A few questions on the content of the previous lecture

The neuron doctrine refers to (choose all that apply)

ⓘ Start presenting to display the poll results on this slide.

slido

The scientists whose research marked the start of the neuron doctrine were (choose all that apply)

ⓘ Start presenting to display the poll results on this slide.

slido

Phrenology was promoted by ....., who hypothesized that ....

ⓘ Start presenting to display the poll results on this slide.

Any questions/remarks before we begin today’s lecture?

Nervous system structure and organization

Dr. Lavinia Carmen Uscătescu

October 23rd 2023

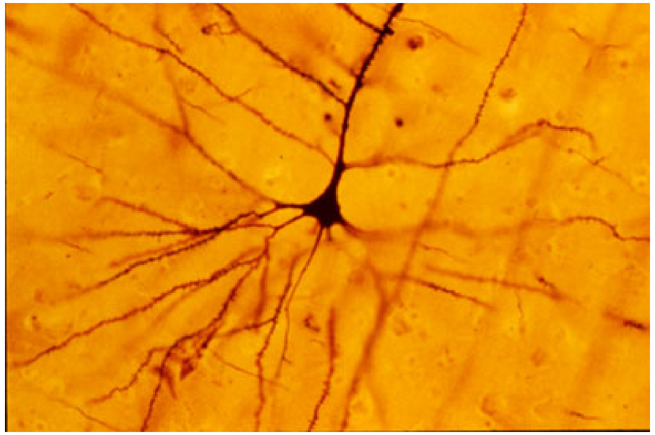
What you can gain from this course

- Basic knowledge of neurohistology;
- Insight into the role of neurons and glia;
- Insight into the role of brain cells in health and disease.

Outline

1. The brain, by the numbers
2. The neuron
3. Cell components (organelles)
4. The glia
5. Neurodegenerative disorders

REMINDER: The neuron doctrine



A human neocortical pyramidal neuron stained via Golgi technique
https://tinyurl.com/258ece5e

neuron = a single, **independent**

unit of the nervous system

The Nobel Prize in Physiology or Medicine 1906

"in recognition of their work on the structure of the nervous system"

Camillo Golgi

1/2 of the prize

Italy

Pavia University
Pavia, Italy

b. 1843
d. 1926

Santiago Ramón y Cajal

1/2 of the prize

Spain

Madrid University
Madrid, Spain

b. 1852
d. 1934

www.nobelprize.org

Drawing of a Purkinje cell in the cerebellum cortex done by Cajal, using the Golgi stain
https://tinyurl.com/258ece5e

> Brain Res Rev. 2007 Oct;55(2):490-8. doi: 10.1016/j.brainresrev.2006.11.004. Epub 2007 Jan 9.

How the 1906 Nobel Prize in Physiology or Medicine was shared between Golgi and Cajal

Gunnar Grant [1]

Affiliations + expand

PMID: 17306375 DOI: 10.1016/j.brainresrev.2006.11.004

https://tinyurl.com/2xwunam6

Camillo Golgi
Biographical
https://www.nobelprize.org/prizes/medicine/1906/golgi/biographical/

Santiago Ramón y Cajal
Biographical
https://www.nobelprize.org/prizes/medicine/1906/cajal/biographical/

The brain, by the numbers

The modern human brain *(~ 1370 g & 1260 cm^3 in the average male)*

> J Comp Neurol. 2009 Apr 10;513(5):532-41. doi: 10.1002/cne.21974.

Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain

Frederico A C Azevedo [1], Ludmila R B Carvalho, Lea T Grinberg, José Marcelo Farfel, Renata E L Ferretti, Renata E P Leite, Wilson Jacob Filho, Roberto Lent, Suzana Herculano-Houzel

Affiliations + expand

PMID: 19226510 DOI: 10.1002/cne.21974

Abstract

The human brain is often considered to be the most cognitively capable among mammalian brains and to be much larger than expected for a mammal of our body size. Although the number of neurons is generally assumed to be a determinant of computational power, and despite the widespread quotes that the human brain contains 100 billion neurons and ten times more glial cells, the absolute number of neurons and glial cells in the human brain remains unknown. Here we determine these numbers by using the isotropic fractionator and compare them with the expected values for a human-sized primate. We find that the adult male human brain contains on average 86.1 +/- 8.1 billion NeuN-positive cells ("neurons") and 84.6 +/- 9.8 billion NeuN-negative ("nonneuronal") cells. With only 19% of all neurons located in the cerebral cortex, greater cortical size (representing 82% of total brain mass) in humans compared with other primates does not reflect an increased relative number of cortical neurons. The ratios between glial cells and neurons in the human brain structures are similar to those found in other primates, and their numbers of cells match those expected for a primate of human proportions. These findings challenge the common view that humans stand out from other primates in their brain composition and indicate that, with regard to numbers of neuronal and nonneuronal cells, the human brain is an isometrically scaled-up primate brain.

https://pubmed.ncbi.nlm.nih.gov/19226510/

Front Hum Neurosci. 2009; 3: 31. PMCID: PMC2776484
Published online 2009 Nov 9. Prepublished online 2009 Aug 5. doi: 10.3389/neuro.09.031.2009 PMID: 19915731

The Human Brain in Numbers: A Linearly Scaled-up Primate Brain

Suzana Herculano-Houzel[1,*]

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Abstract

Go to: ▸

The human brain has often been viewed as outstanding among mammalian brains: the most cognitively able, the largest-than-expected from body size, endowed with an overdeveloped cerebral cortex that represents over 80% of brain mass, and purportedly containing 100 billion neurons and 10× more glial cells. Such uniqueness was seemingly necessary to justify the superior cognitive abilities of humans over larger-brained mammals such as elephants and whales. However, our recent studies using a novel method to determine the cellular composition of the brain of humans and other primates as well as of rodents and insectivores show that, since different cellular scaling rules apply to the brains within these orders, brain size can no longer be considered a proxy for the number of neurons in the brain. These studies also showed that the human brain is not exceptional in its cellular composition, as it was found to contain as many neuronal and non-neuronal cells as would be expected of a primate brain of its size. Additionally, the so-called overdeveloped human cerebral cortex holds only 19% of all brain neurons, a fraction that is similar to that found in other mammals. In what regards absolute numbers of neurons, however, the human brain does have two advantages compared to other mammalian brains: compared to rodents, and probably to whales and elephants as well, it is built according to the very economical, space-saving scaling rules that apply to other primates; and, among economically built primate brains, it is the largest, hence containing the most neurons. These findings argue in favor of a view of cognitive abilities that is centered on absolute numbers of neurons, rather than on body size or encephalization, and call for a re-examination of several concepts related to the exceptionality of the human brain.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776484/

How do we know this?

Suzana Herculano-Houzel

J Neurosci. 2005 Mar 9;25(10):2518-21. doi: 10.1523/JNEUROSCI.4526-04.2005.

Isotropic fractionator: a simple, rapid method for the quantification of total cell and neuron numbers in the brain

Suzana Herculano-Houzel [1], Roberto Lent

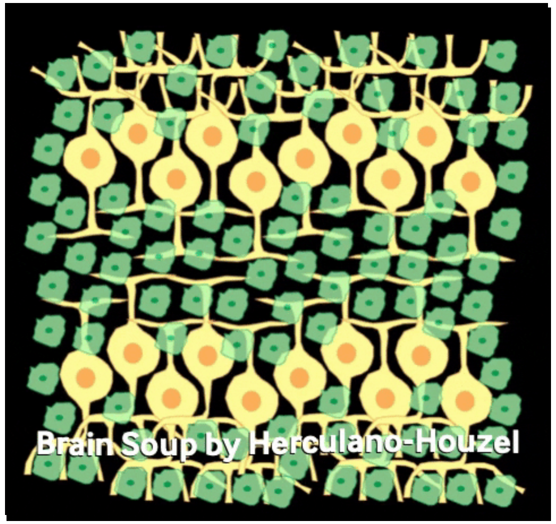
https://pubmed.ncbi.nlm.nih.gov/15758160/

SUZANA HERCULANO-HOUZEL

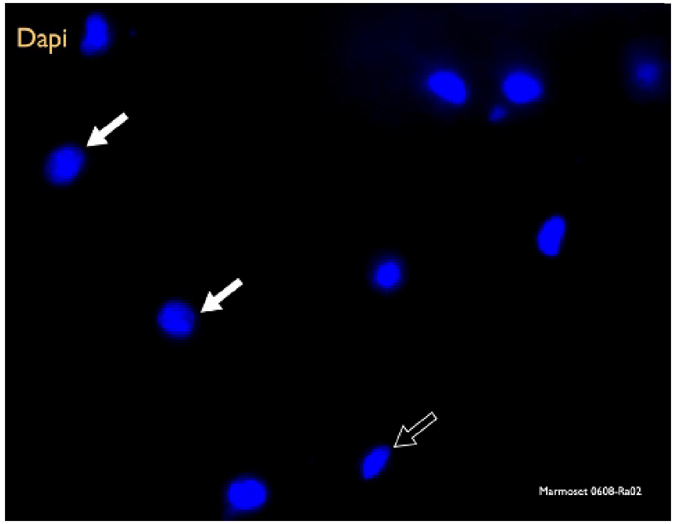
HOME LAB WRITTEN & SPOKEN NEUROSCIENCE OFFICE HOUR LOG IN

The lab

The Herculano-Houzel lab started in 2005, with the publication of the cell-counting method created by the PI, the isotropic fractionator, which really consists of... **turning brains into soup**. The motivation was figuring out **how many cells composed the brains of different animals**, because only one thing was certain then: the human brain was NOT made of "100 billion neurons and 10 times as many glial cells", for the simple reason that nobody had really counted yet.



Take your fixed brain structure of interest, slice and dice it, and dissolve it in a salty detergent solution, using a glass homogenizer. You end up with a suspension of free cell nuclei that can be made homogeneous ("isotropic") by agitation.



As long as every cell in the tissue has one and only one nucleus, counting DAPI-labeled nuclei - which can be done very quickly under a fluorescence microscope - is equivalent to counting cells. Next, fluorescent markers that make only your cells of interest red will let you work out in a couple of hours what fraction of the cells are of that type.

https://www.suzanaherculanohouzel.com/lab.html

Why so many neurons?!

The Expensive-Tissue Hypothesis (ETH)

The Expensive-Tissue Hypothesis: The Brain and the Digestive System in Human and Primate Evolution

Leslie C. Aiello, Peter Wheeler

Current Anthropology, Volume 36, Issue 2 (Apr., 1995), 199-221.

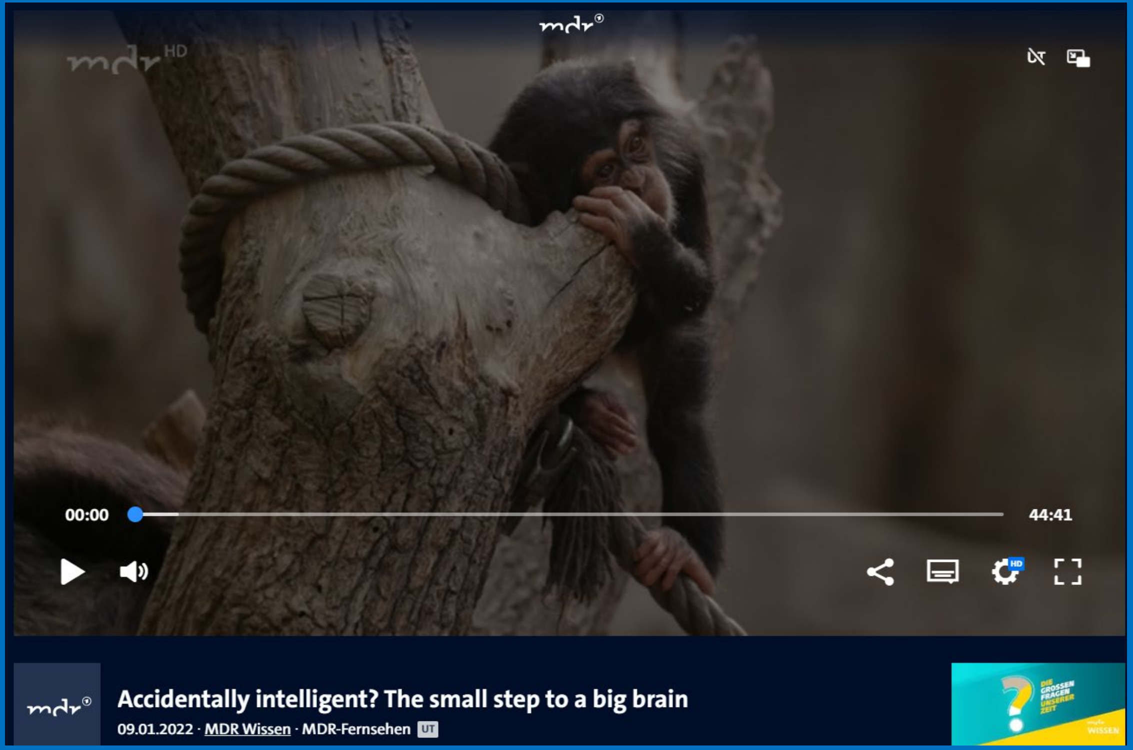
Brain tissue is metabolically expensive, but there is no significant correlation between relative basal metabolic rate and relative brain size in humans and other encephalized mammals. The expensive-tissue hypothesis suggests that the metabolic requirements of relatively large brains are offset by a corresponding reduction of the gut. The splanchnic organs (liver and gastrointestinal tract) are as metabolically expensive as brains, and the gut is the only one of the metabolically expensive organs in the human body that is markedly small in relation to body size. Gut size is highly correlated with diet, and relatively small guts are compatible only with high-quality, easy-to-digest food. The often-cited relationship between diet and relative brain size is more properly viewed as a relationship between relative brain size and relative gut size, the latter being determined by dietary quality. No matter what is selecting for relatively large brains in humans and other primates, they cannot be achieved without a shift to a high-quality diet unless there is a rise in the metabolic rate. Therefore the incorporation of increasingly greater amounts of animal products into the diet was essential in the evolution of the large human brain. https://www.jstor.org/stable/2744104

Int J Mol Sci. 2018 Jun; 19(6): 1792. PMCID: PMC6032294
Published online 2018 Jun 17. doi: 10.3390/ijms19061792 PMID: 29914188

The Expensive-Tissue Hypothesis in Vertebrates: Gut Microbiota Effect, a Review

Chun Hua Huang,[1,2] Xin Yu,[1,2] and Wen Bo Liao[1,2,*]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6032294/



https://tinyurl.com/2s4k2939

The neuron

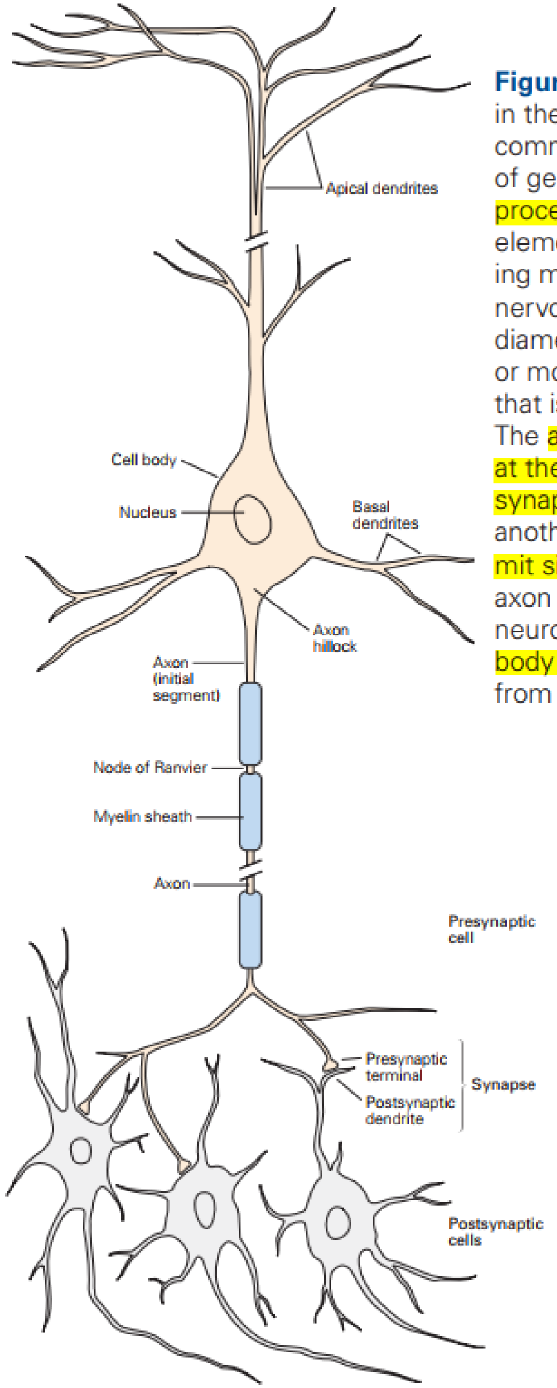


Figure 3–1 (Right) **The structure of a neuron.** Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes: axons and dendrites. Axons are the transmitting element of neurons; they vary greatly in length, some extending more than 1 m within the body. Most axons in the central nervous system are very thin (between 0.2 μm and 20 μm in diameter) compared with the diameter of the cell body (50 μm or more). Many axons are insulated by a sheath of fatty myelin that is regularly interrupted at gaps called the nodes of Ranvier. The action potential, the cell's conducting signal, is initiated at the initial segment of the axon and propagates to the synapse, the site at which signals flow from one neuron to another. Branches of the axon of the presynaptic neuron transmit signals to the postsynaptic cell. The branches of a single axon may form synapses with as many as 1,000 postsynaptic neurons. The apical and basal dendrites together with the cell body are the input elements of the neuron, receiving signals from other neurons.

Kandel et al., 2021, pg. 57

* 1 μm (micrometer) = 10^{-6} m

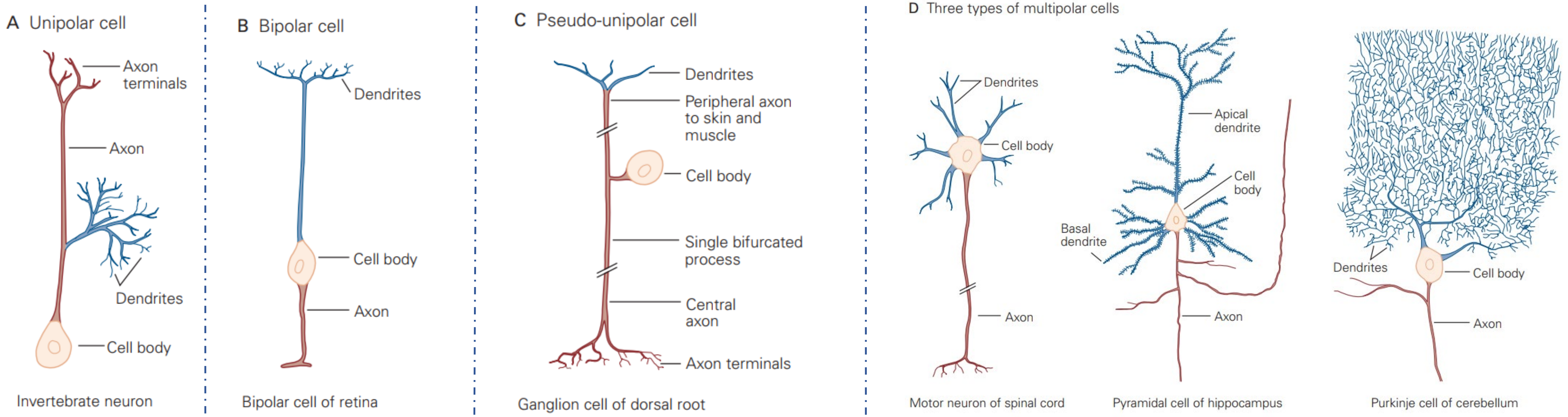
Individual nerve cells, or neurons, are the basic signaling units of the brain. The human brain contains a huge number of these cells, on the order of 86 billion neurons, that can be classified into at least a thousand different types. Yet this great variety of neurons is less of a factor in the complexity of human behavior than is their organization into anatomical circuits with precise functions. Indeed, one key organizational principle of the brain is that nerve cells with *similar* properties can produce different actions because of the way they are interconnected.

Because relatively few principles of organization of the nervous system give rise to considerable functional complexity, it is possible to learn a great deal about how the nervous system produces behavior by focusing on five basic features of the nervous system:

1. The structural components of individual nerve cells;
2. The mechanisms by which neurons produce signals within themselves and between each other;
3. The patterns of connection between nerve cells and between nerve cells and their targets (muscle and gland effectors);
4. The relationship of different patterns of interconnection to different types of behavior; and
5. How neurons and their connections are modified by experience.

Kandel et al., 2021, pg. 56

Neuronal **diversity** (a) based on the **number of processes** that originate from the cell body



A single process *emanating from the cell*

Two types of processes that are functionally specialized: ***one axon*** *for transmitting signals,* ***and dendrites*** *for receiving input*

Variants of bipolar cells, and carry somatosensory information to the spinal cord. During development, the two processes of the embryonic bipolar cell fuse and emerge from the cell body as a single process that has two functionally distinct segments. ***Both segments function as axons****; one extends to peripheral skin or muscle, the other to the central spinal cord.*

One axon and **many dendrites**.

The most common type of neuron in the mammalian nervous system.

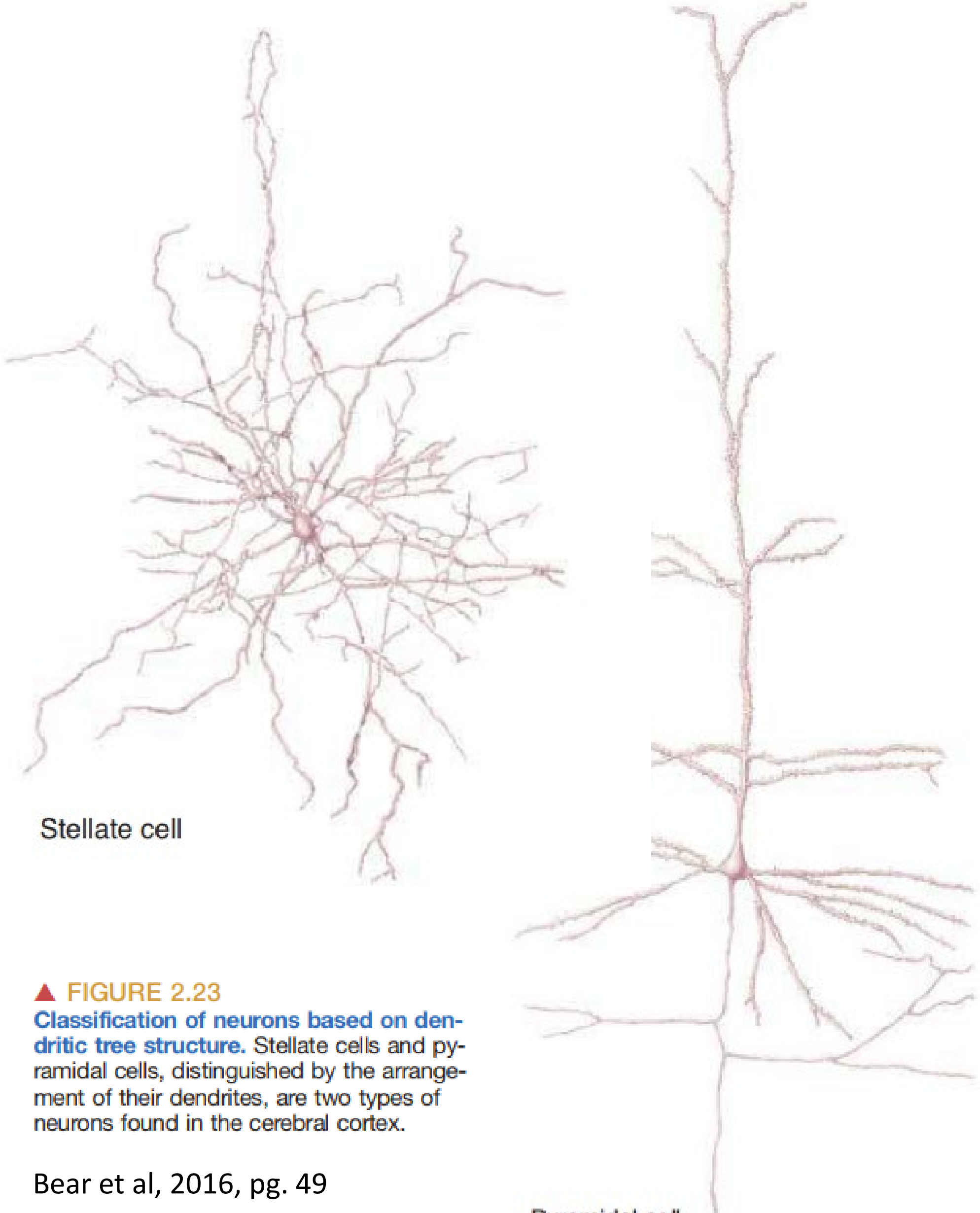
Spinal motor neurons innervate skeletal muscle fibers .

Pyramidal cells have dendrites emerging from both the apex (the apical dendrite) and the base (the basal dendrites); found in the hippocampus and throughout the cerebral cortex.

Purkinje cells of the cerebellum have a rich and extensive dendritic tree that accommodates an enormous number of synaptic inputs.

Kandel et al., 2021, pg. 60

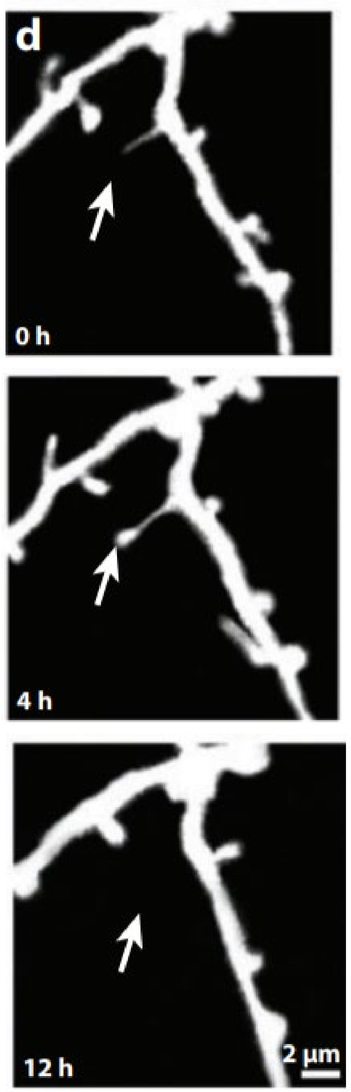
(b) based on the **shape** of the dendritic tree



▲ FIGURE 2.23
Classification of neurons based on dendritic tree structure. Stellate cells and pyramidal cells, distinguished by the arrangement of their dendrites, are two types of neurons found in the cerebral cortex.

Bear et al, 2016, pg. 49

(c) based on the presence or absence of dendritic **spines**

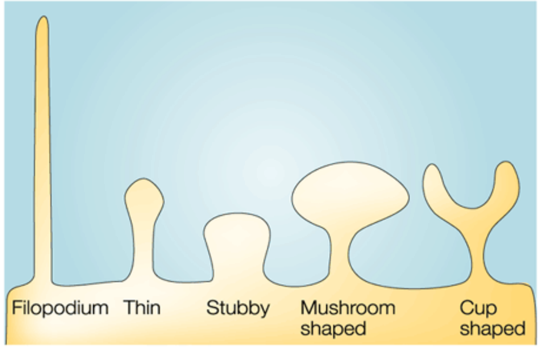


Bhatt et al. (2009)
https://pubmed.ncbi.nlm.nih.gov/19575680/

dendritic spines

small protrusions on the dendritic membrane; receive synaptic input

In the cerebral cortex, all pyramidal cells are spiny, but stellate cells can be either **spiny** or **aspinous**.



Hering & Sheng (2001)
https://tinyurl.com/4npmfkyz

(d) based on the type of **connection**

primary sensory neurons

have neurites in the sensory surfaces of the body (e.g., skin or retina)

motor neurons

form synapses in the muscles and control movement

interneurons

form synapses with other neurons;

most numerous

(e) based on axon **length**

Golgi Type I

projection neurons

have long axons that extend across different areas of the brain

Golgi Type II

local circuit neurons

have short axons that only extend in the vicinity of the cell

(f) based on the type of **neurotransmitter**

Over 100 types of neurotransmitters enabling diverse chemical signalling.

Neuropeptides/peptide neurotransmitters

large molecules (3 to 36 amino acids)

e.g., oxytocin and vasopressin

Small-molecule neurotransmitters

(a) acetylcholine

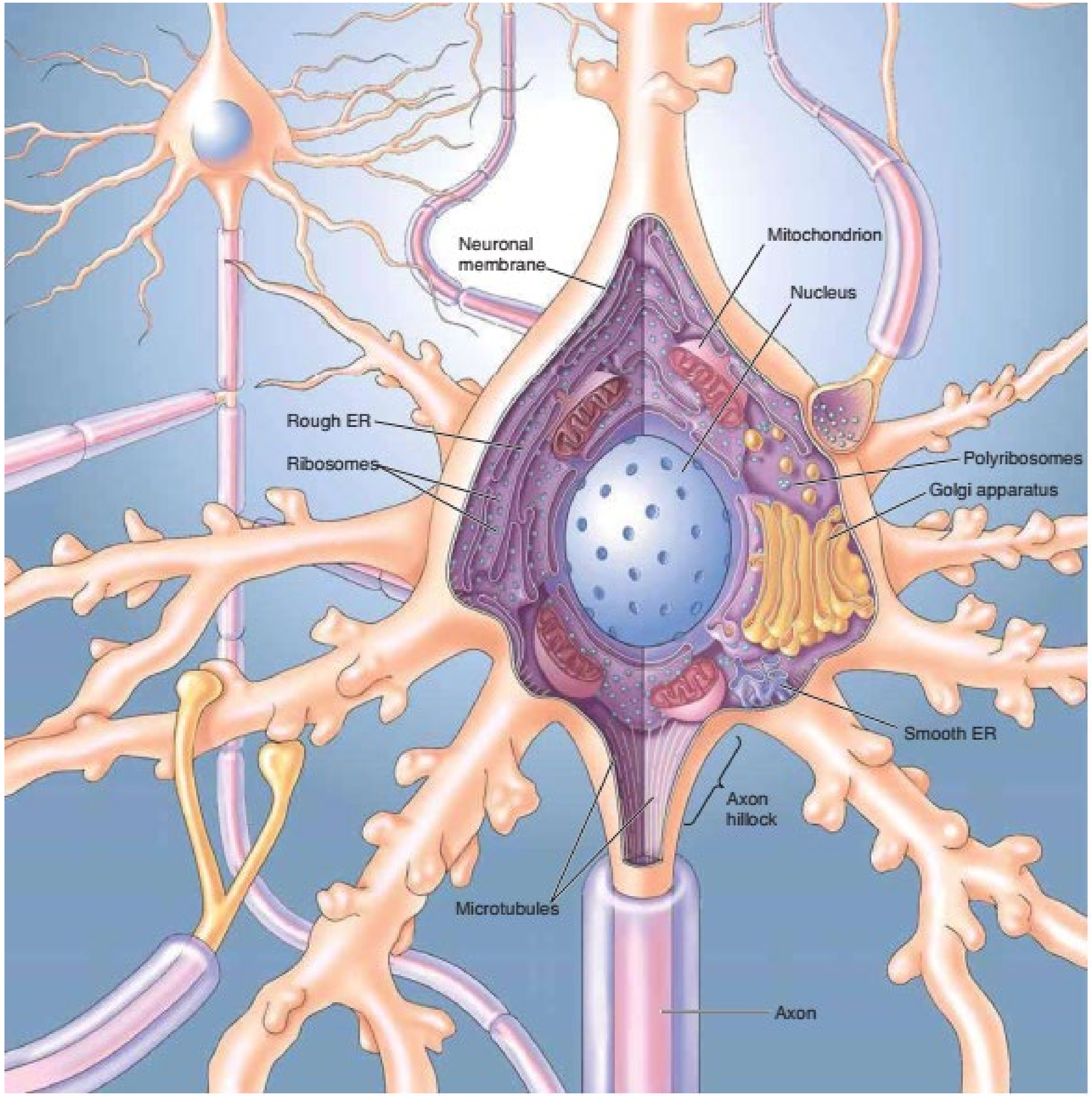
(b) monoamines

- catecholamines (dopamine, norepinephrine, and epinephrine)
- indolamines (serotonin)

(c) soluble gases (nitric oxide)

(d) amino acids (GABA, glycine, glutamate)

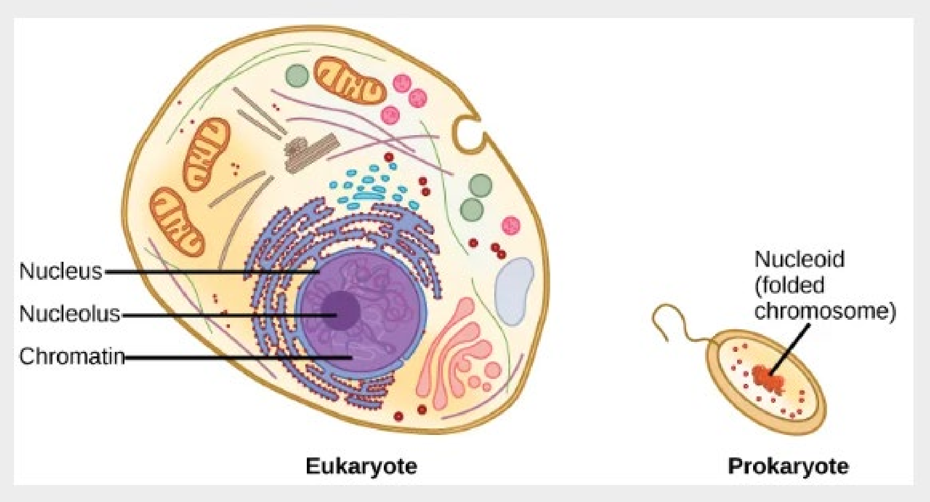
The **cell body** (soma)



▲ FIGURE 2.8
The internal structure of a typical neuron.

Bear et al, 2016, pg. 30

REMINDER: **Eukaryotic** v. **Prokaryotic** cells



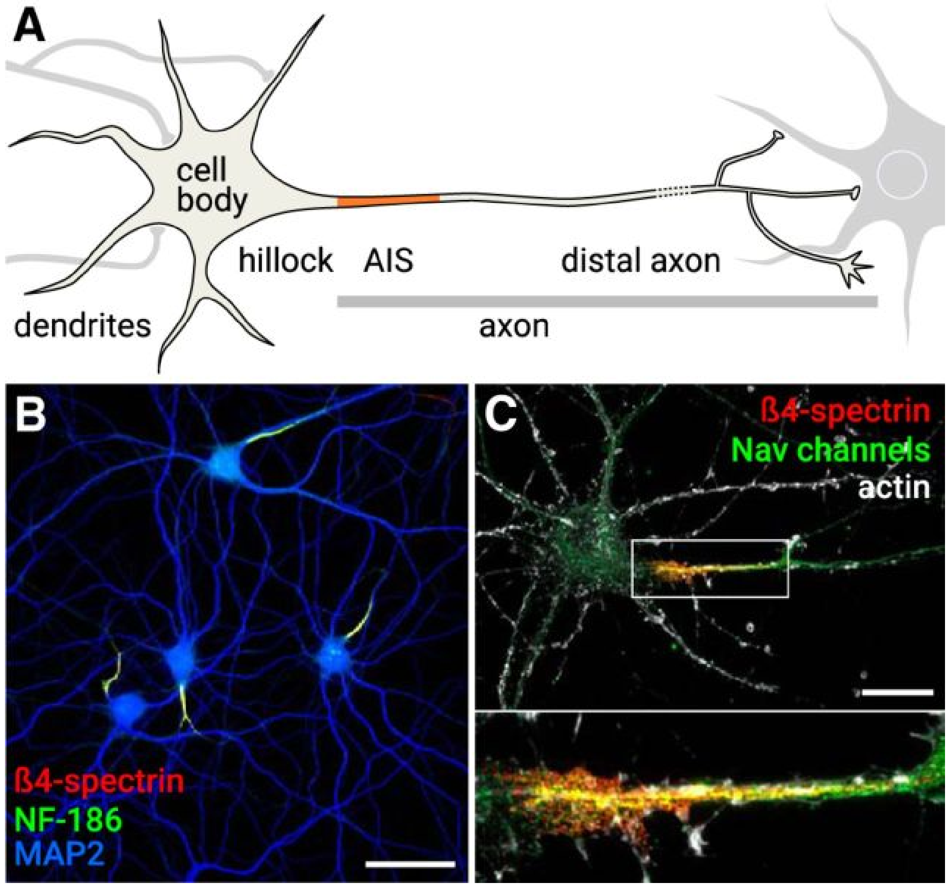
- *well-defined nucleus containing chromosomes*

https://tinyurl.com/8n3jmn74

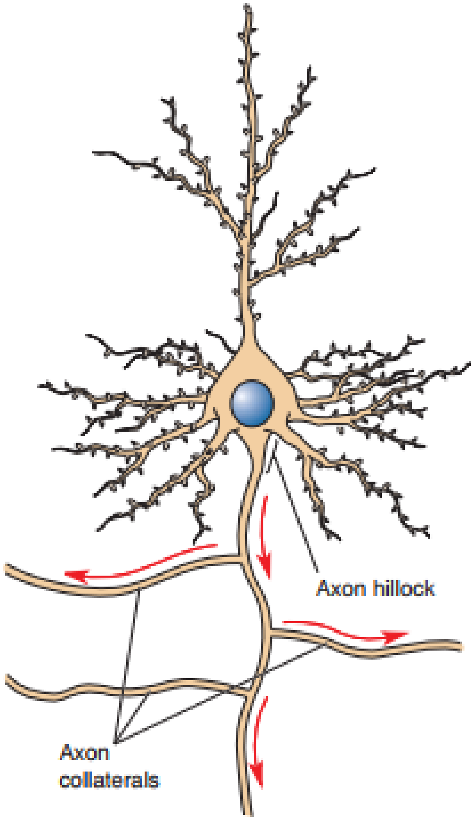
- *the chromosome lies in the cytoplasm in an area called the **nucleoid***

- neurons are **eukaryotic** cells
- typical soma diameter ~ 20 µm
- delineated by **membrane**
- contains **cytoplasm** (**organelles** + **cytosol)**

The **axon**

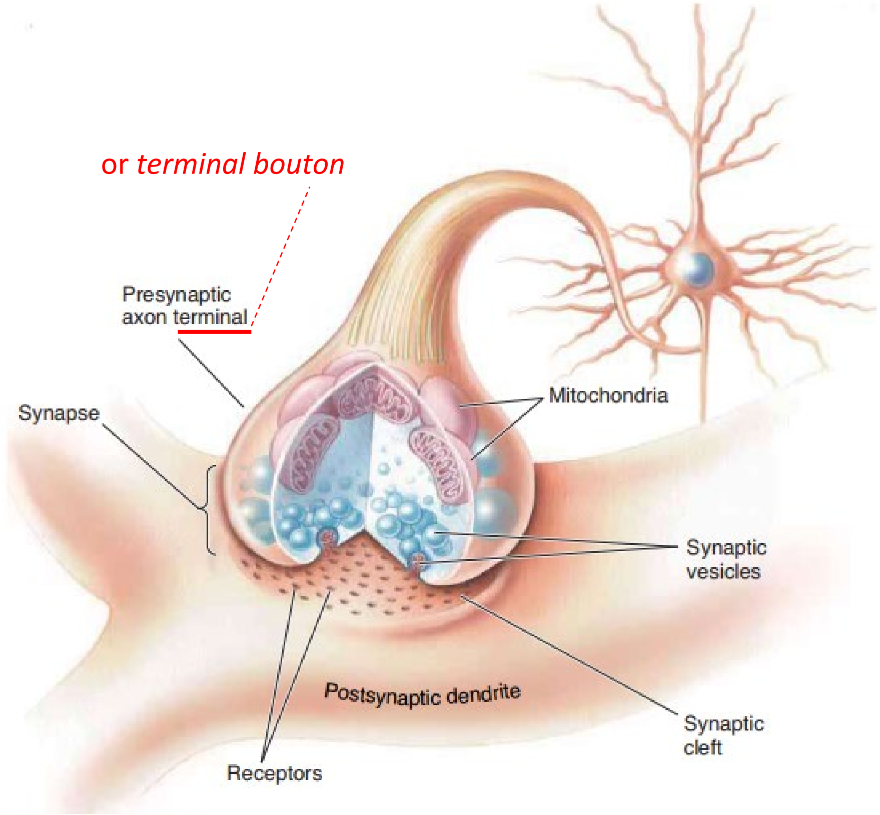


*The **[axon initial segment] AIS**. **A**, A typical neuron receives input on the cell body and dendrites (left). The **[axon] hillock** leads to the axon, which contains the **AIS** (orange). The **distal axon contacts downstream neurons** (right). B, Hippocampal neurons [...]in culture labelled for the AIS.* [*https://tinyurl.com/tcdrfvsk*](https://tinyurl.com/tcdrfvsk)



▲ FIGURE 2.15
The axon and axon collaterals. The axon functions like a telegraph wire to send electrical impulses to distant sites in the nervous system. The arrows indicate the direction of information flow.

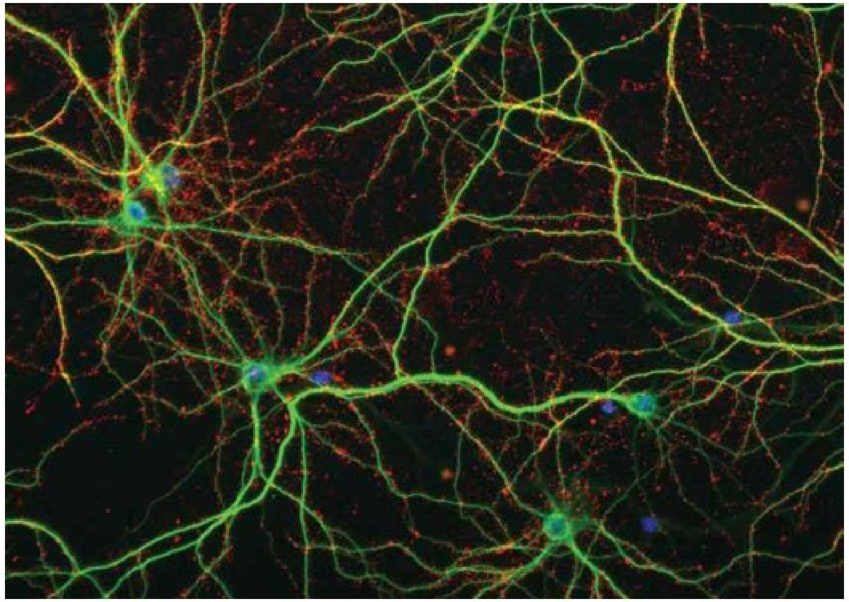
Bear et al, 2016, pg. 42



▲ FIGURE 2.16
The axon terminal and the synapse. Axon terminals form synapses with the dendrites or somata of other neurons. 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 postsynaptic cell.

Bear et al, 2016, pg. 42

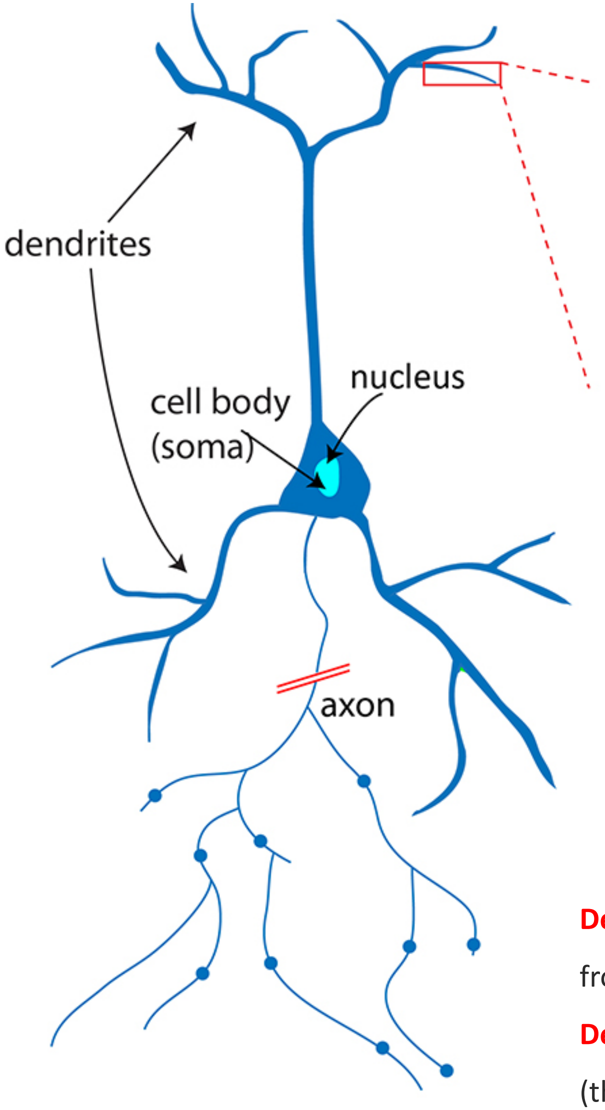
The **dendrites**

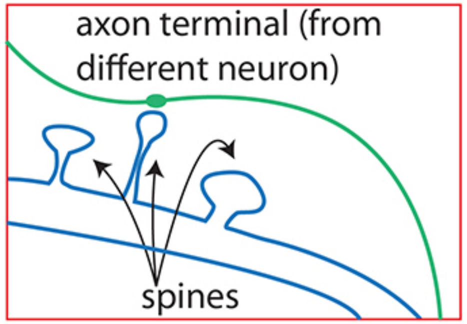


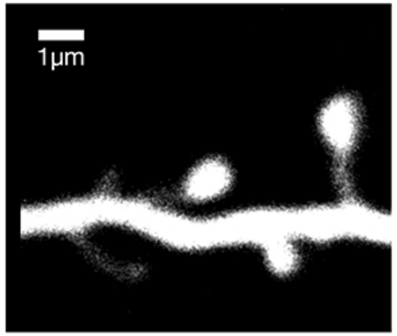
◀ FIGURE 2.19

Dendrites receiving synaptic inputs from axon terminals. Neurons have been made to fluoresce green using a method that reveals the distribution of a microtubule-associated protein. Axon terminals have been made to fluoresce orange-red using a method to reveal the distribution of synaptic vesicles. The nuclei are stained to fluoresce blue. (Source: Dr. Asha Bhakar, Massachusetts Institute of Technology.)

Bear et al, 2016, pg. 45







https://tinyurl.com/48bhmzc6

Dendrite – receiving part of the neuron; receive synaptic inputs from axons of other neurons

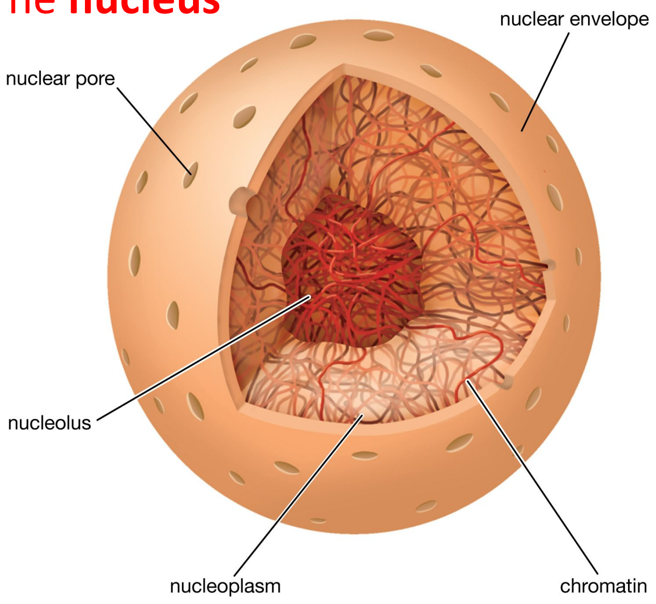
Dendritic spine – small protrusions found on dendrites (the postsynaptic contact site)

Dendritic tree – total of a neuron's dendrites

Dendritic branch – each branch of a dendritic tree

Cell components (organelles)

The nucleus



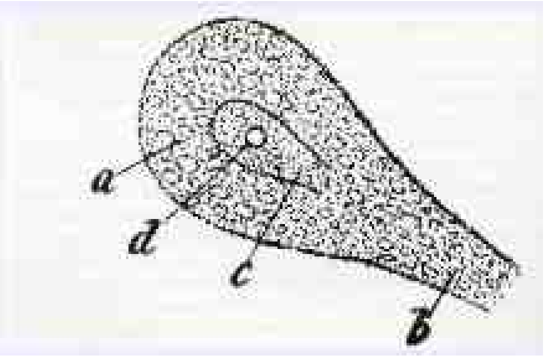
https://www.britannica.com/science/nucleolus

The **nucleus** is ~ 5–10 µm in diameter, and is surrounded by a double membrane called the **nuclear envelope/membrane**. It is filled with a suspension liquid called **nucleoplasm/karyoplasm.**

The nuclear envelope is perforated by **nuclear pores** ~ 0.1 µm in diameter.

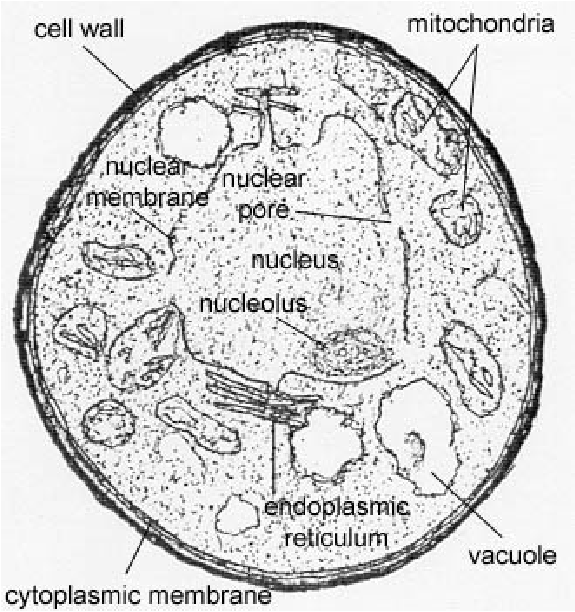
The nucleus contains at least one **nucleolus** (pl: nucleoli; described by Gabriel Gustav Valentin in 1839), which is involved in the **synthesis of ribosomal RNA** (rRNA) and the **formation of ribosomes**.

Drawing of a neuron by Gabriel Valentin, showing the protoplasm (a), the nucleus (c), the **nucleolus** (d) and the axonal cone (b).



https://cerebromente.org.br/n17/history/neurons2_i.htm

The pores in the nuclear membrane allow ribosomal subunits and mRNA transcribed off genes in the DNA to leave the nucleus, enter the cytoplasm, and participate in protein synthesis.



https://tinyurl.com/3jwanezx

Refresher and clarifications

cytosol

the liquid inside a cell

cytoplasm

the cytosol + the organelles inside a cell, except for the nucleus

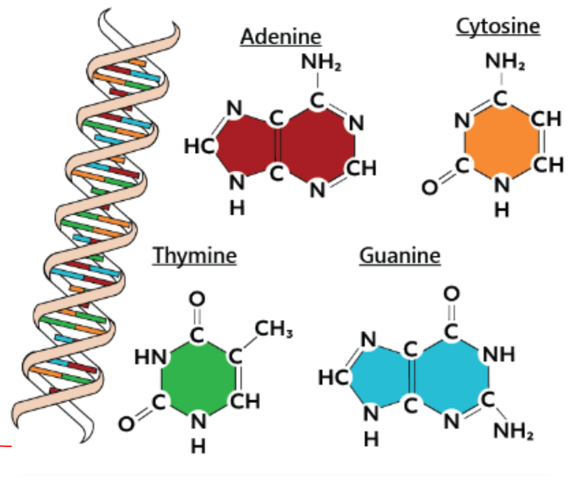
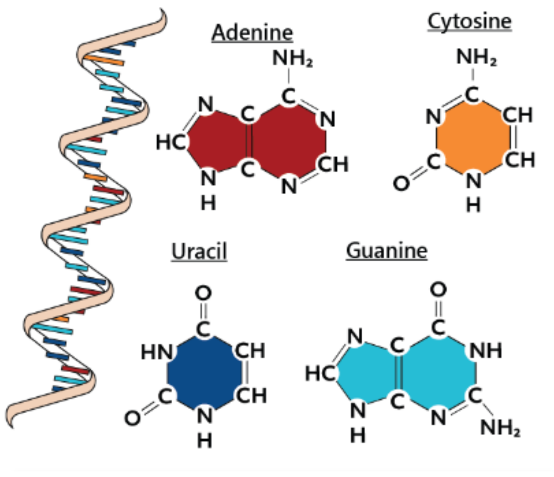
protoplasm

the cytoplasm + the nucleus

nucleoplasm

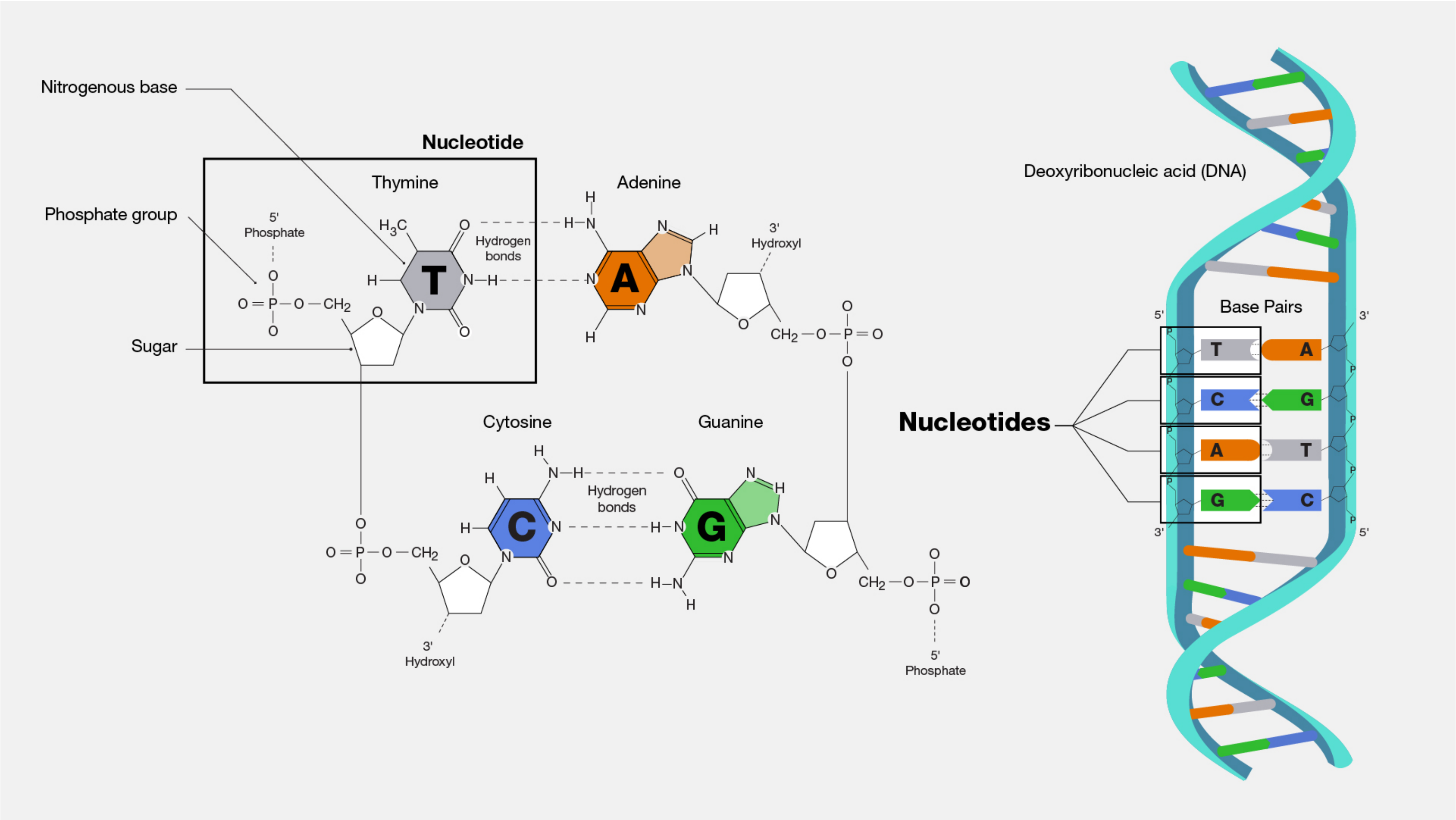
the liquid inside a nucleus

if we stretched the DNA of one cell, it would be ~ 2 m long

DNA (DeoxyriboNucleic Acid)	**RNA** (RiboNucleic Acid)
	
Long-term storage of genetic information; transmission of genetic information to make other cells and new organisms.	Used to transfer the genetic code from the nucleus to the ribosomes to make proteins.
Is a double-stranded molecule consisting of a long chain of nucleotides.	Is a single-strand helix consisting of shorter chains of nucleotides.
Is self-replicating.	Is synthesized from DNA on an as-needed basis.

https://tinyurl.com/ybhw5exf

Refresher and clarifications

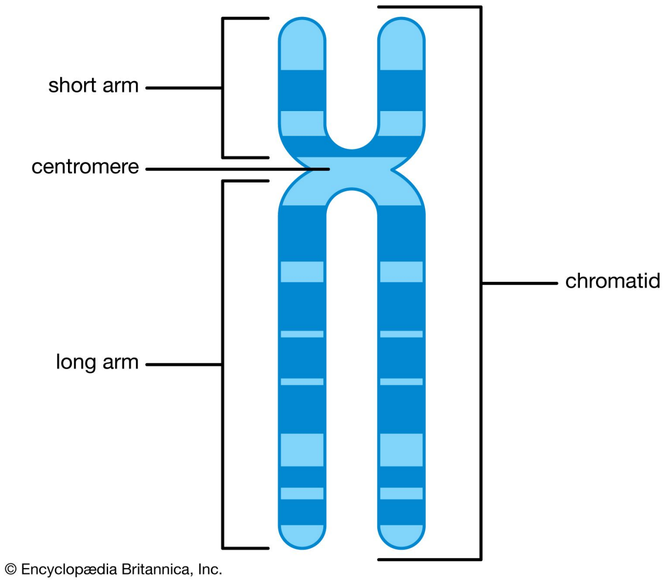


nucleotide

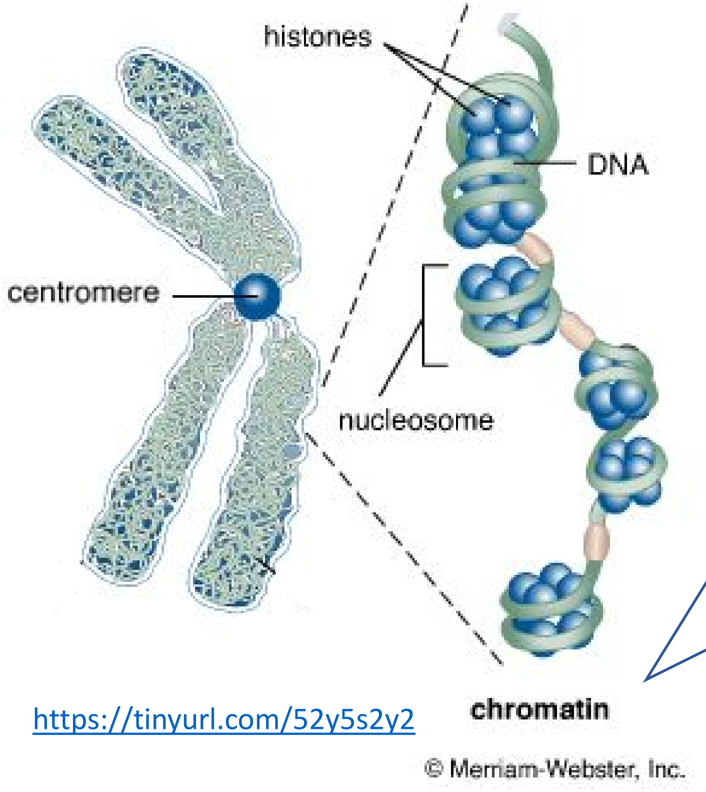
basic building block of DNA and RNA, consisting of: one sugar molecule (i.e., ribose in RNA, or deoxyribose in DNA), a phosphate group, and a nitrogen-containing base (i.e., A, C, T, G in DNA, and A, C, U, G in RNA)

https://www.genome.gov/genetics-glossary/Nucleotide

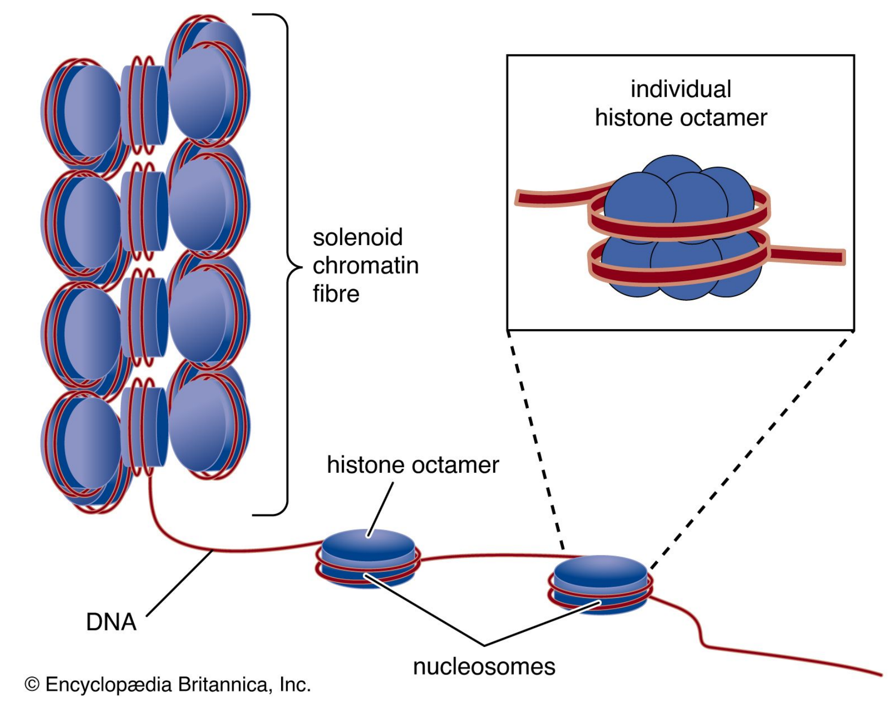
Refresher and clarifications



https://tinyurl.com/ycyycz42



https://tinyurl.com/52y5s2y2



https://tinyurl.com/244ke22e

chromatid

consists of tightly packed chromatin; two chromatids form a **chromosome**

chromatin

combination of nucleic acids (i.e., DNA and RNA) and proteins (i.e., histones)

Histones form packs of eight (i.e., histone **octamer**) around which DNA wraps tightly. This forms the **nucleosome** (i.e., subunit of chromatin)

The genetic information in the DNA is conveyed through **gene expression** and results in **protein synthesis**.

Protein synthesis occurs in the cytoplasm, but remember that the DNA is contained in the nucleus.

So how does the genetic message from the DNA reach the relevant sites of protein synthesis in the cytoplasm?

This is achieved with the help of another long molecule called **messenger ribonucleic acid (mRNA)**.

mRNA is also made of four nucleic acids (see slide 23), whose specific sequence reflects the information in the gene.

The construction of this specific sequence is called **transcription**, and the resulting mRNA is called **transcript**.

These transcripts exit the nucleus through the **nuclear pores** and travel to different sites within the neuron.

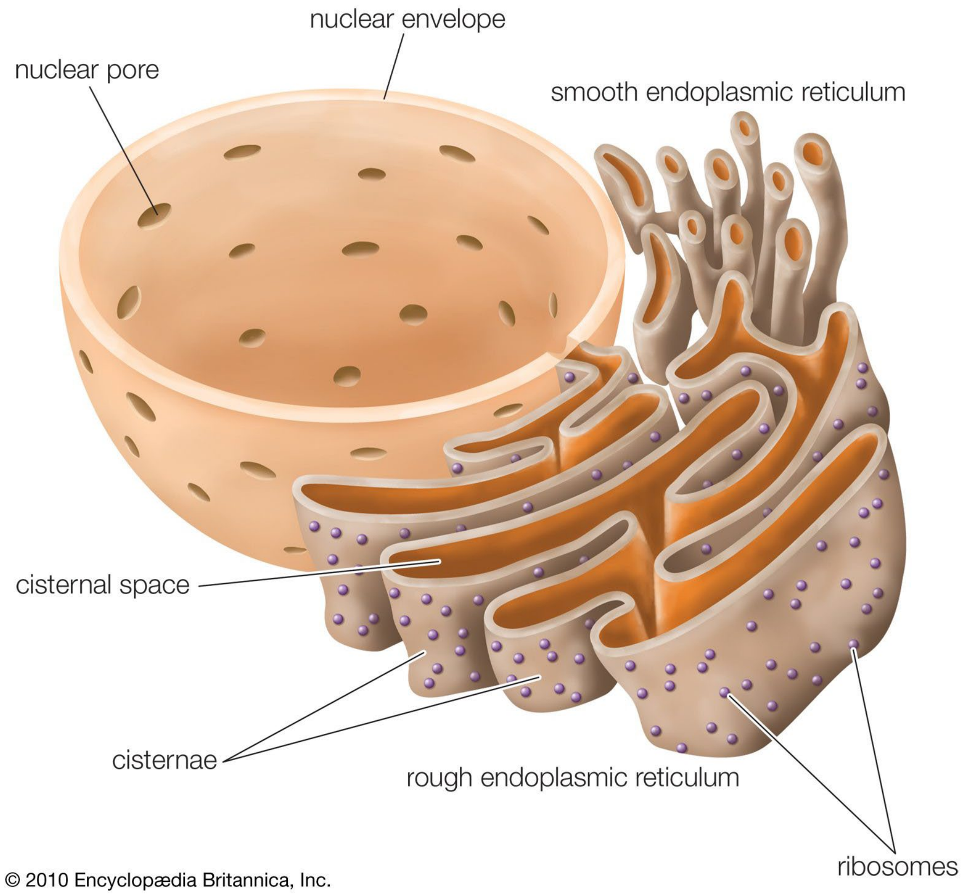
At the final destination, the proteins are assembled with the help of **amino acids**.

This assembling of proteins from amino acids under the direction of the mRNA is called **translation**.

$$\text{DNA} \xrightarrow{\text{Transcription}} \text{mRNA} \xrightarrow{\text{Translation}} \text{Protein}$$

Bear et al, 2016, pg. 32

The **endoplasmic reticulum** and the **ribosomes**



https://www.britannica.com/science/ribosome

The **ribosomes** are the site of protein synthesis. They can be attached to endoplasmic reticulum (i.e., rough endoplasmic reticulum), free floating (i.e., **free ribosomes**), or tied together by a strand of mRNA (i.e., **polyribosomes**).

The **endoplasmic reticulum** is an extension of the nuclear membrane. If ribosomes are attached to it (i.e., **rough** endoplasmic reticulum), then it is the site of protein synthesis. If not (i.e., **smooth** endoplasmic reticulum), then it is mainly involved in hormonal synthesis (depending on cell type)

George E. Palade
Facts

https://www.nobelprize.org/prizes/medicine/1974/palade/facts/

Photo from the Nobel Foundation archive.

George E. Palade
The Nobel Prize in Physiology or Medicine 1974

Born: 19 November 1912, Iasi, Romania

Died: 7 October 2008, Del Mar, CA, USA

Affiliation at the time of the award: Yale University, School of Medicine, New Haven, CT, USA

Prize motivation: "for their discoveries concerning the structural and functional organization of the cell"

Prize share: 1/3

Work

Our bodies are made up of cells that contain organelles, components with various functions. Albert Claude's research with the newly developed electron microscope and his methods for separating the various parts of pulverized cells using a centrifuge opened up new opportunities for studying cells in detail. In 1955 George Palade discovered previously unknown organelles in the cell, ribosomes, where the cell's formation of proteins takes place. He also identified the paths proteins take through the cell.

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https://www.lindau-nobel.org/

Ada E. Yonath
Facts

https://www.nobelprize.org/prizes/chemistry/2009/yonath/facts/

© The Nobel Foundation. Photo: U. Montan

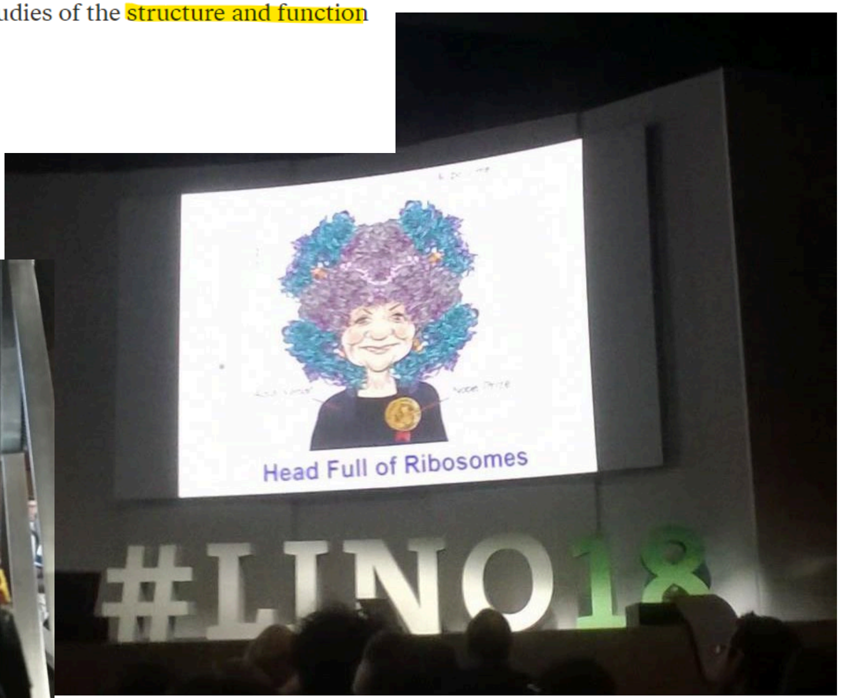
Ada E. Yonath
The Nobel Prize in Chemistry 2009

Born: 22 June 1939, Jerusalem, British Mandate of Palestine (now Israel)

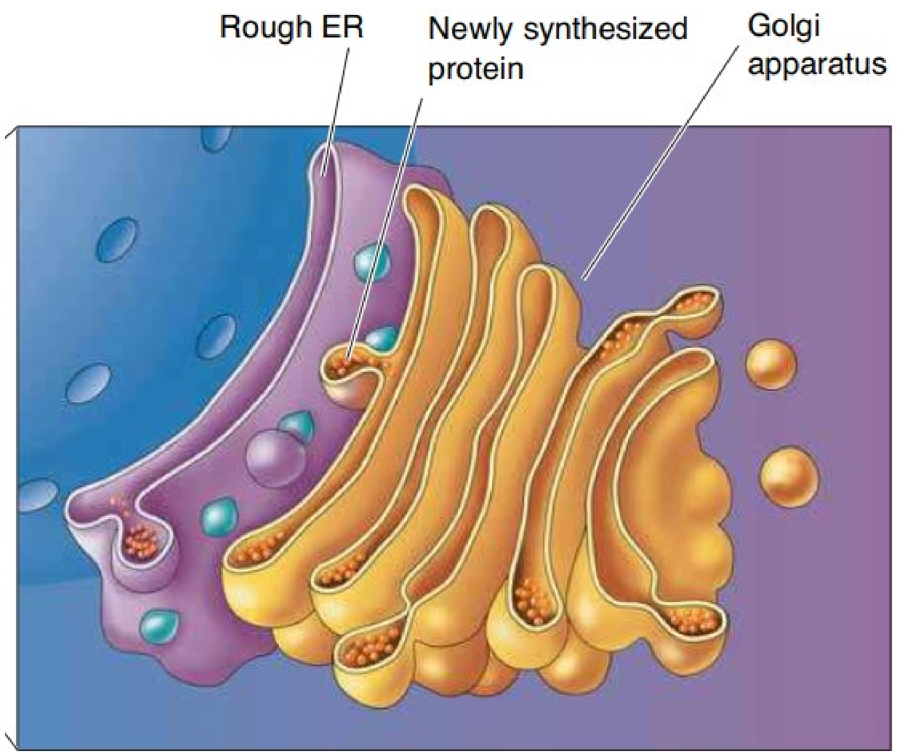
Affiliation at the time of the award: Weizmann Institute of Science, Rehovot, Israel

Prize motivation: "for studies of the structure and function of the ribosome"

Prize share: 1/3



The **Golgi apparatus/body/complex**



◀ FIGURE 2.12
The Golgi apparatus. This complex organelle sorts newly synthesized proteins for delivery to appropriate locations in the neuron.

Bear et al, 2016, pg. 37

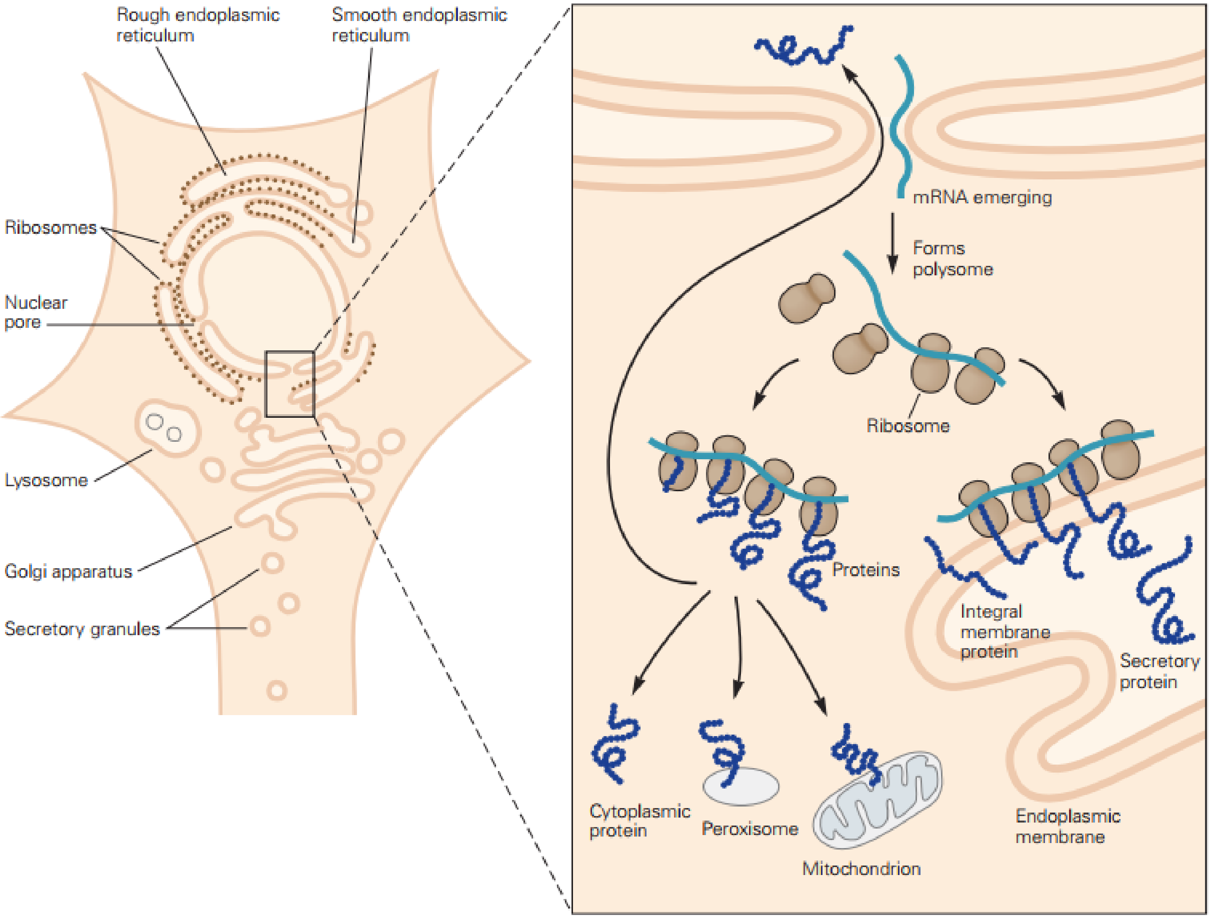
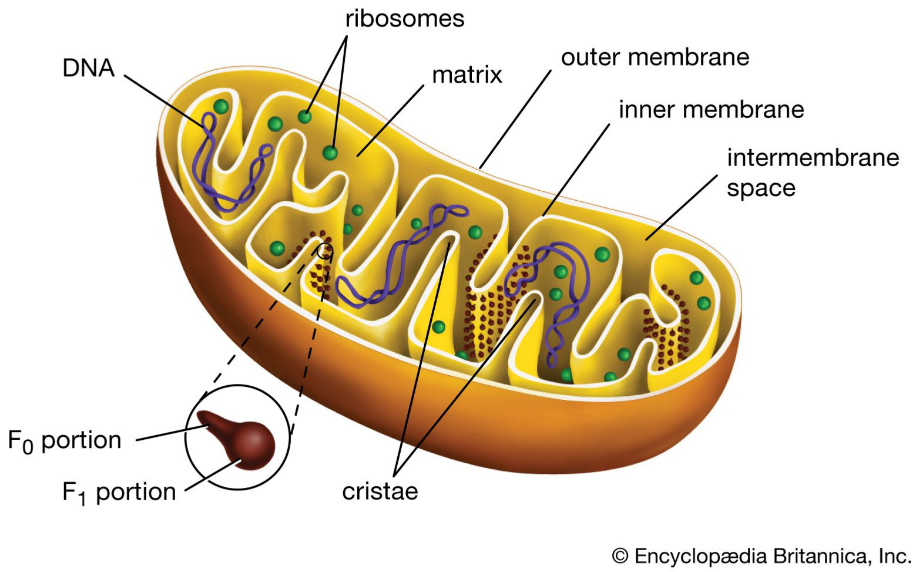


Figure 7–13 Protein synthesis in the endoplasmic reticulum. Free and membrane-bound polysomes translate mRNA that encodes proteins with a variety of destinations. Messenger RNA, transcribed from genomic DNA in the neuron's nucleus, emerges into the cytoplasm through nuclear pores to form polyribosomes (see enlargement). The polypeptides that become secretory and membrane proteins are translocated across the membrane of the rough endoplasmic reticulum.

Kandel et al., 2021, pg. 135

Responsible for **packaging proteins into vesicles** for delivery to targeted destinations.

The **mitochondria**



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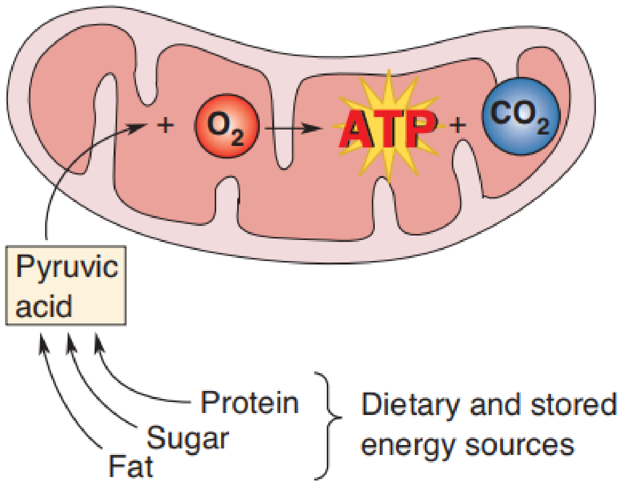


Bear et al, 2016, pg. 38

Biparental Inheritance of Mitochondrial DNA in Humans

Shiyu Luo[a,b], C. Alexander Valencia[a,1], Jinglan Zhang[c], Ni-Chung Lee[d], Jesse Slone[a], Baoheng Gui[a,b], Xinjian Wang[a], Zhuo Li[a,2], Sarah Dell[a], Jenice Brown[a], Stella Maris Chen[c], Yin-Hsiu Chien[d], Wuh-Liang Hwu[d], Pi-Chuan Fan[e], Lee-Jun Wong[c], Paldeep S. Atwal[f,3], and Taosheng Huang[a,3,4]

[a]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229; [b]Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region, Nanning, 530003 Guangxi, China; [c]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030; [d]Department of Pediatrics and Medical Genetics, National Taiwan University Hospital, 100 Taipei, Taiwan; [e]Department of Pediatrics, National Taiwan University Hospital, 100 Taipei, Taiwan; and [f]Department of Clinical Genomics, Center for Individualized Medicine, Mayo Clinic Hospital, Jacksonville, FL 32224

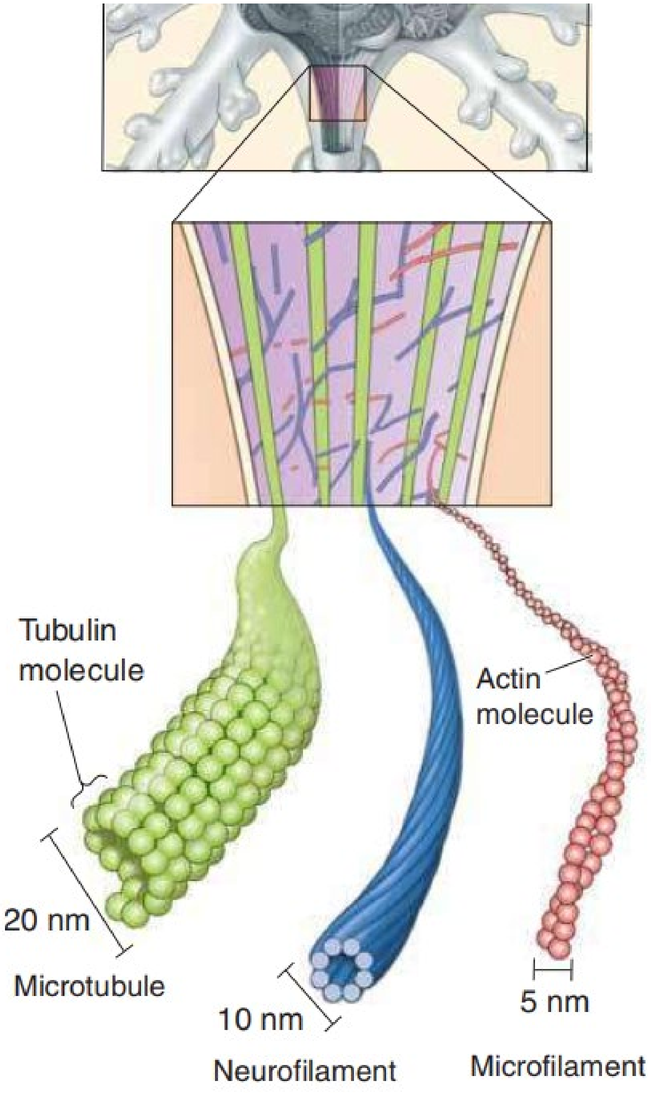
Edited by Douglas C. Wallace, Children's Hospital of Philadelphia and University of Philadelphia, Philadelphia, PA, and approved October 29, 2018 (received for review June 26, 2018)

https://www.pnas.org/doi/full/10.1073/pnas.1810946115

Sugars, protein an fat, for the basis of **pyruvic acid**.

The mitochondria take the pyruvic acid and the oxygen from the cytosol and transforms them into **adenosine triphosphate (ATP)**, which forms the energy source of the cell.

The **membrane** and the **cytoskeleton**



Bear et al, 2016, pg. 39

* 1 nm (nanometer) = 10^{-9} m

The membrane (*plasmalemma*) is ~ 5 nm thick and is covered in proteins. These proteins vary according to whether the membrane covers the soma, the axon, or the dendrites.

The membrane stretches over a scaffolding called **cytoskeleton**, composed of **microtubules**, **microfilaments**, and **neurofilaments**.

Microtubules run longitudinally down the **neurites** (i.e., axons or dendrites), and look like hollow cylinders. Their wall is made of proteins called **tubulin**, joined into long strands (i.e., **polymers**).

Intermediate filaments (i.e., intermediate in size between microtubules and microfilaments) are called **neurofilaments** when they are found in neurons. The are formed bundles of elongated protein molecules.

Microfilaments are formed by two polymers consisting of proteins called **actin**. They run along the neurites, but are also attached to the membrane.

The glia

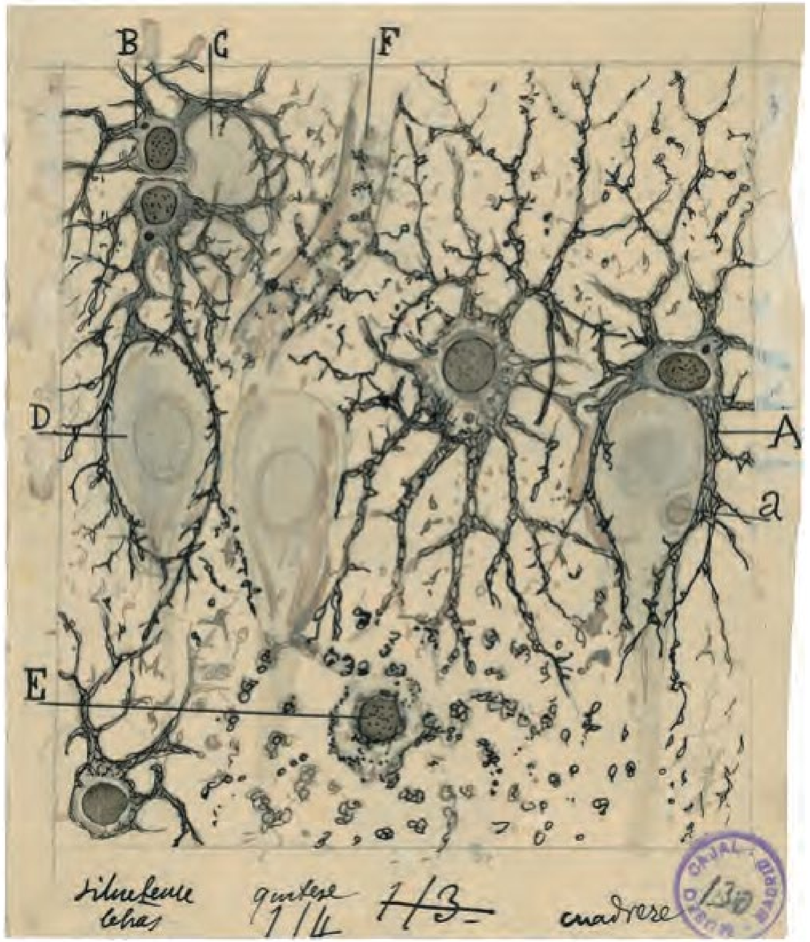


Figure 7–14 Astrocytes interact with neurons and synapses in the brain. This drawing by Ramón y Cajal (based on tissue stained with the sublimated gold chloride method) shows astrocytes of the pyramidal layer and stratum radiatum of Ammon's horn in the human brain. (**A**) A large astrocyte ensheathes a pyramidal neuron. (**B**) Twin astrocytes form a nest around a nerve cell body (**C**). One of the astrocytes sends two branches to form another nest (**D**). (**E**) A cell shows signs of autolysis. (**F**) Capillary vessel. (Reproduced, with permission, from the Instituto Cajal, Madrid, Spain.)

Kandel et al., 2021, pg. 151

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Published in final edited form as: NIHMSID: NIHMS995422

Science. 2018 Oct 12; 362(6411): 181–185. PMID: 30309945

doi: 10.1126/science.aat0473

Glia as Architects of Central Nervous System Formation and Function*

Nicola J. Allen[1,*] and David A. Lyons[2,*]

Abstract Go to: ▸

Glia constitute roughly half of the cells of the central nervous system (CNS), but were long-considered static bystanders to its formation and function. Here we provide an overview of how the diverse and dynamic functions of glial cells orchestrate essentially all aspects of nervous system formation and function. Radial glia, astrocytes, oligodendrocyte progenitor cells, oligodendrocytes and microglia each influence nervous system development, from neuronal birth, migration, axon specification and growth, through to circuit assembly and synaptogenesis. As neural circuits mature, distinct glia fulfil key roles in synaptic communication, plasticity, homeostasis, and networklevel activity, through dynamic monitoring and alteration of CNS structure and function. Continued elucidation of glial cell biology, and the dynamic interactions of neurons and glia, will enrich our understanding of nervous system formation, health and function.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6292669/

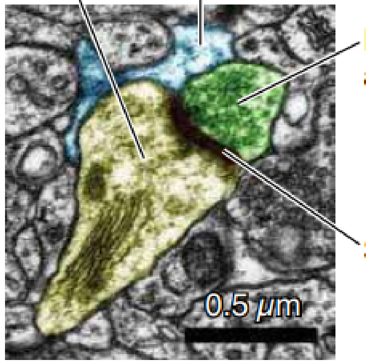
Santiago Ramon y Cajal first identified the presence of glia and suggested they may play an important role.

Initially believed to be no more than the "**glue**" holding neurons together.

Astrocytes

▲ FIGURE 2.24
An astrocyte. Astrocytes fill most of the space in the brain that is not occupied by neurons and blood vessels.

Bear et al, 2016, pg. 37



▲ FIGURE 2.25
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.)

Bear et al, 2016, pg. 37

Most numerous glial cells.

Only present in the **central nervous system** (brain and spinal cord).

Regulate the chemical content of the extracellular space, e.g., by restricting the spread of released **neurotransmitters**, or by removing neurotransmitters from the synaptic cleft.

Help maintain **optimal neuronal function** by controlling the level of **ions** (electrically charged particles) in the extracellular space.

Crucially, astrocytes form and maintain the **blood brain barrier (BBB)**, which regulates the exchange of molecules between the central nervous system (CNS) and the outside environment, thus maintaining **CNS homeostasis**.

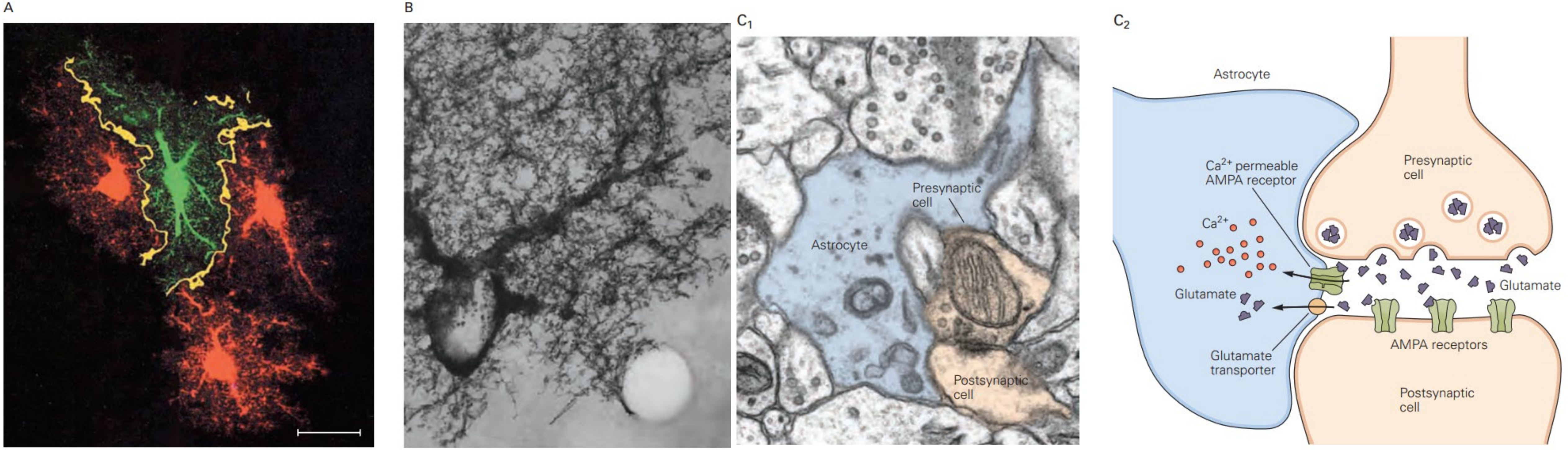


Figure 7–19 Astrocyte processes are intimately associated with synapses.

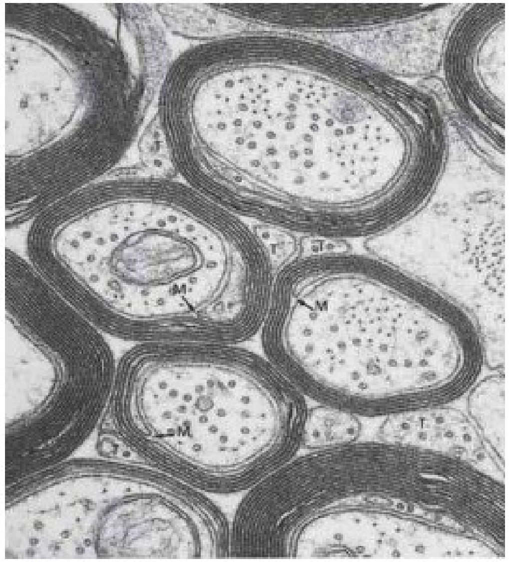
A. Astrocytes occupy discrete volumes. The central astrocyte (**green**) is shown to occupy a volume distinct from its three neighbors (**red**), with only a small overlap (**yellow**) at the ends of their processes, which are interconnected by gap junctions Bar = 20 μm. (Reproduced, with permission, from Bushong et al. 2002. Copyright © 2002 Society for Neuroscience.)

B. This high-voltage electron micrograph shows several thick processes emanating from the cell body of an astrocyte and branching into extraordinarily fine processes. The typical envelopment of a blood vessel is shown at lower right. (Reproduced, with permission, from Hama et al. 1994. Copyright © 1994 Wiley.)

C. The processes of astrocytes are intimately associated with both presynaptic and postsynaptic elements. **1.** The close association between astrocyte processes and synapses is seen in this electron micrograph of hippocampal cells. (Reproduced, with permission, from Ventura and Harris 1999. Copyright © 1999 Society for Neuroscience.) **2.** Glutamate released from the presynaptic neuron activates not only receptors on the postsynaptic neuron but also AMPA-type (α-amino-3-hydroxy-5-methylisoxazole-4-propionate) receptors on astrocytes. Astrocytes remove glutamate from the synaptic cleft by uptake through high-affinity transporters. (Adapted from Gallo and Chittajallu 2001.)

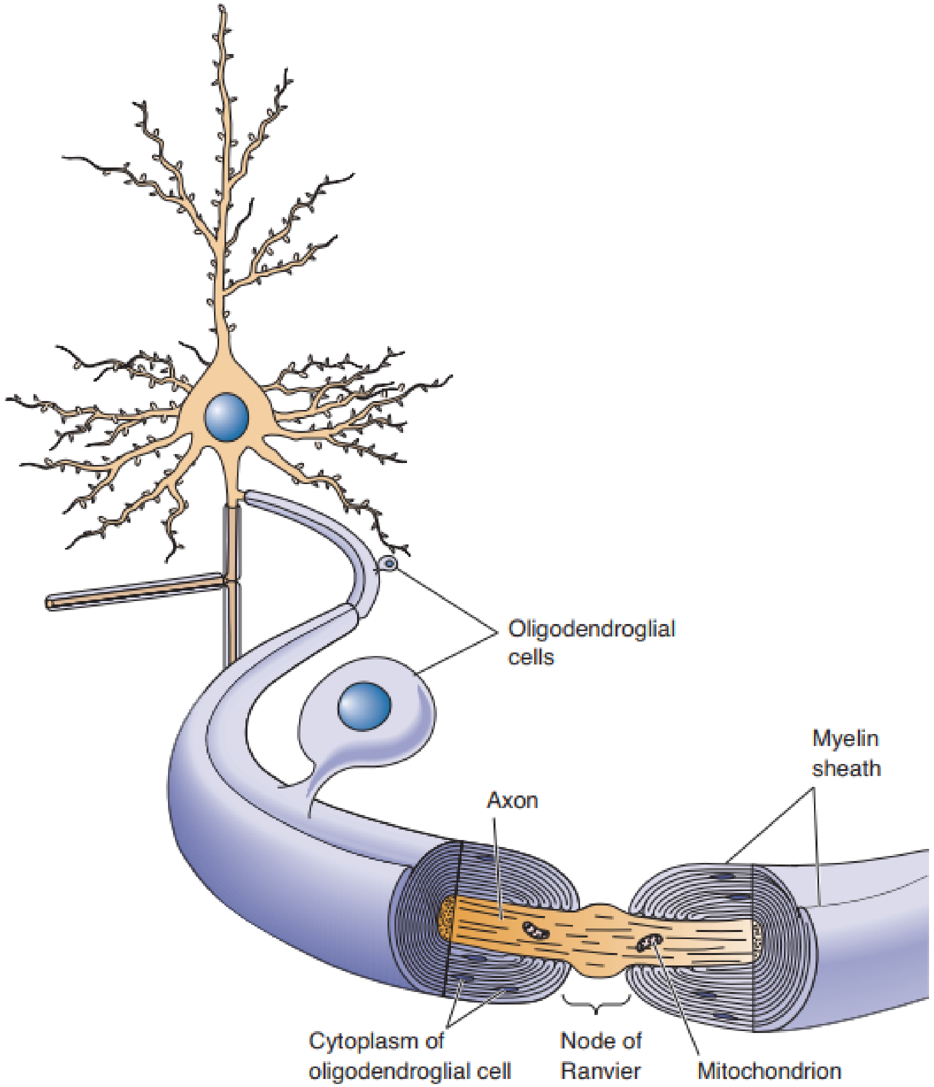
Kandel et al., 2021, pg. 158

Myelinating Glia: **Oligodendrocytes** and **Schwann** cells



▲ FIGURE 2.26
Myelinated optic nerve fibers cut in cross section. (Source: Courtesy of Dr. Alan Peters.)

Bear et al, 2016, pg. 52



▲ FIGURE 2.27
An oligodendroglial cell. Like the Schwann cells found in the nerves of the body, oligodendroglia provide myelin sheaths around axons in the brain and spinal cord. The myelin sheath of an axon is interrupted periodically at the nodes of Ranvier.

myelin

insulating layer of fat and protein

Oligodendrocytes myelinate the axons of the neurons in the **CNS**

Schwann cells myelinate the axons of the neurons in the **peripheral** nervous system

nodes of Ranvier

gaps in between sheaths of myelin increasing the speed of signal transmission

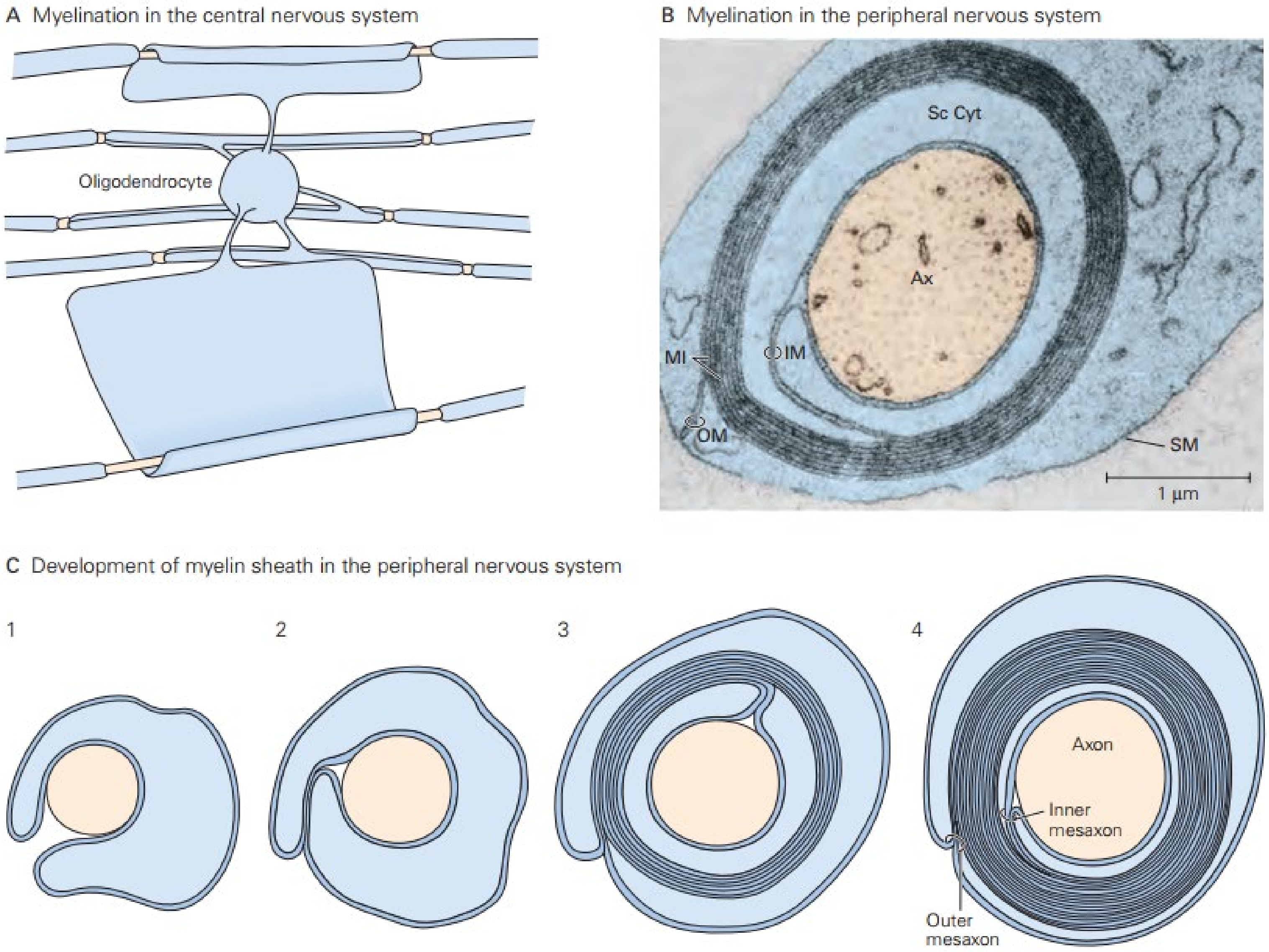


Figure 7–15 Glial cells produce the myelin that insulates the axons of central and peripheral neurons.

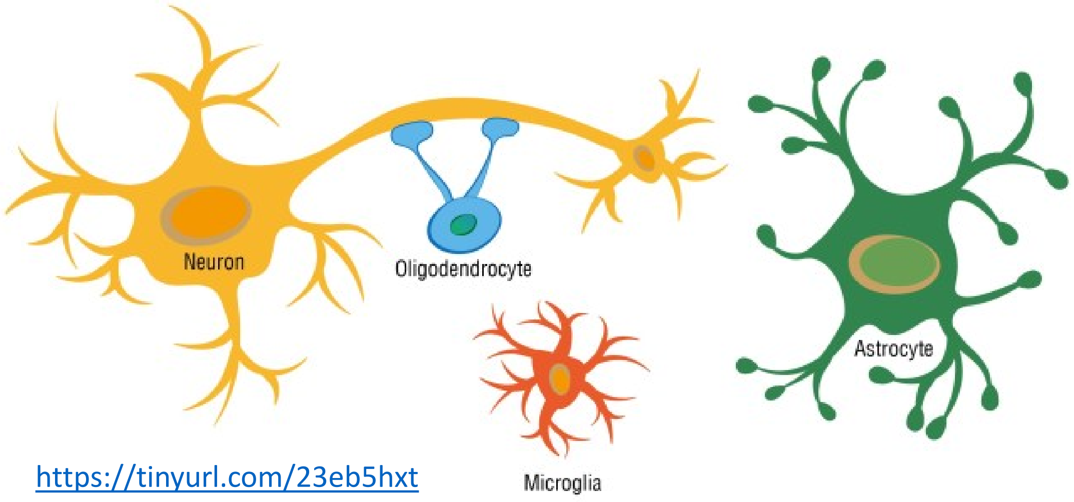
A. Axons in the central nervous system are wrapped in several layers of myelin produced by oligodendrocytes. Each oligodendrocyte can myelinate many axons. (Adapted from Raine 1984.)

B. This electron micrograph of a transverse section through an axon (**Ax**) in the sciatic nerve of a mouse shows the origin of a sheet of myelin (**MI**) at a structure called the inner mesaxon (**IM**). The myelin arises from the surface membrane (**SM**) of a Schwann cell, which is continuous with the outer mesaxon (**OM**). In this image, the Schwann cell cytoplasm (**Sc Cyt**) still surrounds the axon; eventually it is squeezed out and the myelin layers become compact, as shown in part **C**. (Reproduced, with permission, from Dyck et al. 1984.)

C. A peripheral nerve fiber is myelinated by a Schwann cell in several stages. In stage 1, the Schwann cell surrounds the axon. In stage 2, the outer aspects of the plasma membrane have become tightly apposed in one area. This membrane fusion reflects early myelin membrane formation. In stage 3, several layers of myelin have formed because of continued rotation of the Schwann cell cytoplasm around the axon. In stage 4, a mature myelin sheath has formed; much of the Schwann cell cytoplasm has been squeezed out of the innermost loop. (Adapted, with permission, from Williams et al. 1989.)

Kandel et al., 2021, pg. 152

Microglial cells



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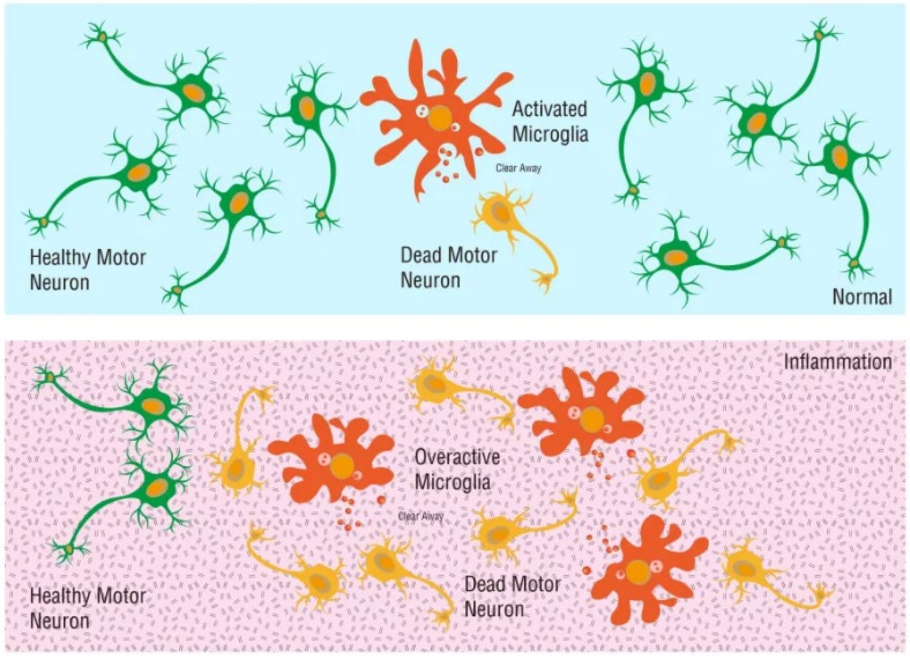


https://tinyurl.com/23eb5hxt

Make up ~ 10% of the glia in the CNS.

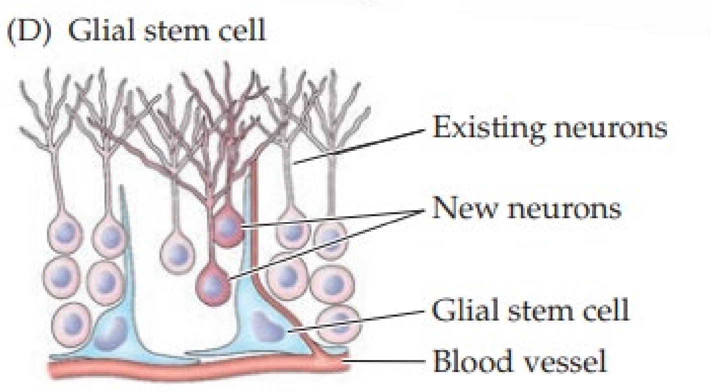
Similar in function to other **macrophage** (*scavenger*) cells, they engage in the **phagocytosis** (ingestion) of the debris resulting from tissue injury or cell turnover.

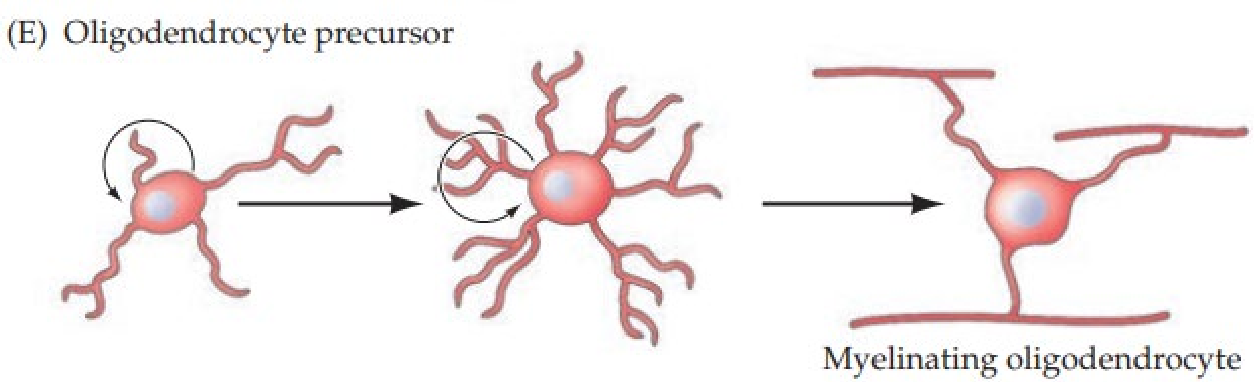
After brain damage, the number of microglia at the site of the injury increases dramatically.

Critical for the immune response to infection or trauma, but can also contribute to pathological neuroinflammation by releasing cytokines and neurotoxic proteins and by inducing neurotoxic reactive astrocytes.

In the early stages of Amyotrophic Lateral Sclerosis (ALS), microglia may have a protective role by detecting and clearing away dead motor neurons (top), but in the presence of chronic inflammation (bottom), overactive microglia can lead to the death of healthy neurons, which may cause the disease to progress more rapidly.

Glial stem cells





(D) Glial stem cells in the mature nervous system include stem cells with properties of astrocytes that **can give rise to neurons, astrocytes, and oligodendrocytes.**

(E) Another class of glial stem cell, the **oligodendrocyte precursor**, has a more restricted potential, giving rise primarily to differentiated oligodendrocytes.

Purves et al., 2018, pg. 8

Reviews

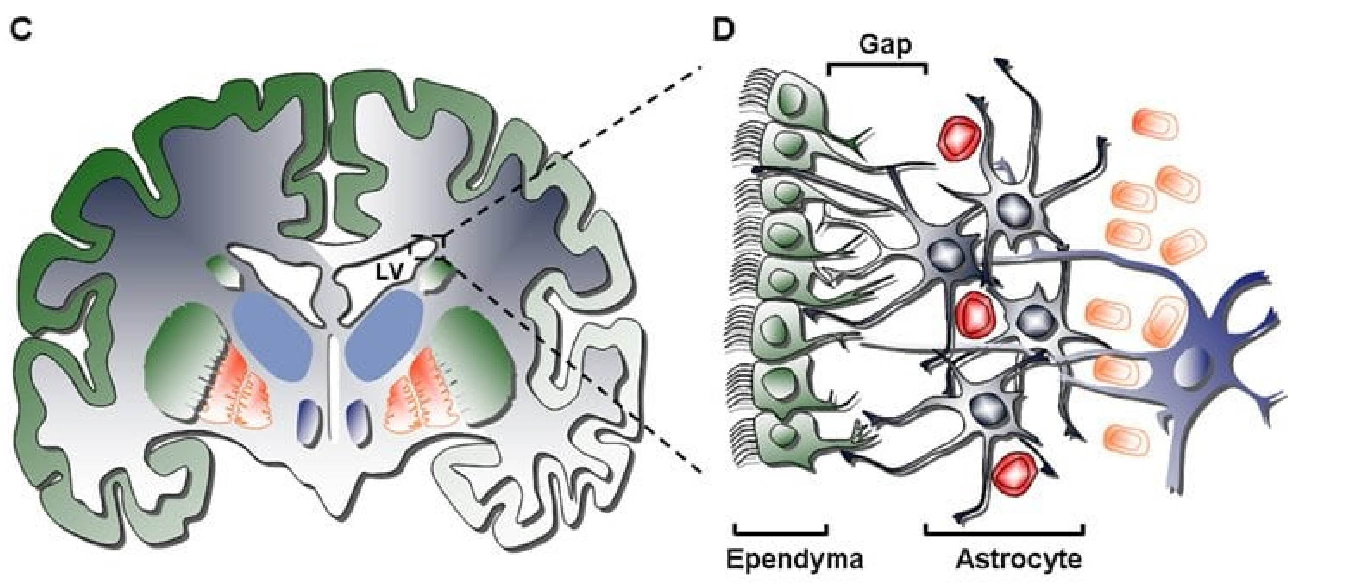
Glial Cells as Progenitors and Stem Cells: New Roles in the Healthy and Diseased Brain

Leda Dimou, and Magdalena Götz

01 JUL 2014 // https://doi.org/10.1152/physrev.00036.2013

https://journals.physiology.org/doi/full/10.1152/physrev.00036.2013

Ependymal cells

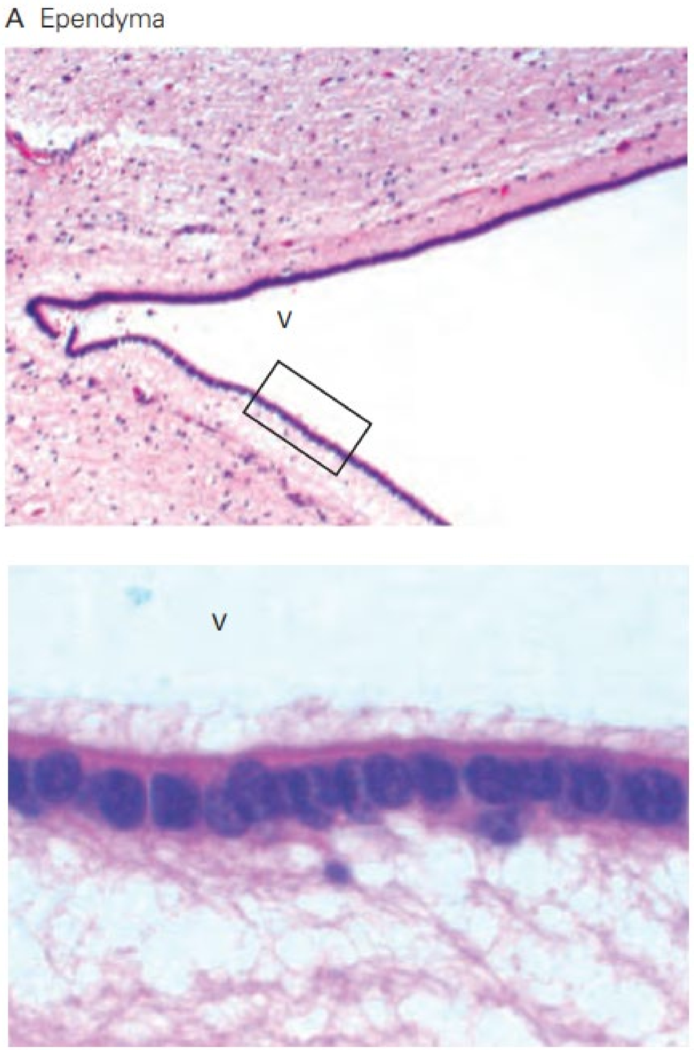


https://tinyurl.com/wvxu77h8

Ependymal cells are **ciliated glial cells** that form an epithelial barrier, called the **ependyma**, lining the brain's ventricular system and the spinal cord's central canal. They **develop from radial glia** along the surface of the ventricles of the brain and spinal canal.

(MacDonald et al., 2021, pg. 1, https://tinyurl.com/wvxu77h8)

Crucial for cerebrospinal fluid (CSF) **homeostasis**, brain **metabolism**, and the **clearance of waste** from the brain



A. The ependyma is a single layer of ciliated, cuboidal cells lining the cerebral ventricles (V). The lower image, a high magnification of the ependymal lining (rectangle in upper image), shows the cilia on the ventricular side of the ependymal cells.

Kandel et al., 2021, pg. 161

Neurodegenerative disorders

Multiple sclerosis (MS)

In MS, the **immune system cells** that normally protect us from viruses, bacteria, and unhealthy cells **mistakenly attack myelin** in the **CNS** (brain, optic nerves, and spinal cord).

https://www.ninds.nih.gov/health-information/disorders/multiple-sclerosis

Guillain-Barré Syndrome (GBS)

In GBS, the **immune system cells mistakenly attack** the **myelin** in the peripheral nervous system, as well as axons.

https://www.ninds.nih.gov/health-information/disorders/guillain-barre-syndrome

Amyotrophic Lateral Sclerosis (ALS)

Formerly known as **Lou Gehrig's disease**.

Caused by the **degeneration of motor neurons**, causing muscle twitching and muscle atrophy.

https://www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral-sclerosis-als

And more

Int J Mol Sci. 2022 Feb; 23(3): 1851.
Published online 2022 Feb 6. doi: 10.3390/ijms23031851

PMCID: PMC8837071
PMID: 35163773

A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics

Richard N. L. Lamptey, Bivek Chaulagain, Riddhi Trivedi, Avinash Gothwal, Buddhadev Layek,* and Jagdish Singh*

https://tinyurl.com/yc58t435

Genomics Proteomics Bioinformatics. 2016 Jun; 14(3): 155–165.
Published online 2016 May 28. doi: 10.1016/j.gpb.2016.04.003

PMCID: PMC4936608
PMID: 27245308

Connecting Malfunctioning Glial Cells and Brain Degenerative Disorders

Natalie Kaminsky,[1,a] Ofer Bihari,[1,2,b] Sivan Kanner,[1,*,c] and Ari Barzilai[1,2,*,d]

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Abstract

Go to: ▸

The **DNA damage response** (DDR) is a complex biological system activated by different types of DNA damage. Mutations in certain components of the DDR machinery can lead to **genomic instability** disorders that culminate in tissue degeneration, premature aging, and various types of cancers. Intriguingly, malfunctioning DDR plays a role in the etiology of late onset brain degenerative disorders such as Parkinson's, Alzheimer's, and Huntington's diseases. For many years, brain degenerative disorders were thought to result from aberrant neural death. Here we discuss the evidence that supports our novel hypothesis that **brain degenerative diseases** involve dysfunction of **glial cells** (**astrocytes**, **microglia**, and oligodendrocytes). Impairment in the functionality of **glial cells** results in pathological neuro-glial interactions that, in turn, generate a "hostile" environment that impairs the functionality of neuronal cells. These events can lead to systematic neural demise on a scale that appears to be proportional to the severity of the neurological deficit.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4936608/

Glial cells have more than a mere trophic role; they contribute to **neurotransmission**, **neuroplasticity** and **neurogenesis.** They also help maintain **homeostasis** and regulate **neuroinflamation**.

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Published online 2020 Dec 2. doi: 10.3390/ijms21239188

PMCID: PMC7730416
PMID: 33276471

Glia in Neurodegeneration: The Housekeeper, the Defender and the Perpetrator

Carrie Sheeler,[1,*] Juao-Guilherme Rosa,[1] Austin Ferro,[1] Brian McAdams,[1] Ella Borgenheimer,[1] and Marija Cvetanovic[1,2]

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Associated Data

▸ **Supplementary Materials**

Abstract

Go to: ▸

Over the past decade, research has unveiled the intimate relationship between neuroinflammation and neurodegeneration. Microglia and astrocytes react to brain insult by setting up a multimodal inflammatory state and act as the primary defenders and executioners of neuroinflammatory structural and functional changes. Microglia and astrocytes also play critical roles in the maintenance of normal brain function. This intricate balance of homeostatic and neuroinflammatory functions can influence the onset and the course of neurodegenerative diseases. The emergent role of the microglial-astrocytic axis in neurodegenerative disease presents many druggable targets that may have broad therapeutic benefits across neurodegenerative disease. Here, we provide a brief review of the basal function of both microglia and astrocytes, how they are changed in disease states, the significant differences between mouse and human glia, and use of human induced pluripotent stem cells derived from patients to study cell autonomous changes in human astrocytes and microglia.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7730416/

Astrocytic modulation of blood brain barrier: perspectives on Parkinson's disease

Ricardo Cabezas [1], Marcos Avila [1], Janneth Gonzalez [1], Ramon Santos El-Bachá [2], Eliana Báez [1], Luis Miguel García-Segura [3], Juan Camilo Jurado Coronel [1], Francisco Capani [4], Gloria Patricia Cardona-Gomez [5], George E Barreto [1]

Affiliations + expand

PMID: 25136294 PMCID: PMC4120694 DOI: 10.3389/fncel.2014.00211

Free PMC article

Abstract

The blood-brain barrier (BBB) is a tightly regulated interface in the Central Nervous System (CNS) that regulates the exchange of molecules in and out from the brain thus maintaining the CNS homeostasis. It is mainly composed of endothelial cells (ECs), pericytes and astrocytes that create a neurovascular unit (NVU) with the adjacent neurons. Astrocytes are essential for the formation and maintenance of the BBB by providing secreted factors that lead to the adequate association between the cells of the BBB and the formation of strong tight junctions. Under neurological disorders, such as chronic cerebral ischemia, brain trauma, Epilepsy, Alzheimer and Parkinson's Diseases, a disruption of the BBB takes place, involving a lost in the permeability of the barrier and phenotypical changes in both the ECs and astrocytes. In this aspect, it has been established that the process of reactive gliosis is a common feature of astrocytes during BBB disruption, which has a detrimental effect on the barrier function and a subsequent damage in neuronal survival. In this review we discuss the implications of astrocyte functions in the protection of the BBB, and in the development of Parkinson's disease (PD) and related disorders. Additionally, we highlight the current and future strategies in astrocyte protection aimed at the development of restorative therapies for the BBB in pathological conditions.

https://pubmed.ncbi.nlm.nih.gov/25136294/

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NIHMSID: NIHMS1636305
PMID: 33127097

Microglial Phagocytosis: A Disease-Associated Process Emerging from Alzheimer's Disease Genetics

Anna Podleśny-Drabiniok,[1,2] Edoardo Marcora,[1,2] and Alison M. Goate[1,2,*]

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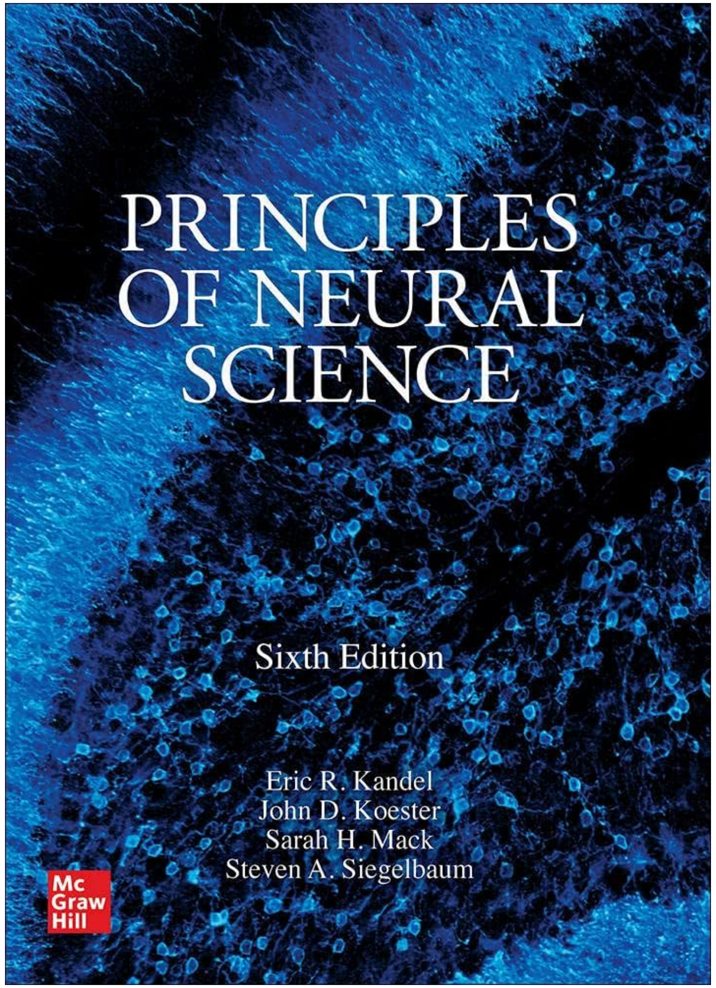
Abstract

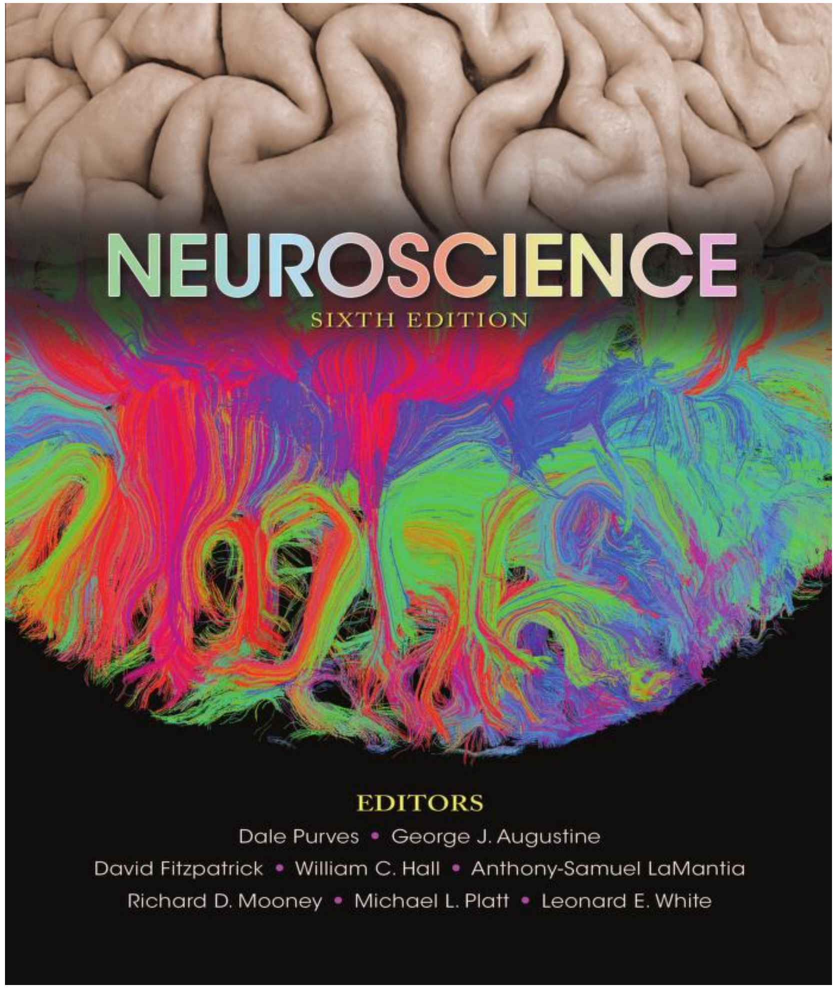
Go to: ▸

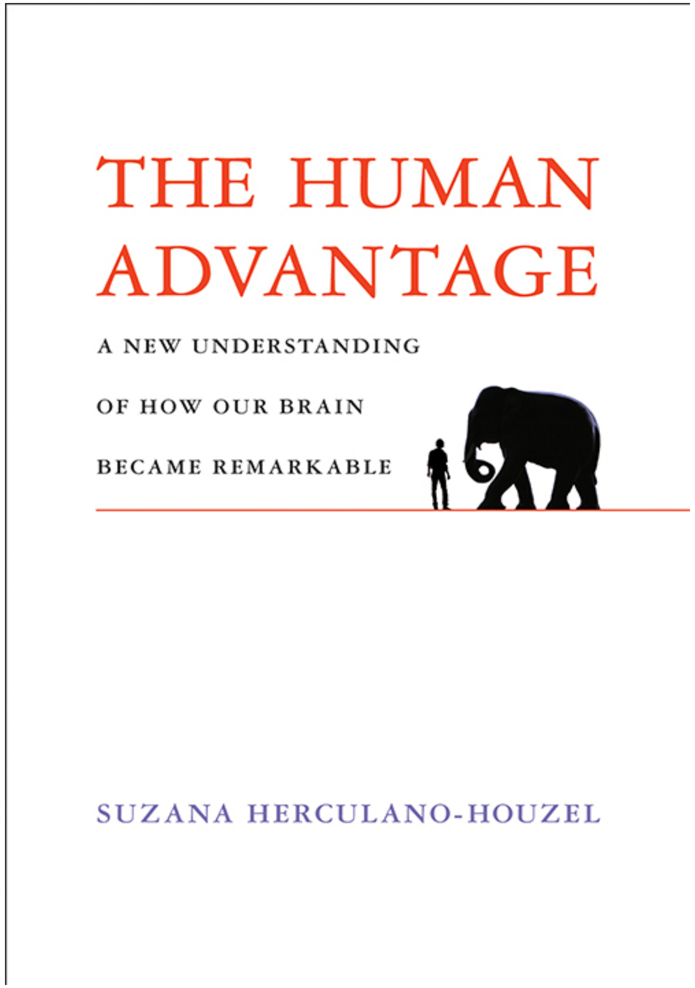
Alzheimer's disease (AD) is a debilitating, chronic neurodegenerative disease. Genetic studies involving genome-wide association studies (GWAS) and meta-analysis have discovered numerous genomic loci associated with AD; however, the causal genes and variants remain unidentified in most loci. Integration of GWAS signals with epigenomic annotations has demonstrated that AD risk variants are enriched in myeloid-specific enhancers, implicating myeloid cells in AD etiology. AD risk variants in these regulatory elements modify disease susceptibility by regulating the expression of genes that play crucial roles in microglial phagocytosis. Several of these AD risk genes are specifically expressed in myeloid cells, whereas others are ubiquitously expressed but are regulated by AD risk variants within myeloid enhancers in a cell type-specific manner. We discuss the impact of established AD risk variants on microglial phagocytosis and debris processing via the endolysosomal system.

https://tinyurl.com/52z6pajb

Further reading







REVIEW article

Front. Neuroanat., 16 May 2011

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The evolution of the brain, the human nature of cortical circuits, and intellectual creativity

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The tremendous expansion and the differentiation of the neocortex constitute two major events in the evolution of the mammalian brain. The increase in size and complexity of our brains opened the way to a spectacular development of cognitive and mental skills. This expansion during evolution facilitated the addition of microcircuits with a similar basic structure, which increased the complexity of the human brain and contributed to its uniqueness. However, fundamental differences even exist between distinct mammalian species. Here, we shall discuss the issue of our humanity from a neurobiological and historical perspective.

Homo sum, humani nihil a me alienum puto
(I am a human being, and therefore, nothing human is strange to me)
Publius Terentius Afer (195/185–159 BC)

https://www.frontiersin.org/articles/10.3389/fnana.2011.00029/full#B52

The Transylvanian Institute of Neuroscience

https://www.youtube.com/watch?v=07btnKn90dw

** also ask your tutors, Ana and Andrei, about ways to get involved*