Review

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University of Minnesota

Course News

Coffee Hour

Tuesday (Oct 16)
9:30-10:30am

Surdyks Café in Northrop Auditorium

Stop by for a minute or an hour!

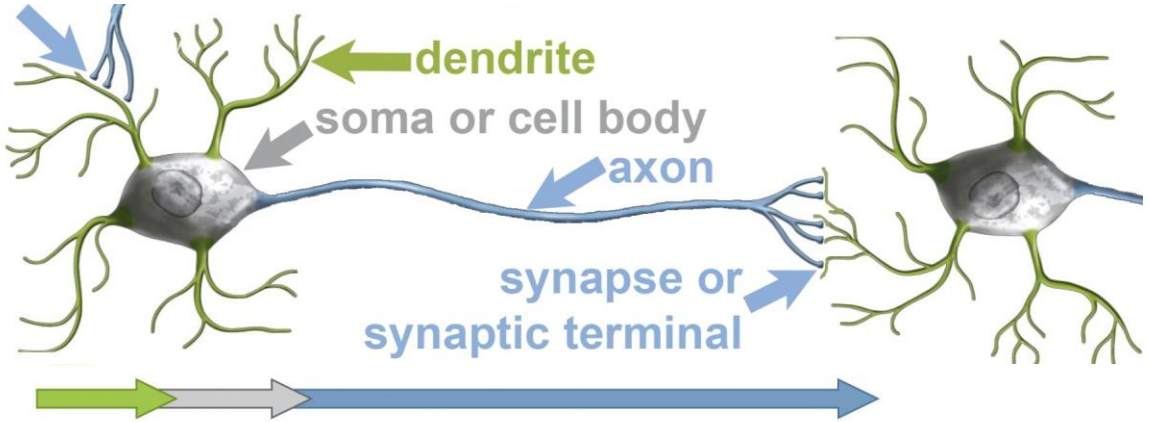
Course News

Midterm Exam

Monday, October 15
9:30am-11:00am???

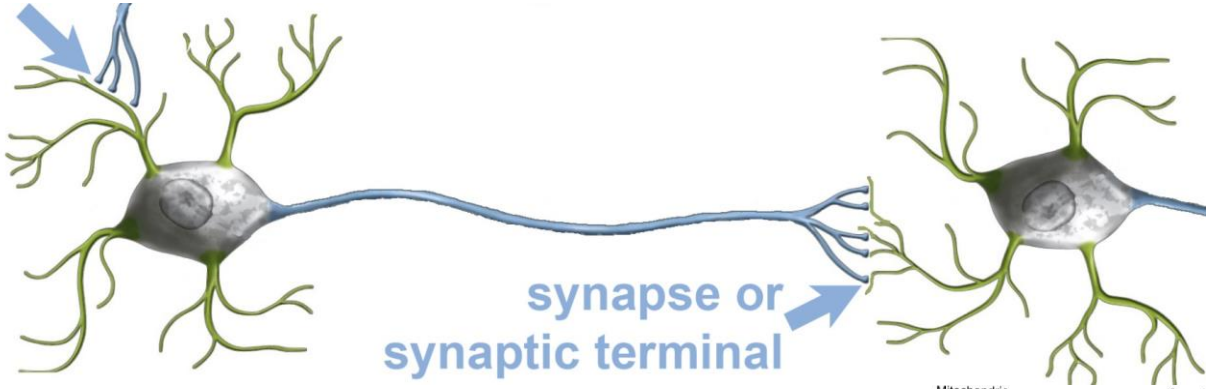
Bring a #2 pencil !!

Neurons communicate with other cells via synapses.



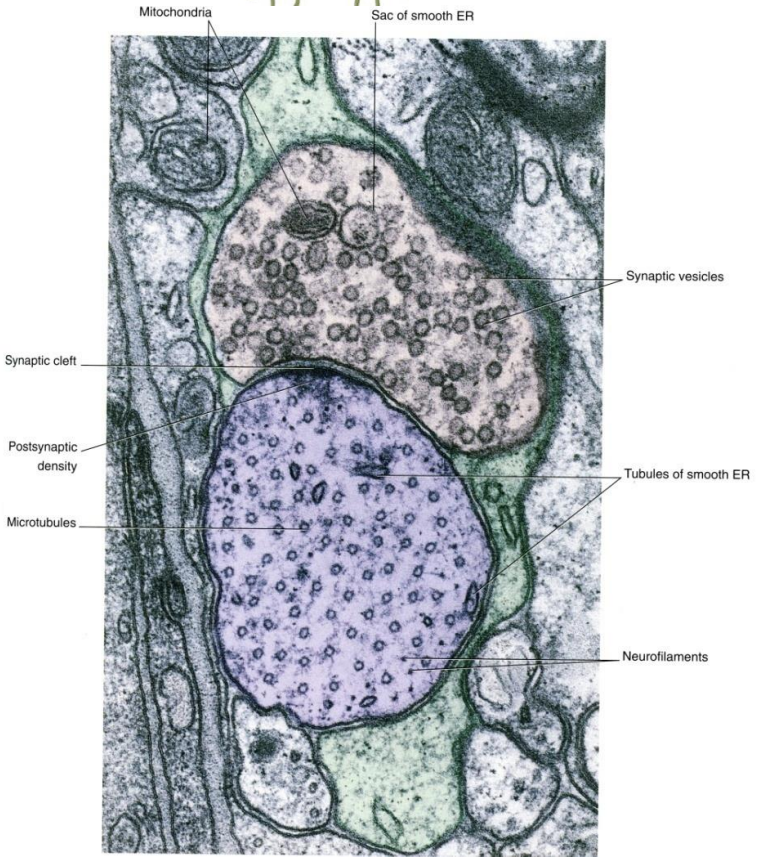
- Flow of information:
  dendrite > soma > axon > synapse
- Neurotransmitter is released from the presynaptic cell at the synapse.
- The transmitter diffuses across the synaptic cleft to the postsynaptic cell.

Neurons communicate with other cells via synapses.



Structure of a typical synapse:

- Presynaptic terminal
    - Synaptic vesicles containing neurotransmitter
    - Presynaptic density
- Synaptic cleft
- Postsynaptic element
    - Neurotransmitter receptors
    - Postsynaptic density



Neurons communicate with other cells via synapses.

- Different types of neurons release different neurotransmitters.
- Some common neurotransmitters:

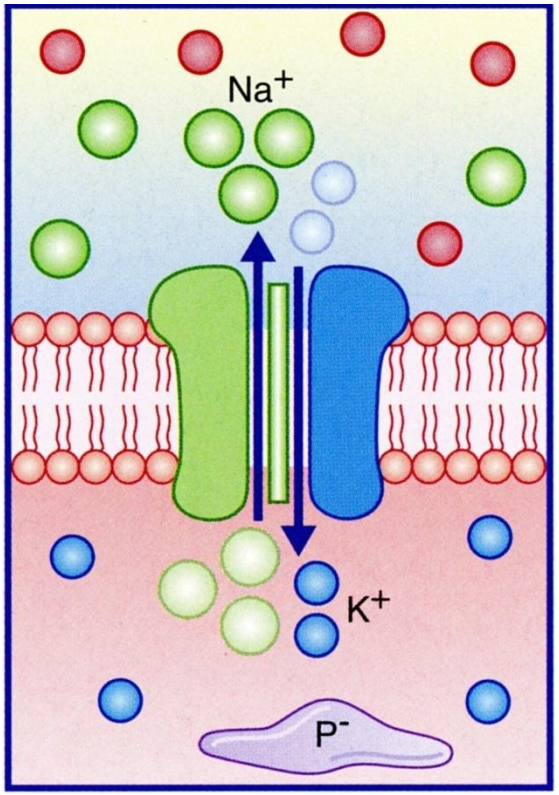
class	***transmitter***
biogenic amines	acetylcholine
	dopamine
	norepinephrine (noradrenaline)
	epinephrine (adrenaline)
	serotonin
amino acids	γ-aminobutyric acid (GABA)
	glutamate
	glycine
peptides	vasoactive intestinal polypeptide
	substance P
	enkephalin
	endorphin

Electrical Properties of Neurons

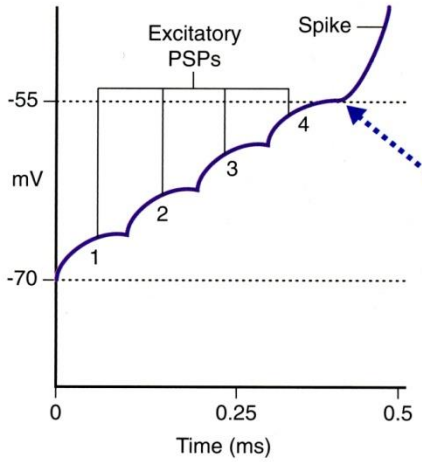
- A neuron at rest, that is a neuron receiving no synaptic input, maintains a higher concentration of K^+ and a lower concentration of Na^+ and Cl^- in its cytoplasm than outside the cell.

- A sodium-potassium pump maintains this ion differential.

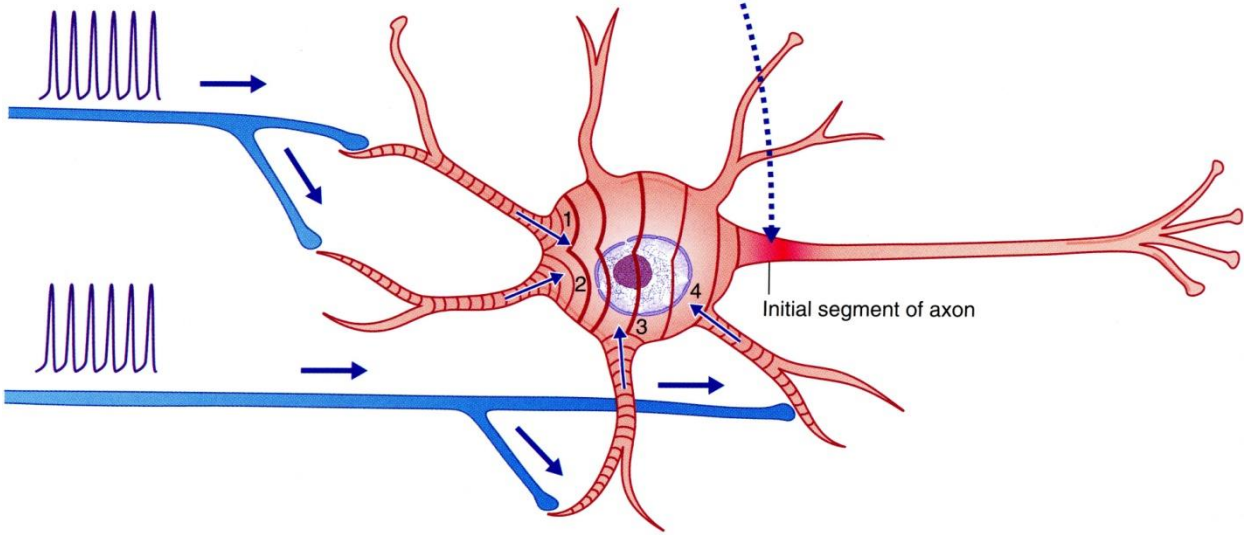
- A ‘resting membrane potential’ can be measured with electrodes on the inside and outside of the cell; this is typically -65mV.



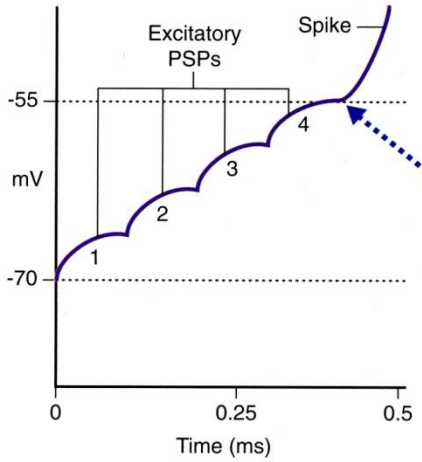
Electrical Properties of Neurons



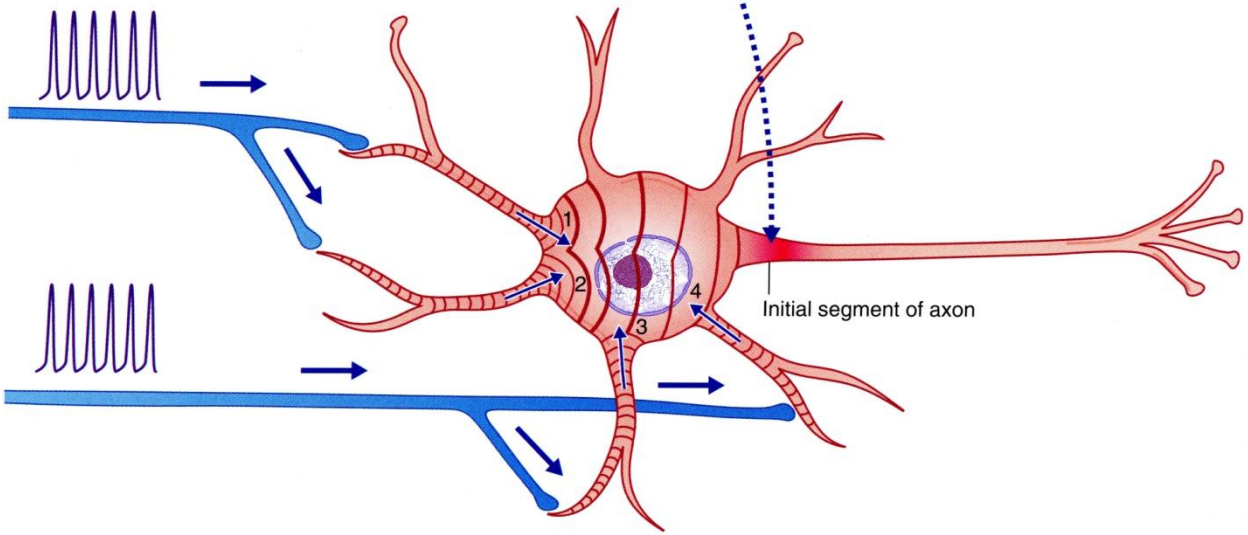
- Activation of neurotransmitter receptors causes changes in the ion conductance in the dendrites and soma.
- Inhibitory synaptic activity hyperpolarizes the neuron (i.e. the membrane potential becomes more negative).
- Excitatory synaptic activity depolarizes the neuron (i.e. makes it more positive).



Electrical Properties of Neurons

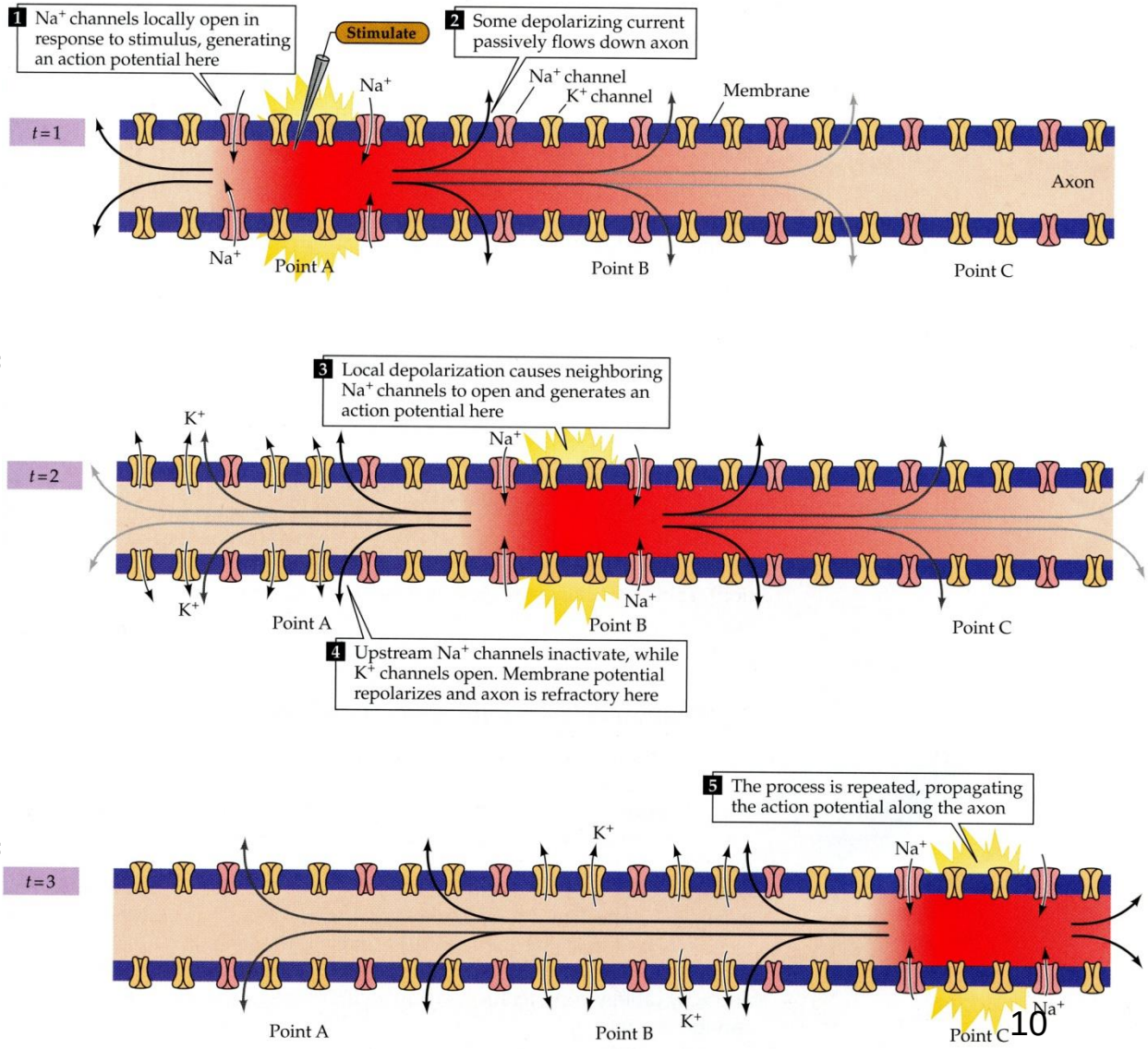


- The graded effect of all the synapses is summed at the initial segment of the axon.
- When the initial segment becomes sufficiently depolarized, voltage-gated sodium channels open and an action potential is generated.
- The influx of Na^+ into the axon is followed by an outflow of K^+.



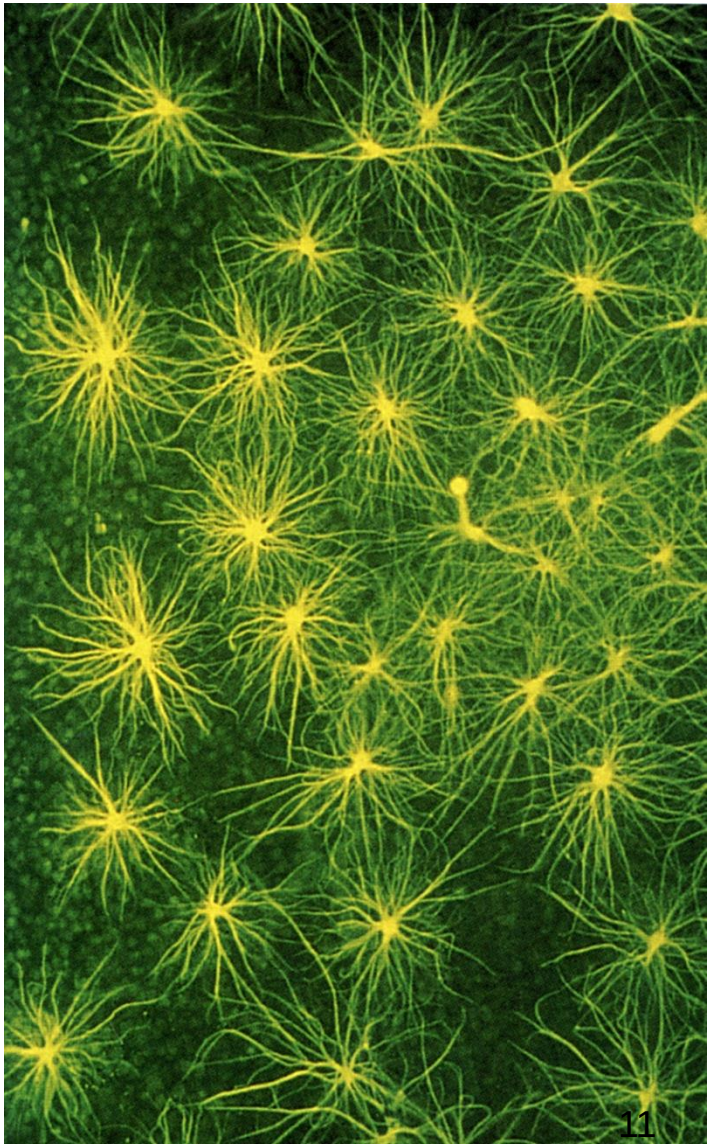
Electrical Properties of Neurons

- The influx of Na^+ into one segment of the axon results in opening of the sodium channels in the next part of the axon.
- The action potential is self propagated down the axon.
- The strength of the action potential is unchanged along the entire length of the axon.
- When an action potential reaches the synapse, it initiates release of neurotransmitter into the synaptic cleft.



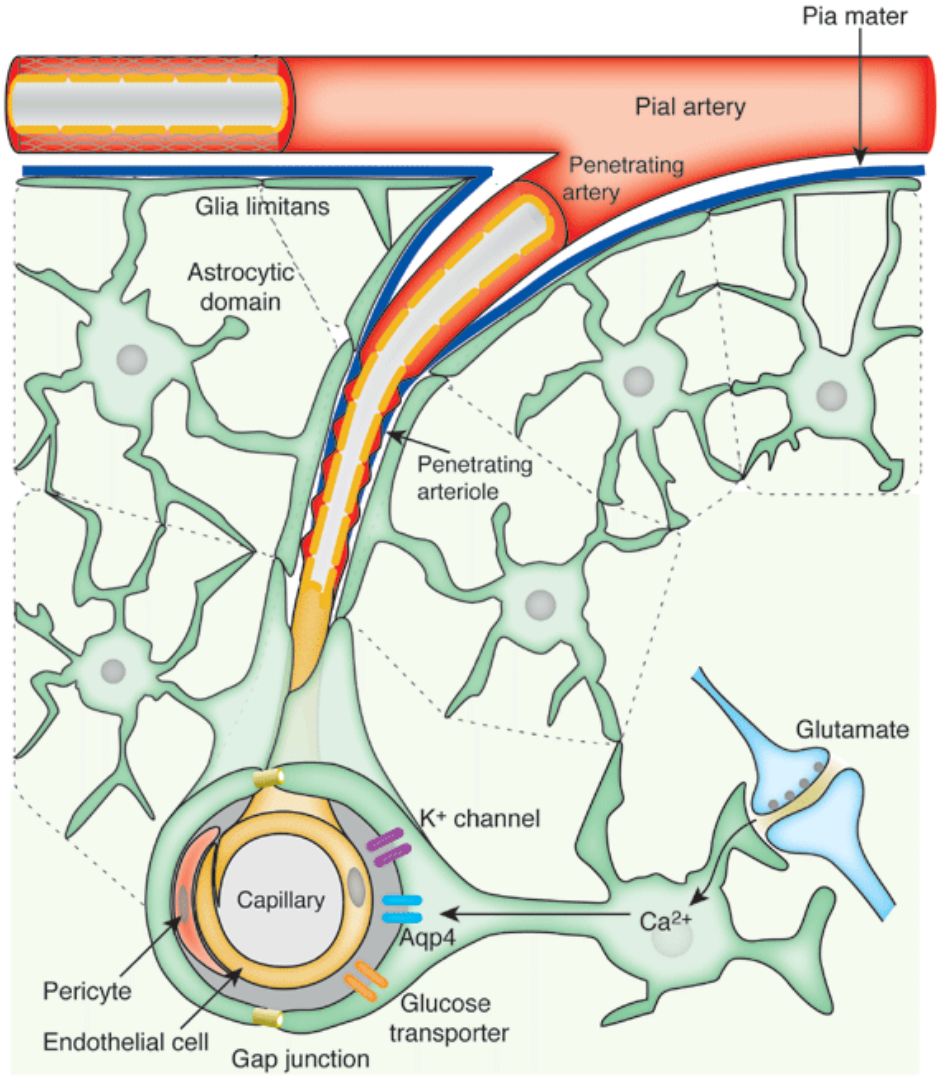
Astrocytes

- Star-shaped glial cells in the CNS
- Most abundant cell type of the brain and spinal cord
- Surround most synaspes



Astrocytes

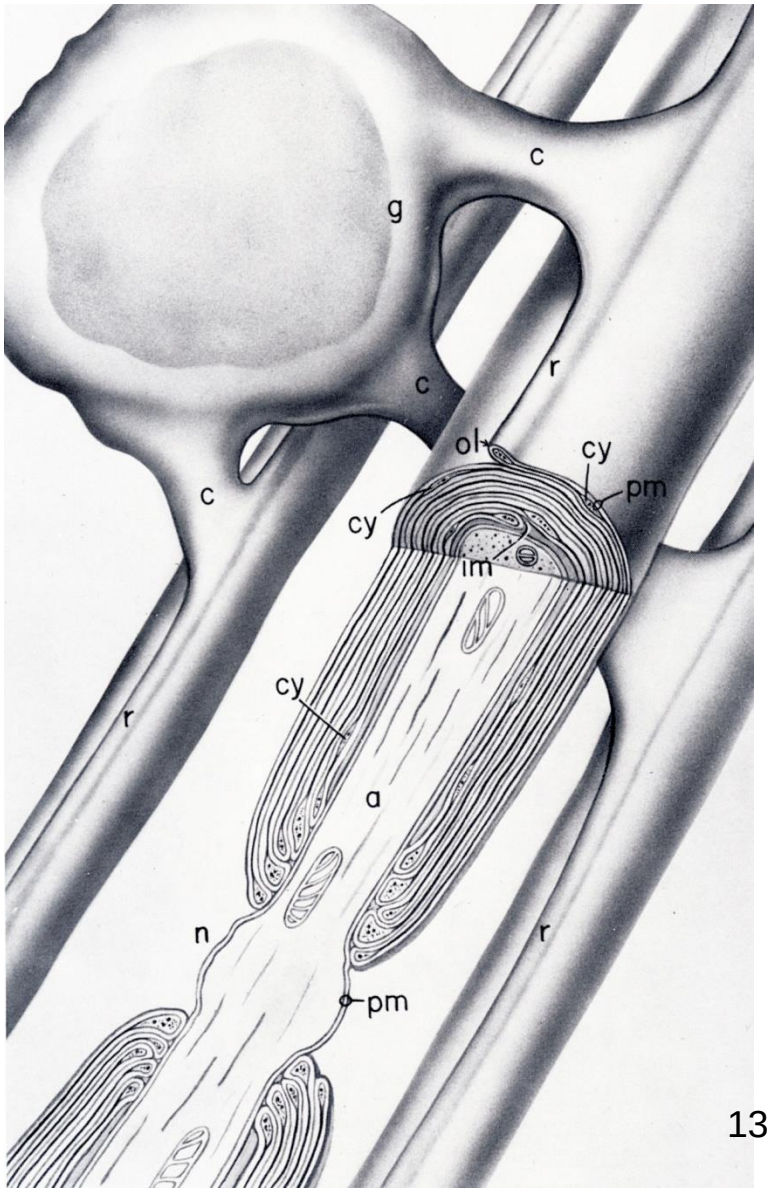
- Mediate exchange between capillaries and neurons; contribute to the blood-brain barrier



Myelin

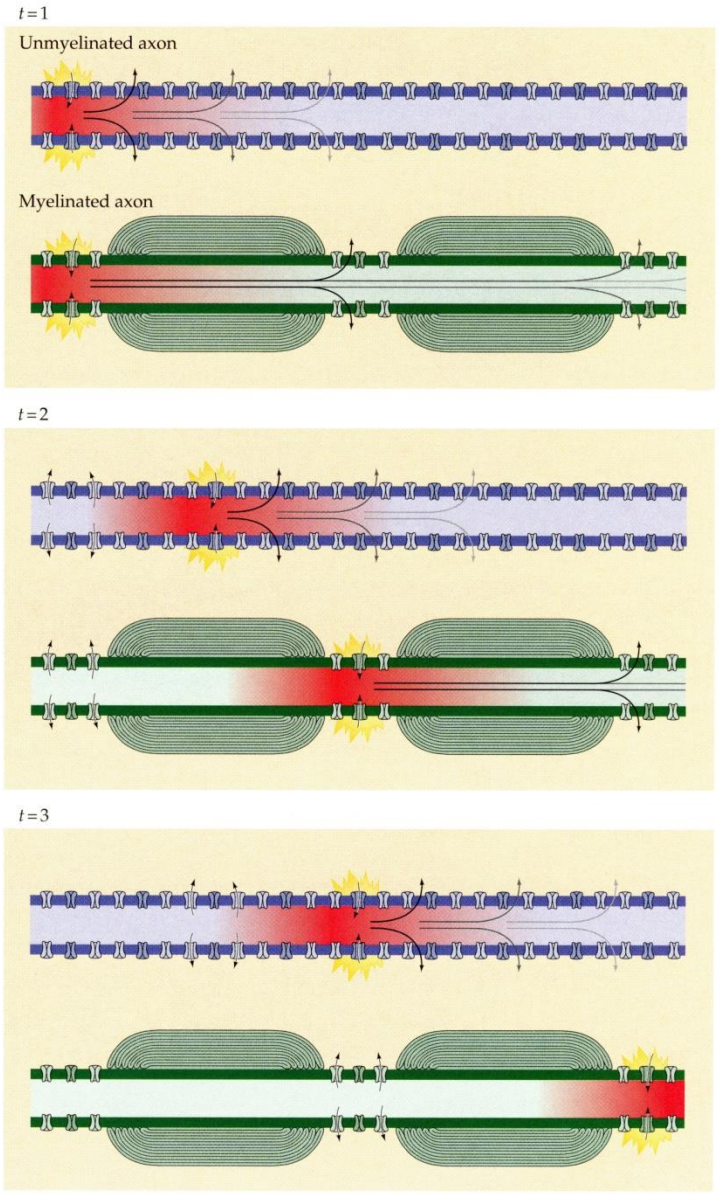
Myelin or a wrapping of glial cell membranes around axons is formed by:

- Schwann cells in the PNS
- Oligodendrocytes in the CNS



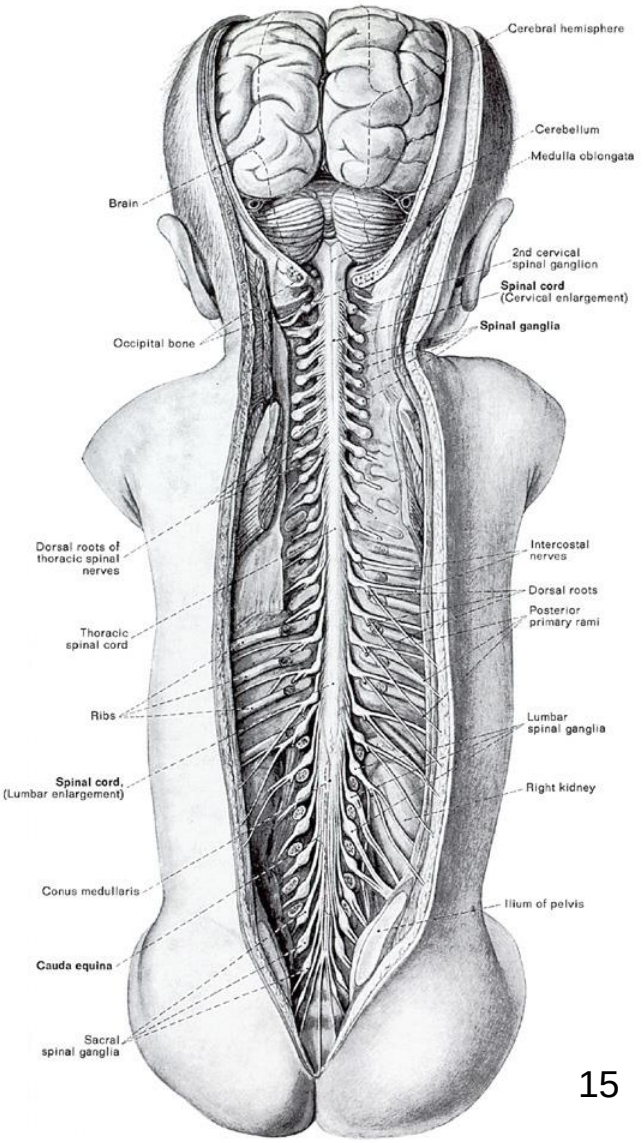
Myelin

- Myelin allows saltatory conduction or rapid advance of the action potential down the axon.

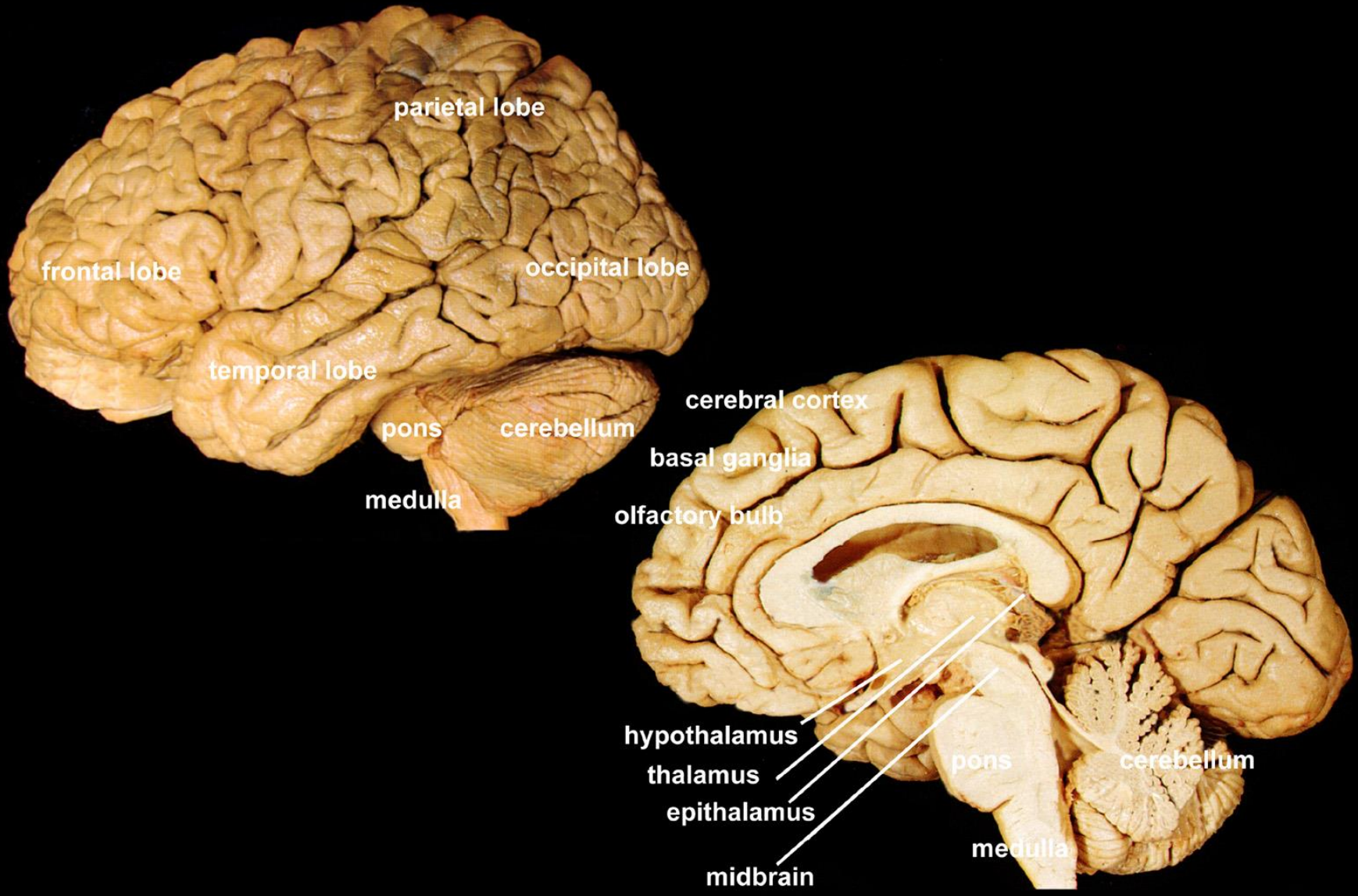


Nervous System Organization

- Peripheral nervous system (PNS) includes nerves and ganglia.
  - Nerves are bundles of axons.
  - Nerves connect to the brain (cranial nerves) or to the spinal cord (spinal nerves).
  - Ganglia are collections of neuronal cell bodies.
- Central nervous system (CNS) includes the brain, spinal cord and retina.
  - Tracts are bundles of axons (white matter).
  - Neuronal cell bodies are in nuclei or layered structures (grey matter).



Major Brain Regions



Inputs and Outputs of the Central Nervous System

Input - Sensory Systems:

- Somatosensory
- Visceral sensory
- Special sensory
  - Vision
  - Auditory
  - Vestibular
  - Gustatory (taste)
  - Olfactory (smell)

> general sensory

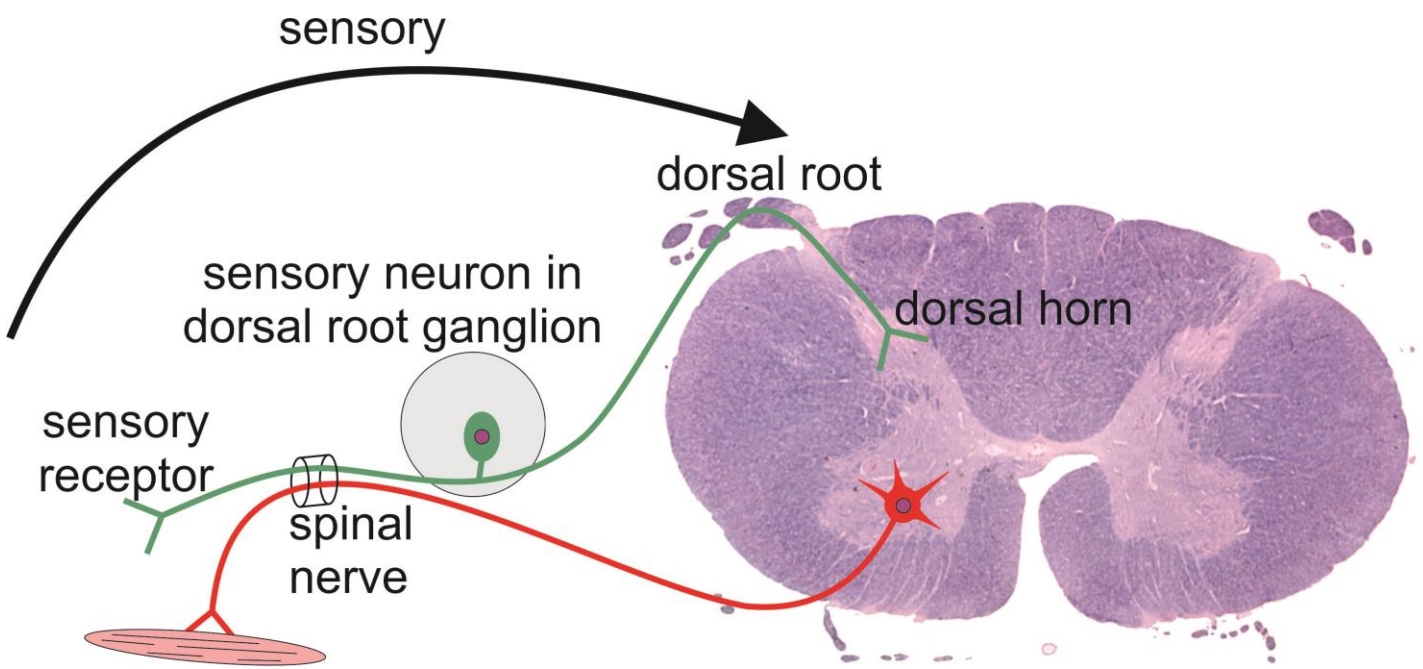
Output – Motor & Endocrine Systems:

- Somatomotor
- Branchial motor
- Autonomic (visceral) motor
  - Parasympathetic
  - Sympathetic
  - Enteric
- Neuroendocrine systems (hormones)
  - Hypothalamus / Pituitary
  - Pineal gland
  - Adrenal medulla

> general motor

Primary Somatosensory Neurons

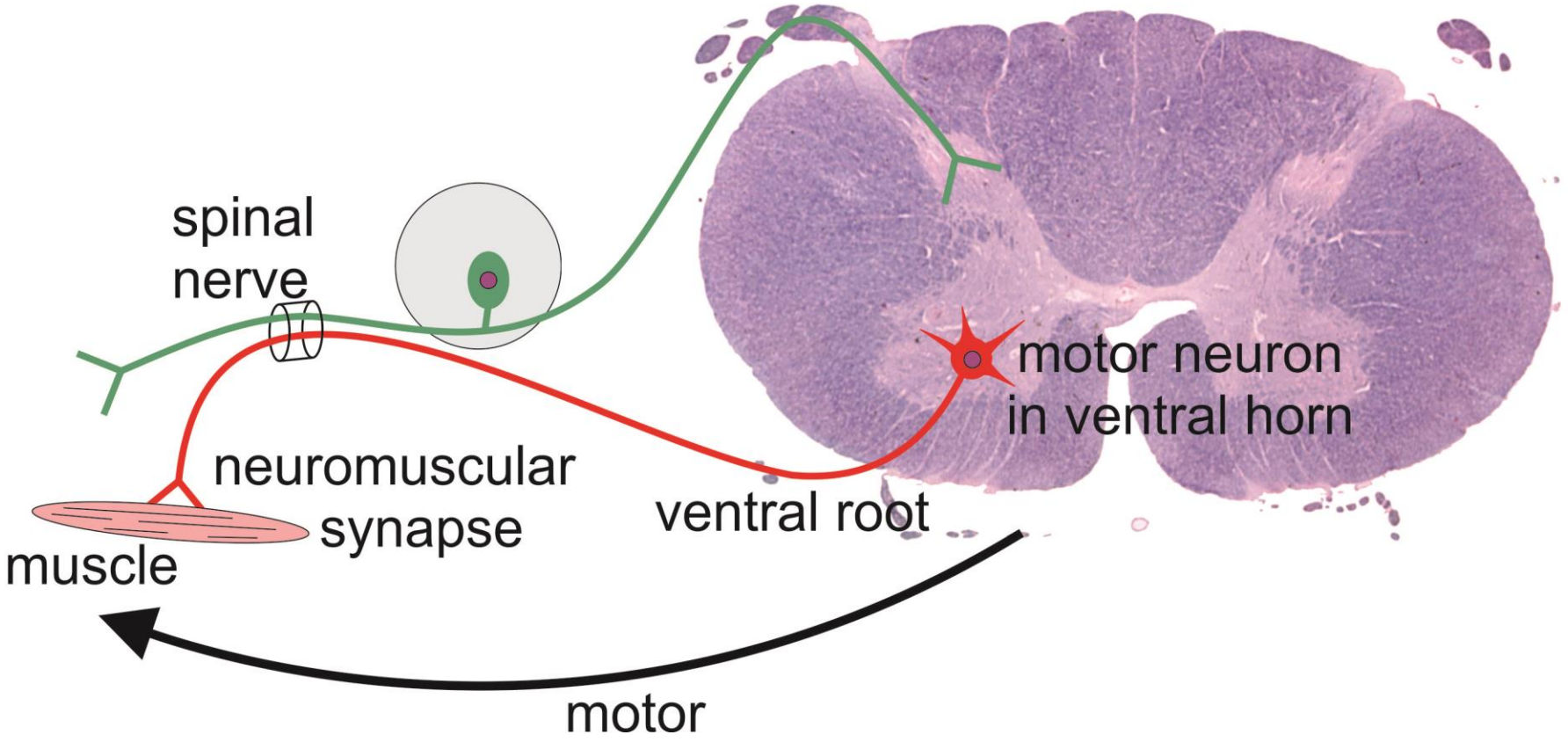
- The somas of primary somatosensory neurons are in:
  - cranial nerve sensory ganglia
  - dorsal root (spinal) ganglia



The somatosensory system detects multiple sensations.

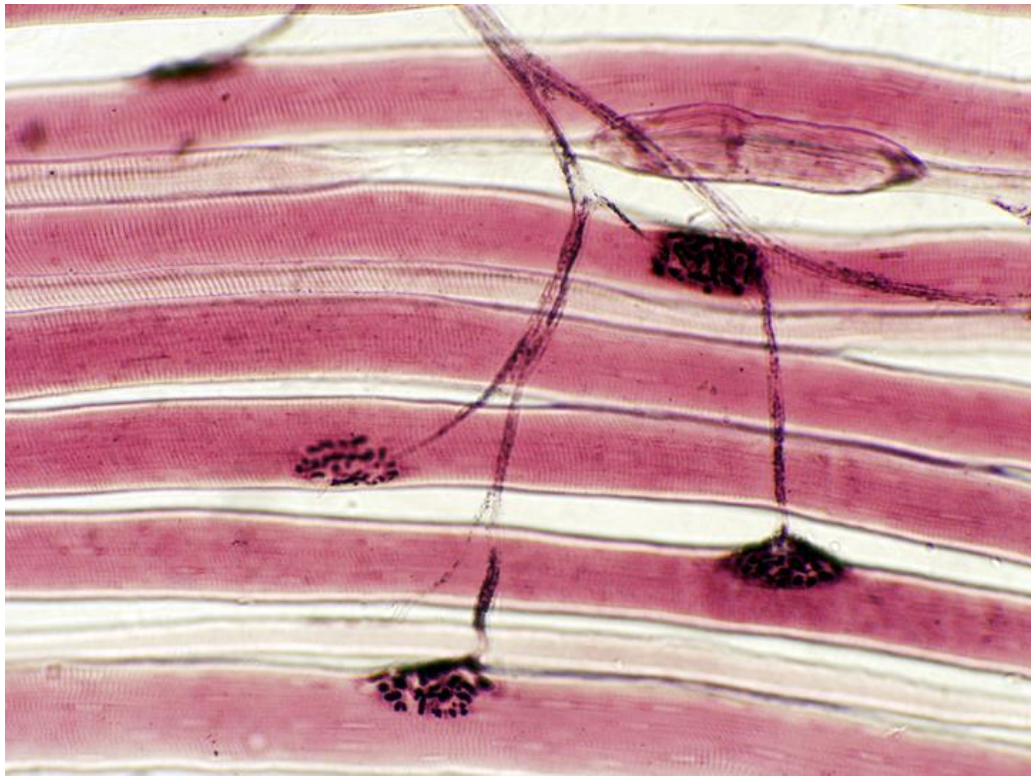
- Touch
  - fine touch
  - pressure
  - vibration
  - movement against the skin
- Proprioception
  - limb & trunk position
  - movement
  - load
- Thermoception (temperature)
  - heat
  - cold
- Nociception (pain – tissue damage)
- Pruritic reception (itch)

General Motor System



Neuromuscular Junction

- Each muscle fiber (myofiber) has a synapse with a single motor neuron in the adult.
- A motor neuron can synapse with more than one myofiber.
- Acetylcholine is the neurotransmitter used at neuromuscular junctions.
- Activation by a motor neuron initiates contraction of the myofiber.

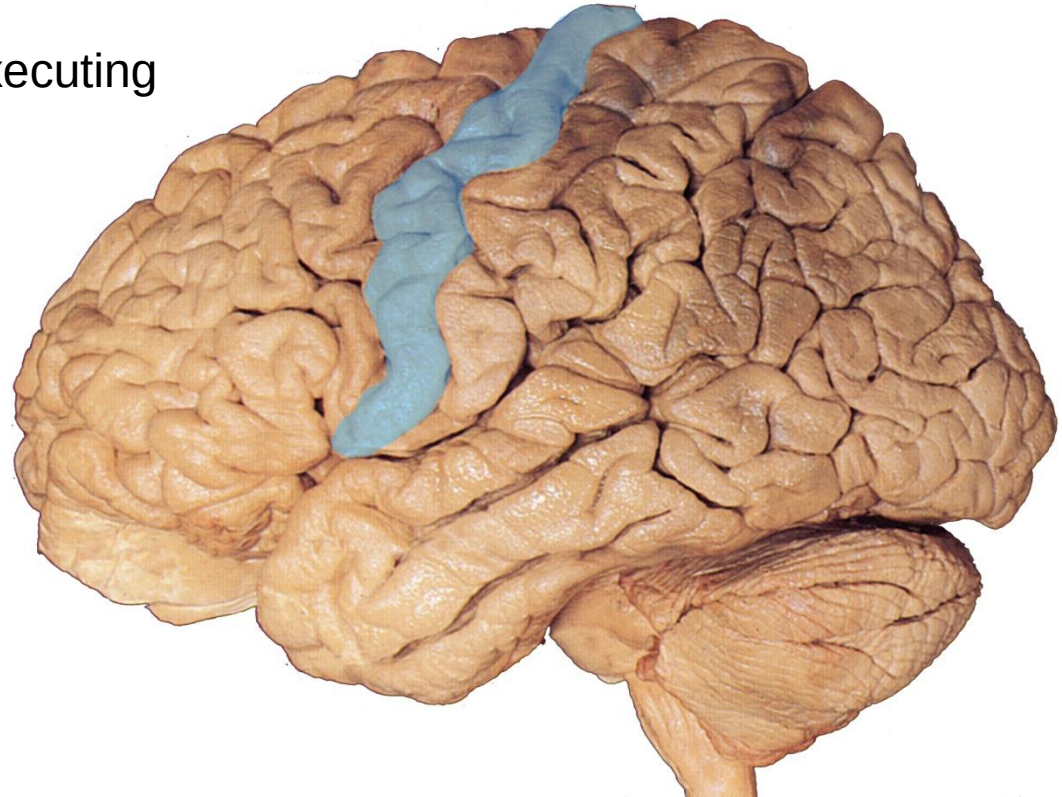


Motor Cortex

- The largest descending input to motor neurons is from primary motor cortex in the precentral gyrus of the frontal lobe.

- Axons descending from motor cortex are from upper motor neurons in cortical layer V.

- Motor cortex is essential for executing voluntary movements.



General Motor System

- Upper motor neuron in motor cortex

  (most axons cross to the opposite side of the body)

  -synapses with-

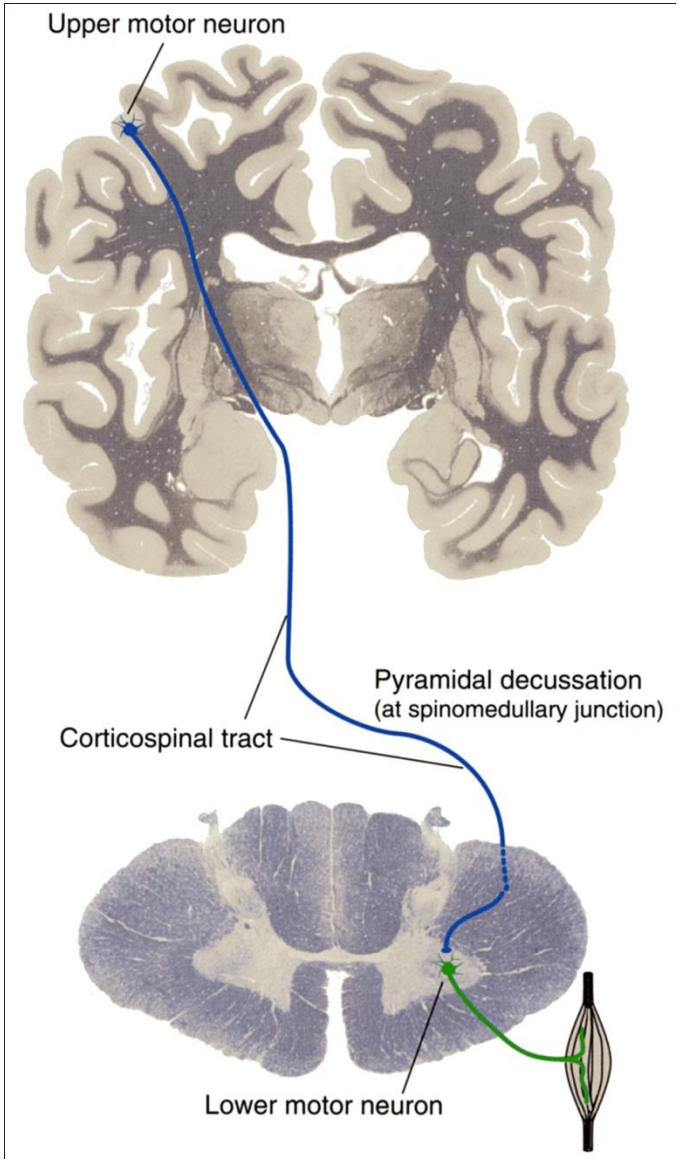
- (Lower) motor neuron in a cranial nerve nucleus in the brainstem or the ventral horn of the spinal cord

  (axons exit CNS via a cranial nerves or ventral roots)

  -synapses with-

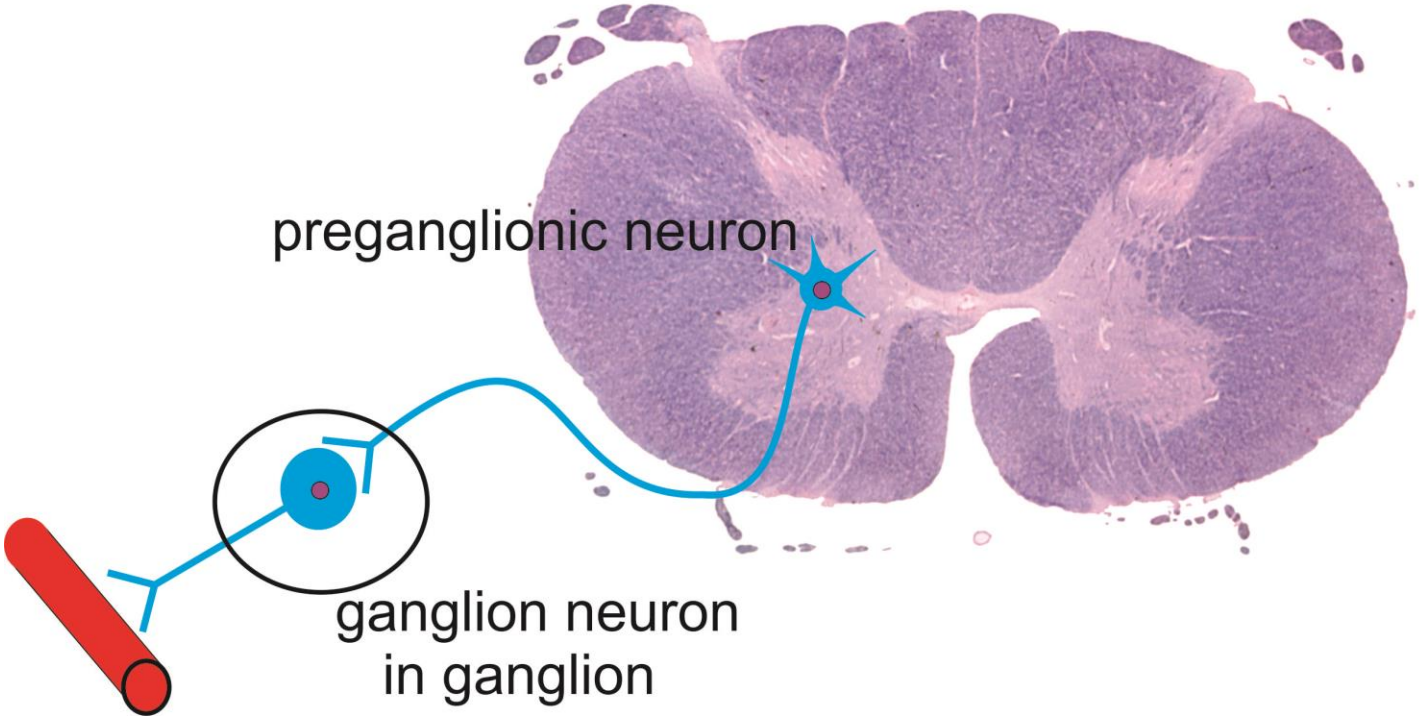
- Muscle fiber

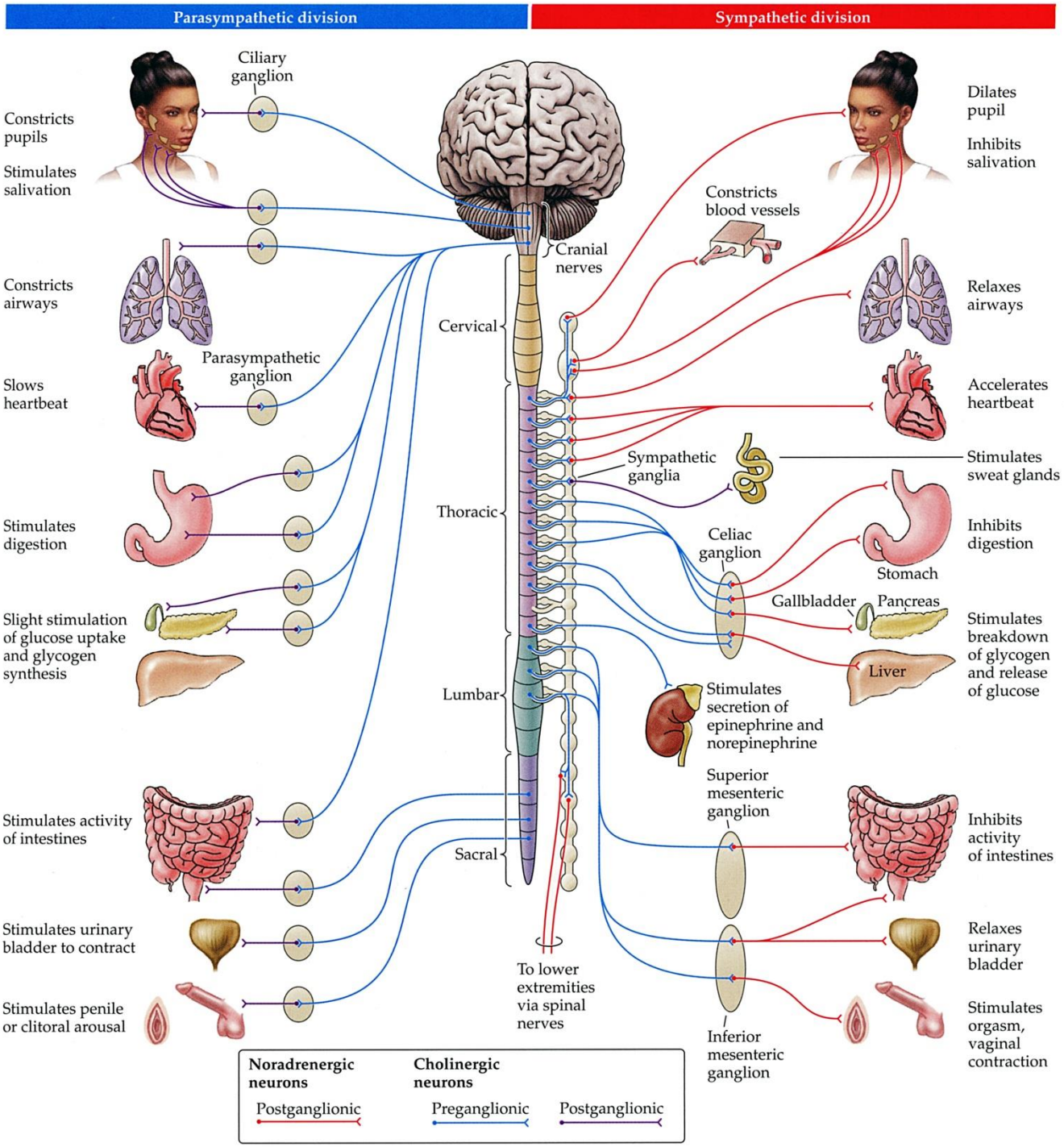
  (each muscle fiber has a single neuromuscular synapse; a single motor neuron can innervate multiple muscle fibers)



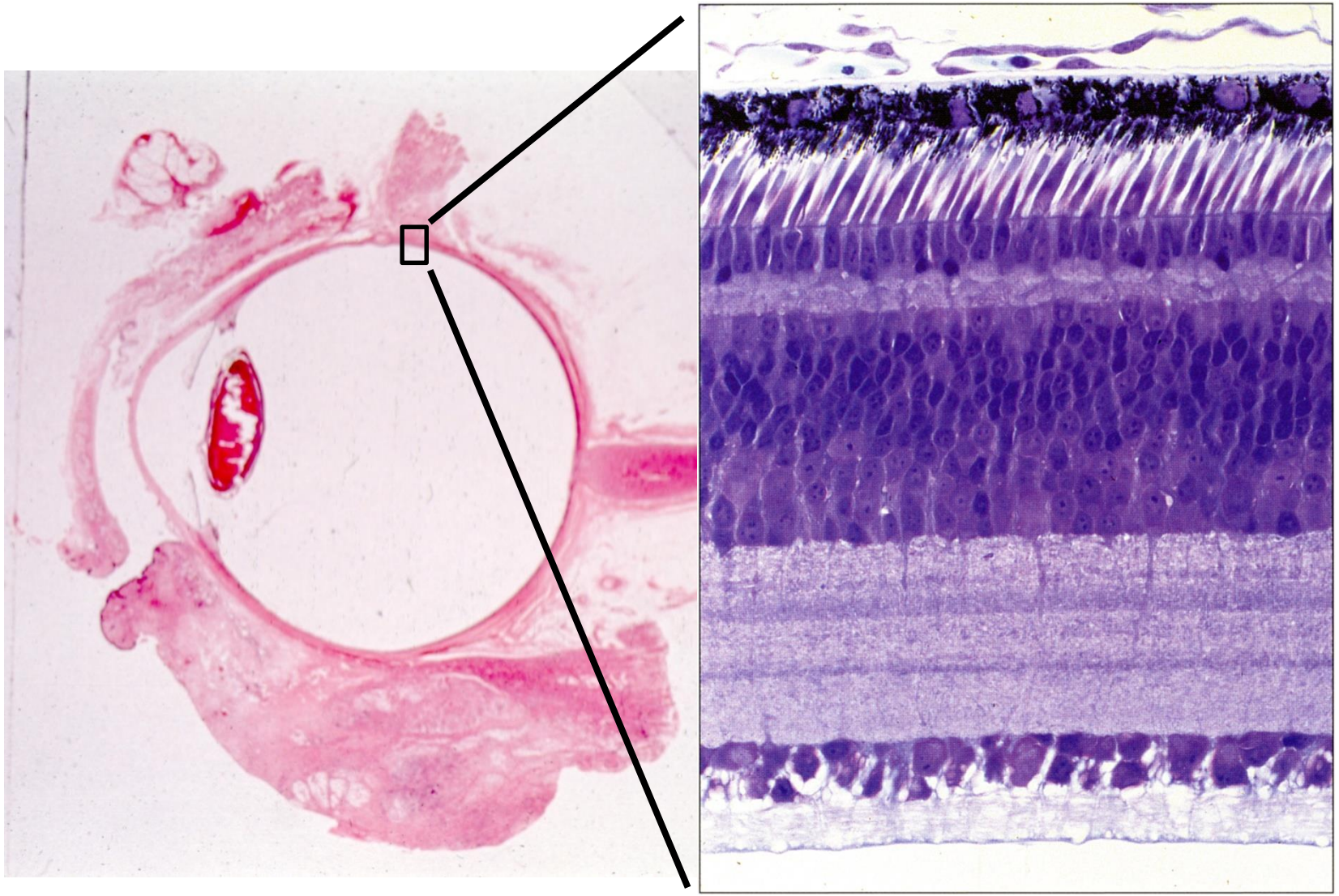
Autonomic Nervous System

- Two neuron chain:
  - Preganglionic neuron in brainstem or spinal cord
  - Ganglion neuron in PNS ganglion




Parasympathetic division
Sympathetic division
Ciliary ganglion
Constricts pupils
Stimulates salivation
Constricts airways
Parasympathetic ganglion
Slows heartbeat
Stimulates digestion
Slight stimulation of glucose uptake and glycogen synthesis
Stimulates activity of intestines
Stimulates urinary bladder to contract
Stimulates penile or clitoral arousal
Cranial nerves
Cervical
Thoracic
Lumbar
Sacral
To lower extremities via spinal nerves
Dilates pupil
Inhibits salivation
Constricts blood vessels
Relaxes airways
Accelerates heartbeat
Sympathetic ganglia
Stimulates sweat glands
Celiac ganglion
Inhibits digestion
Stomach
Gallbladder
Pancreas
Stimulates breakdown of glycogen and release of glucose
Liver
Stimulates secretion of epinephrine and norepinephrine
Superior mesenteric ganglion
Inhibits activity of intestines
Relaxes urinary bladder
Inferior mesenteric ganglion
Stimulates orgasm, vaginal contraction
Noradrenergic neurons
Postganglionic
Cholinergic neurons
Preganglionic
Postganglionic

Retina



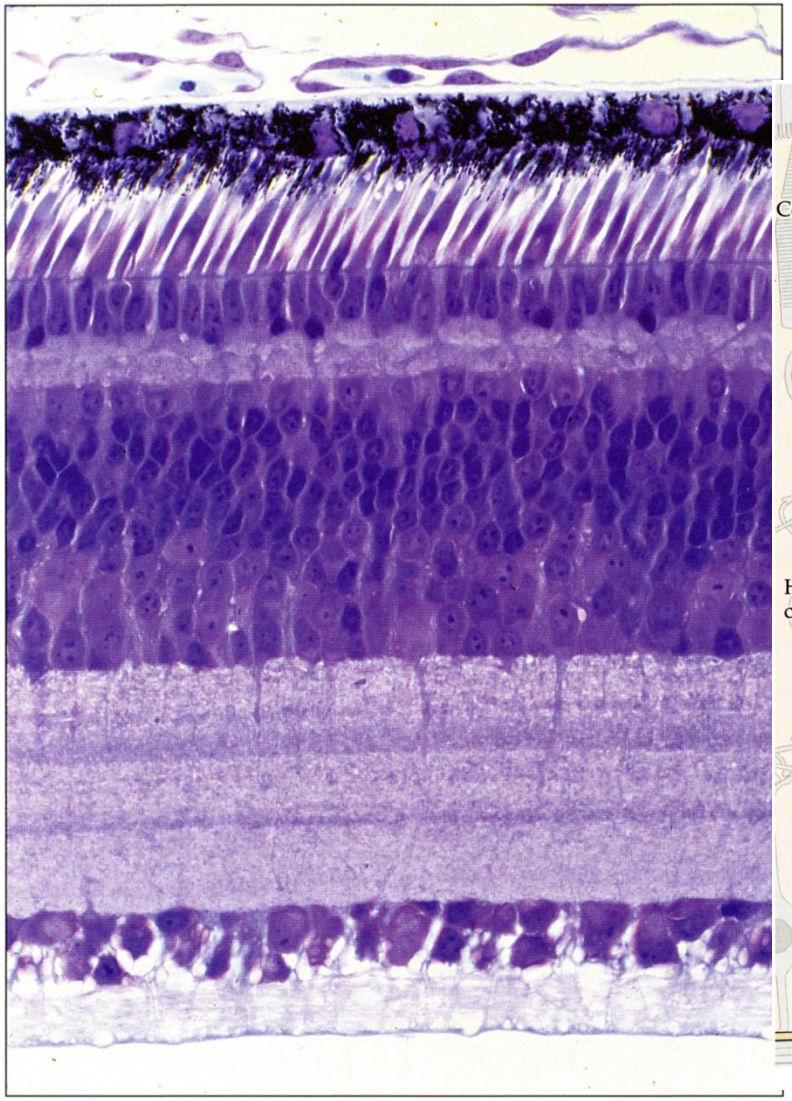
Retina

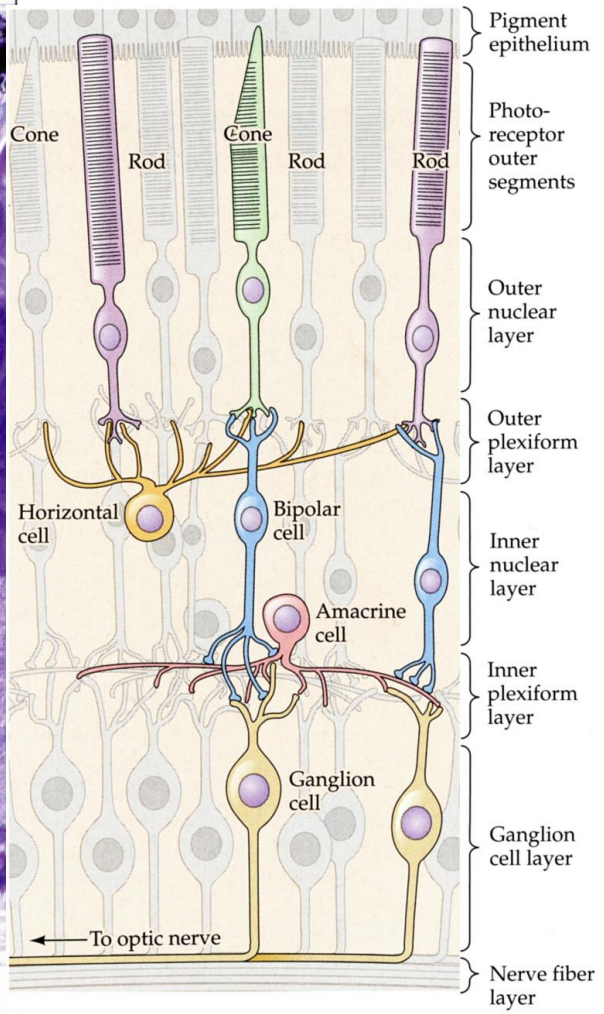
pigment epithelial cells

photoreceptor neurons (rod and cone cells)

interneurons and glial cells (horizontal, amacrine, bipolar and Muller cells)

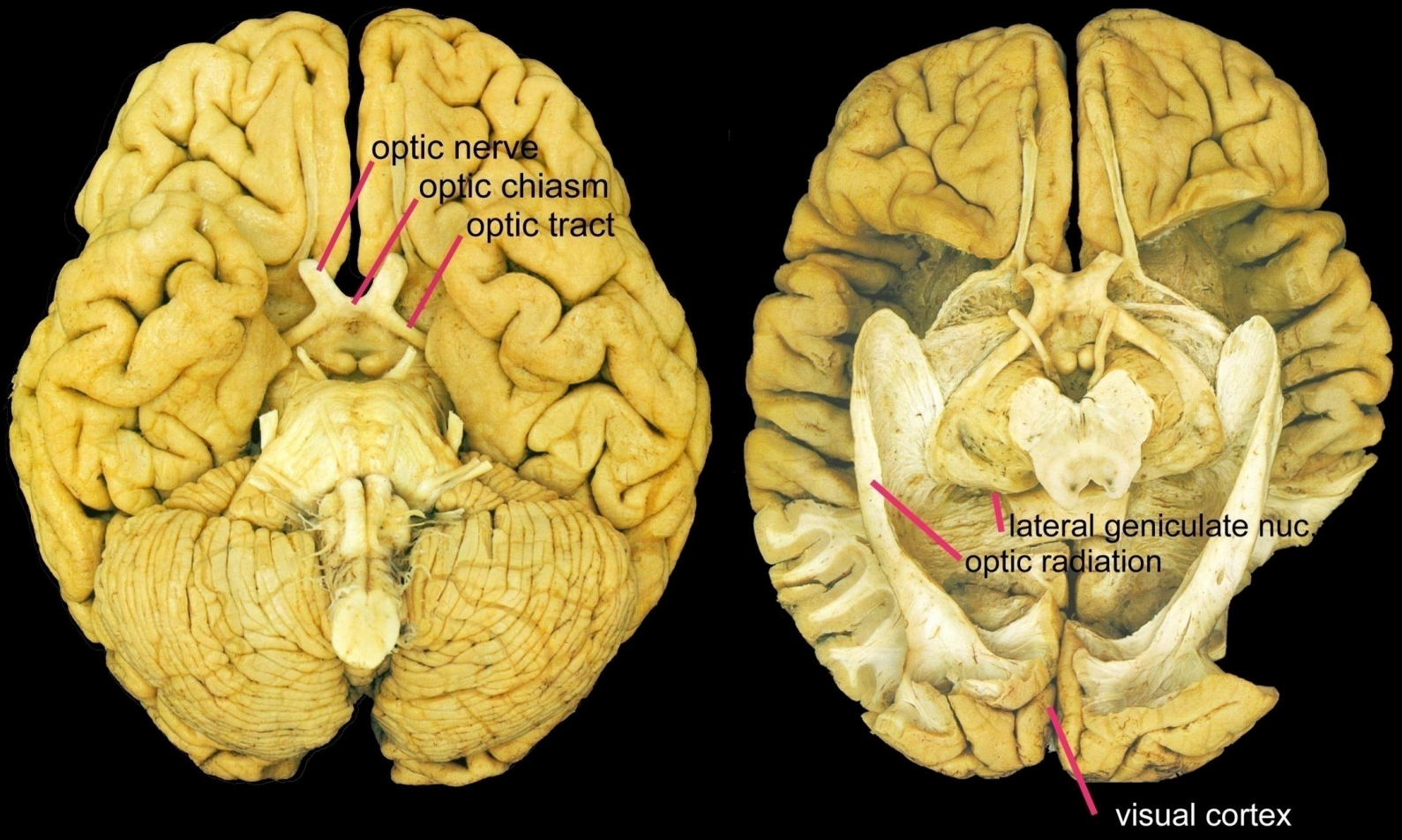
ganglion cells





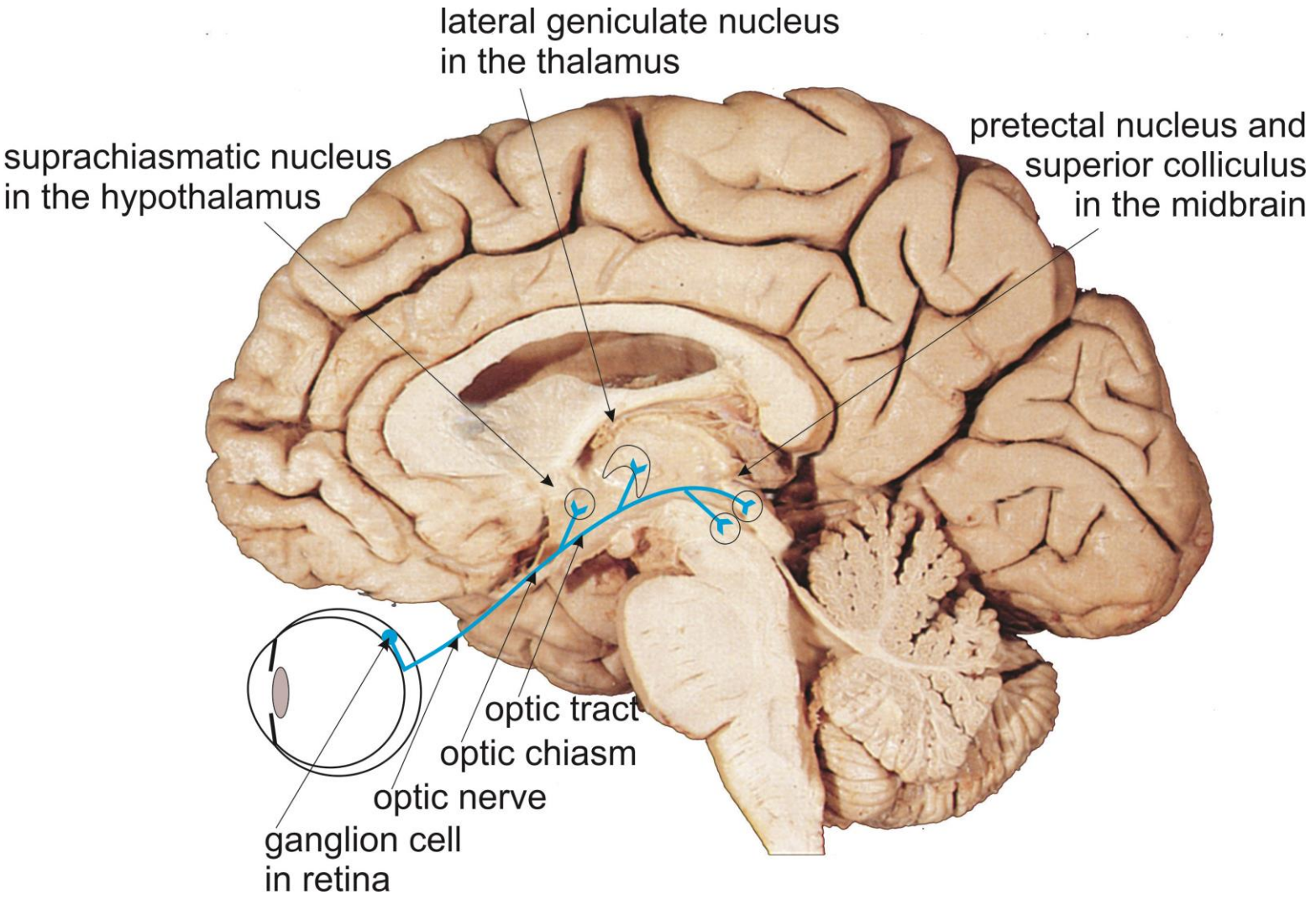
Central Visual Pathways

- The optic nerve attaches to the brain at the optic chiasm.
- The retinal axons continue in the optic tract.



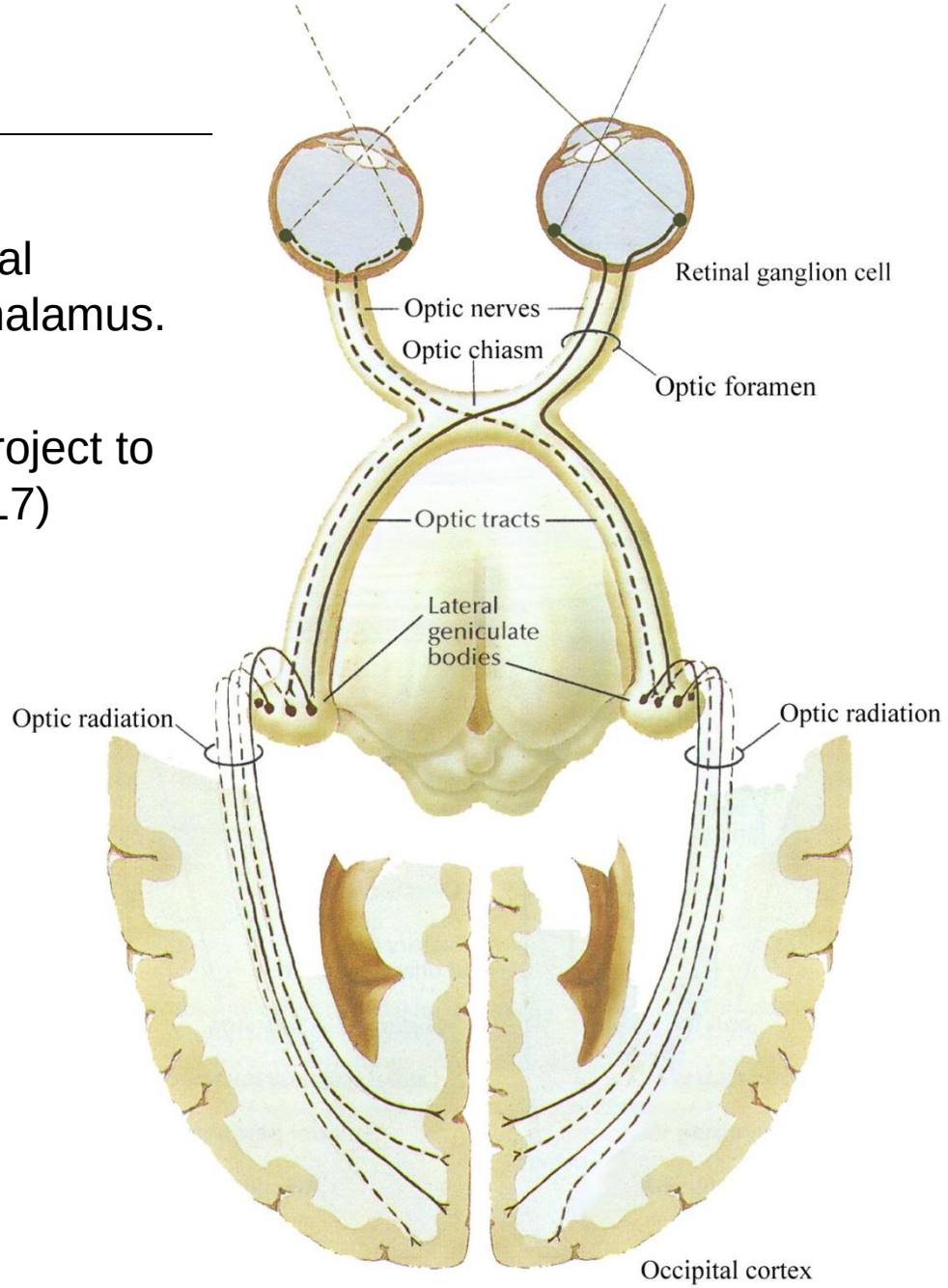
Central Visual Pathways

- Retinal axons synapse in several visual centers in the brain.



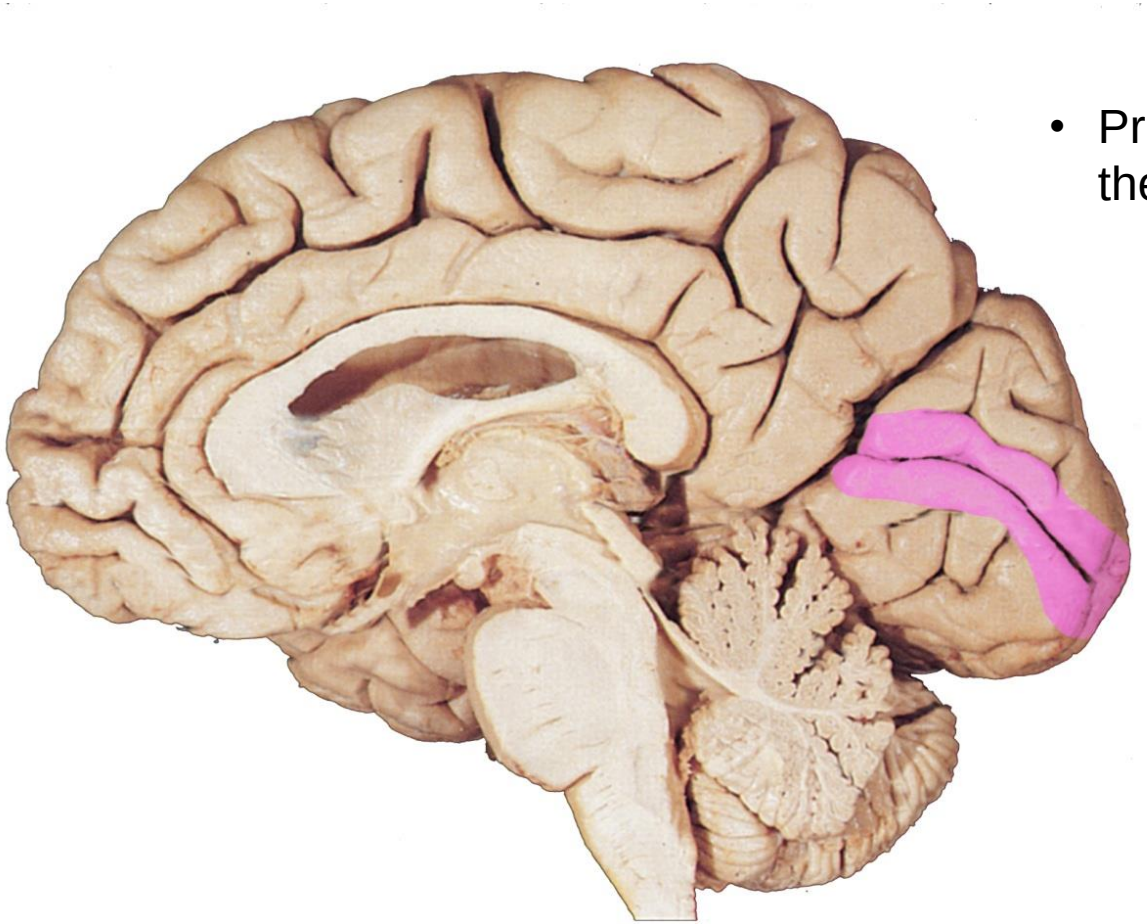
Central Visual Pathways

- Retinal axons synapse in the lateral geniculate nucleus (LGN) of the thalamus.
- Axons from neurons in the LGN project to primary visual cortex (V1 or area 17)



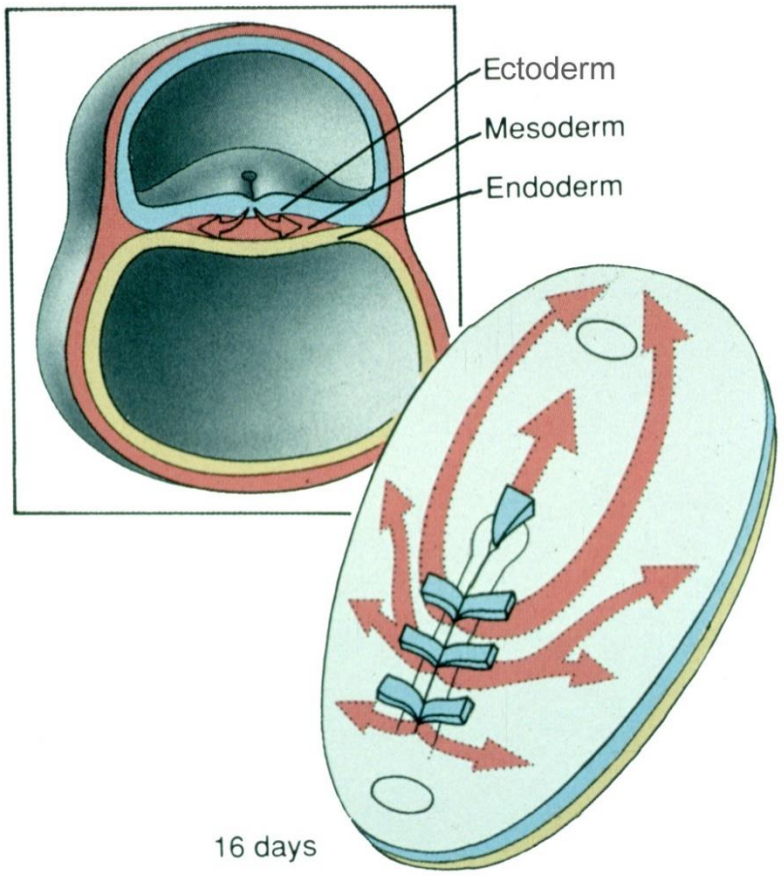
Central Visual Pathways

- Primary visual cortex is essential for conscious visual perception.

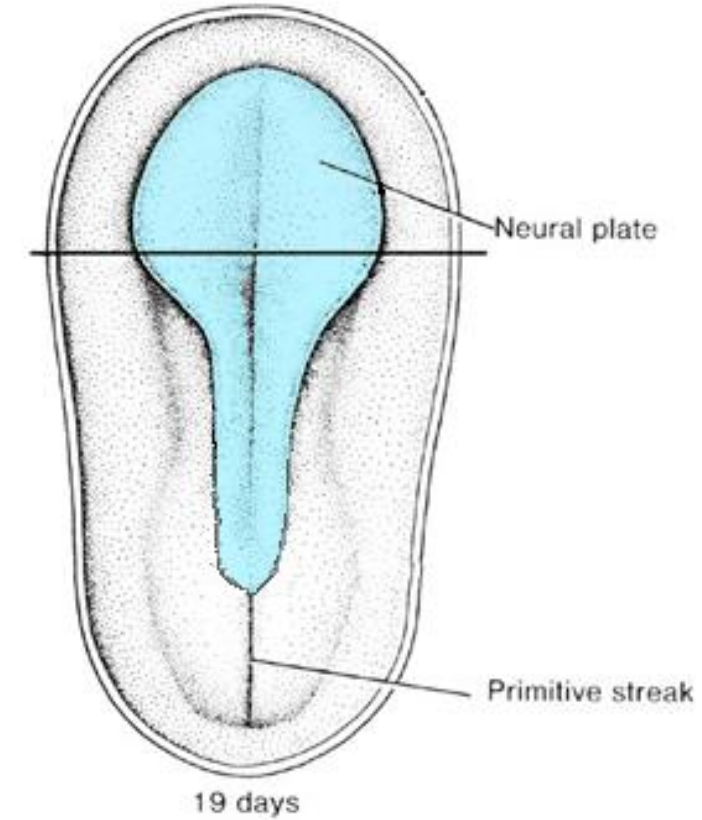


- Primary visual cortex is in the occipital lobe.

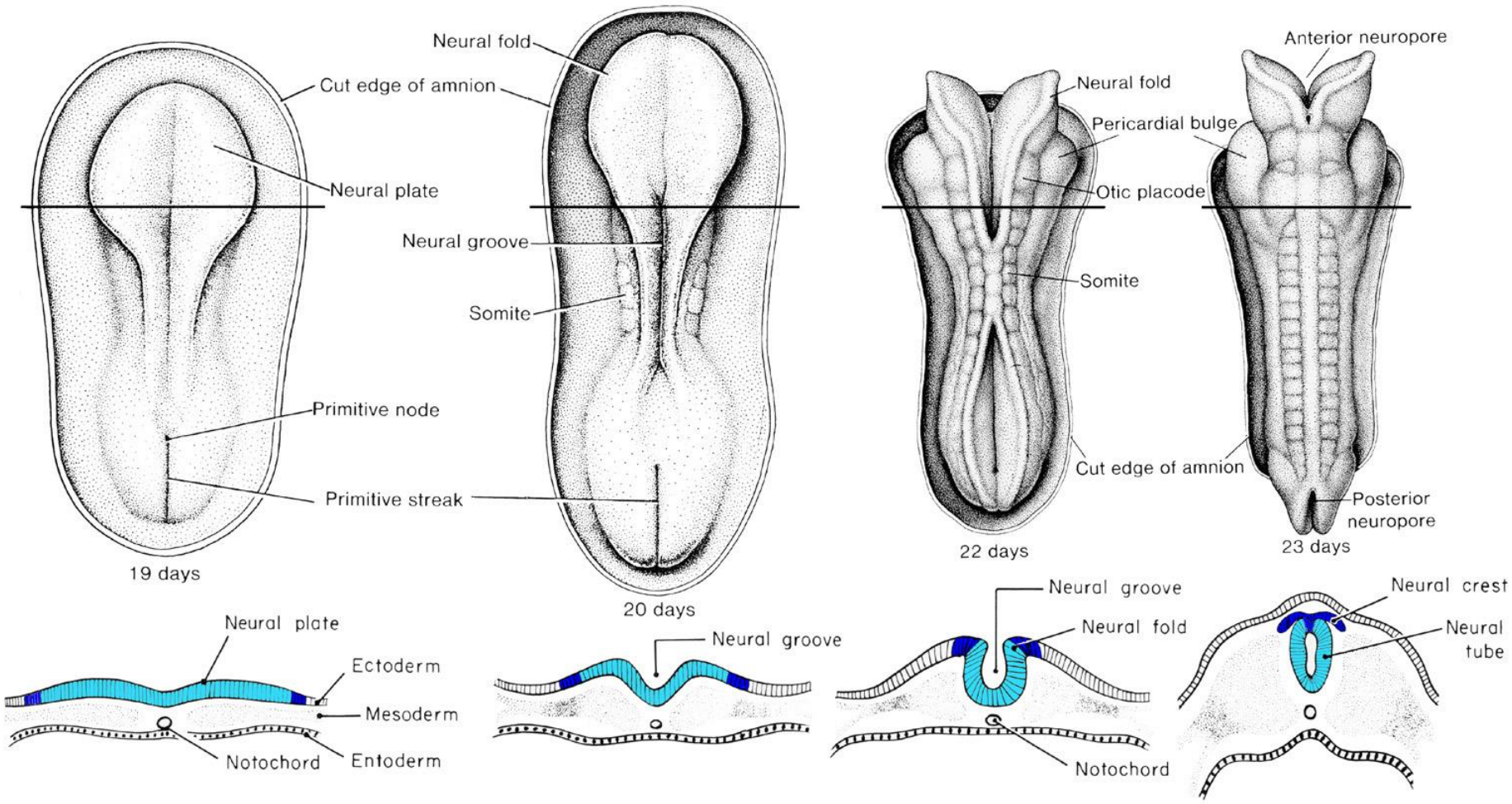
During gastrulation, epiblast cells migrate through the primitive streak to form a three layered embryo.



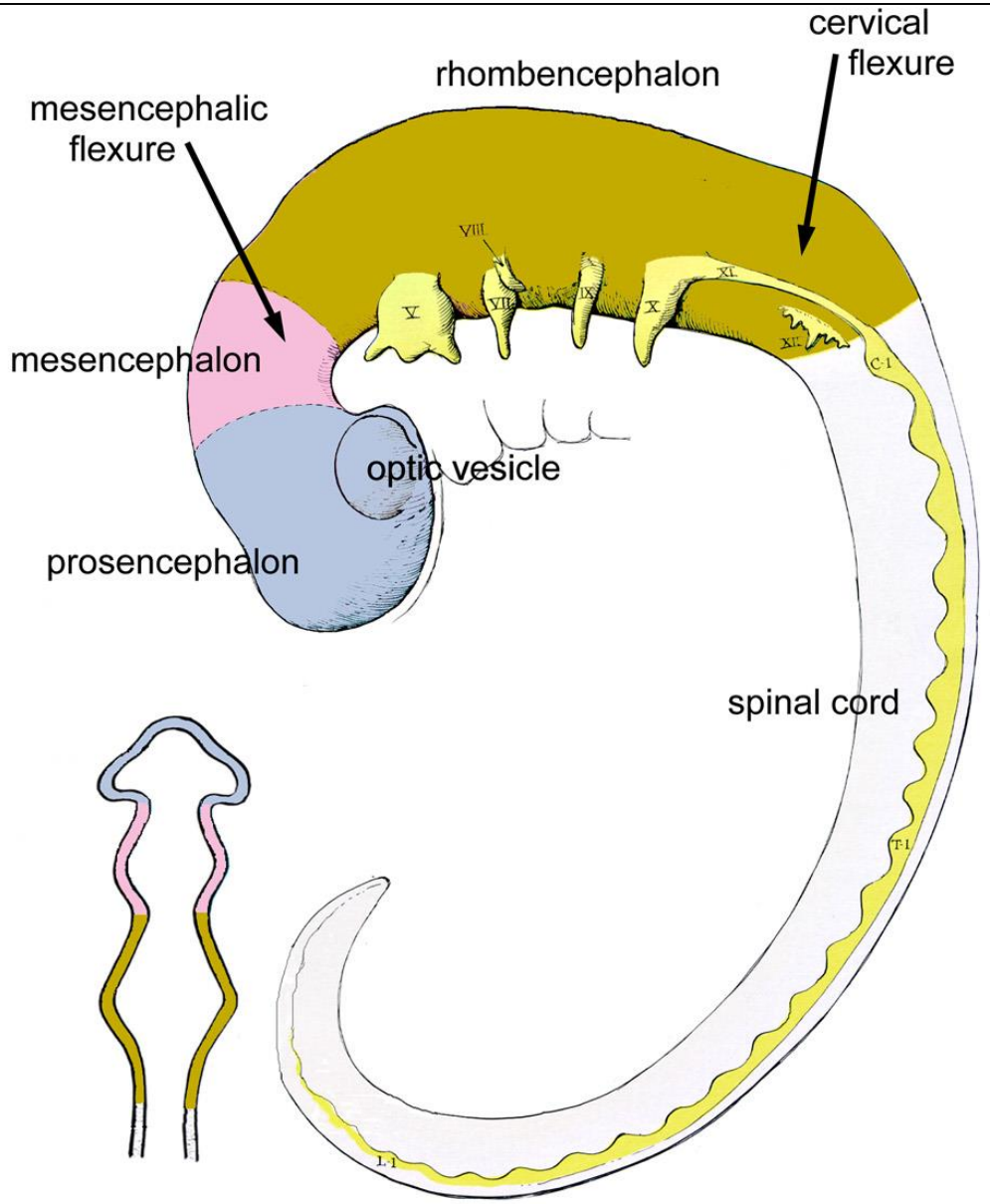
Factors from the midline mesoderm induce nervous system in the overlying ectoderm, and the neural plate forms from ectoderm.



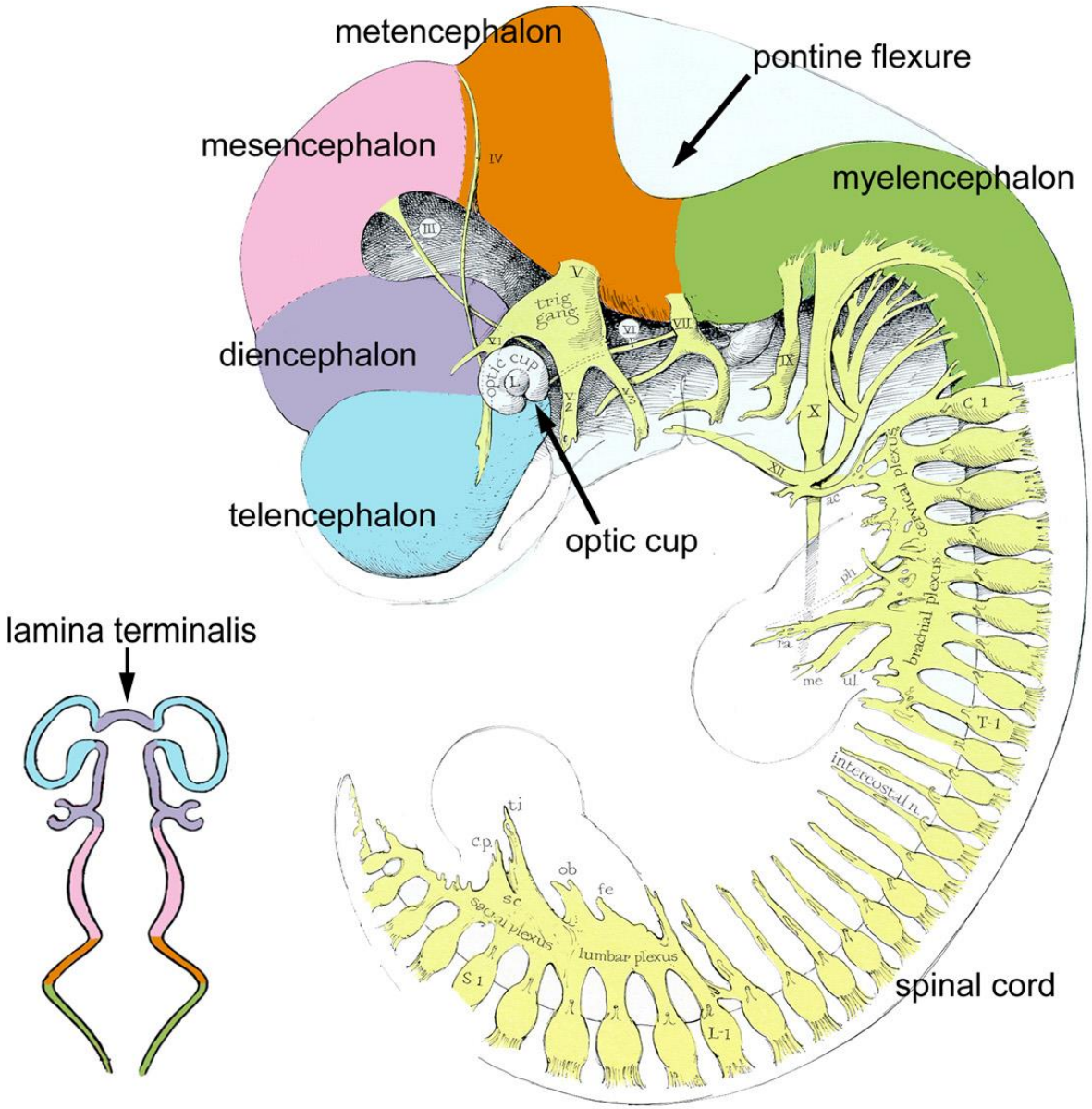
Neurulation



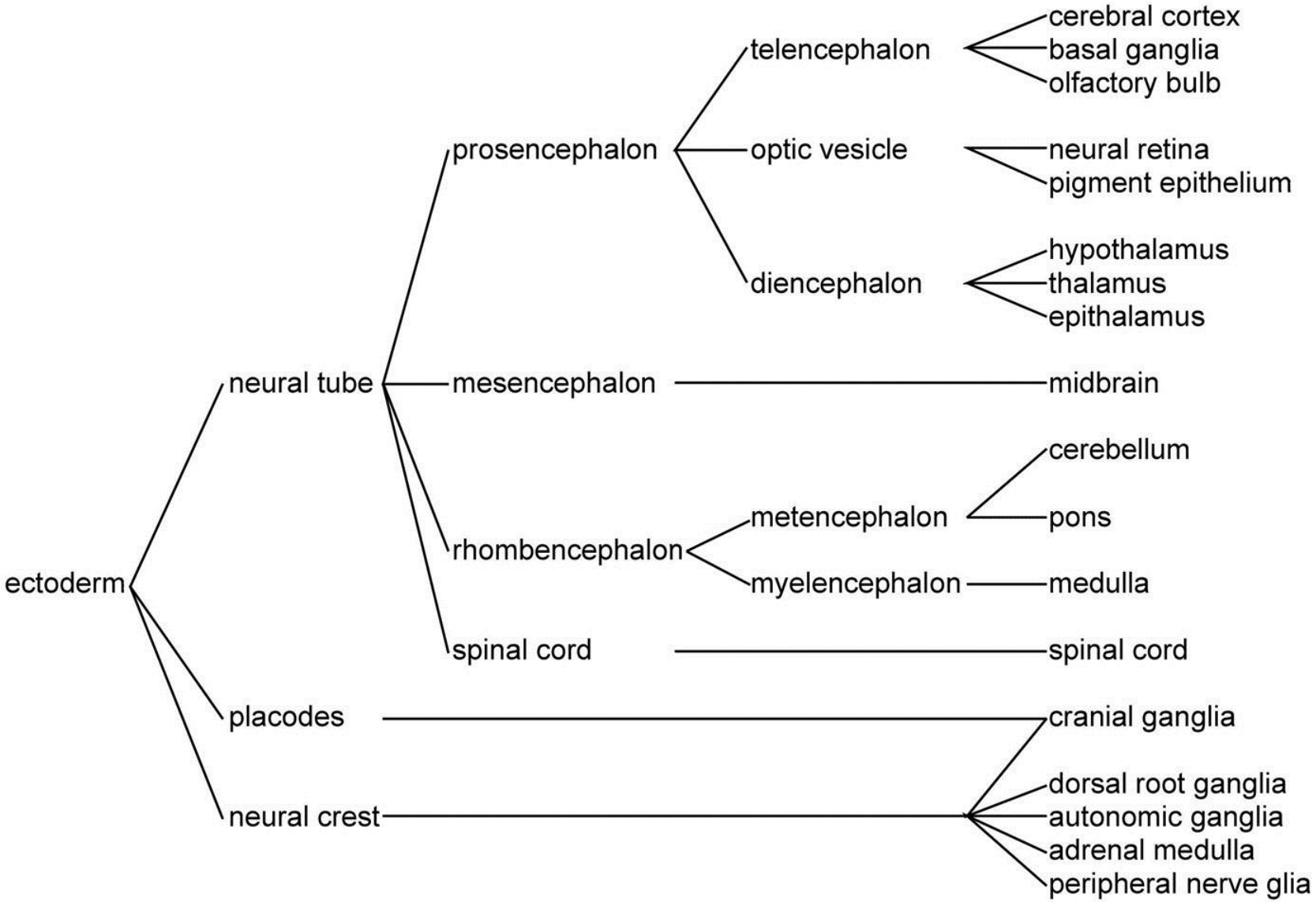
Primary Brain Vesicles



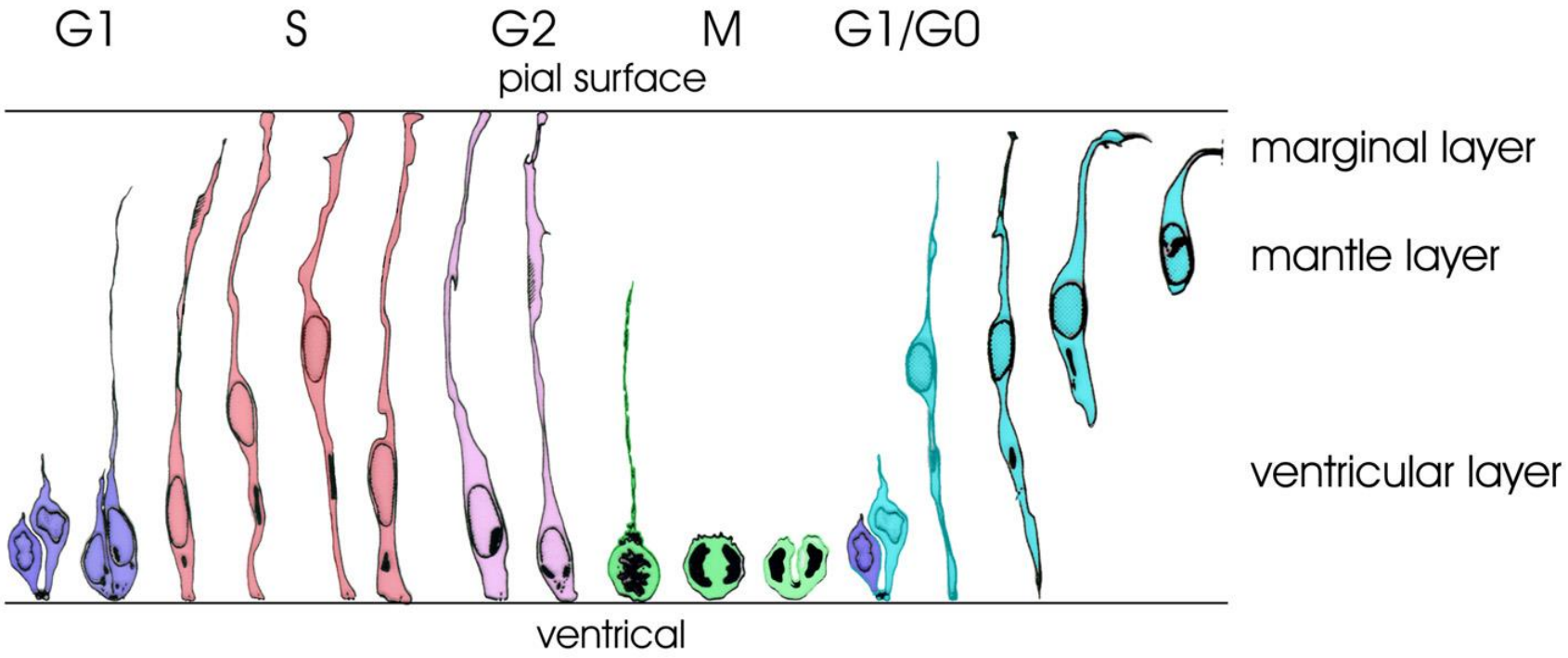
Secondary Brain Vesicles and Optic Vesicles



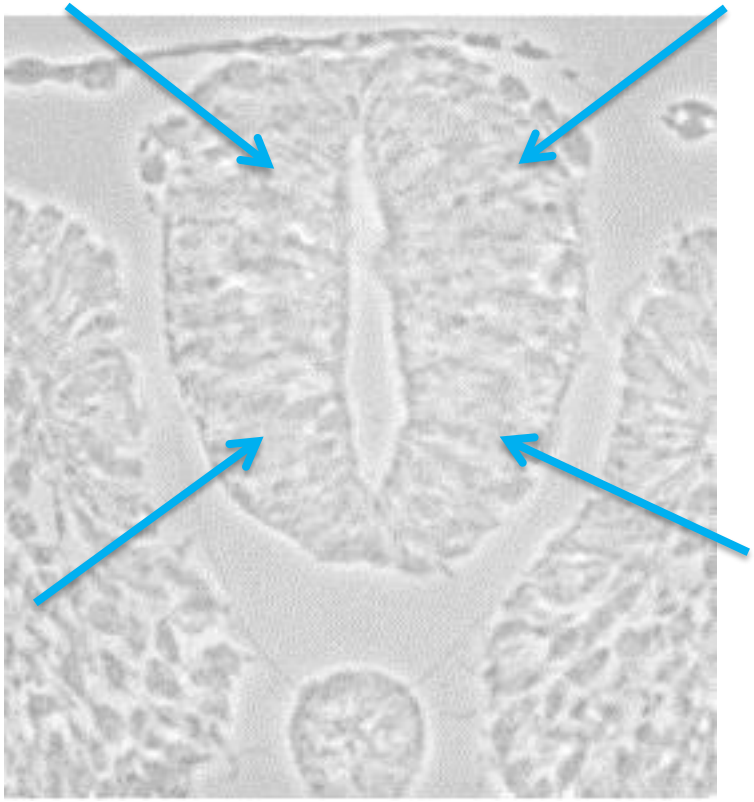
Origin of the Nervous System



Layers of the Early Neural Tube

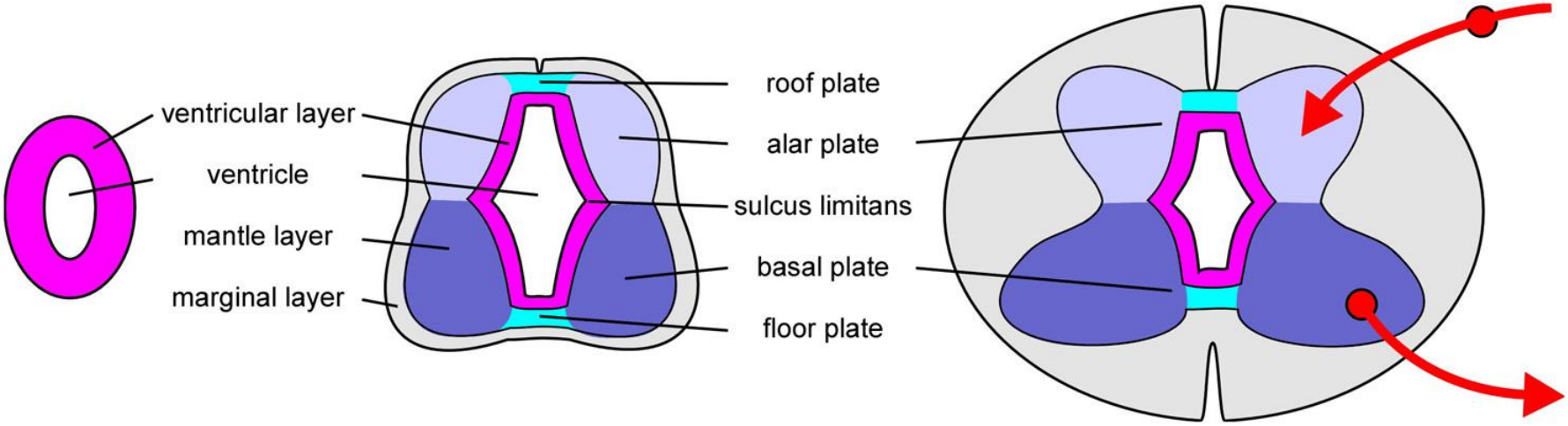


Cell division is not uniform around the neural tube.

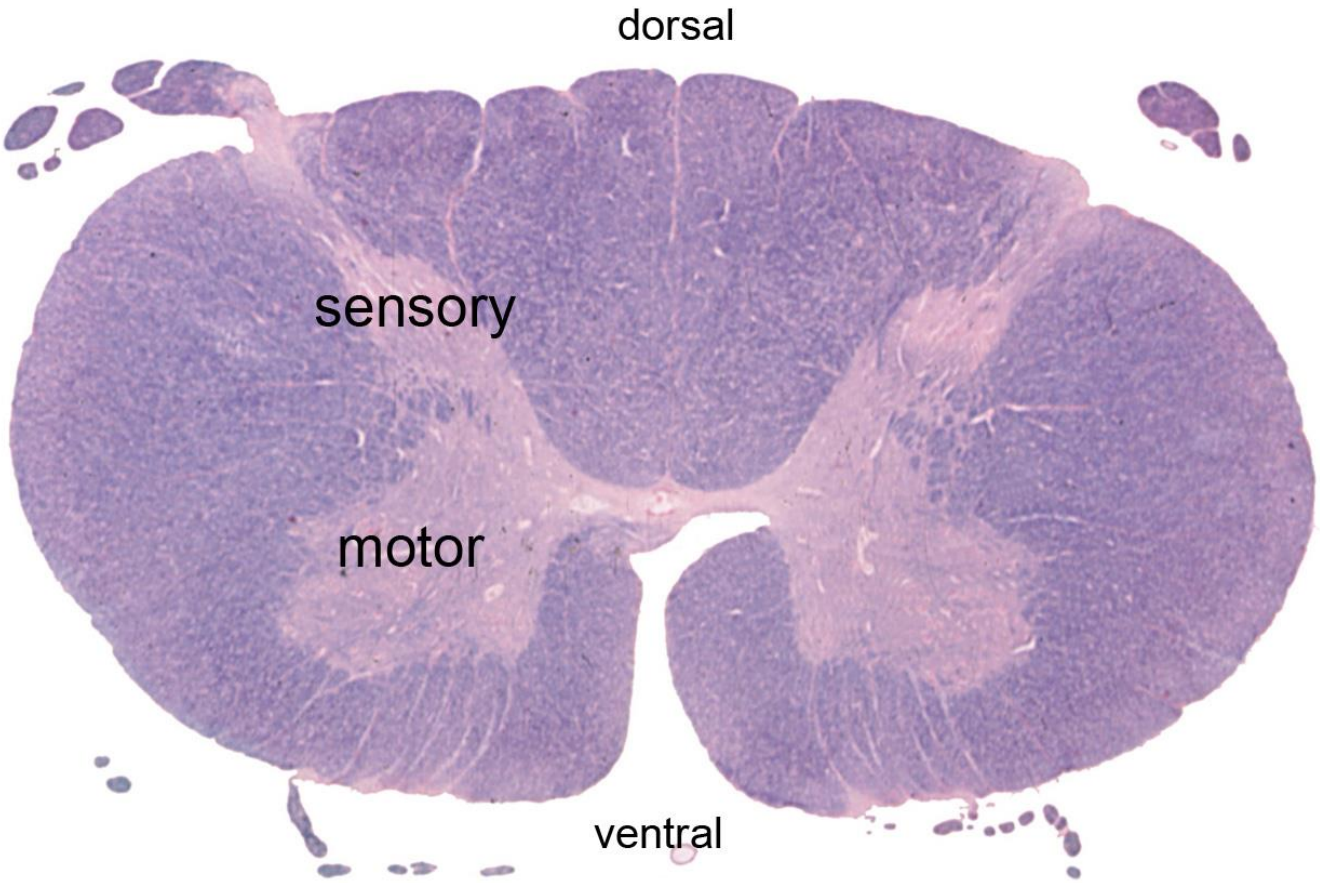


Arrows indicate areas of more cell division.

Roof Plate, Alar Plate, Sulcus Limitans, Basal Plate & Floor Plate

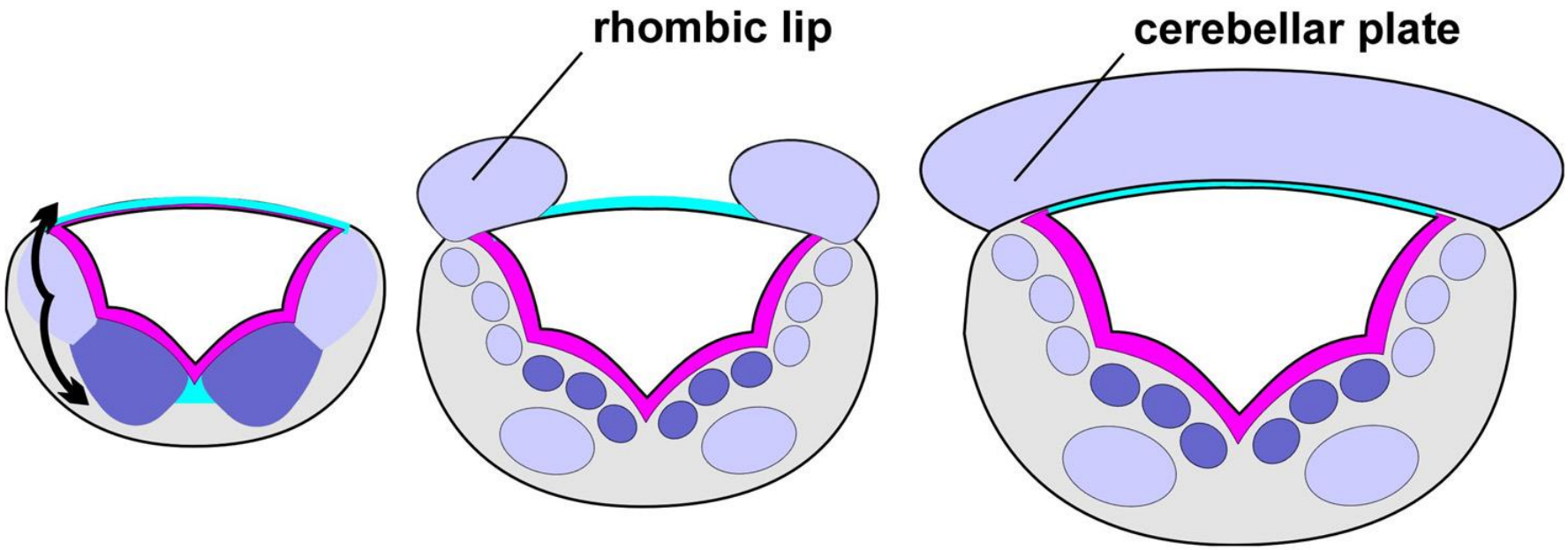


Sensory structures of the CNS develop from alar plate (dorsal), and motor structures develop from basal plate (ventral).

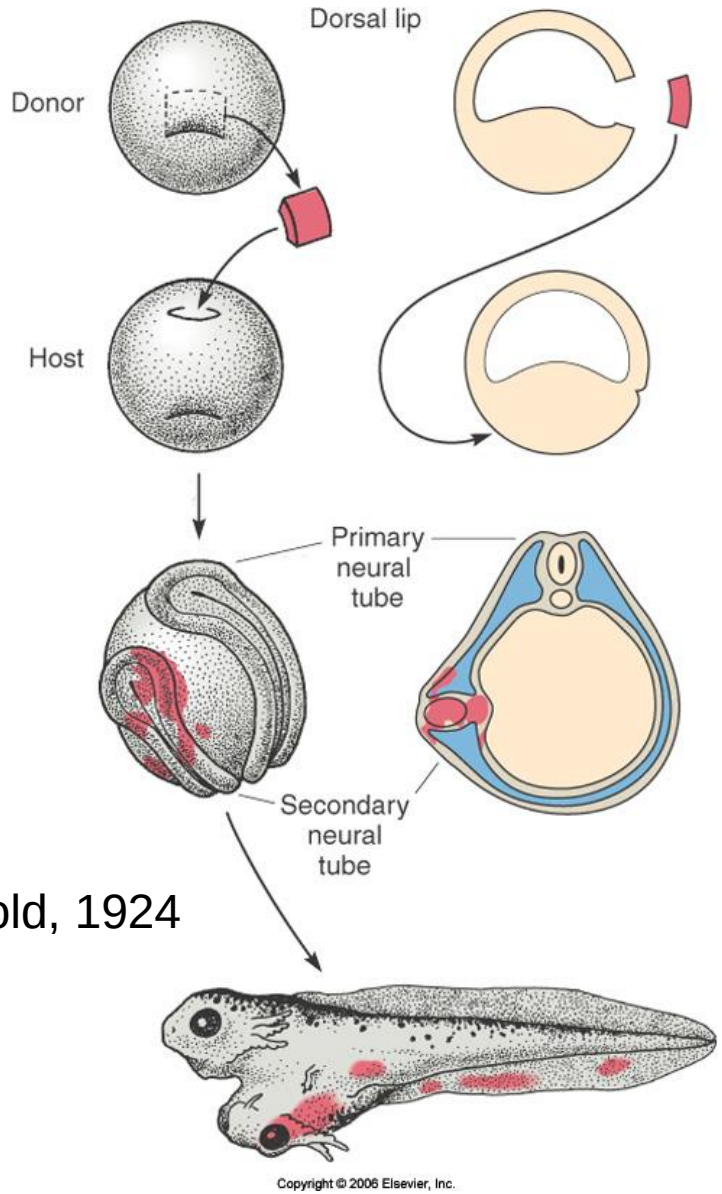


Metencephalon (Pons and Cerebellum)

Some cells migrate from the alar and basal plates and undergo further cell division.

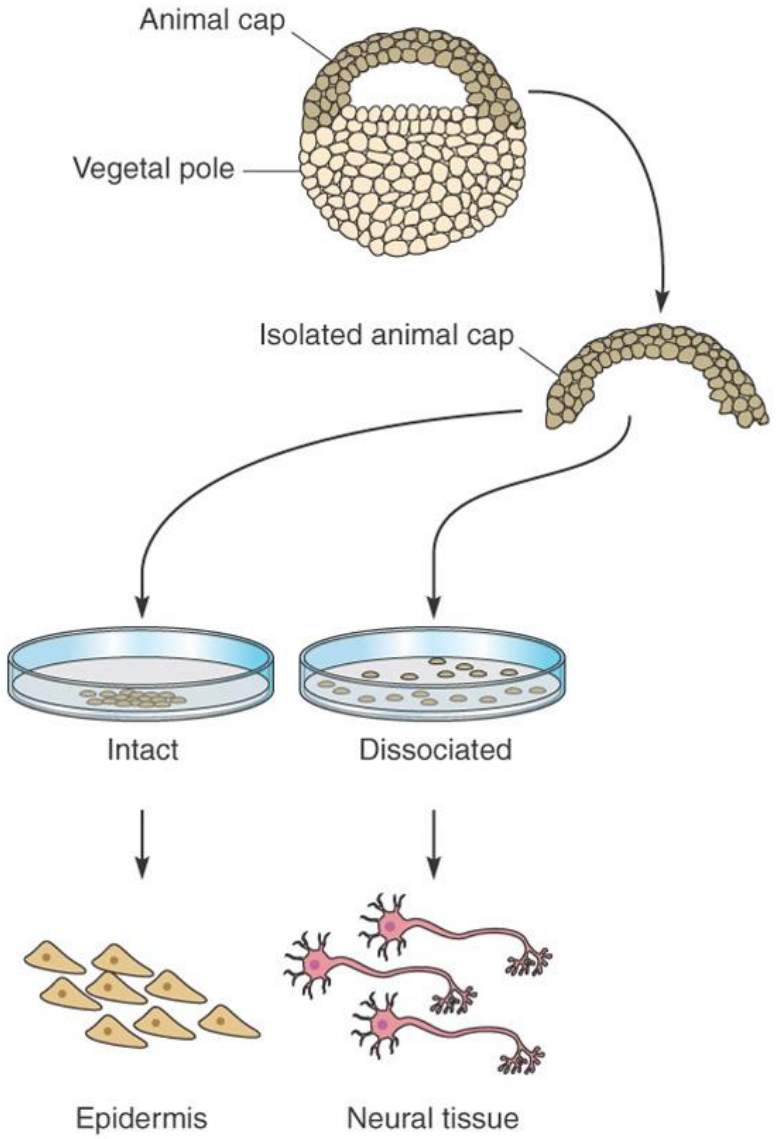


The organizer/mesoderm induces nervous system.



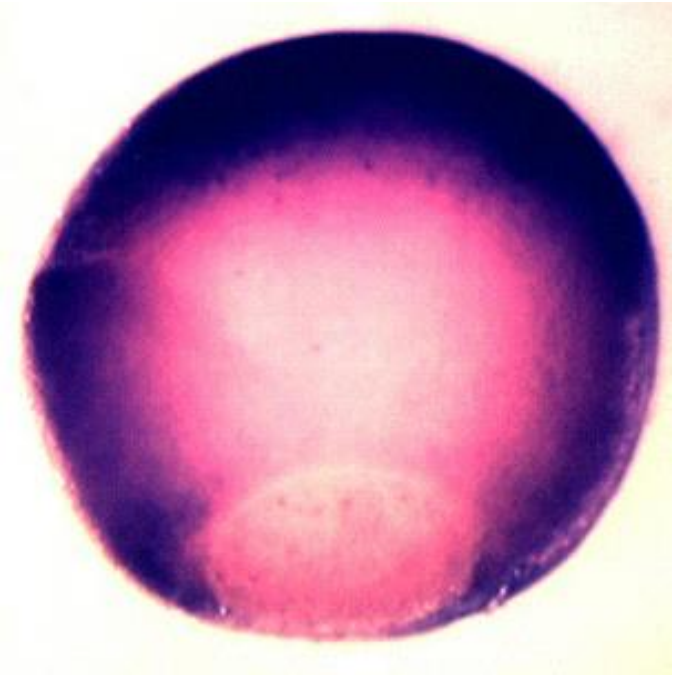
Spemann and Mangold, 1924

Nervous system is the default state of ectoderm.

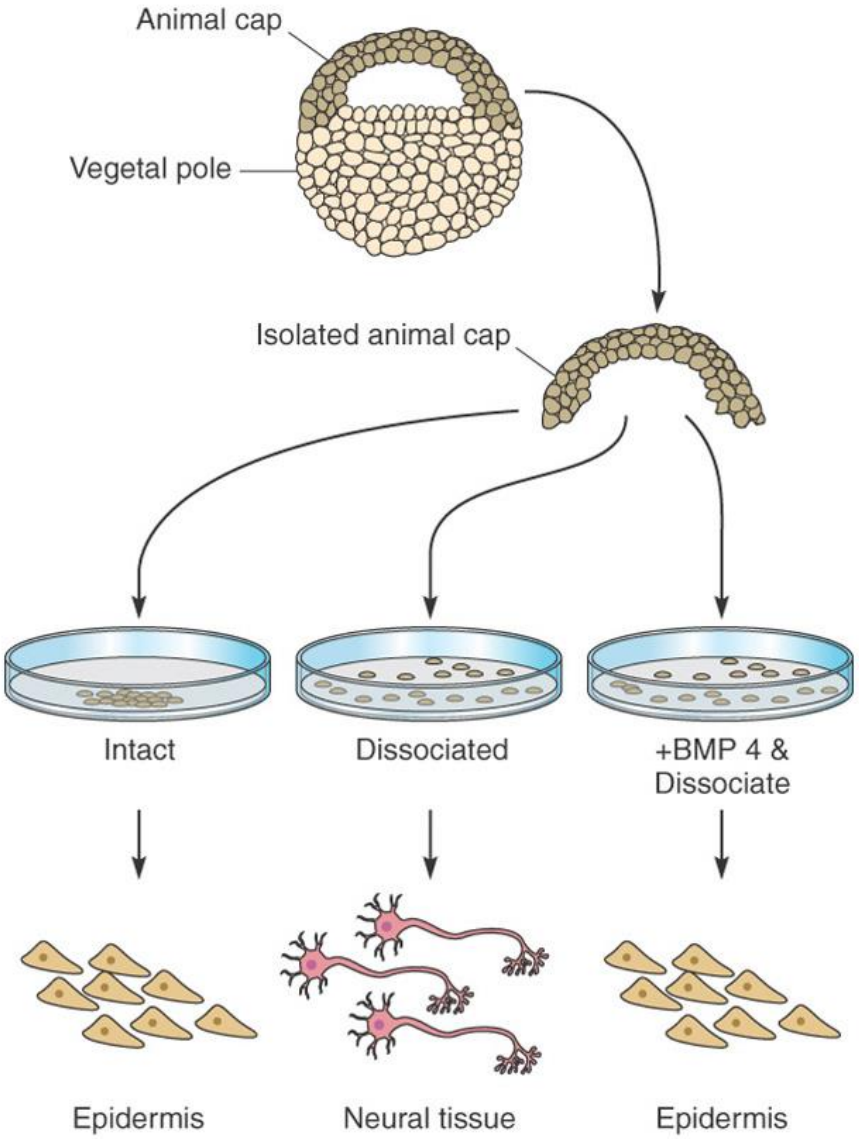


Bone morphogenetic protein 4 (BMP4), a TGFβ-family member, is expressed by all cells of the ectoderm in the blastula and early gastrula stage embryo.

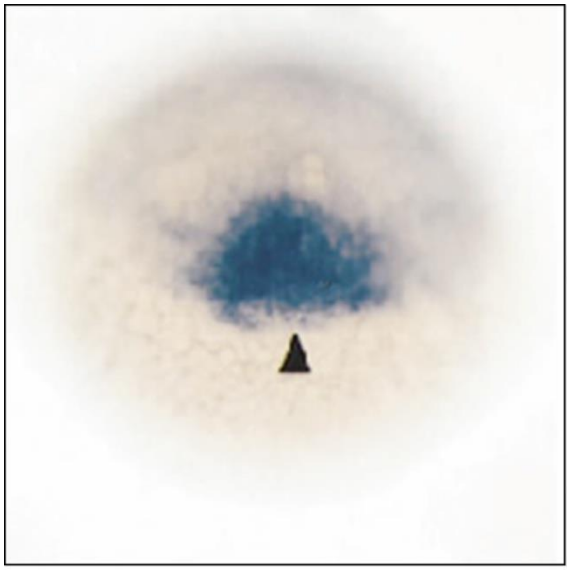
Expression of BMP4 is lost by cells induced to be nervous system.



BMP4 blocks neuralization and promotes an epidermal fate .



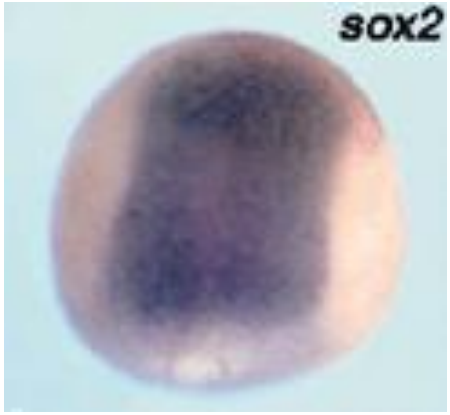
Noggin, Chordin & Follistatin are secreted proteins expressed by the organizer that have neuralizing activity .

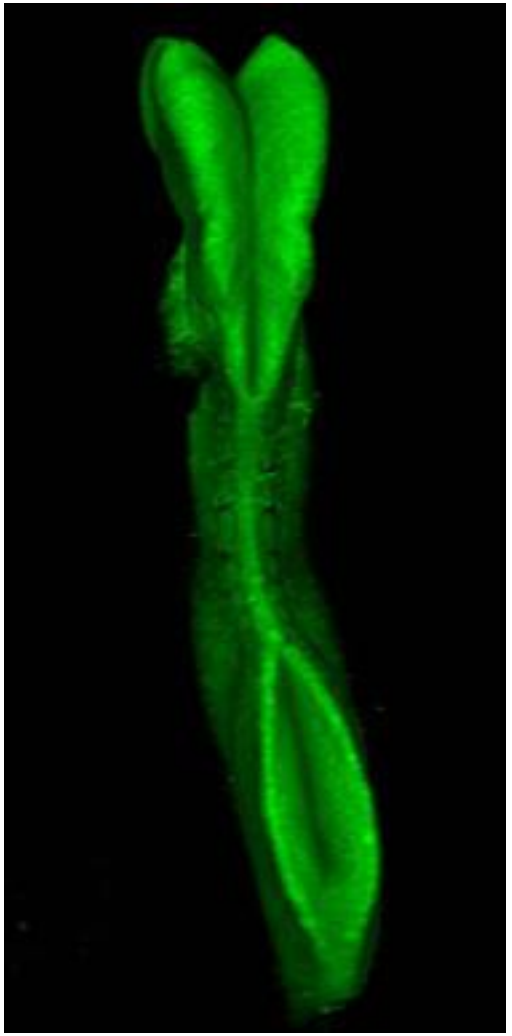


(From Sasai et al., 1994)

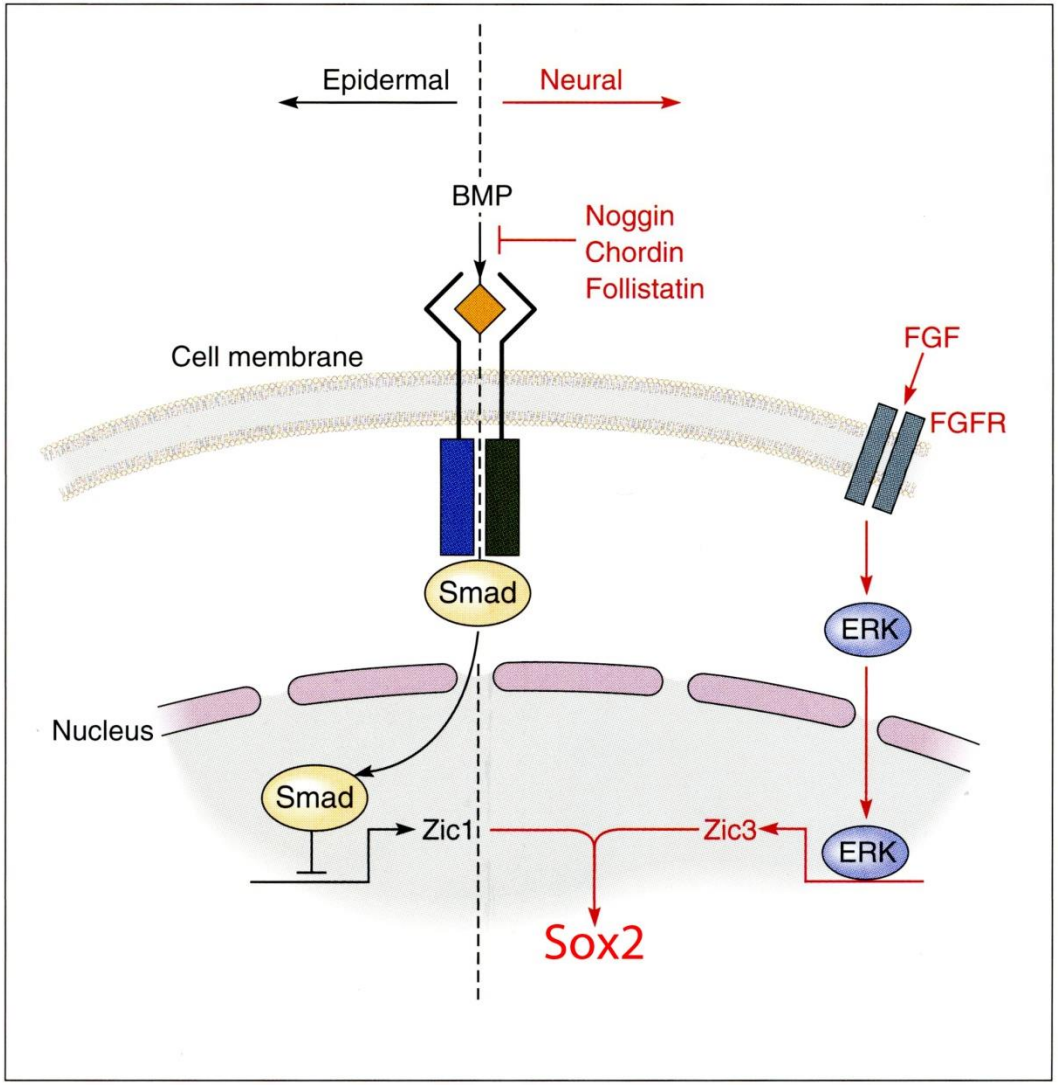
Chordin expression by the organizer

Expression of the transcription factor Sox2 defines neuralized cells . BMP4 signaling represses Sox2 expression.





The Working Model



Patterning the Nervous System

-There are four major steps in regionalization of the brain:

1. Ectodermal cells acquire neural identity (neural induction)

BMP inhibition results in the formation of anterior neural tissue.

2. Adoption of <u>crude</u> positional character (anterior vs posterior)

Opposition between caudalizing factors and their inhibitors (especially Wnts and Wnt inhibitors) establish crude AP patterning.

3. Formation of cell populations ("secondary organizers") <u>within</u> the neural tissue that secretes signaling molecules (morphogens)

4. These secondary organizers modulate and refine initial regional patterning such that the differential gene expression subdivides the neural plate into discrete territories that prefigure the various structures of the mature CNS.

-Same molecular pathways (Wnt, BMP, FGF, RA, Shh, etc.) play a role in more than one steps at different times and places.

Early regionalization is linked to neural induction

-BMP inhibition induces anterior neural tissue (default neural fate).

-Posterior identity is induced independently of BMP inhibition.

- •caudalizing (transforming) activity: Wnts, FGFs, RA
- •Inhibitors of Wnt proteins are expressed underneath the anterior neural tissue and prevent the neural tissue from becoming caudalized.

Signaling pathways and molecules involved in regionalization of the vertebrate nervous system were initially discovered in fly genetics

-Signaling pathway

- •cascade of gene regulation
- •graded expression of transcription factors forms discrete boundaries within embryos

-Molecules

- •*Hox* genes (encodes a family of transcription factors) are involved in identity of specific body segments.
- •secreted signaling molecules and their receptors

A-P axis in vertebrates is also controlled by Hox genes

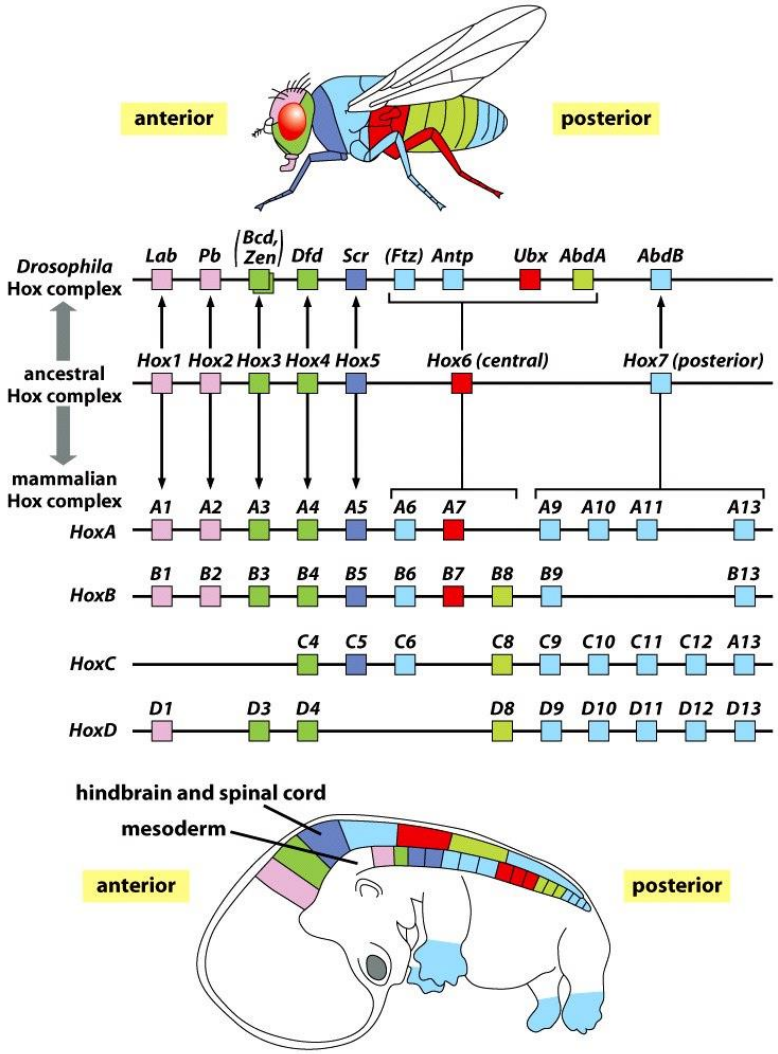


Figure 22-46 Molecular Biology of the Cell 5/e (© Garland Science 2008)

In the mouse, there are four complexes, *HoxA*, *HoxB*, *HoxC* and *HoxD* complexes, each on different chromosomes.

Each of the four complexes is the equivalent of the Drosophila set.

Members of each complex are expressed in a head-to-tail series along the AP axis, just as in Drosophila (the pattern is most clearly seen in the neural tube, from the hindbrain to the spinal cord, but is visible in other tissues such as the mesoderm).

Regulation and functions of the Hox genes in vertebrate nervous system will be discussed later.

Hox genes ≠ Homeobox genes

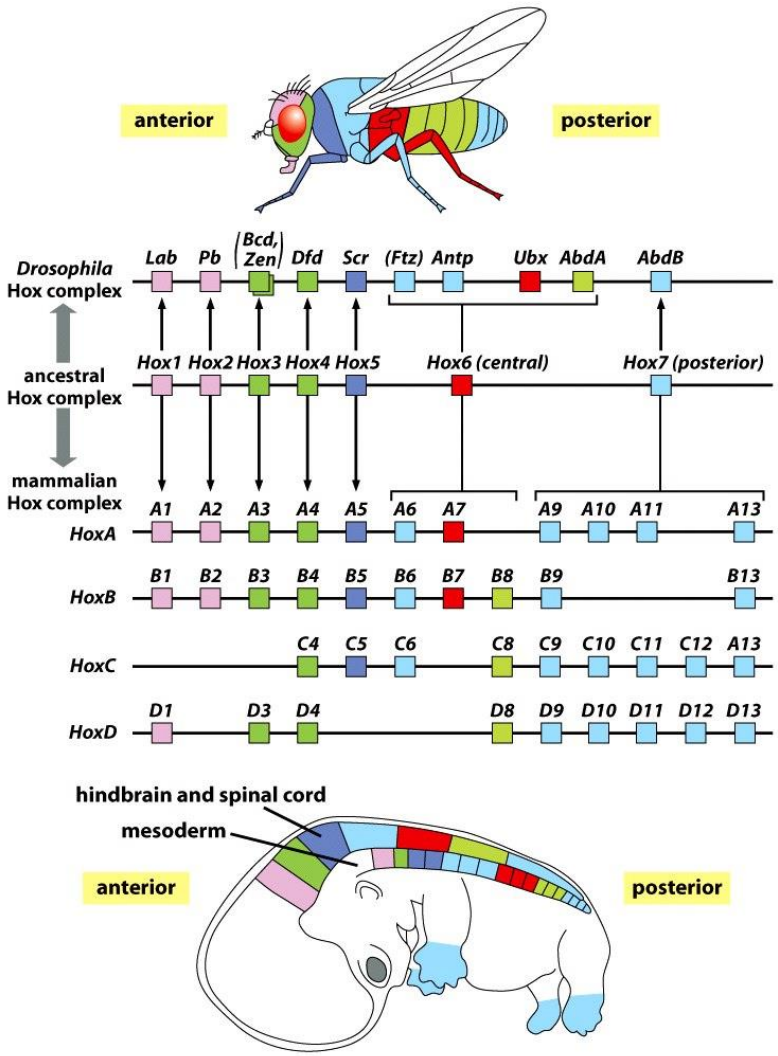


Figure 22-46 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Homeobox: 180 nucleotide DNA sequence (encoding 60 amino acid of the conserved DNA-binding domain called the *homeodomain*

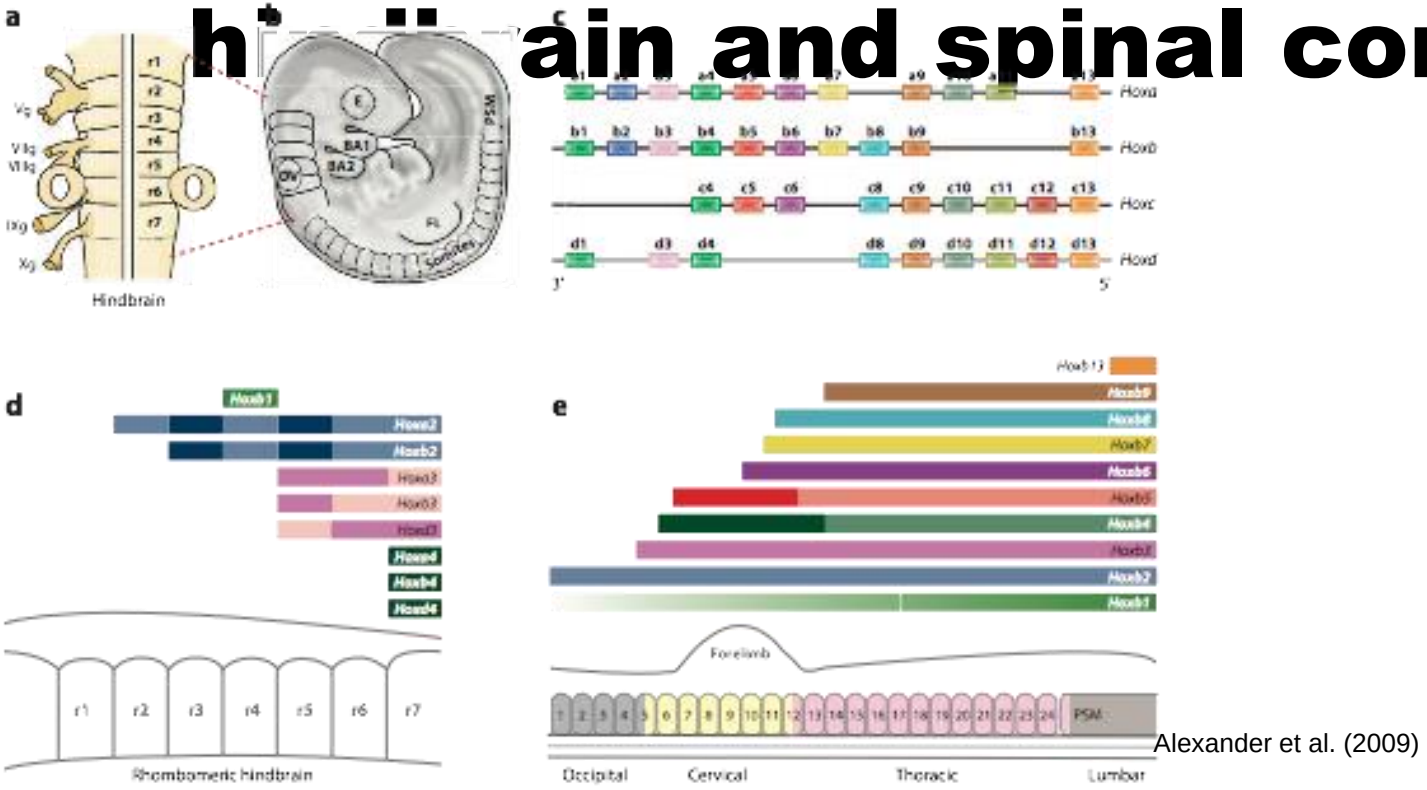
Homeobox genes: genes containing a homeobox

Hox genes: genes on the Hox cluster on Drosophila chromosome or the Hox A-D clusters in the vertebrates (some vertebrates have fewer than four clusters). They only comprise a small portion of homeobox genes.

In the vertebrate brain, Hox genes are not expressed rostral to the hindbrain. Many homeobox genes that are not Hox genes are expressed in the midbrain and forebrain.

"Homeotic": functional term that describes the homeotic transformation (not the same as homeobox)

Segmental expression patterns of mammalian Hox genes in the hindbrain and spinal cord

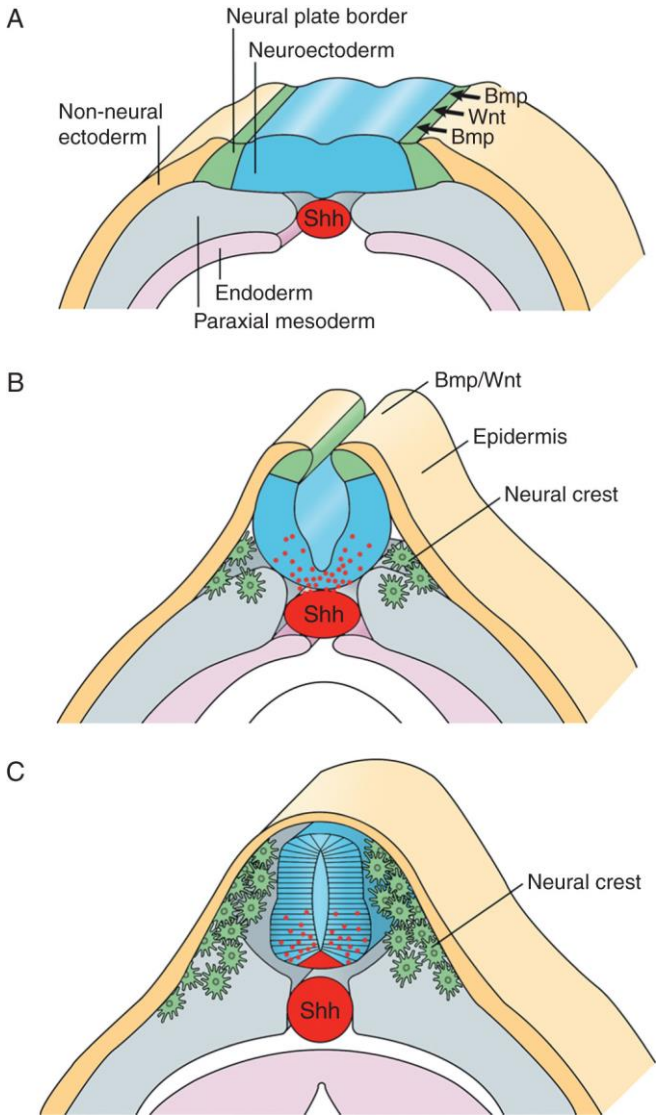


Alexander et al. (2009)

Colineality: Anterior expression borders of *Hox* genes are correlated with the positions of their locations on the chromosome (the more 3' the gene is, the more anterior the border of expression is).

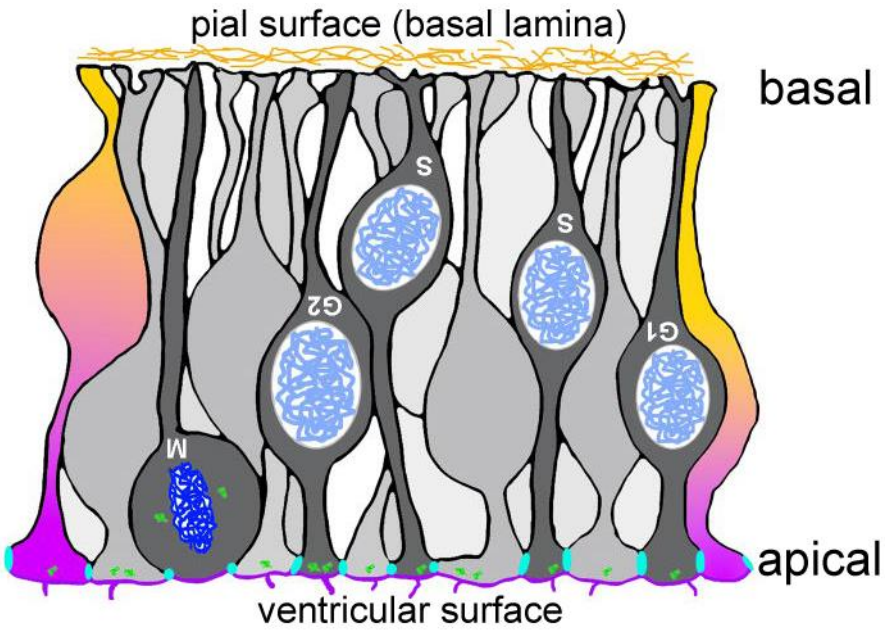
The most anterior border of *Hox* gene expression is between r1 and r2.

Factors from ectoderm and mesoderm pattern dorsal-ventral identity of the neural tube.



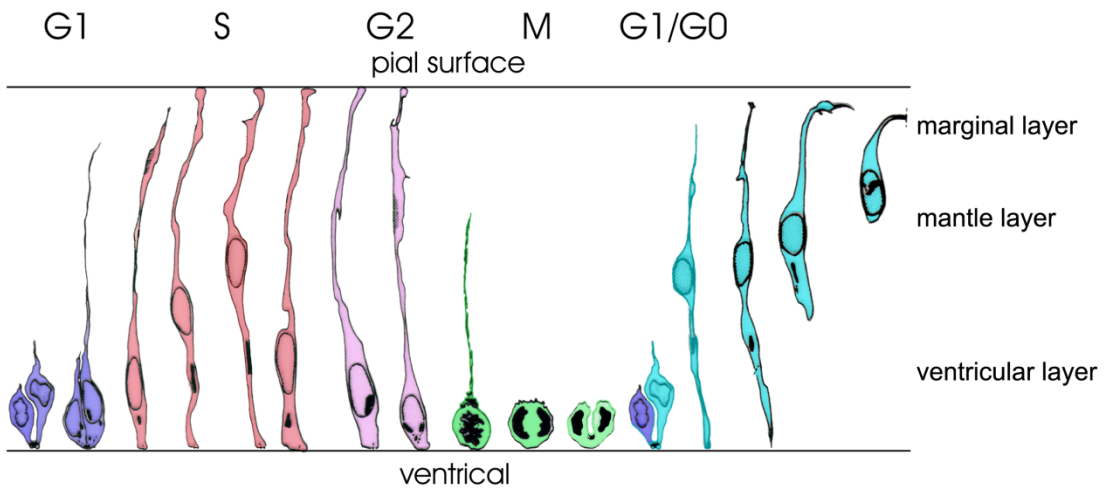
Sanes, Fig.2.26

Neuroepithelial Cells



- Bipolar cells with apical and basal ends
- Neighboring progenitor cells are linked at the apical ends by adherens junctions.
- Apical end has a cilium projecting into the ventricle, which is lost during M-phase.
- Basal end is in contact with the basal lamina.
- Many regulatory proteins are asymmetrically distributed in the apical-basal axis.

Interkenetic Nuclear Migration during the Cell Cycle in the Early Neural Tube



G1 nucleus translocates from the ventricular surface towards the pial surface

S DNA replicates

G2 nucleus translocates to the ventricular surface

M cell divides at the ventricular surface

G0 cell loses attachment to the ventricular surface and migrates towards the pial surface to differentiate

Cell Cycle Length

- varies; 12 hrs is typical
- tends to increase during development
- difference between slow and fast dividing cells is generally the time spent in G_1
- length of S, G_2 and M phases are nearly constant for all cells of an organism

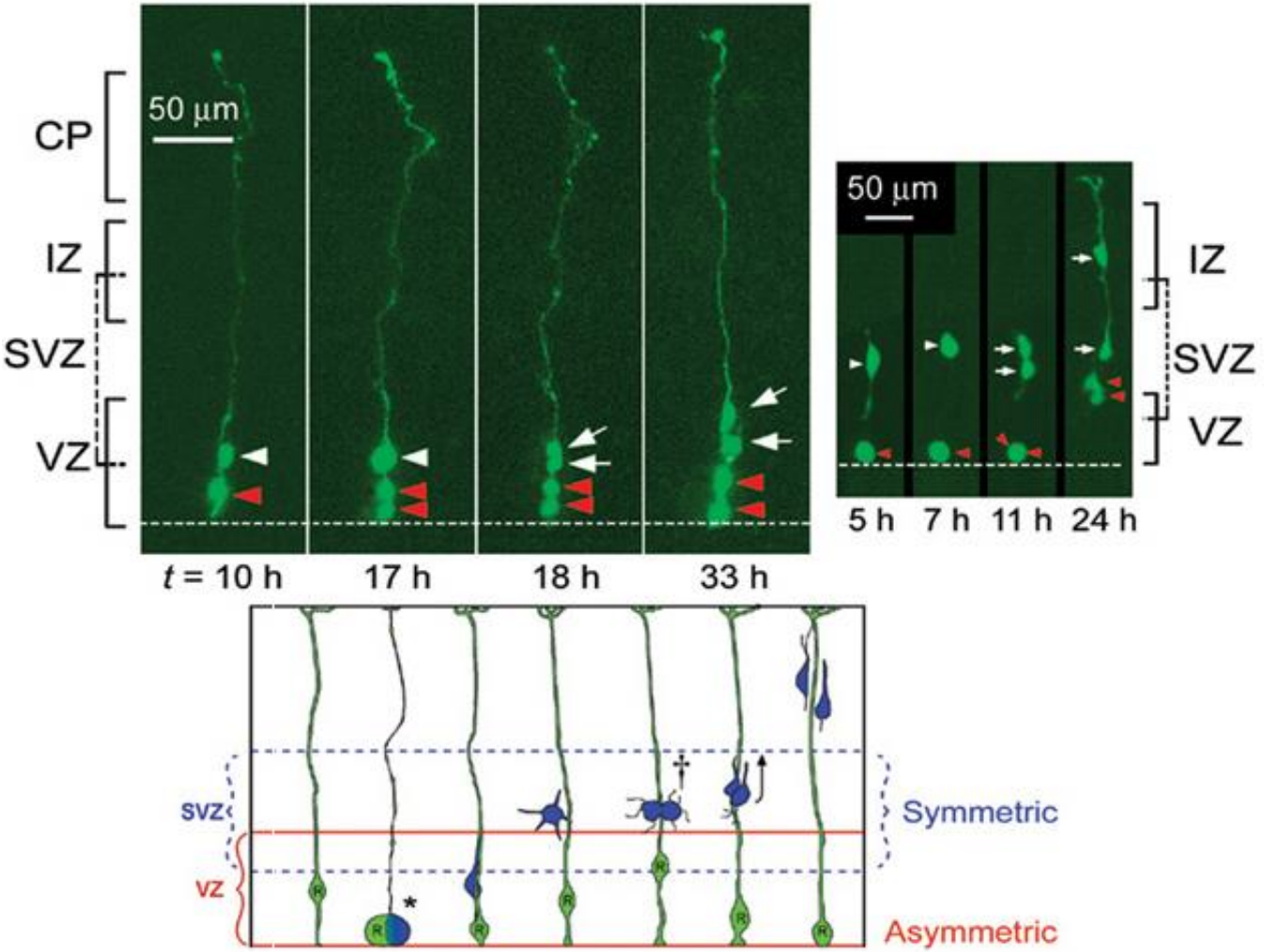
Secondary Sites of Cell Division

In some regions, cells migrate away from the ventricular zone and establish a secondary site of cell division

e.g. subventricular zone of developing cortex

In some regions, progenitor cells migrate away from the ventricular zone and establish a secondary site of cell division.

e.g. subventricular zone of developing cortex



Methods Used to Study Cell Division Experimentally

S-phase labeling bromodeoxyuridine (BRDU) or 3H-Thymidine:

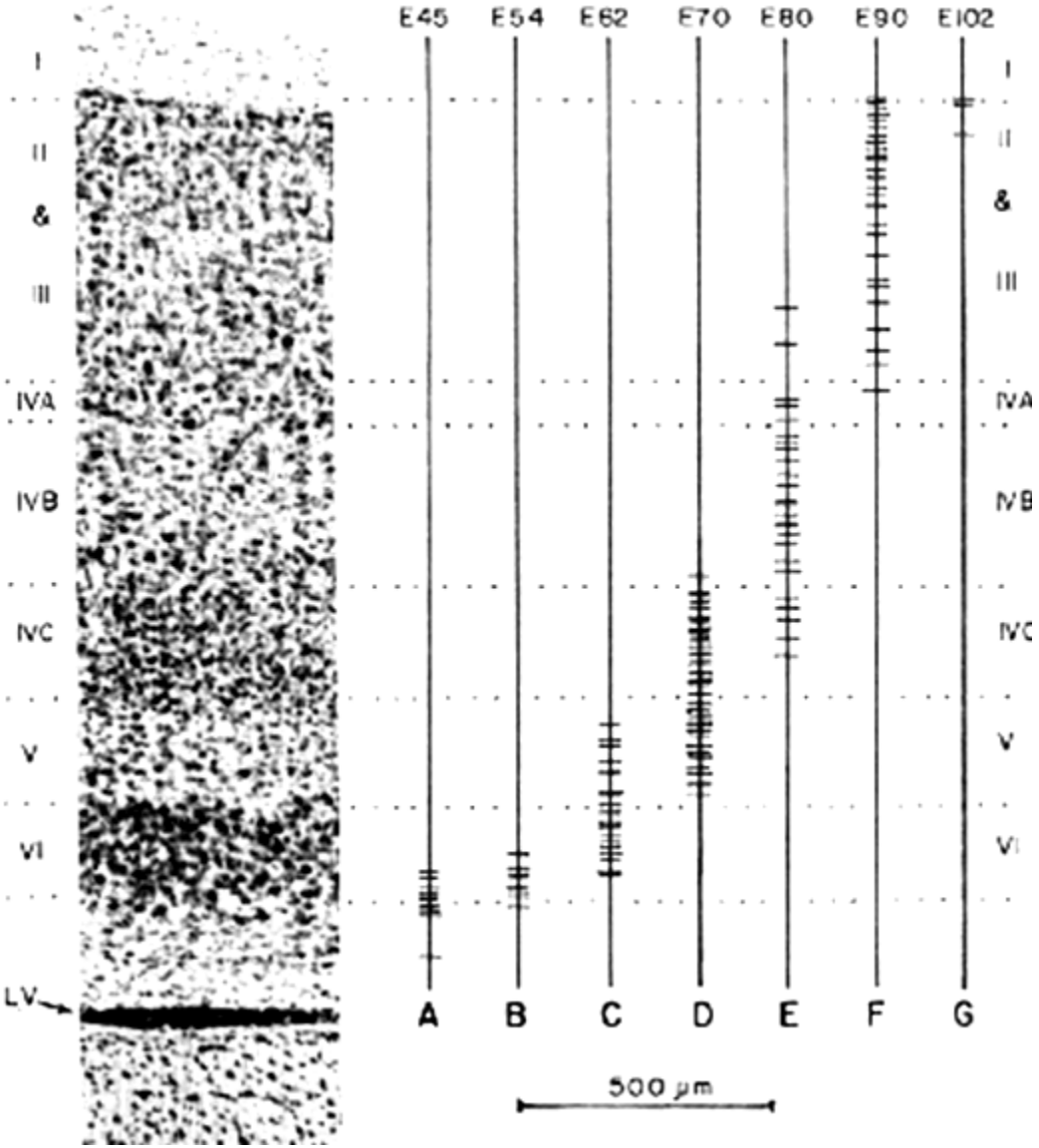
- in mammals, label is available for 1-4 hrs following the injection into the mother or the baby

- increased post-injection survival time results in labeled cells at progressively later phases of the cell cycle

- labeled cells that differentiate following division, retain the label throughout life

- label will be diluted in cells that continue to divide

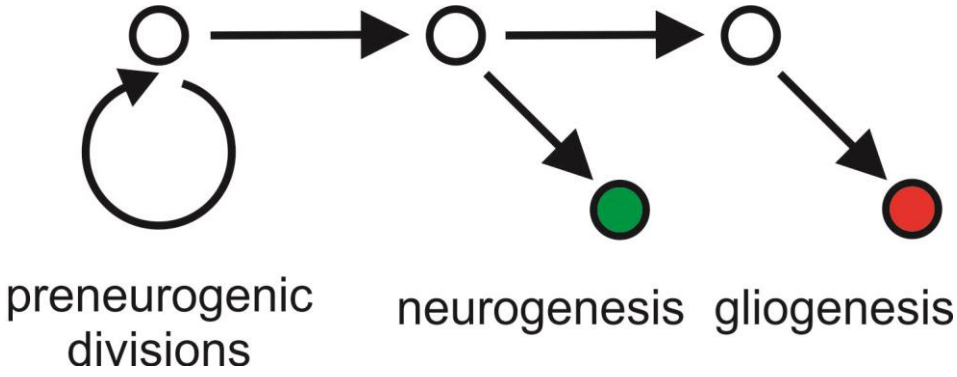
Cell Birth Dates in Cerebral Cortex



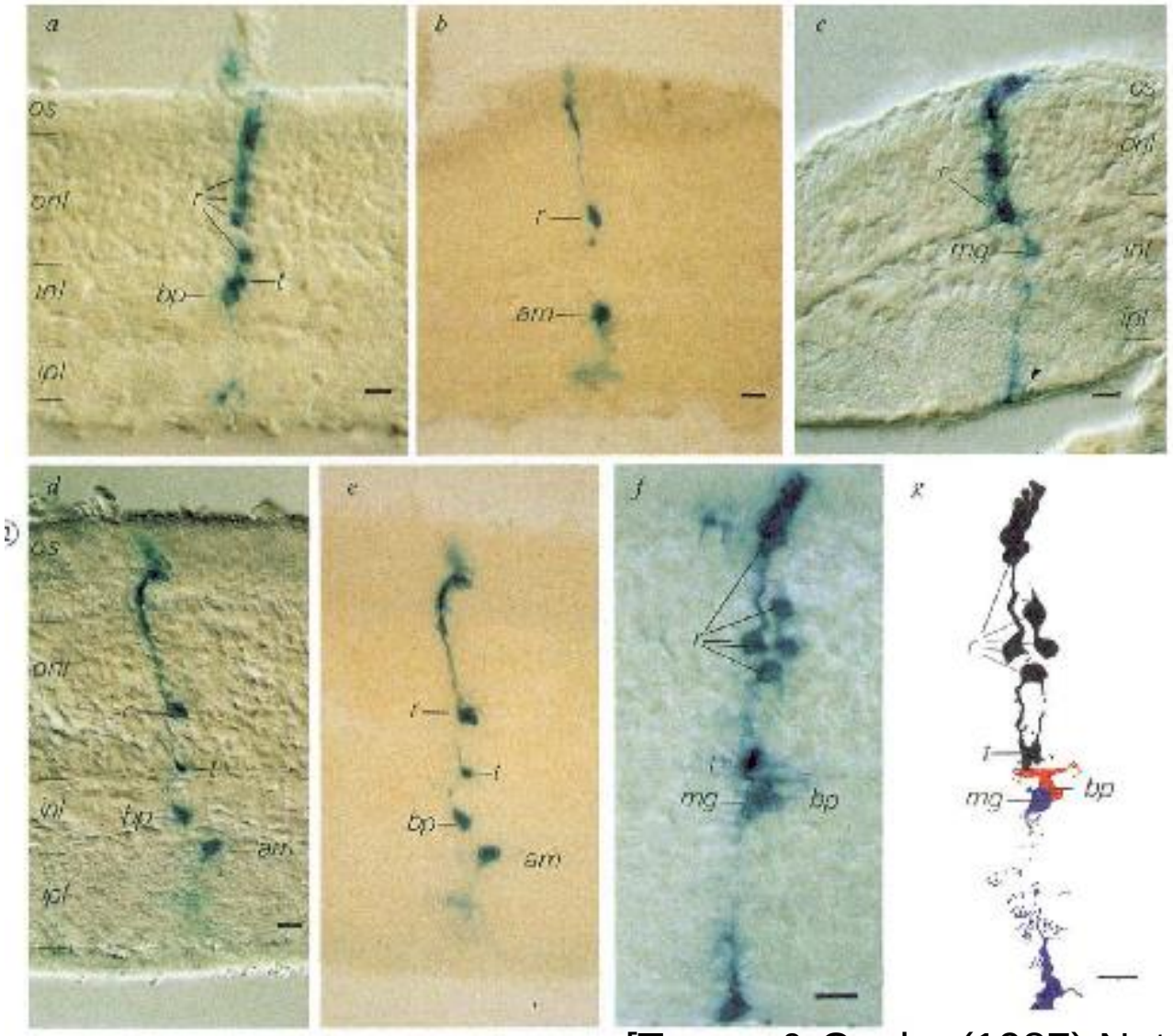
[Rakic (1974) Science 183]

Generalizations on the Pattern of Differentiation in the CNS

- neurons before glia
- large, projection neurons before small interneurons

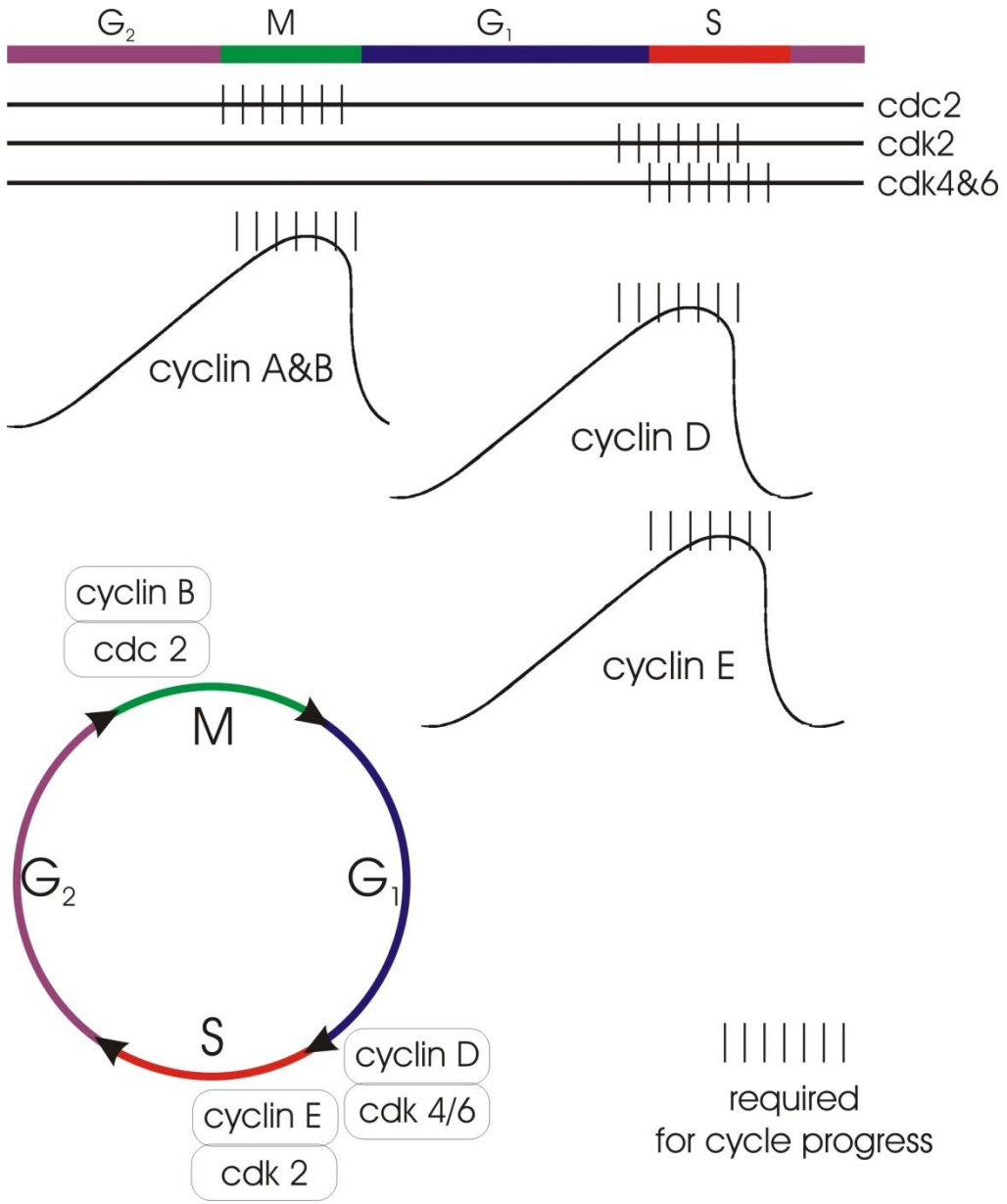


Generally individual progenitor cells give rise to multiple cell types.

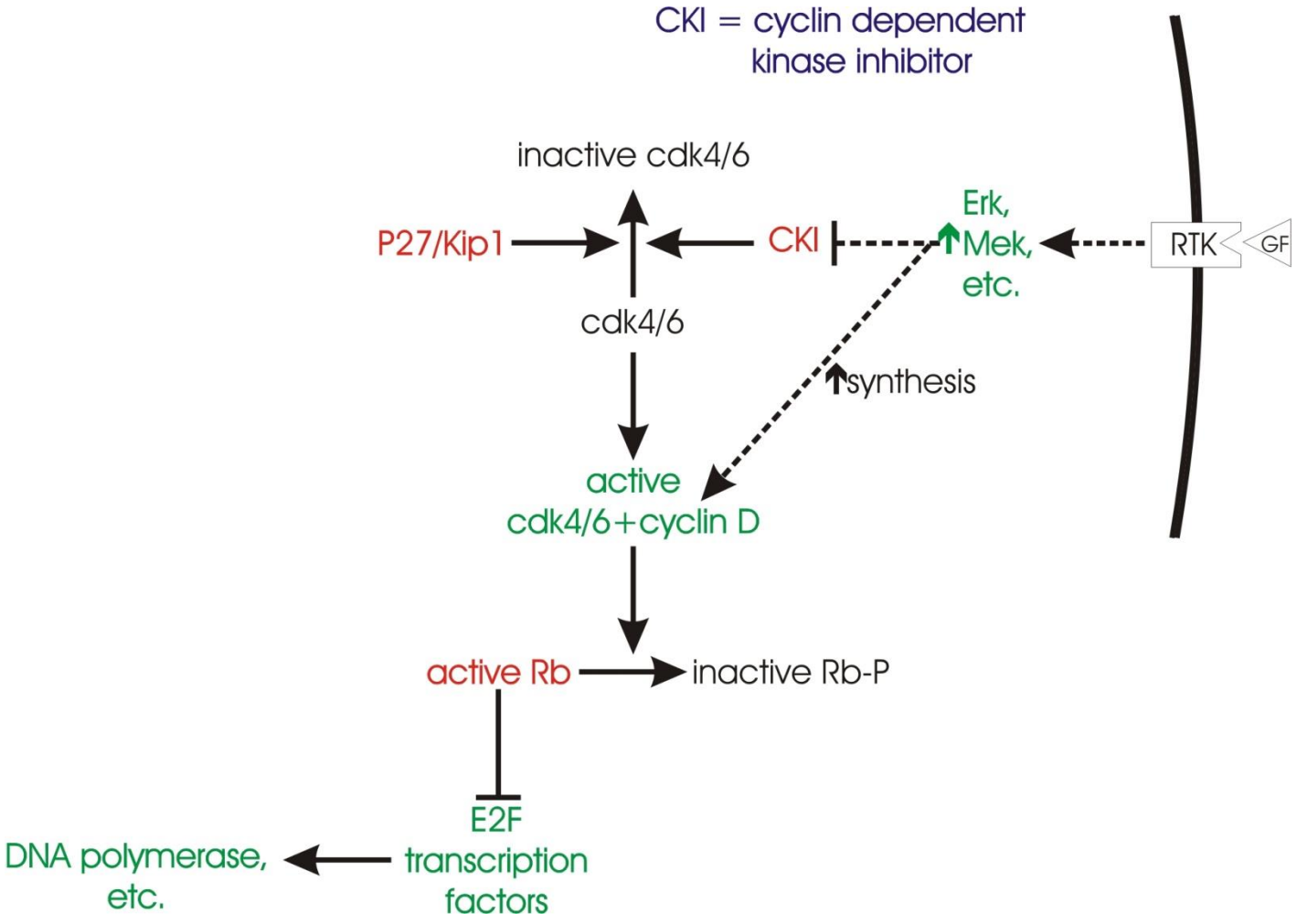


[Turner & Cepko (1987) Nature 328]

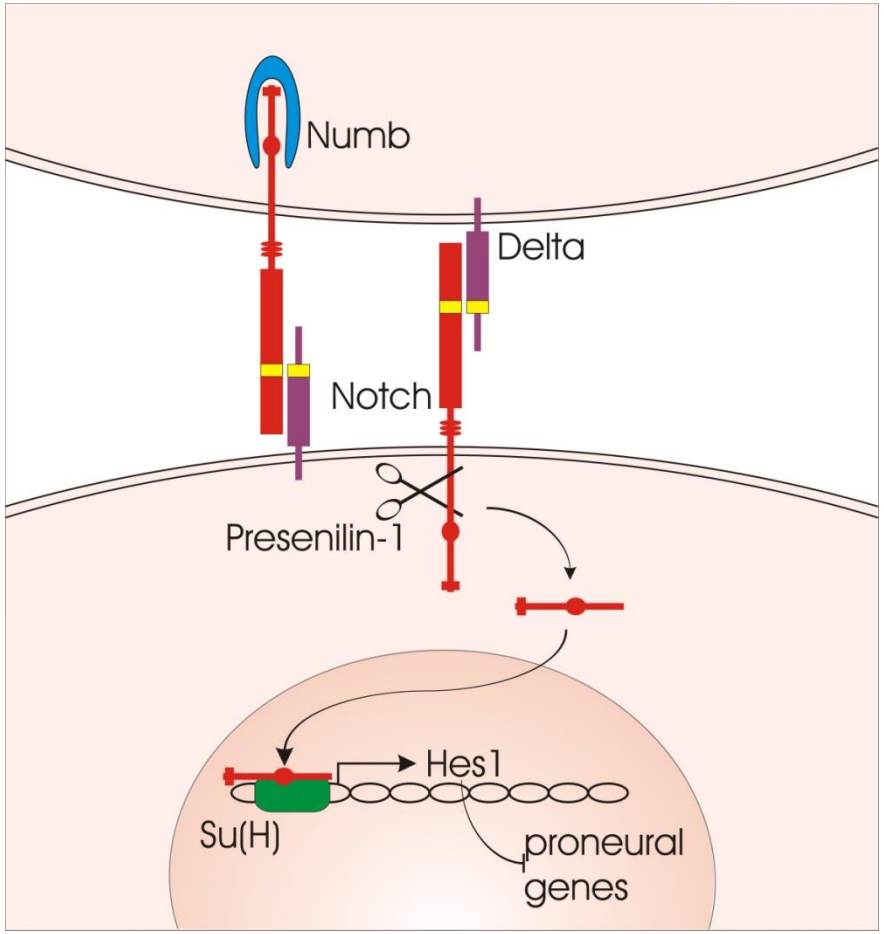
Progress through the cell cycle is regulated by multiple cyclin dependent kinases and cyclins.



Control of Entry into S-Phase of the Cell Cycle

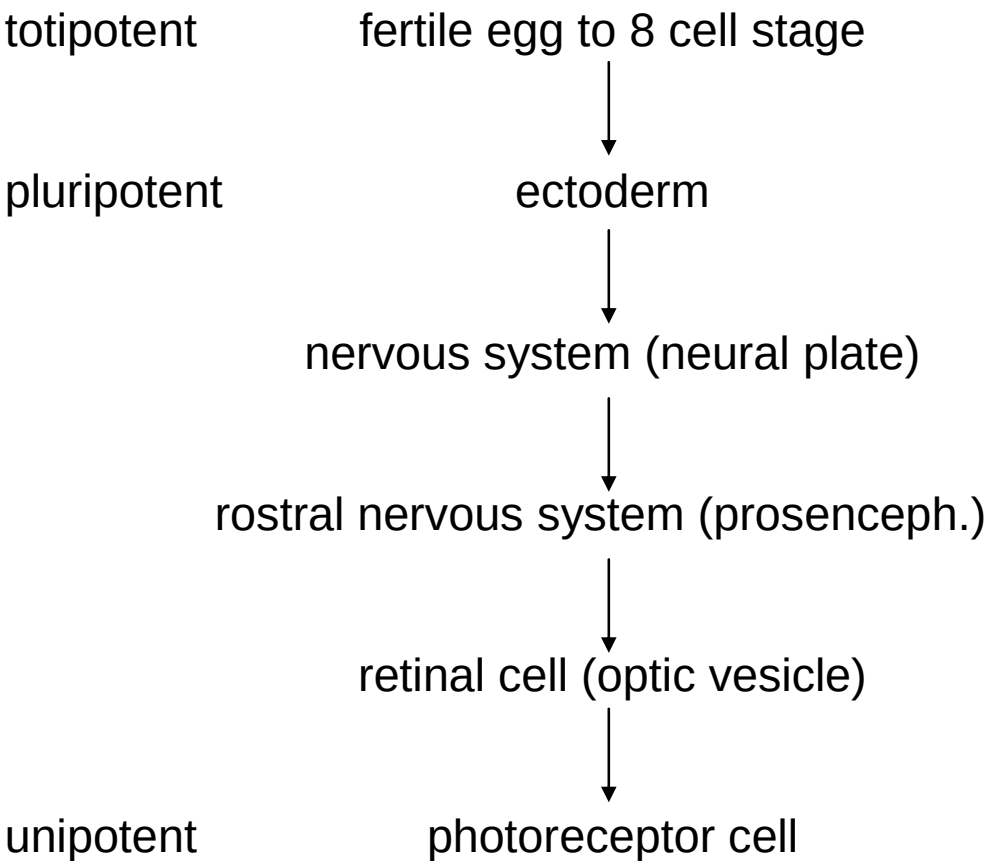


Notch signaling can block differentiation and promote cell division.



Determination of cell fate is due to the sequential restriction of possible fates.

- Fate restrictions are unidirectional.



What determines cell fate?

- Intrinsic program – inherited fate
- Extrinsic cue - features in the environment to which a cell can respond with a change in potential fate

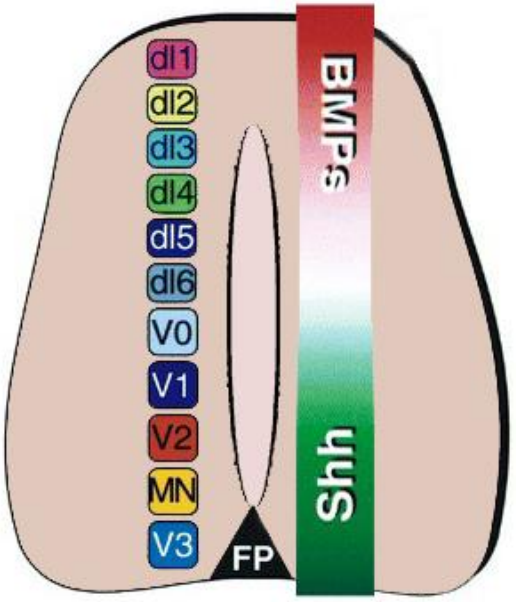
  [Extrinsic cues induce intrinsic changes.]

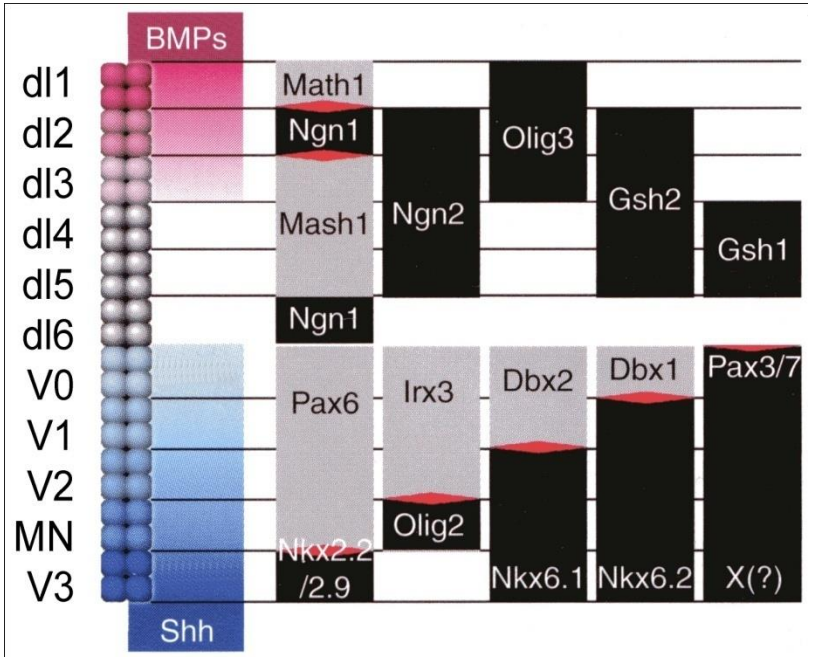
Factors that induce regional differences determine the initial cell fate in each domain.

e.g. spinal cord

- The relative levels of Shh and BMPs determine the transcription factors expressed in each dorsal-ventral domain of the developing spinal cord.

- The combination of factors expressed in each domain determines the cell types that develop there.



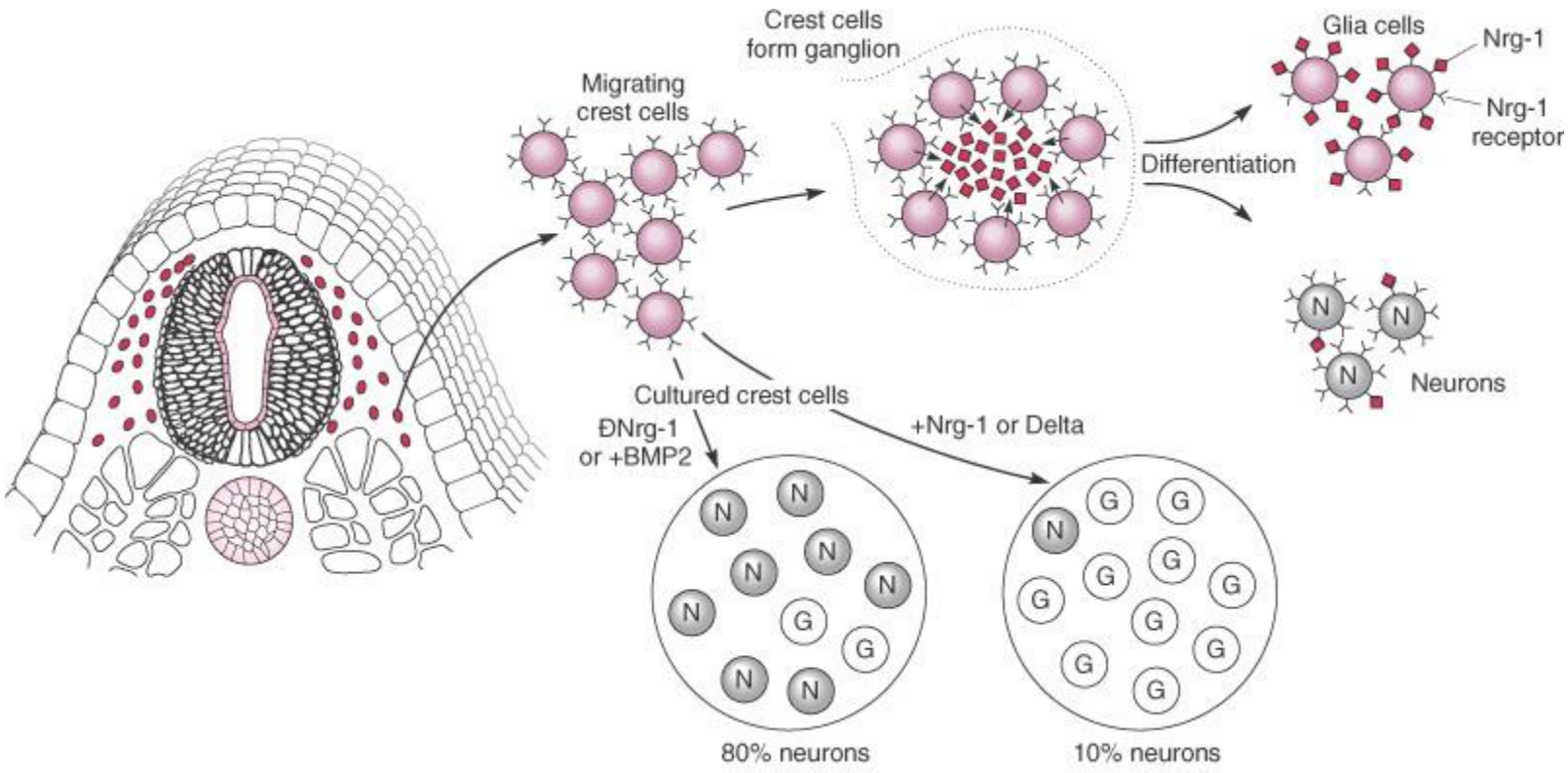


Factors that induce regional differences determine the initial cell fate in each domain.

- The first cell type generated in a domain is the ‘default fate’.

Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

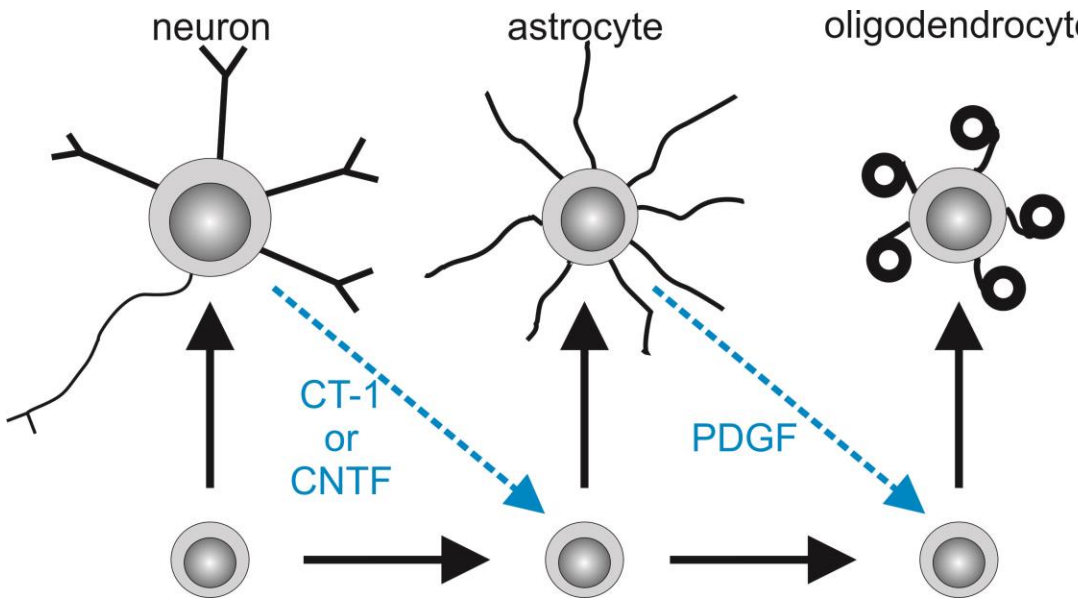
- Crest cells in culture develop into neurons and glia.
- With Nrg-1 added to the medium, they all become glia.
- Blocking expression of Nrg-1 in the cultured cells caused them all to become neurons.



Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

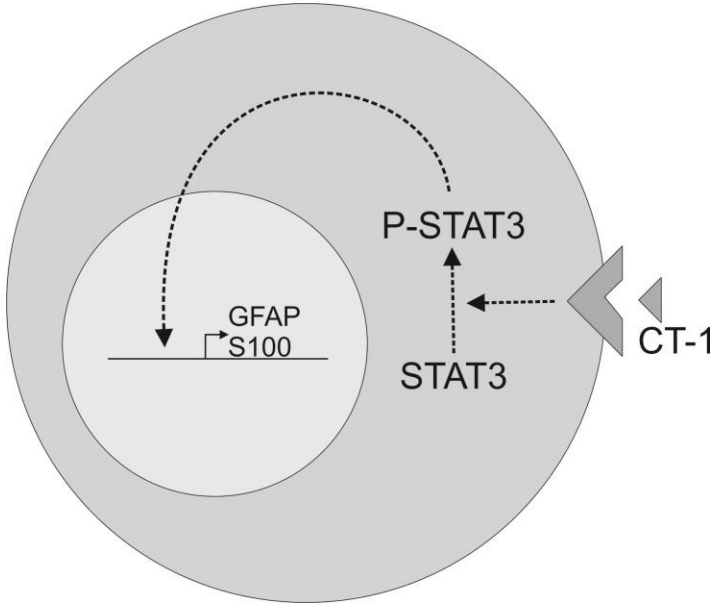
In cultures of cortical progenitor cells:

- The cytokines Cardiotrophin-1 (CT-1) or ciliary neurotrophic factor (CNTF) terminate neurogenesis and promote astrocyte genesis.
- PDGF promotes oligodendrocyte genesis.



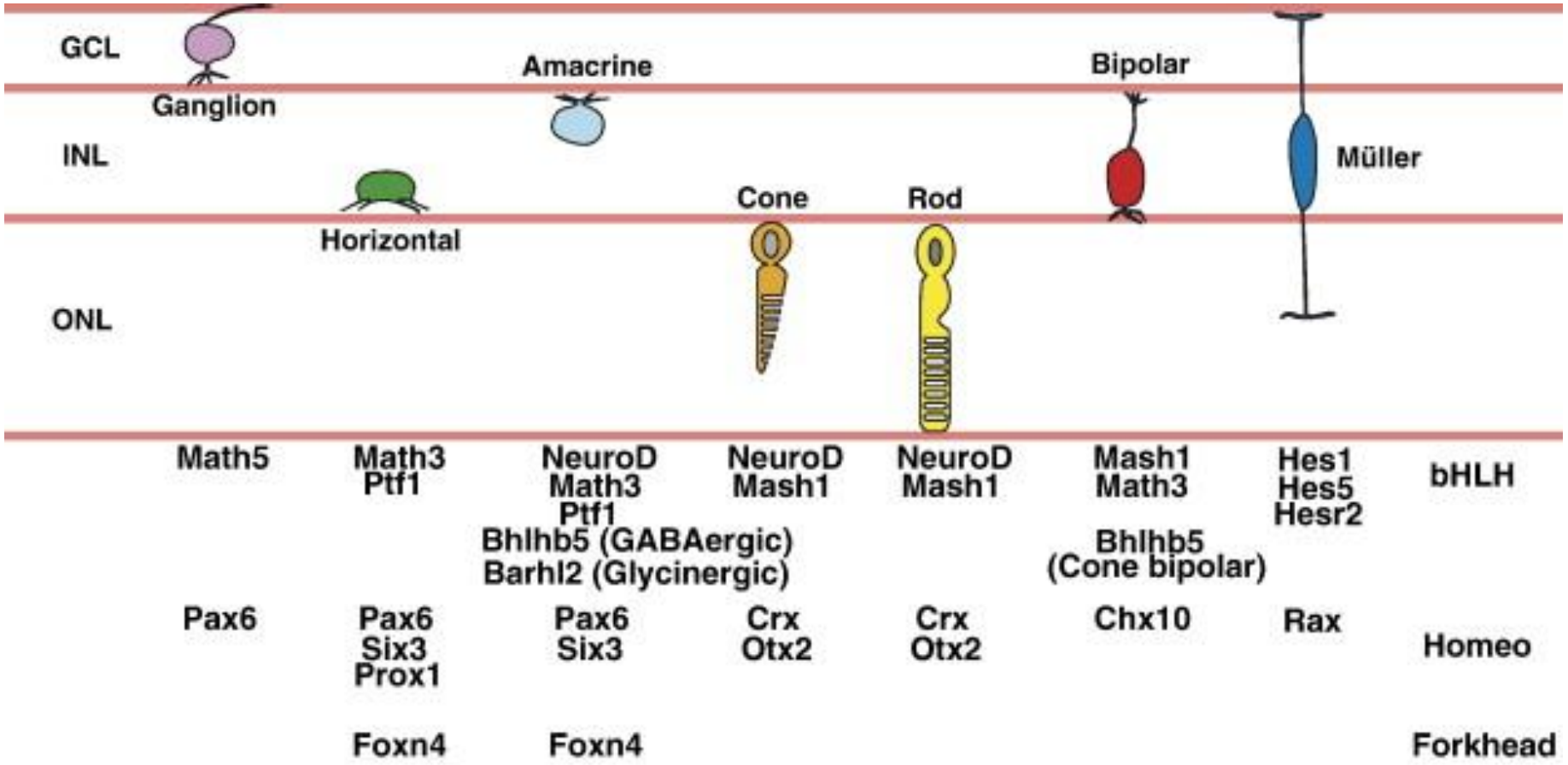
Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

- CT-1 and CNTF act via cell surface receptors to activate STAT3 by phosphorylation.
- Active STAT3 binds the promoter of astrocyte specific proteins including GFAP and S100.
- In early development, the STAT3 binding sites in the promoters of these genes are methylated, so STAT cannot bind and only neurons are generated.
- Notch activation demethylates these STAT binding sites.



Molecular Basis of Determination

- Seven retinal cell types are each determined by expression of a specific complement of transcription factors.



Concept …

Sequential steps in the restriction of possible fates are controlled by different mechanisms.

Early steps: Differences among cells through the blastula stage are due to asymmetric distribution of maternal mRNAs during cell division.

Mid steps: Large scale patterning of tissues is due to secretion of inducing factors that act over large distances. Generally factors released from one population of cells acts on another population of cells. These factors are often in gradients and the relative concentration of a factor determines its effect. Generally it is the sum action of multiple factors that defines the nature of a cell.

Final steps: The possible fates of differentiated cells in a tissue are determined by the previous patterning events (i.e. early and mid steps). Local cell-cell interactions specify the fate of individual cells. Local cell-cell interactions can be a combination of secreted factors and cell contact mediated signaling systems.

What is the molecular basis of cell fate?

- The specific proteins expressed by a cell determines its fate.

What determines the proteins expressed by a cell?

- transcription factors (promoters and repressors)
- epigenetics (chromatin modifications and DNA methylation)
- microRNAs

Midterm Exam

Monday, October 15
9:30am-11:00am???

Bring a #2 pencil !!

Good luck!