Introduction to Cognitive Neuroscience

Lecture Neurons and Glia

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© Paul De Koninck- https://www.sott.net/article/200134-Glia-The-Other-Brain
Hippocampal neurons (green) and glial cells (red).

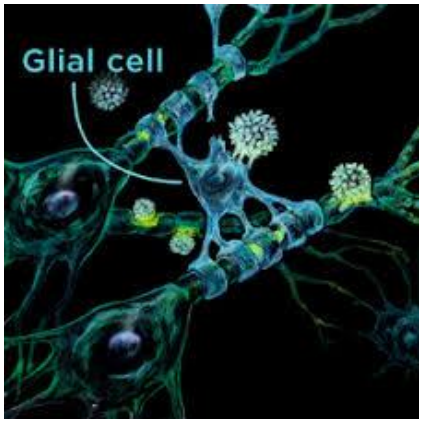
Brain as an organ

- The most sophisticated and complex organ that nature has devised
- All tissues and organs, including brain, in the body consist of **cells**
  - Unlike other organs, We should learn how brain cells work individually and then see how they are assembled to work together
- In neuroscience, there is no need to separate *mind* from *brain*;
- **Neurophilosophy** of brain studies:
  - Fully understanding of the individual brain cells entails understanding the origins of our **mental abilities**

https://snowbrains.com/13-facts-about-the-human-brain-you-didnt-know/human_brain_hands00_2/

Different types of cells in the nervous system

- **Neurons** (about100 billion):
  - **Sense** changes in the environment
  - **Communicate** these changes to other neurons
  - **Command** the body's responses to these sensations
- **Glia** (outnumber neurons by tenfold):
  - **Insulating**
  - **Nourishing** neighboring neurons.
  - Derived from the Greek word for "**glue**,"
    - keep the brain from running out of our ears!



http://www.synapticpotential.com/wp-content/uploads/2018/01/

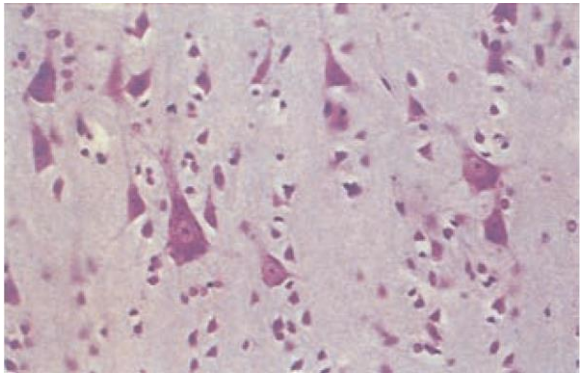
- Chocolate-chip cookie:
  - Neurons are chocolate chips and glia would be the cookie dough
- We focus **90%** of our attention on **10%** of brain cells (big ignorance ☺)

Problems for studying brain cells

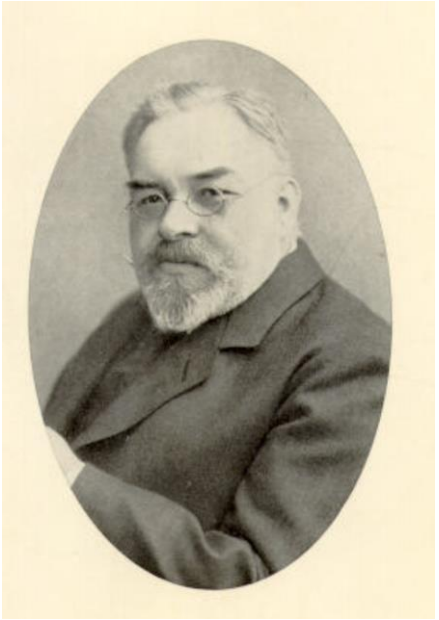
- They are **too small** (~ 0.01–0.05 mm)
  - Using microscope
- The tissue is like a **bowl of Jello**
  - Fixing them by **formaldehyde**
  - Make thick slice by **microtome**
- Brain tissue has **cream-colored** appearance under the microscope
  - Using **stain** to color some, but not all, parts of the cells
- **Histology**:
  - The **microscopic study** of the **structure of tissues**

Nissl stain

- This method stains the **nuclei of all** cells and also stain **clumps of material** surrounding the nuclei of neurons
- These **clumps** are called ***Nissl bodies***
- Advantages:
  - It **distinguishes** neurons and glia
  - It enables histologists to study the arrangement, or **cytoarchitecture**, of neurons in different parts of the brain



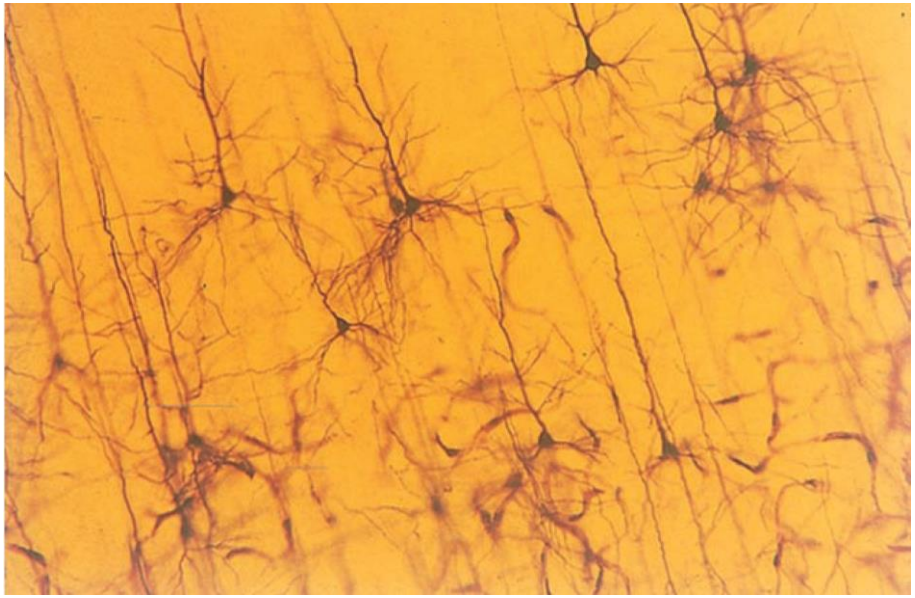
Nissl-stained neurons. A thin slice of brain tissue has been stained with cresyl violet, a Nissl stain. The clumps of deeply stained material around the cell nuclei are Nissl bodies. (Source: Hammersen, 1980, Fig. 493.)



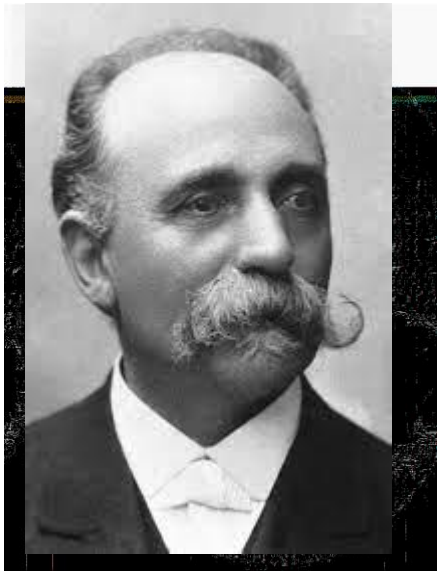
German neurologist in the late nineteenth century

The Golgi Stain

- Soaking brain tissue in a **silver chromate solution**
- This showed **more complex** structure **around the nucleus** that is shown with the Nissl stain



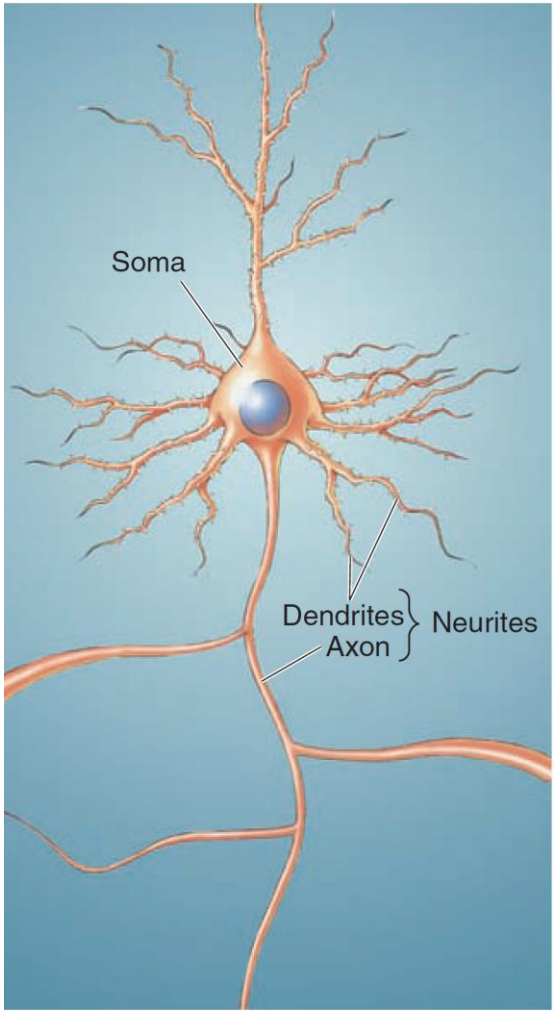
Golgi-stained neurons. (Source: Hubel, 1988, p. 126.)



Camillo Golgi (1843–1926).
(Source: Finger, 1994, Fig. 3.22.)

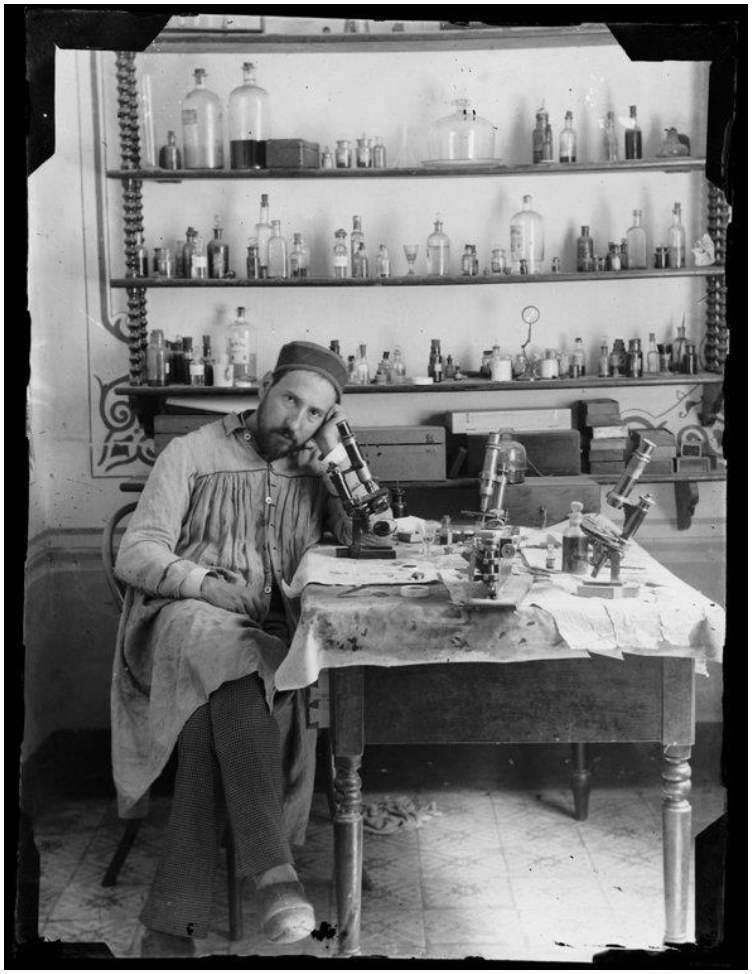
Golgi stain shows that neurons have at least two distinguishable parts:

- **Central region** that contains the **cell nucleus**:
  - **cell body, soma** (plural: somata)
- Numerous thin tubes that radiate away from the central region (**neurites**)
- **Neurites** are of two types: **axons** and **dendrites**
  - Axons must act like "**wires**"
  - Dendrites come in contact with many axons, so they seem act as the "**antennae**"

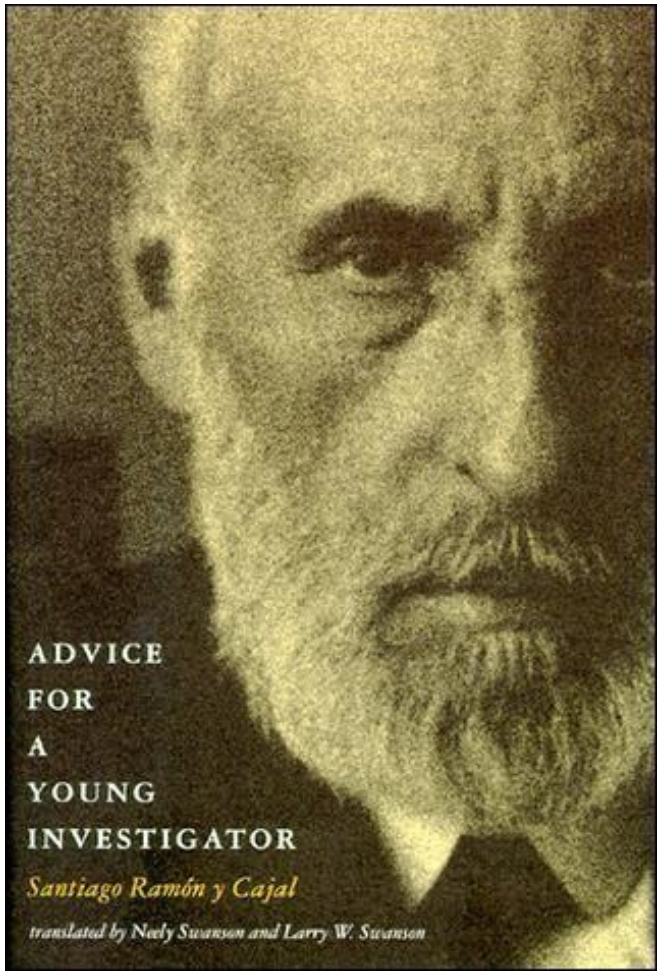


Cajal's Contribution

- He used Golgi method to **greatest effect**
- A skilled histologist and artist who learned about Golgi's method in 1888
- Ironically, Golgi and Cajal drew **completely opposite** conclusions about neurons (as discussed in last lecture)
- **Neuron doctrine (Cajal's view)**, *neurons communicate by contact, not continuity*, vs. Golgi's view that neurites of different cells are *fused together* to form a *continuous reticulum*
- They shared the Nobel Prize in **1906**, although they remained **rivals to the end**



Santiago Ramón y Cajal (1852–1934).



Overview Author(s)

Summary

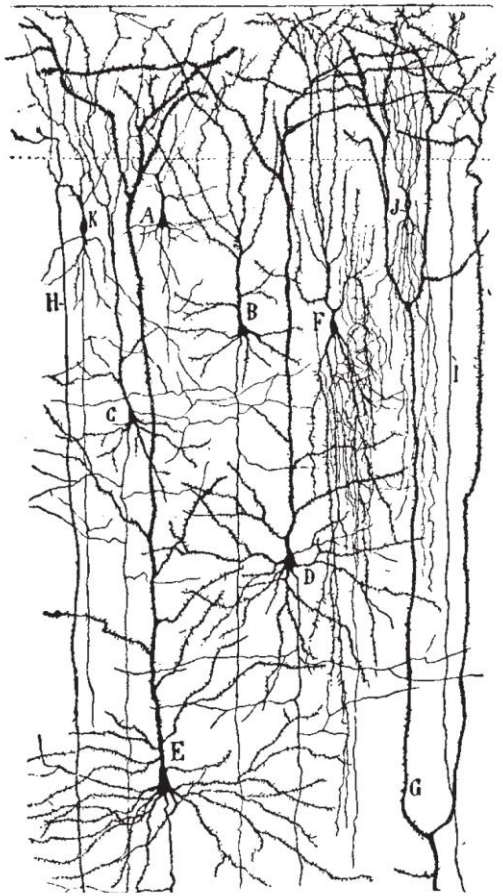
An anecdotal guide for the perplexed new investigator as well as a refreshing resource for the old pro, covering everything from valuable personality traits for an investigator to social factors conducive to scientific work.

Santiago Ramón y Cajal was a mythic figure in science. Hailed as the father of modern anatomy and neurobiology, he was largely responsible for the modern conception of the brain. His groundbreaking works were *New Ideas on the Structure of the Nervous System* and H*istology of the Nervous System in Man and Vertebrates*. In addition to leaving a legacy of unparalleled scientific research, Cajal sought to educate the novice scientist about how science was done and how he thought it should be done. This recently rediscovered classic, first published in 1897, is an anecdotal guide for the perplexed new investigator as well as a refreshing resource for the old pro.

Cajal was a pragmatist, aware of the pitfalls of being too idealistic – and he had a sense of humor, particularly evident in his diagnoses of various stereotypes of eccentric scientists. The book covers everything from valuable personality traits for an investigator to social factors conducive to scientific work.

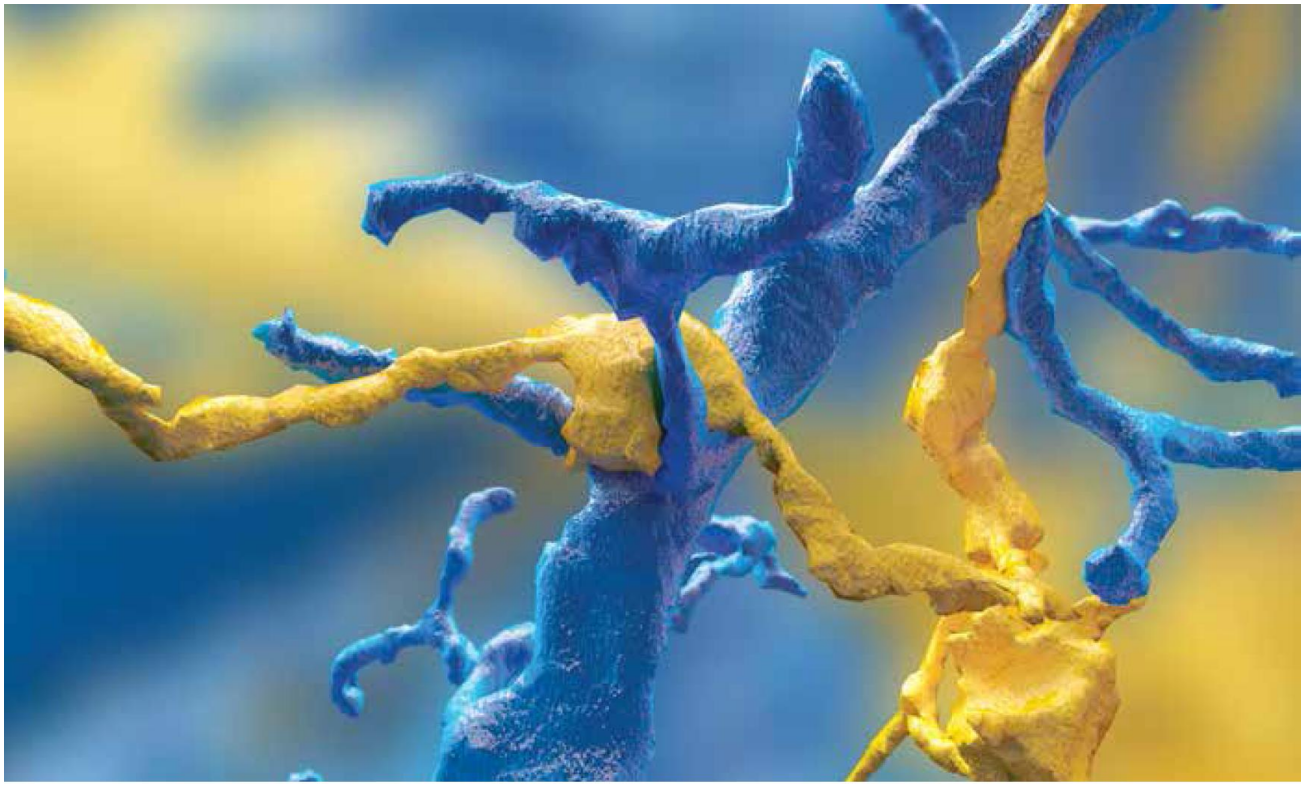
The proof of neuron doctrine 1950s

- **Some scales**:
  - **Neuron diameter**: ~*20 μ m*
  - **Unaided eye** resolution: ~*0.1 mm*
  - **Light microscope** resolution : ~*0.1 μ m*
  - Space **between neurons** measures: ~*0.02 μ m (20 nm).*
- **Electron microscope** resolution : *0.1 nano m* (a million times better than the unaided eye)
- It help us to peer into brain tissue **that is still alive**



One of Cajal's many drawings of brain circuitry

Neurites in contact, not continuity

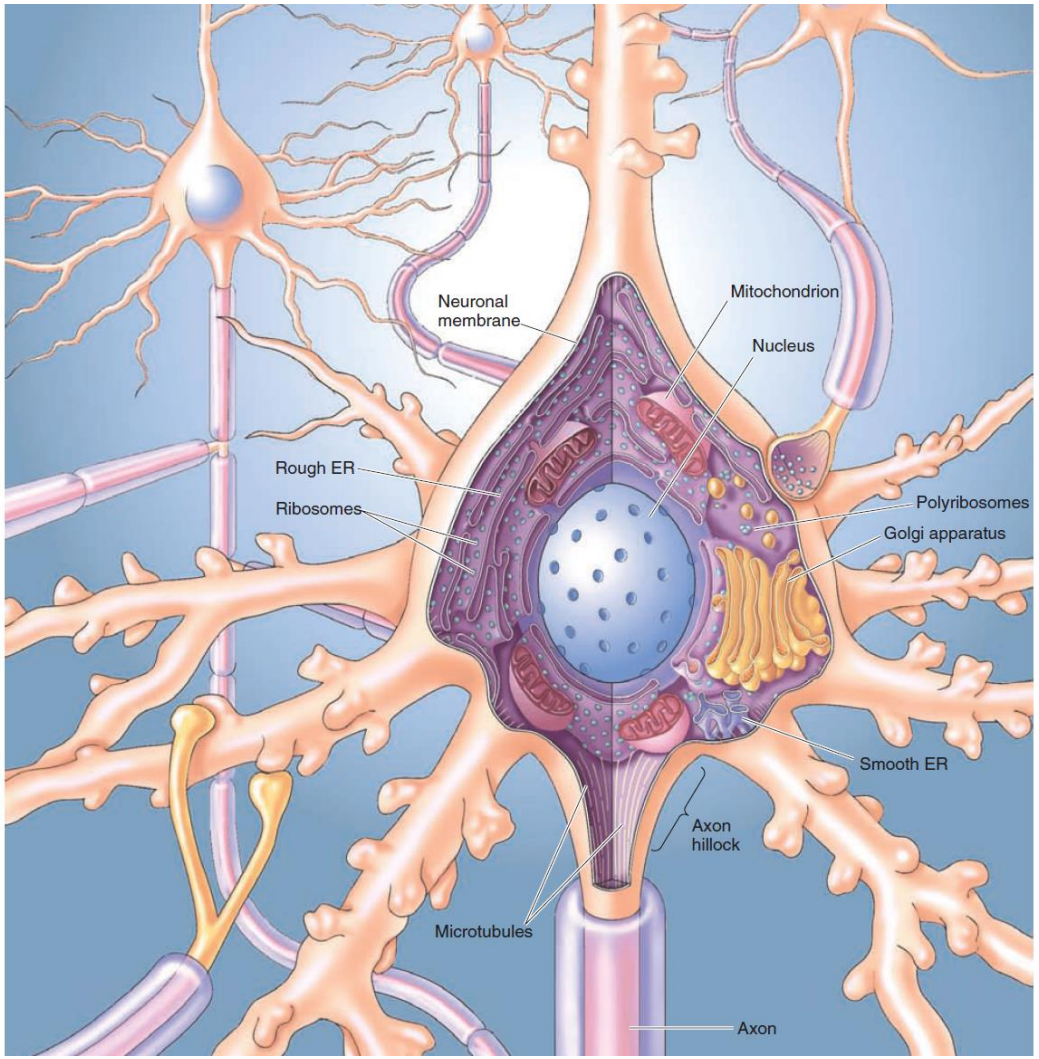


Neurites in contact, not continuity. These neurites were reconstructed from a series of images made using an electron microscope. The axon (colored yellow) is in contact with a dendrite (colored blue). (Source: Courtesy of Dr. Sebastian Seung, Princeton University, and Kris Krug, Pop Tech.)

Prototypical neuron

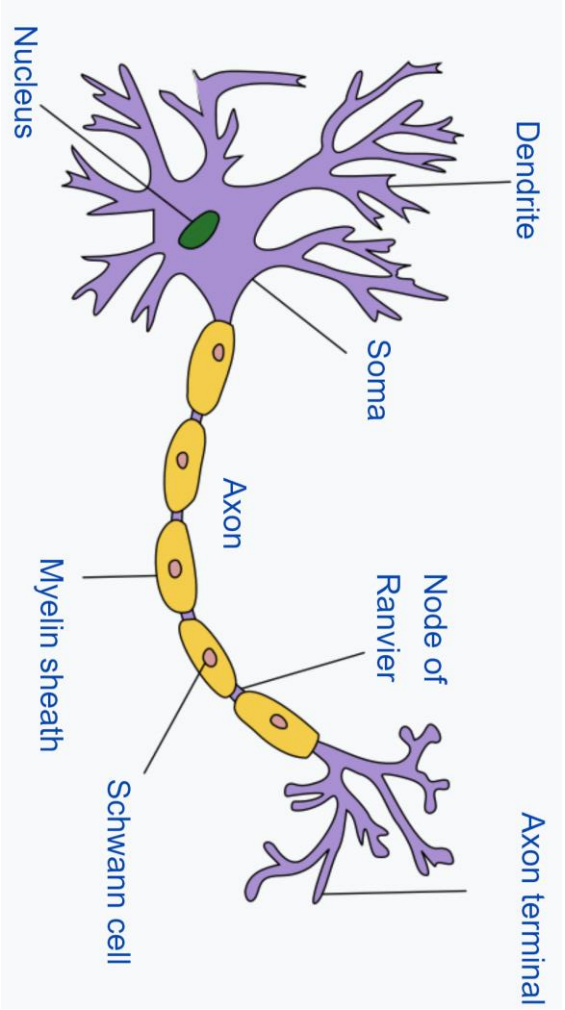
- Consists of several parts: the **soma**, the **dendrites**, and the **axon**

- Neuronal membrane lies like a circus tent on internal scaffolding, giving each part of the cell its special three-dimensional appearance



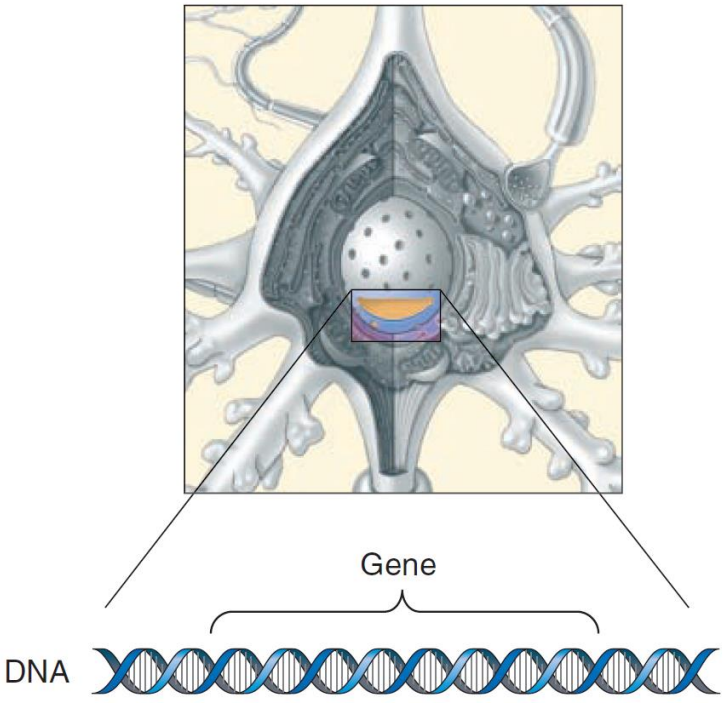
The Soma

- Cell body of the typical neuron is about **20 µm** in diameter.
- **Cytosol:**
  - Watery fluid inside the cell separated by membrane
  - It is a salty, potassiumrich solution
- **Organelles**:
  - **Membrane-enclosed structures** within the soma
  - Neuron contains the same organelles that are found in all animal cells:
    - Most important ones: nucleus, the rough endoplasmic reticulum, the smooth endoplasmic reticulum, the Golgi apparatus, and the mitochondria.
- **Cytoplasm**:
  - All things inside membrane except for **nucleus**

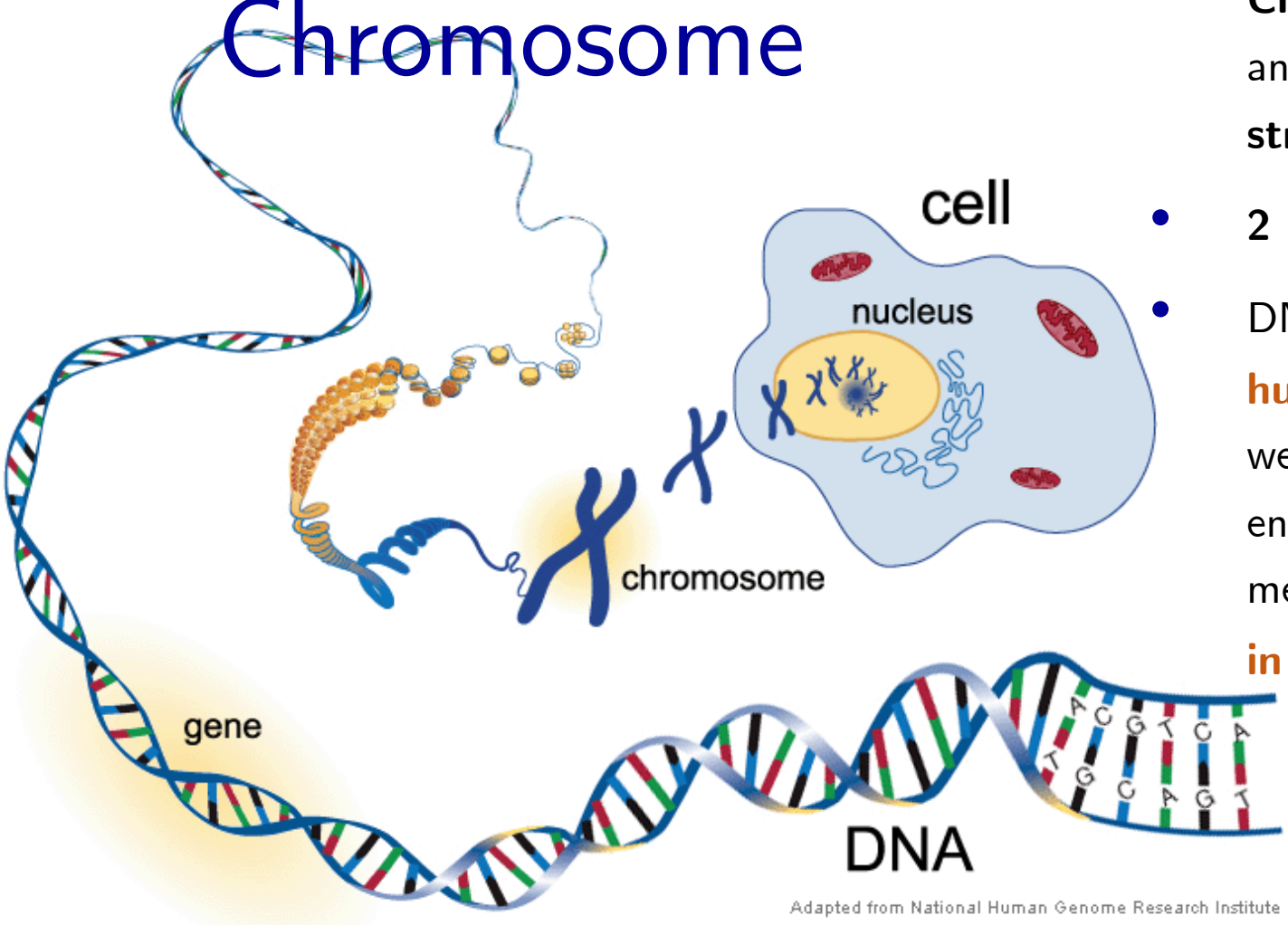


The Nucleus

- Within the nucleus are **Chromosomes** which contain the **genetic material**, **DNA** (**deoxyribonucleic acid**)
- **DNA** was **passed on to you by parents** and contains the *blueprint for your entire body*
- DNA are **similar** for all cells; **genes** make differences
- Genes: **specific parts of the DNA** that are used to assemble the cell
  - **Genes length**: from 0.1 µm to several micrometers



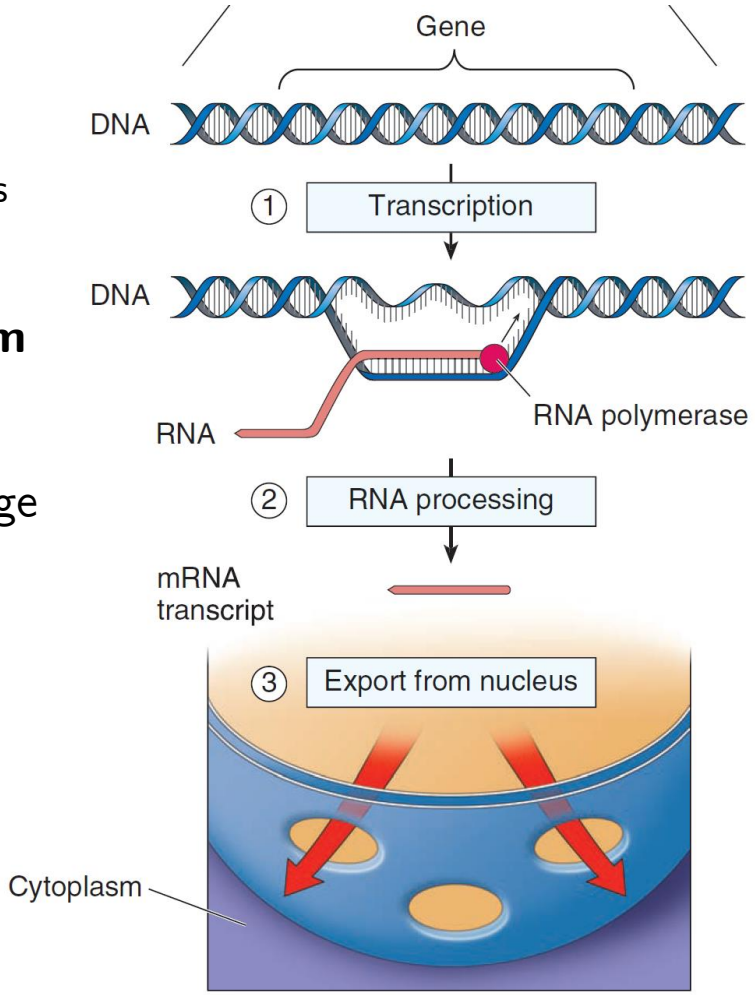
Chromosome



- **Chromosome** contains an uninterrupted **double-stranded braid of DNA**,
- **2 nm wide**
- DNA from the **46 human chromosomes** were laid out straight, end to end, it would measure more than **2 m in length**

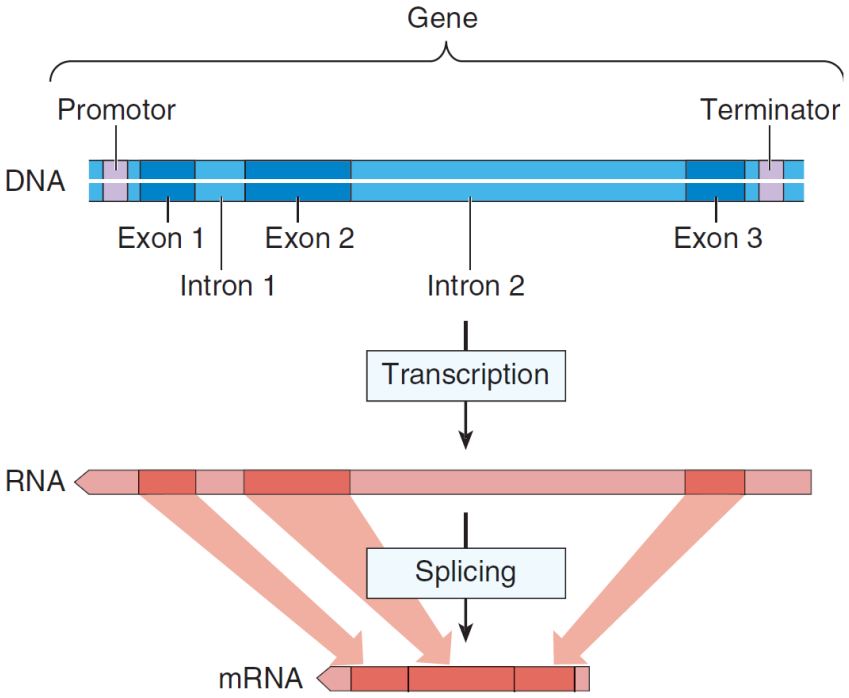
Gene expression

- **Gene expression**
  - **Reading of the DNA** to synthesis of molecules called **proteins**
- Synthesis of proteins occurs in the **cytoplasm**
- DNA **never leaves the nucleus** so there is **intermediary** that carries the genetic message named **messenger ribonucleic acid**, or **mRNA**.
- RNA molecules are synthesized by **RNA polymerase** and then processed into messenger RNA to carry the genetic instructions



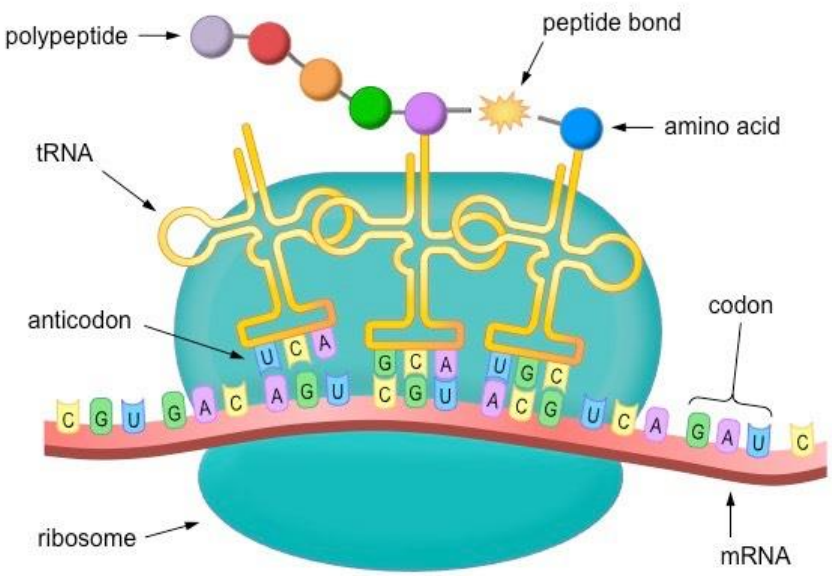
Transcription

- The process of assembling a piece of mRNA that **contains the information of a gene**
- Transcription is initiated at the **promoter** region of the gene and stopped at the **terminator** region.
- The initial RNA must be **spliced** to remove the *introns* that do not code for protein.
- Coding sequences are called *exons*.
- **Single gene** can ultimately give rise to several different mRNAs and **protein**



Translation and protein synthesis

Assembling of proteins from amino acids (20 kinds) under the **direction of the mRNA**



https://hypothes.is/a/0blB3PDQEeiSQN-OCuNKiQ

Molecular biology and molecular neurobiology

- Studying **the DNA of the nucleus** and the **synthesis of protein** molecules in the cell
- Molecular neurobiologists use the information contained in the genes to determine the **structure and functions of neuronal proteins**

Expressing the mind ☺

- **Human Genome Project** identified all of the approximately **20,000 genes** in human DNA.
- The **brain is the product of the genes expressed** in it.
- Differences in gene expression between a normal brain and a diseased brain, or a brain of unusual ability, can be used to identify the **molecular basis** of the observed symptoms or traits.

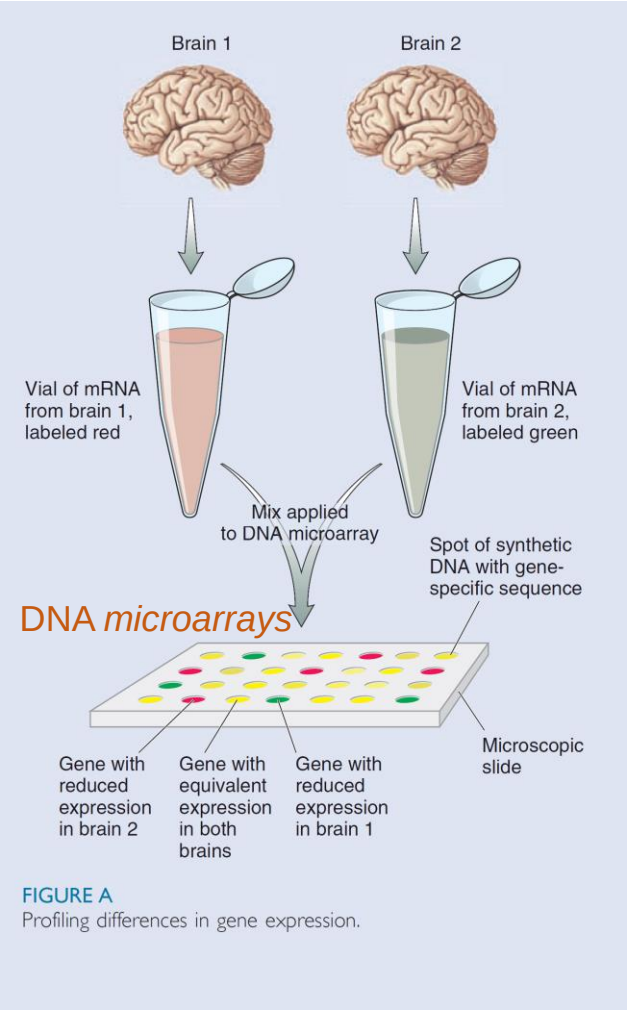
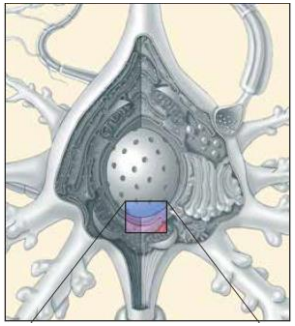
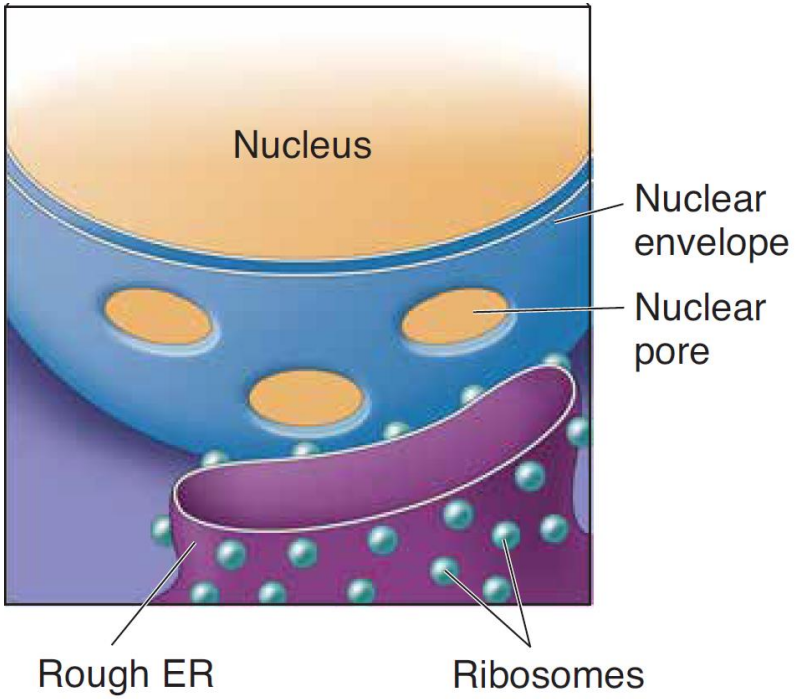


FIGURE A
Profiling differences in gene expression.

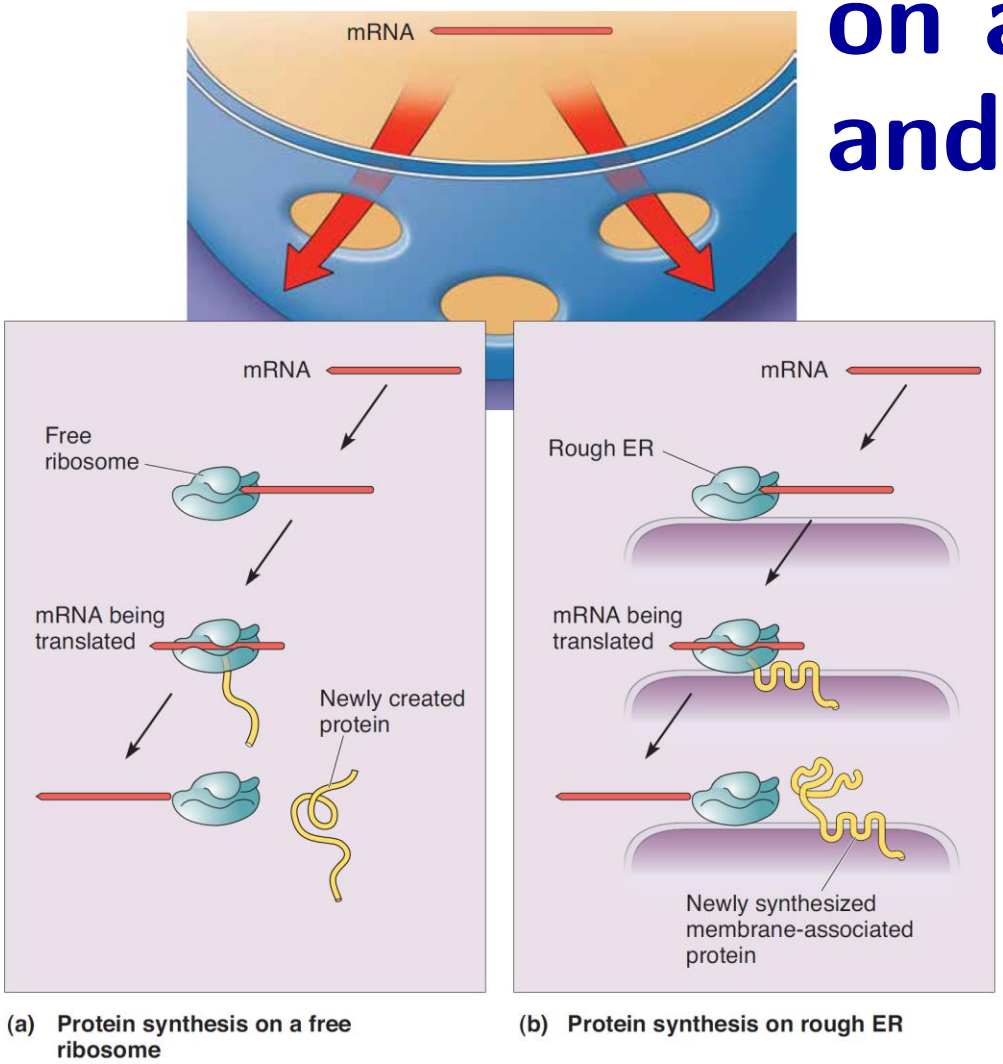
Rough Endoplasmic Reticulum

- The **stacks near nucleus**, **abounds** in neurons, far more than in glia. (another name: Nissl bodies, it **stains** with Nissl dyes).
- Rough ER is a **major site of protein synthesis** in neurons
- RNA transcripts **bind** to the **ribosomes**, and the ribosomes translate the instructions contained in the **mRNA** to assemble a protein molecule **from raw material in the form of amino acids**.
- **Ribosomes:** dense globular structures (25 nm)





Protein synthesis on a free ribosome and on rough ER.



(a) Protein synthesis on a free ribosome

(b) Protein synthesis on rough ER

(a) Proteins synthesized on **free** ribosomes are **destined for the cytosol**.

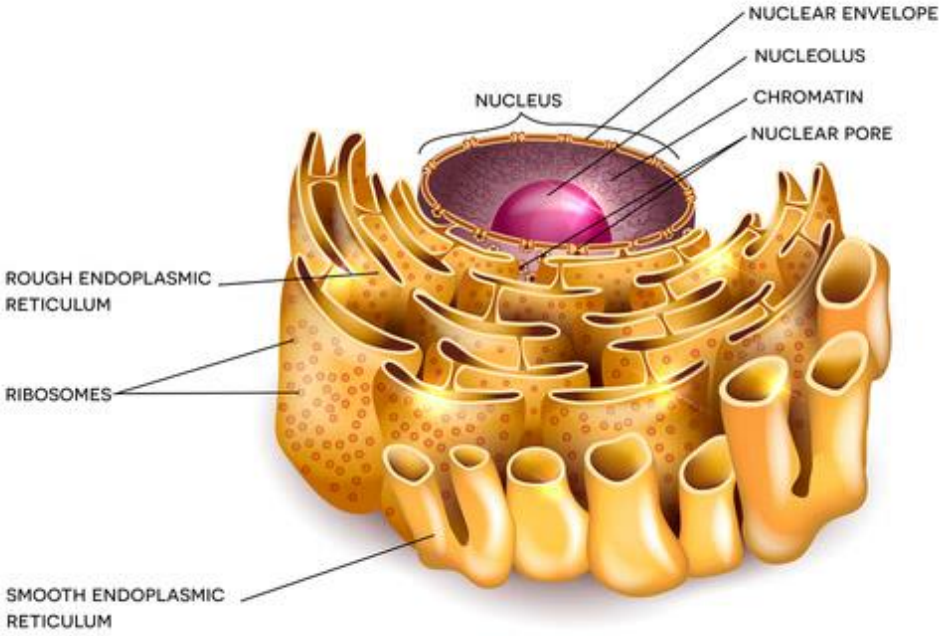
(b) Proteins synthesized on the **rough ER** are destined to be enclosed by or **inserted into the membrane**.

Neurons have **so much** rough ER because, special membrane proteins are what give these cells their remarkable information-processing abilities.

Smooth Endoplasmic Reticulum

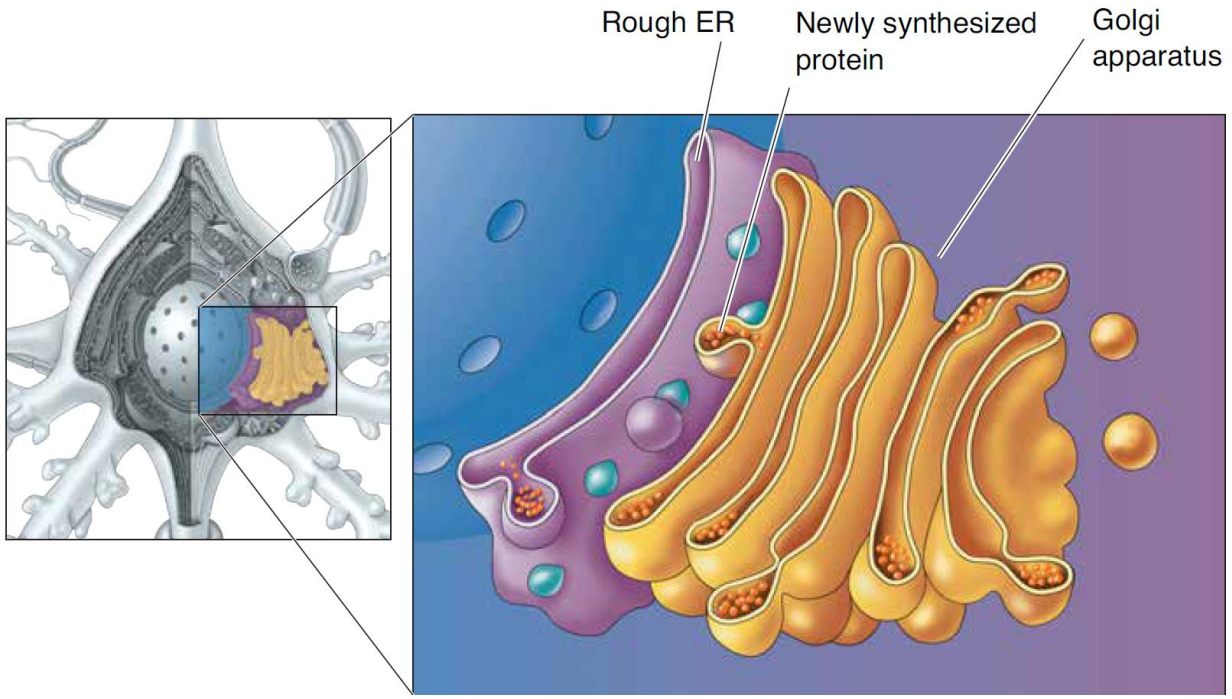
- Look a lot like **rough ER without the ribosomes**

- **Function of smooth ER:**
  - **Folding** protein, giving them their three-dimensional structure
  - **Regulating** internal concentrations of substances such as **calcium**.

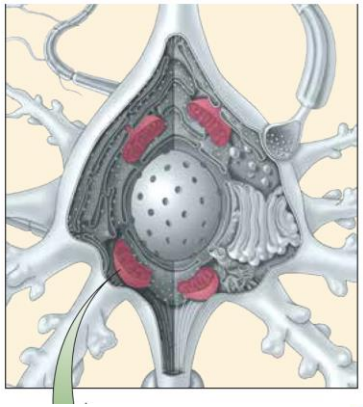


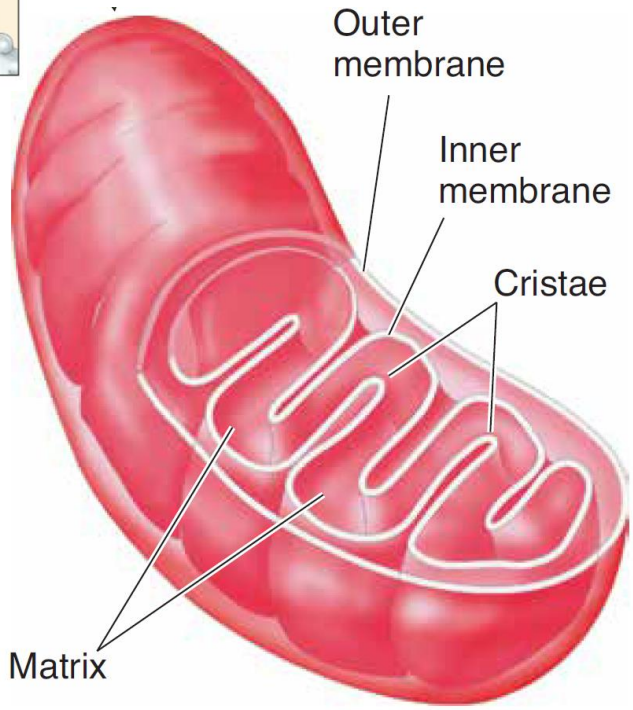
Golgi Apparatus

- The stack of **membrane-enclosed disks** in the soma
- First described in 1898 by **Camillo** Golgi
- **Function**: **Sorting** of certain proteins that are **destined** for **delivery** to different parts of the neuron, such as the axon and the dendrites
  - it packages proteins into membrane-bound vesicles inside the cell before the vesicles are sent to their destination



The Mitochondrion (plural: mitochondria)



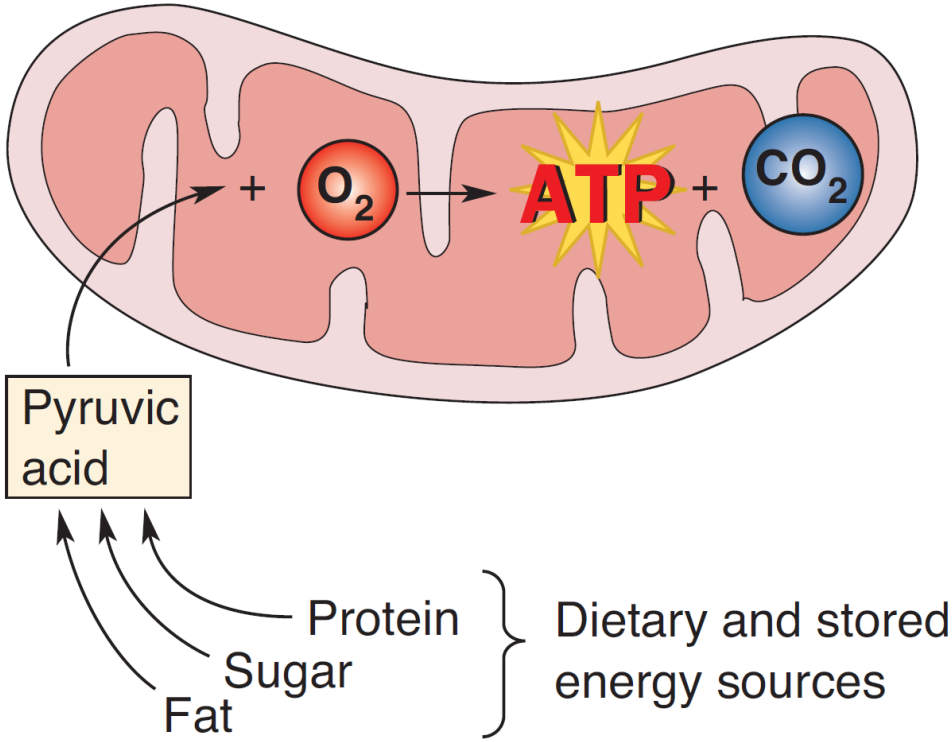


- The **1 μm sausage** shaped structures

- **Components of a mitochondrion:**
  - Multiple folds of inner membrane called ***cristae*** (singular: crista)
  - Inner space called ***matrix***

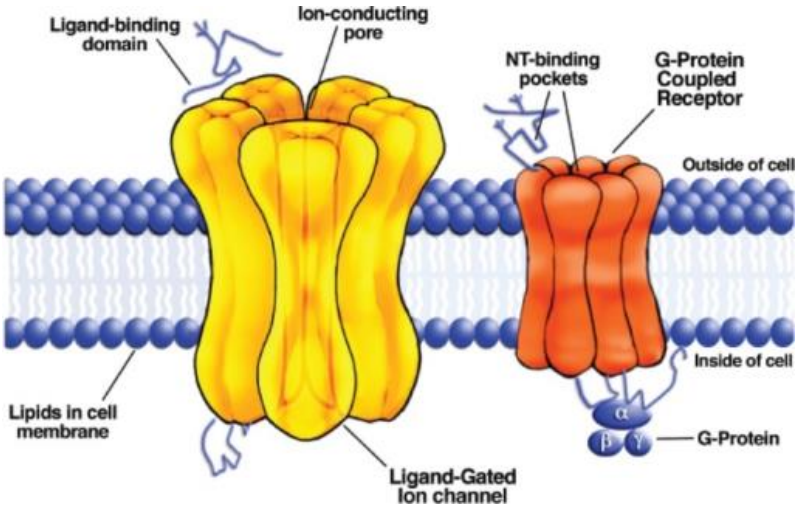
Cellular respiration

- Mitochondrion **inhales**:
  - it pulls inside **pyruvic acid** (derived from sugars and digested proteins and fats) and oxygen, both of which are floating in the cytosol
- **Within** mitochondrion (***Krebs Cycle***):
  - ***Electron-transport chain*** results in the **addition of phosphate** to adenosine diphosphate (**ADP**), yielding **adenosine triphosphate (ATP)**
- Mitochondrion **exhales**:
  - 17 ATP molecules are released for every molecule of pyruvic acid
- ***ATP*** *is the* ***energy currency*** *of the cell:*
  - The **chemical energy** **stored in ATP** **fuels** most of the biochemical reactions of the neuron
  - **e. g. breakdown** of ATP into ADP to pump certain substances



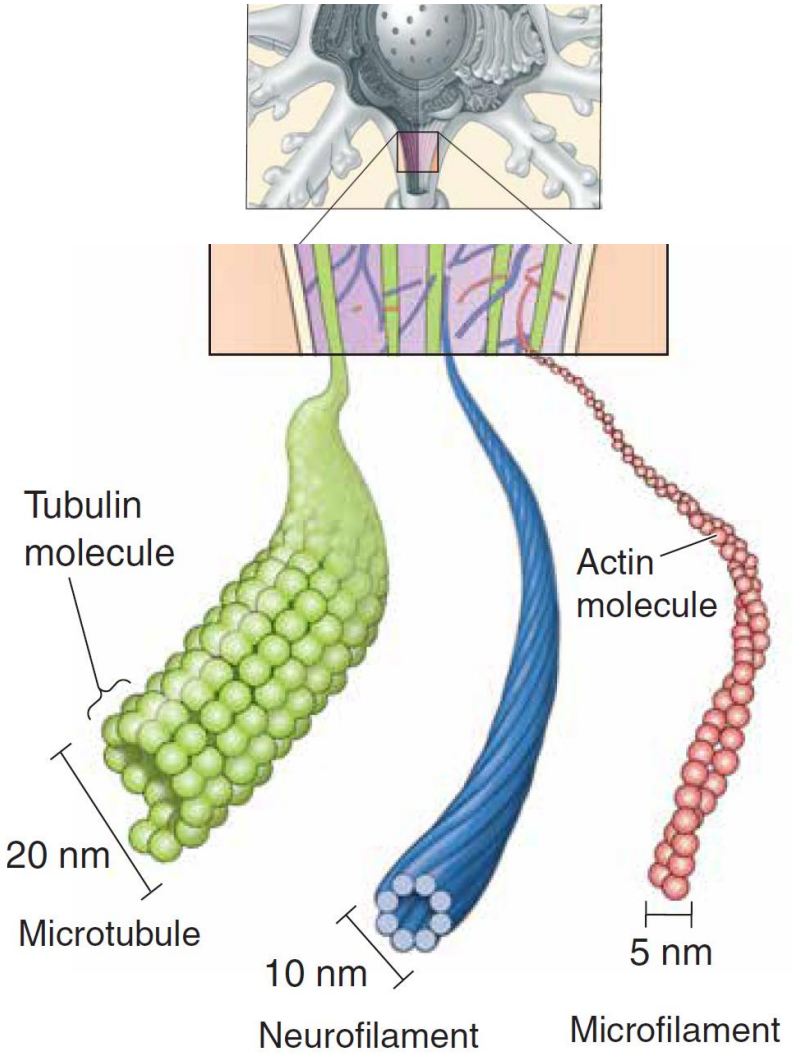
The Neuronal Membrane

- **5 nm** thick
- Membrane-associated proteins:
  - **Protein composition** varies depending on whether it is in the soma, the dendrites, or the axon
- We'll spend much of three of the next lectures looking at how the membrane

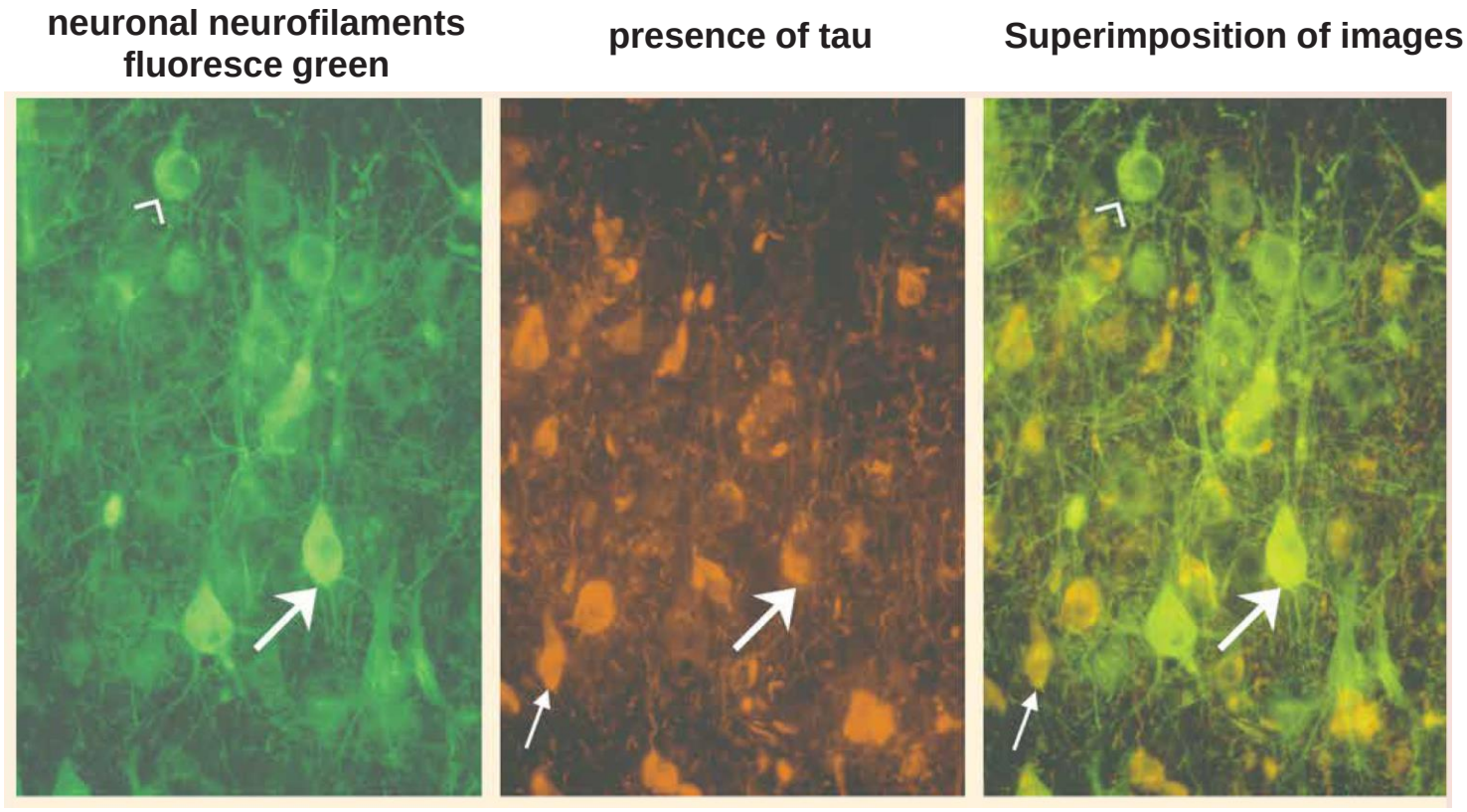


Cytoskeleton

- The **scaffolding** that gives the neuron its **characteristic shape**
- The "**bones**" of the cytoskeleton:
  - Microtubules
  - Microfilaments
  - neurofilaments
- ***Alzheimer's disease*** characterized by the disruption of the cytoskeleton
  - *microtubule-associated proteins*, *MAPs*, anchor the **microtubules**
  - Pathological changes in an axonal MAP, **called *tau***, have been implicated in the **dementia** that accompanies Alzheimer's disease

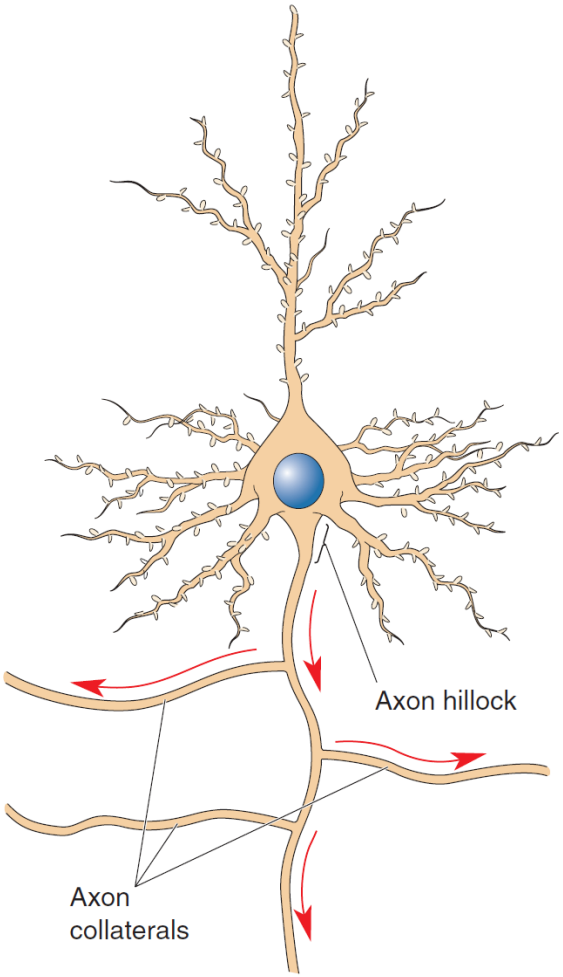


In Alzheimer's disease, the tau detaches from the microtubules and accumulates in the soma



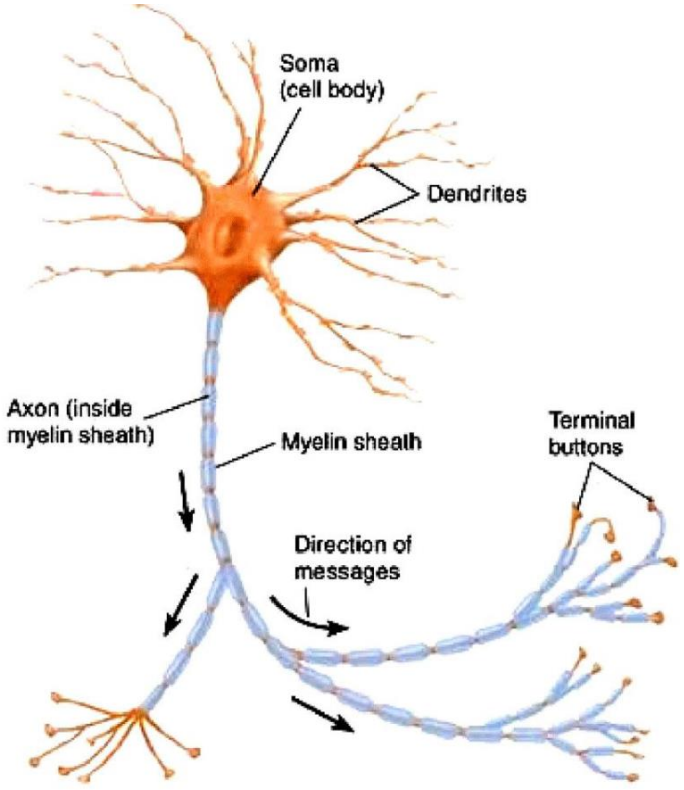
The Axon

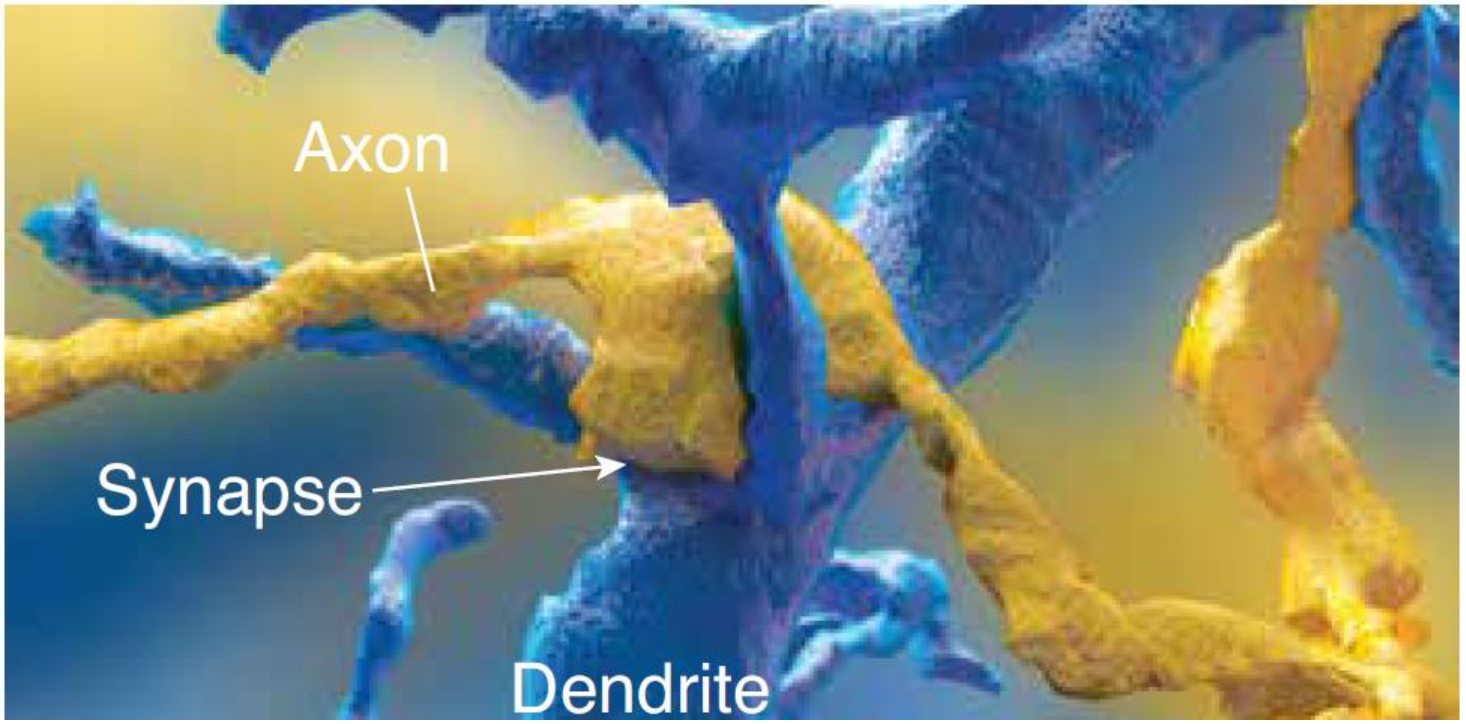
- The **Structure found only in neurons** that is highly specialized for the **transfer of information** over distances in the nervous system.
- **Differences**:
  - **No rough ER** and few, if any, free ribosomes(there is no protein synthesis in the axon)
  - **Protein composition** of the axon **membrane** is fundamentally different
- **Size**:
  - from less than a **millimeter** to over a **meter** long
- **Axon collaterals**
  - Axon branches to communicate with different parts of the nervous system
  - **Exception** is ***recurrent collaterals***: **self** or neighbors contact.
- **Diameter:**
  - From 1 to 25 µm; 1mm in squid
  - The **thicker** the axon, the **faster** the impulse travels



The Axon Terminal

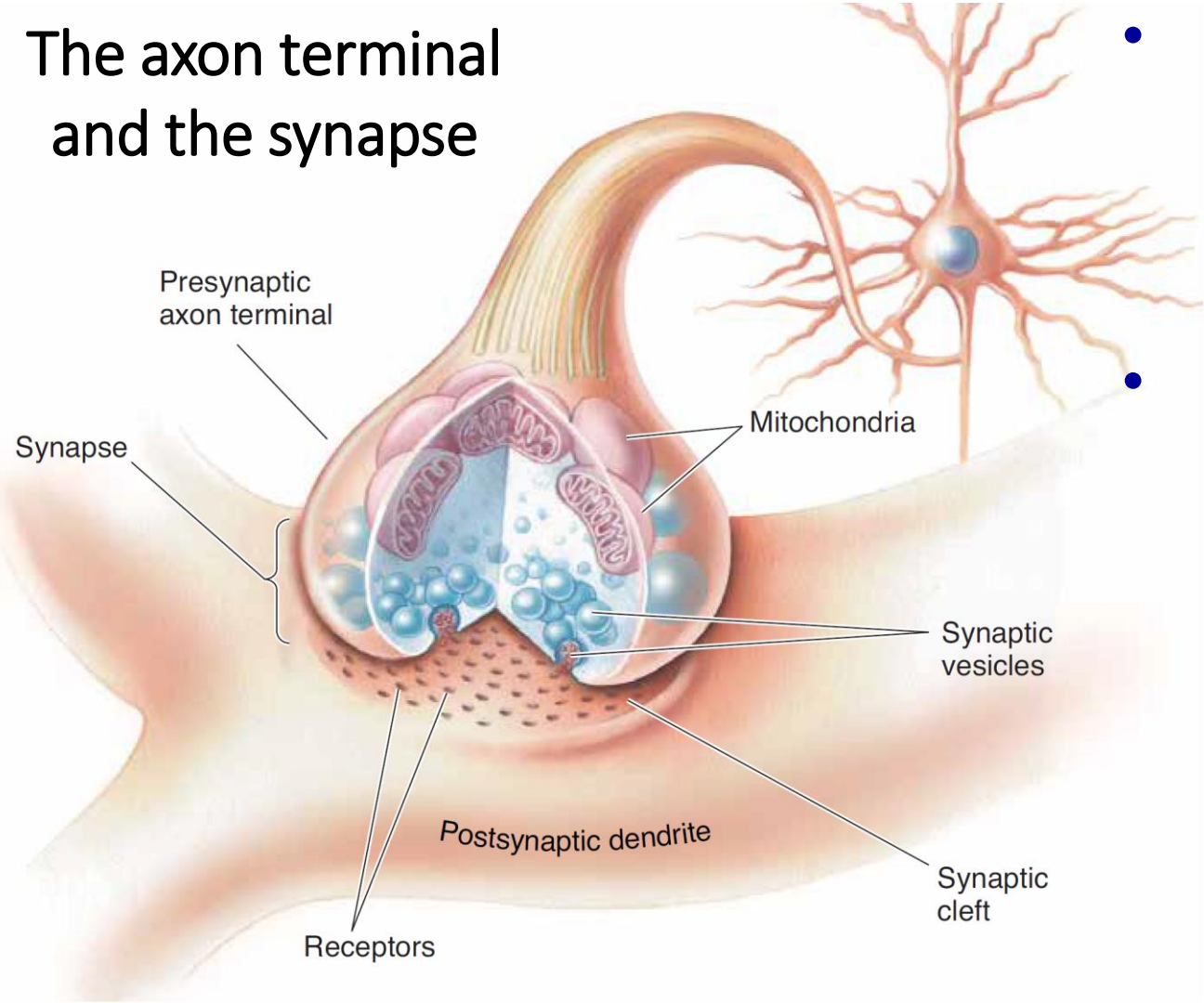
- Terminal is a **site** where the axon comes in **contact** **with other neurons**
- **Also named as terminal bouton**
  - **(**French for "button") **:** appears as a swollen disk
- Point of contact is called the **synapse:**
  - from the Greek, meaning **"to fasten together."**
- **Making synapse** provides **innervation**.
- **Terminal features**
  - No **microtubules**
  - Small bubbles of membrane, called **synaptic vesicles** (~50 nm in diameter)
  - **Numerous mitochondria**, indicating a high energy demand





An axon (colored yellow) makes a synapse on a dendrite (colored blue) as they cross. This synapse was reconstructed from a series of images made using an electron microscope

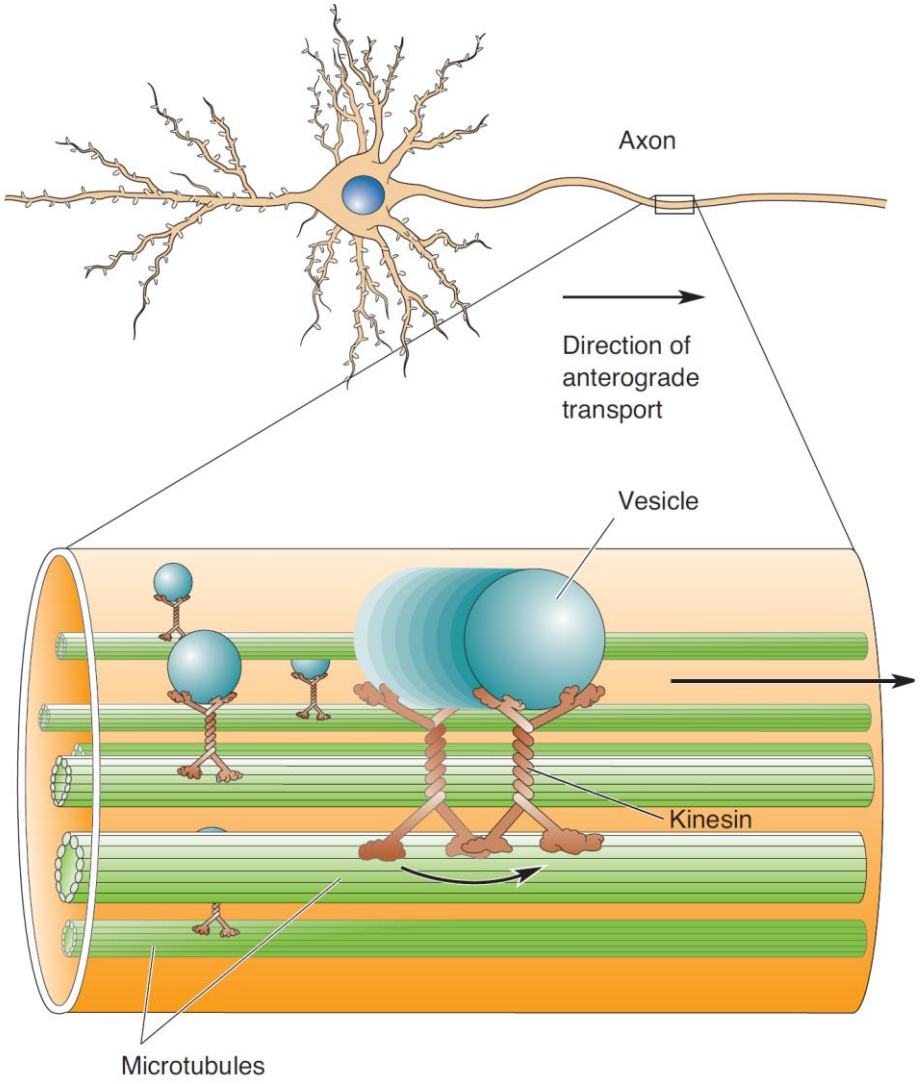
The axon terminal and the synapse



- **Electrical-to-chemical-to-electrical** transformation of information makes possible many of the brain's **computational abilities**
- **When a nerve impulse arrives in the presynaptic axon terminal:**
  - **neurotransmitter** molecules are released from synaptic vesicles into the **synaptic cleft**.
  - Neurotransmitter then binds to specific **receptor proteins**, causing the generation of electrical or chemical signals in the **postsyaptic** cell.

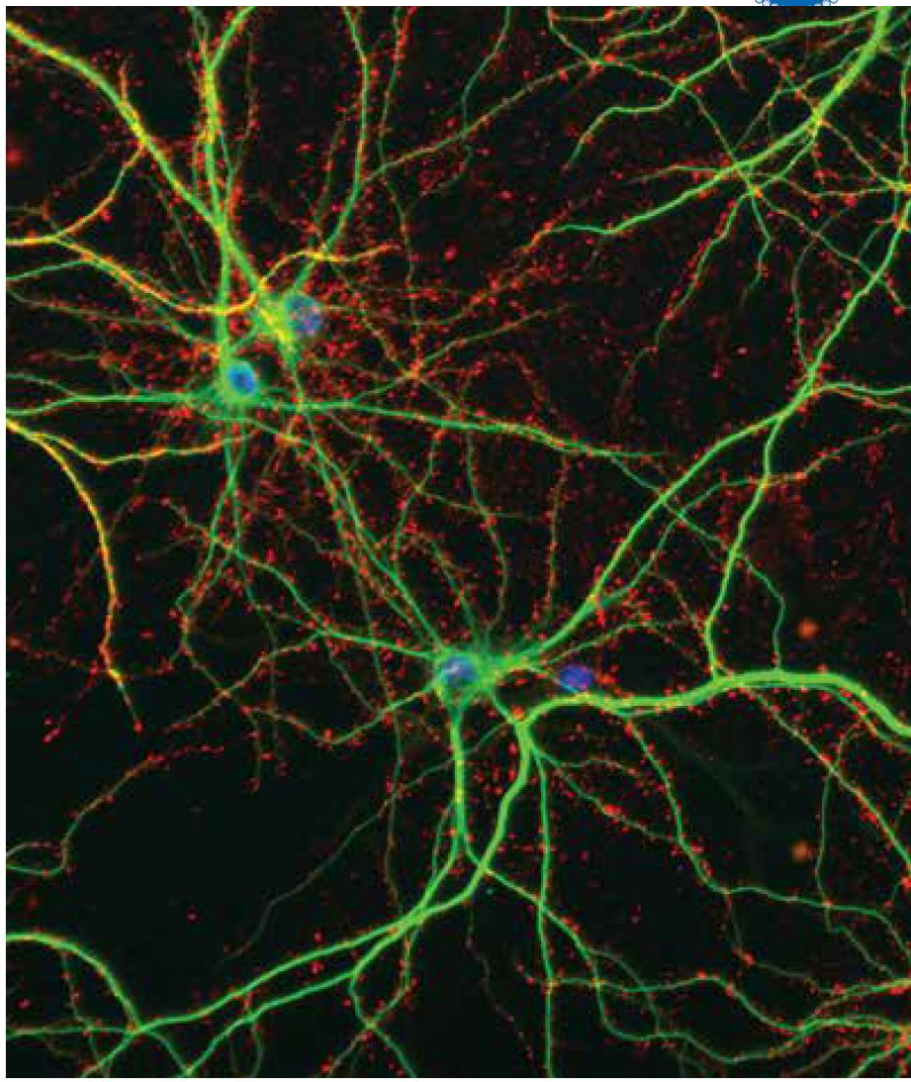
Axoplasmic Transport

- **Absence of ribosomes** in axones means that the proteins of the axon must be synthesized in the soma and then **shipped** down the axon
- ***Slow axoplasmic transport*** (1–10 mm per day)
  - Tiding a thread around an axon and found accumulation of material on the soma side
- ***Fast axoplasmic transport*** (1000 mm per day)
  - Discovered by **injecting** the somata of neurons with **radioactive amino acids**
- **Axoplasmic Transport**
  - A mechanism for the movement of material **on the microtubules** of the axon **using ATP**
  - **Anterograde transport** (kiesin)
  - **Retrograde transport** (from terminal to soma, dynein)



Dendrites

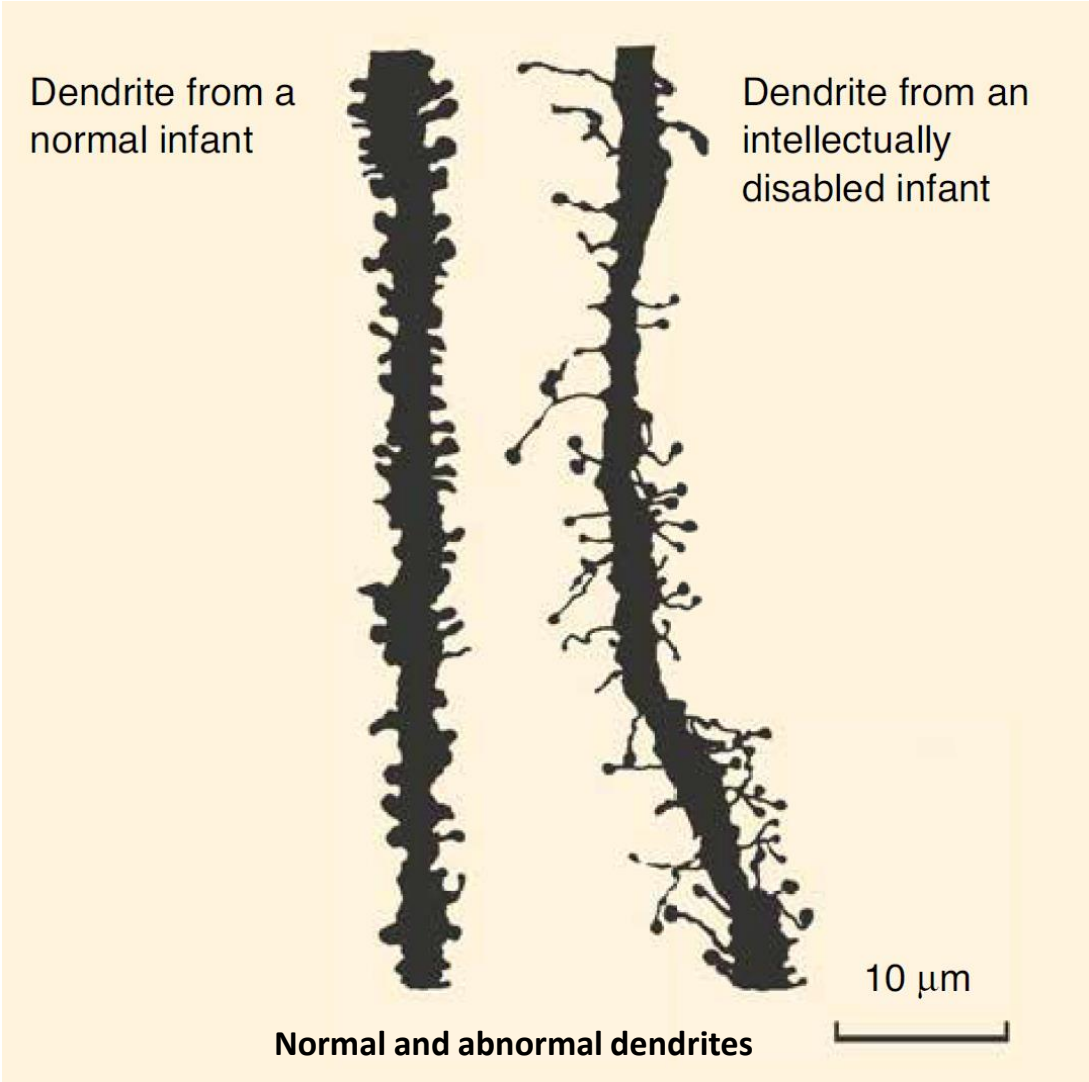
- Derived from the Greek for "**tree**"
- The **wide variety of shapes** and sizes of **dendritic trees** and dendritic branches are used to **classify** different groups of neurons.
- Function as the **antennae** of the neuron; therefore they are covered with thousands of **synapses**
- **Receptors:**
  - **Specialized protein molecules** that **detect the neurotransmitters** in the synaptic cleft.



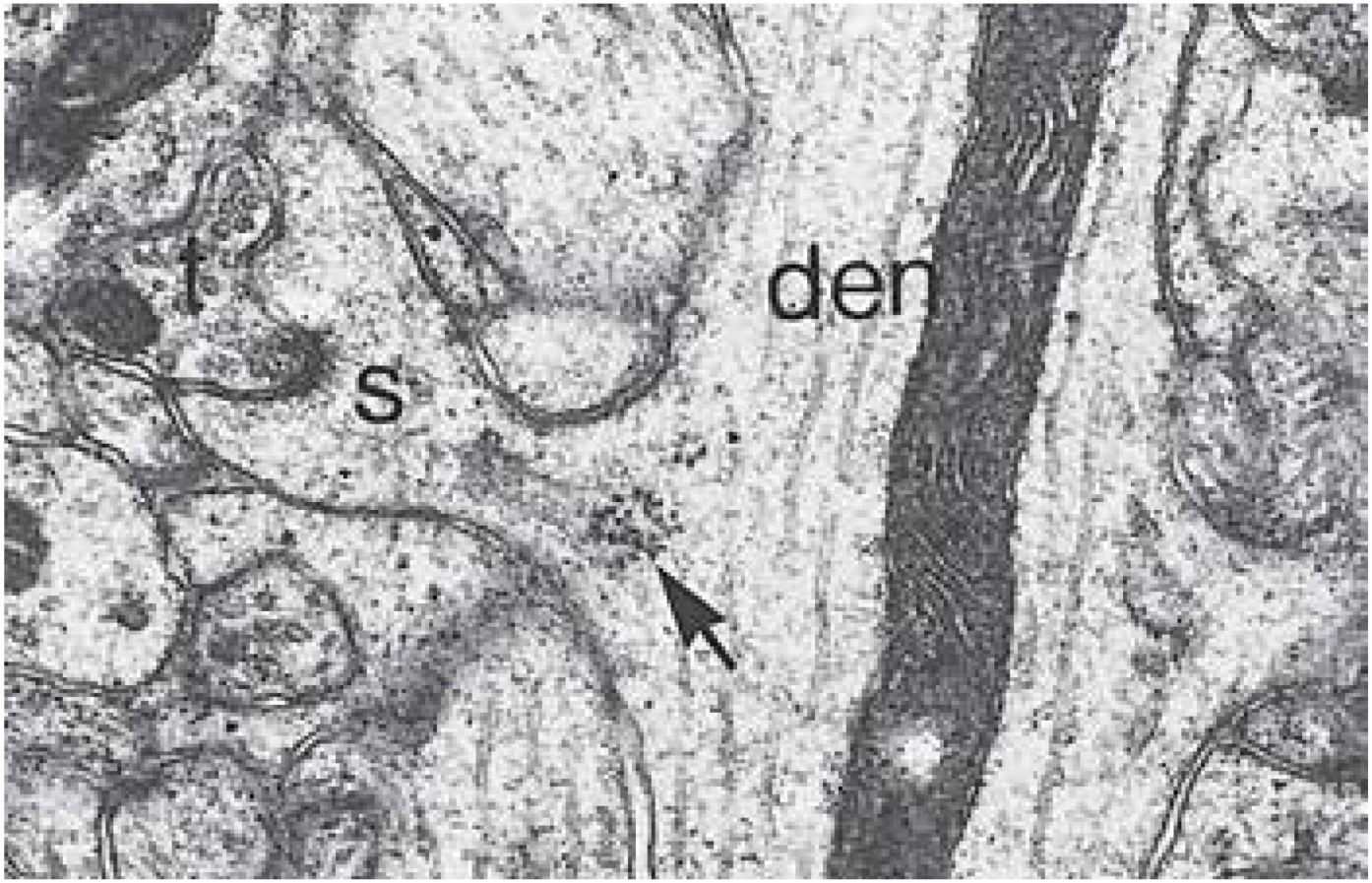
Dendritic spines

- Dendrites of some neurons are covered with **specialized structures** called **dendritic spines**
- Spine structure is sensitive to the **type and amount of synaptic activity**.
- **Changes in spines** have been shown to occur in the brains of individuals with **cognitive impairments**
- **Polyribosomes** can be observed in dendrites:
  - Often right **under spines**
  - **Protein synthesis** for information storage

Intellectual Disability and Dendritic Spines



Normal and abnormal dendrites

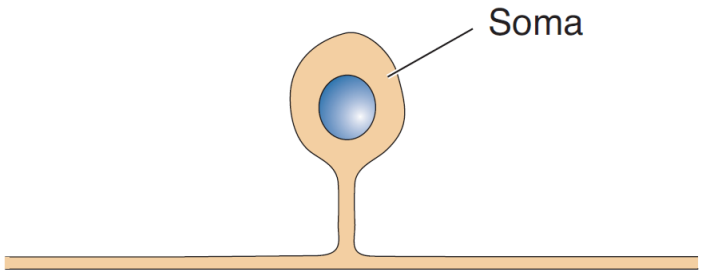


Postsynaptic polyribosomes. This electron micrograph shows a dendrite (den) with a cluster of polyribosomes (arrow) at the base of a dendritic spine (s) receiving a synapse from an axon terminal (t).

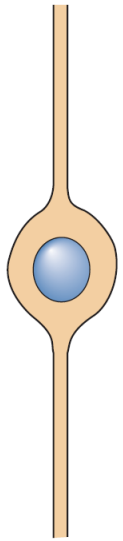
Classifying Neurons

- **Classification Based on Neuronal Structure**
  - **Number of Neurites**
  - **Dendrites**
  - **Connections**
  - **Axon Length**
- **Classification Based on Gene Expression**

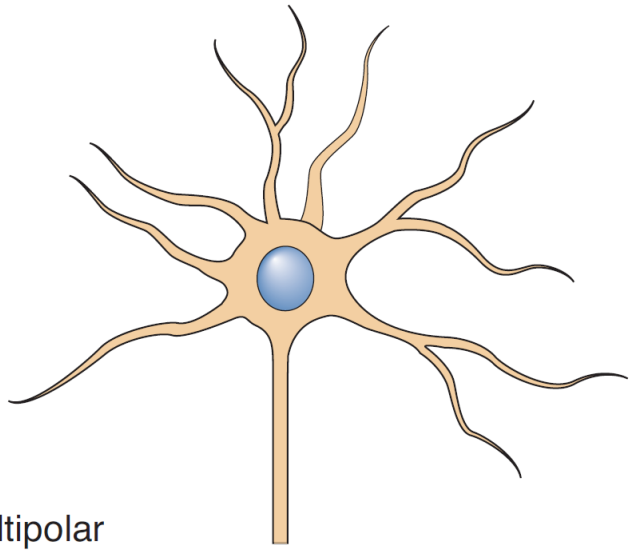
Classification Based on the Number of Neurites



Unipolar



Bipolar

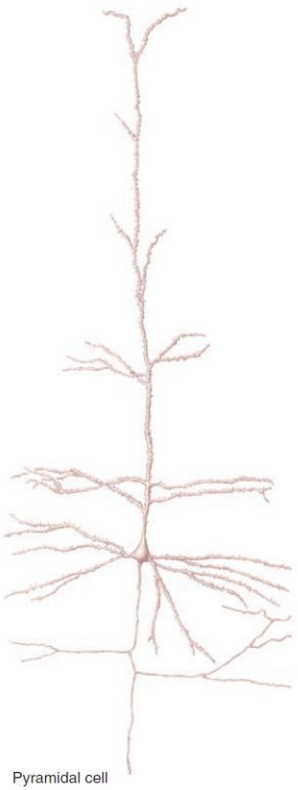


Multipolar

Most neurons in the brain are **multipolar**

Classification Based on Dendrites

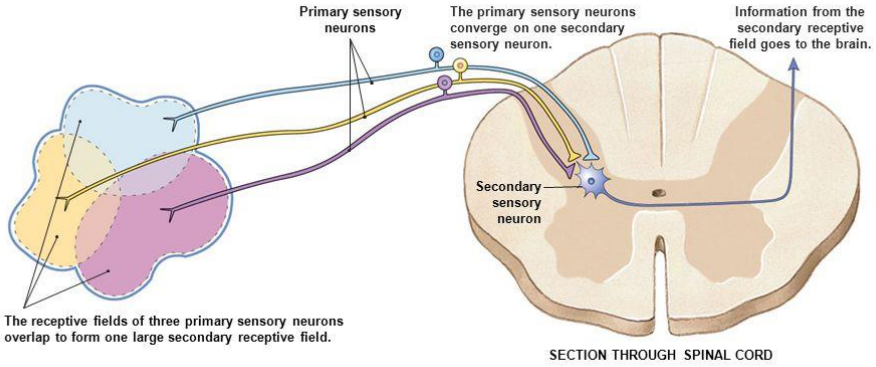
- They vary **widely**
  - Double bouquet cells
  - Chandelier cells
  - Alpha cells
- in the **cerebral cortex:**
  - **Pyramidal** (pyramid shaped)
  - **Stellate** (star shaped)
- **Spine**:
  - **Spiny:** dendrites have spines
  - **Aspinous:** those that do not
- All **pyramidal** cells are **spiny**. However **stellate** cells can be either spiny or aspinous.


Pyramidal cell

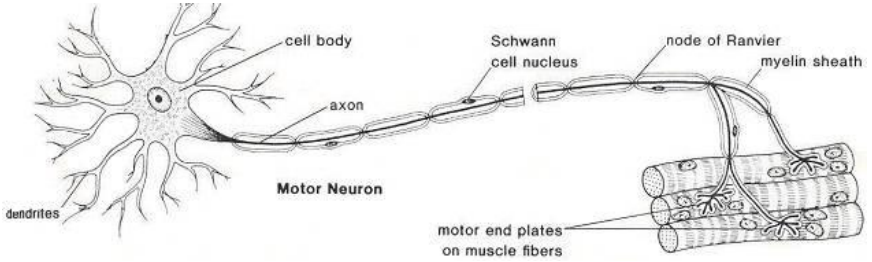

Stellate cell

Classification Based on Connections

primary sensory neurons



motor neurons



Classification Based on Axon Length

- **Long axons** that extend from one part of the brain to the other
  - **Golgi type I neurons , or projection neurons**
  - **e. g. pyramidal cells**

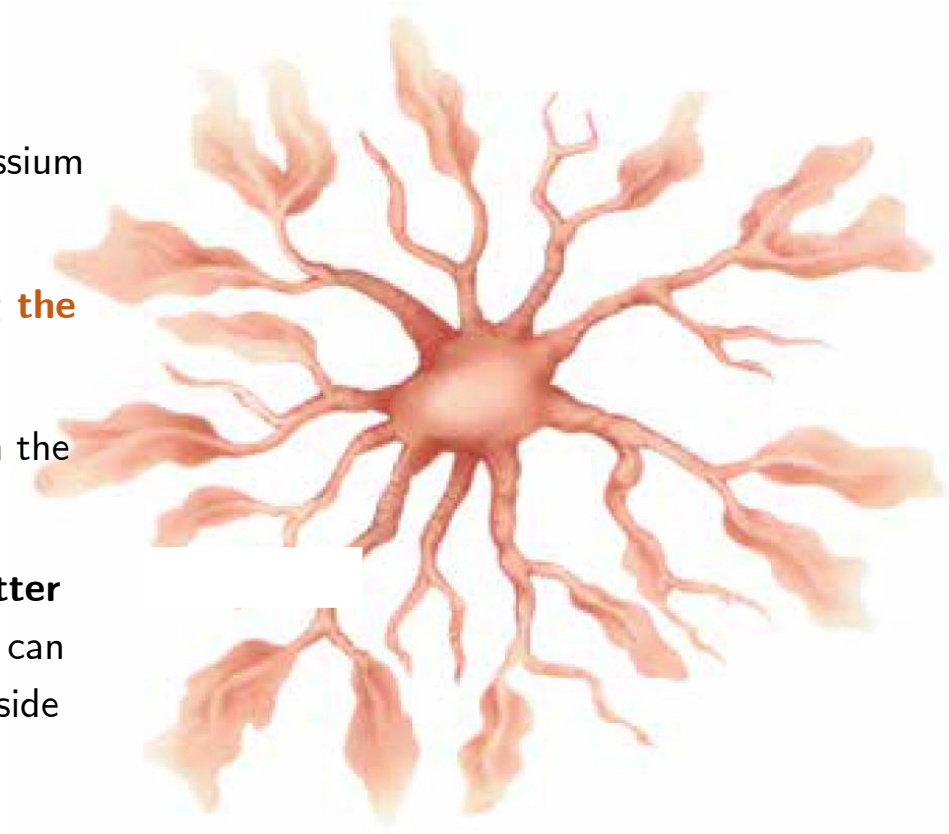
- **Short axons** that do not extend beyond the vicinity of the cell body
  - **Golgi type II neurons , or local circuit neurons**
  - **e. g. Stellate cells**

Classification Based on Gene Expression

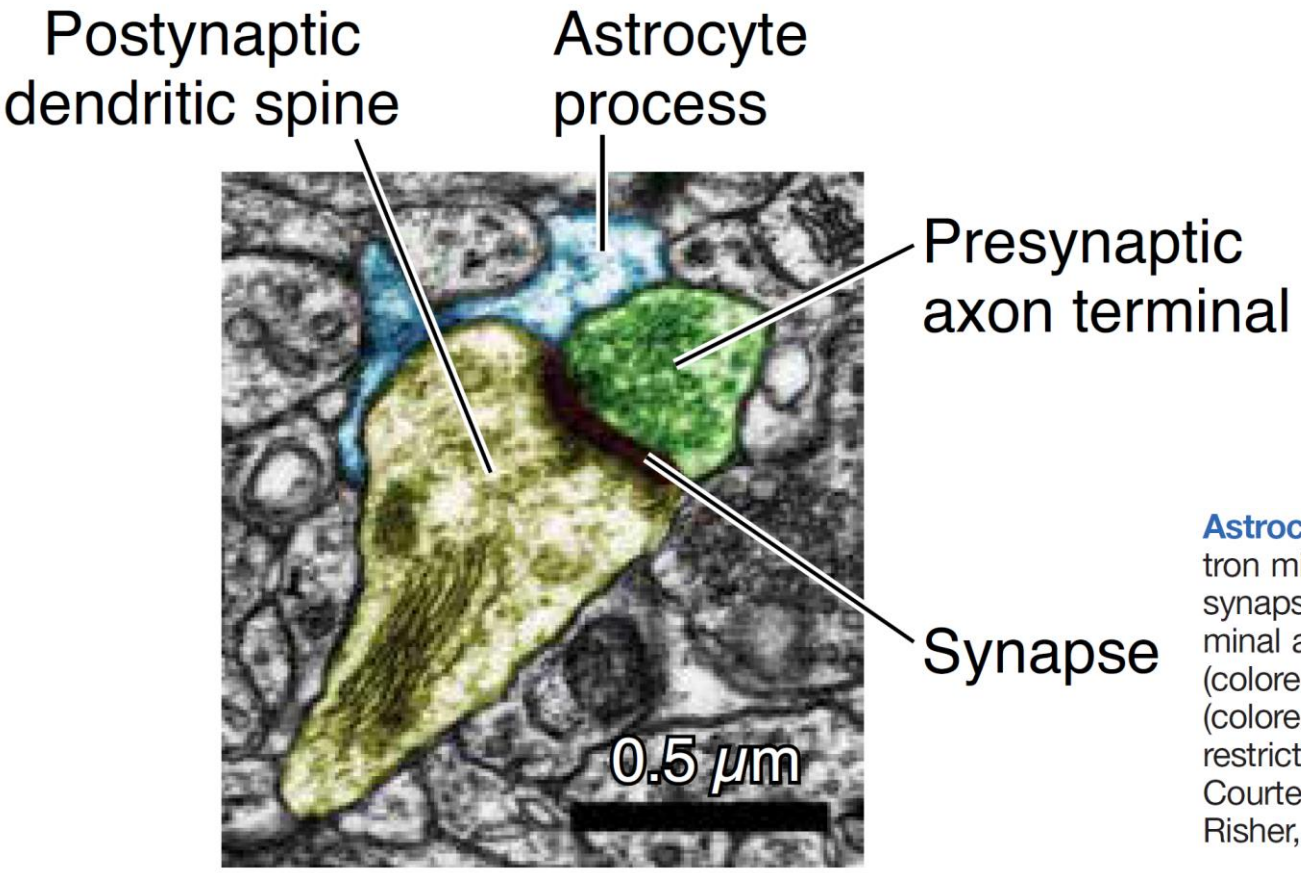
- One type of cell (e.g. neurons) in the body can be **distinguished from another** by the unique **pattern of genes** it expresses as proteins.
- **Green fluorescent protein** (**GFP**),
  - Foreign gene **encoding** a fluorescent protein
  - discovered in jellyfish
  - It placed in specific gene promoter (**genetic engineering**)
- Express the genes of the **particular neurotransmitter**
  - **e.g. Cholinergic neurons**

Glia; "sleeping giants" of neuroscience
Astrocytes:

- **Most numerous** glia in the brain
- **Regulating** the **chemical content** of this *extracellular space* (e.g. concentration of potassium ions)
- Envelop synaptic junctions thereby **restricting the spread** of neurotransmitter molecules
- Actively **remove** many neurotransmitters from the synaptic cleft
- Astrocytic membranes **possess neurotransmitter receptors** that, like the receptors on neurons, can **trigger electrical and biochemical** events inside the glial cell.



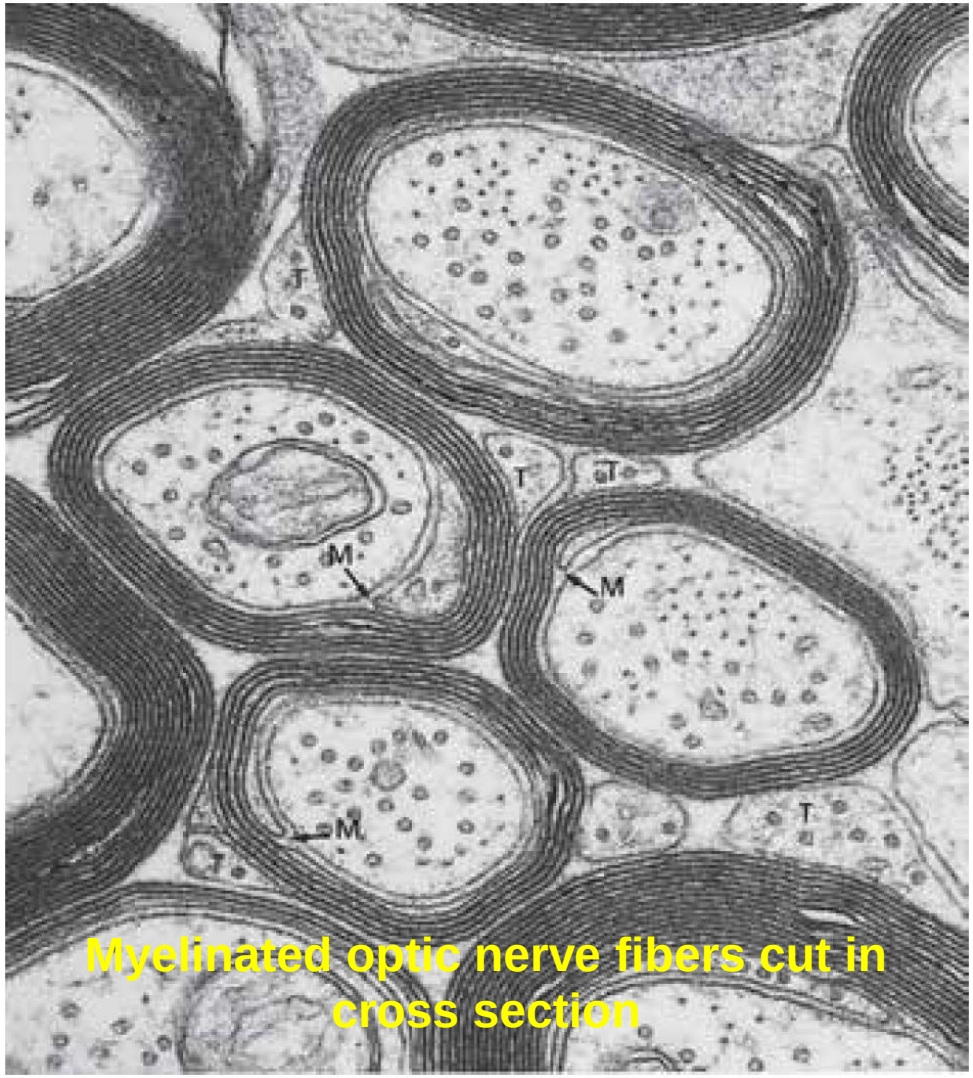
Astrocytes envelop synapses



Astrocytes envelop synapses. An electron micrograph of a thin slice through a synapse showing the presynaptic axon terminal and the postsynaptic dendritic spine (colored green) and an astrocyte process (colored blue) that wraps around them and restricts the extracellular space. (Source: Courtesy of Drs. Cagla Eroglu and Chris Risher, Duke University.)

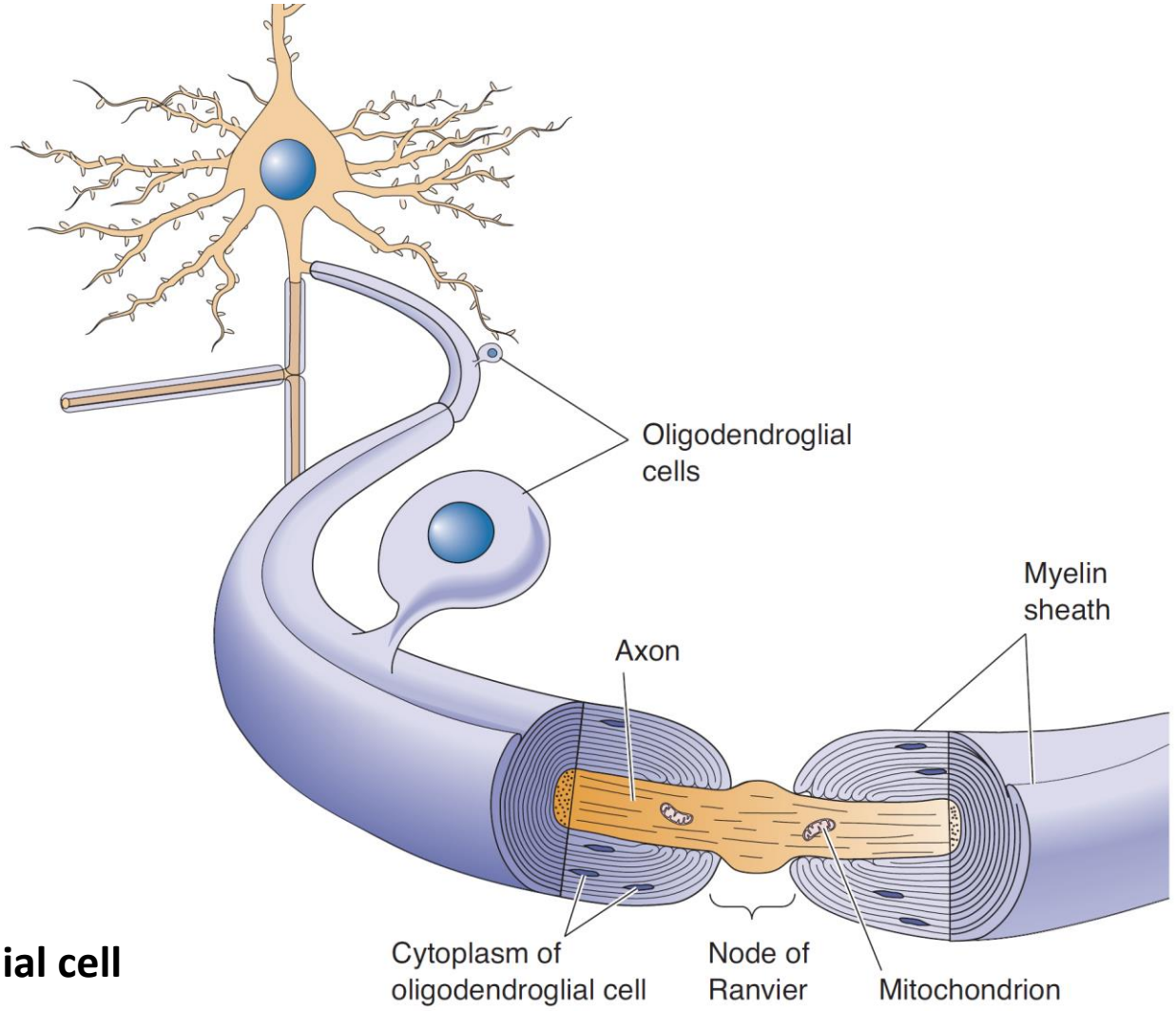
Myelinating Glia

- Provide layers of membrane that **insulate** axons.
- **Oligodendroglial** (only in CNS) and **Schwann cells** (only in PNS)
- **Myelin:**
  - A **spirals wrapping** around axons in the brain
- **Node of Ranvier**
  - The sheath is interrupted periodically
- **Oligodendroglial** cell share myelin to several axons, whereas each **Schwann** cell myelinates only a single axon.



Myelinated optic nerve fibers cut in cross section

Node of Ranvier



An oligodendroglial cell

Other types

- **Ependymal cells:**
  - Provide the lining of fluid-filled **ventricles** and cell migration

- **Microglia**
  - function as **phagocytes**
  - It involved in **remodeling synaptic connections**