Lecture 15. Development

Learning Objectives:

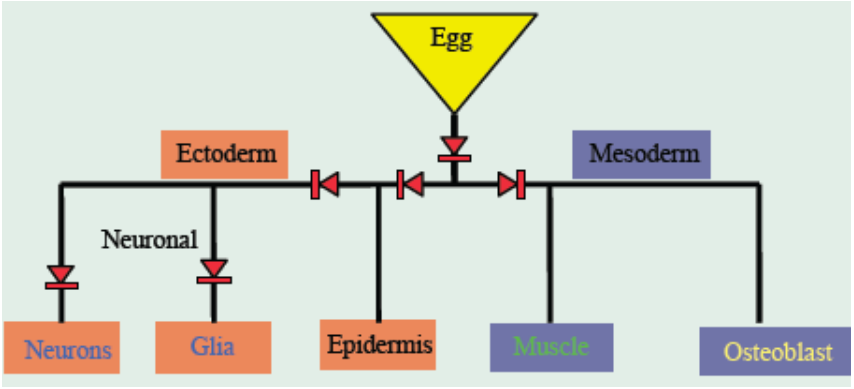
1. Understand the central role of cell signaling in the induction of neural tissue.
2. Be able to explain how a cell's response to the repeated exposure to the same signaling molecule depends on the cell's developmental history.
3. Understand the Hebbian "wire together fire together" rule in synapse formation.

Reading Assignment: Bear figures 23.10, 23.13, 23.14. Optional: read box 23.3 for learning more about why CNS neurons don't normally regenerate (a topic of considerable medical interest)

Lecture Outline

A. Nature versus Nurture: Cues that influence Neural Development

- Intrinsic cues/factors (Nature)
- Extrinsic cues/factors (Nurture)



B. Initial Formation of the Vertebrate Nervous System: the **dorsal ectoderm** is the source of the neural tissue

-- During embryogenesis, cell-cell interactions induce, or organize, neural identity; *the fate of cells depends on their environment.*

-- in the absence of extrinsic signals neural is the ***default fate***

-- *Bone Morphogenic Proteins (BMPs)* are expressed in the ectoderm, and they *suppress* the default neuronal fates, promote epidermal fates.

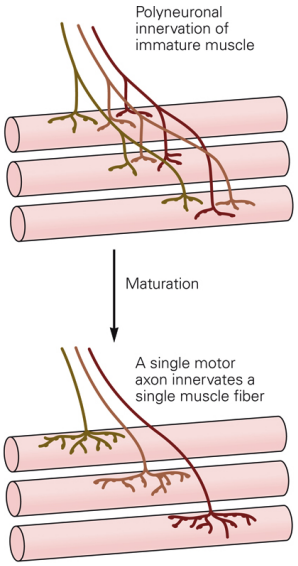
-- *Chordin and Noggin* are expressed in the organizer and antagonize the BMPs, thus restoring neuronal fates.

C. Regional Specification of Neural Tissue

- **All nervous systems are patterned,** meaning that cells in the developing nervous system acquire distinct identities according to their specific spatial position

- **Fate depends on both environment and history**, in that once cells have made irrevocable developmental changes during **critical periods** they lose pluripotency
- Two-Step Model
  - **Step 1.** Primary inducers (Chordin, Noggin) induce anterior neural tissue
  - **Step 2.** Transformer signals act on the anterior neural tissue to specify posterior neural tissue (hindbrain, spinal cord)

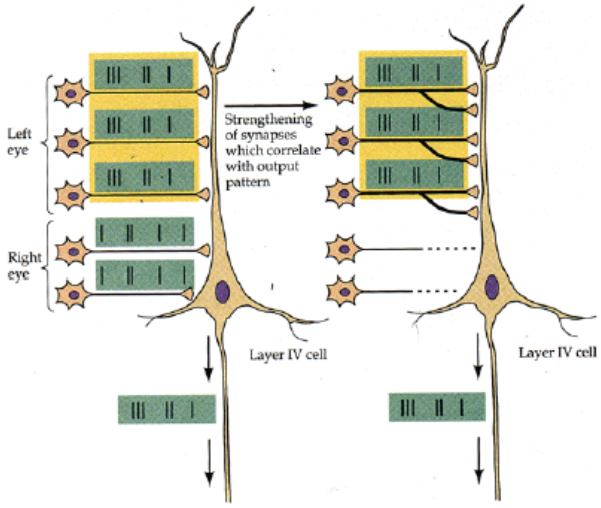
D. Axon outgrowth and synaptic refinement



• Guidance cues like cadherins, immunoglobulins, and ephrins direct the movements of migrating neurons and growth cones
• Once a growth cone makes contact with its target a synapse matures
• The maturation of the nervous system usually involves the pruning of the arrangement and number of synapses.

E. A combination of competition and cooperation is involved in Hebbian synaptic refinement

- The synapses from neighboring neurons tend to fire synchronously
- They cooperate to depolarize the target cell
- Synapses that cooperate are strengthened
- Asynchronous synapses are weakened
- "Fire together, wire together"



Lecture 15: development of the central nervous system

Learning goals:

1. Understand that at both the level of individual cells and the organism developmental outcomes depend on both intrinsic and extrinsic signals.

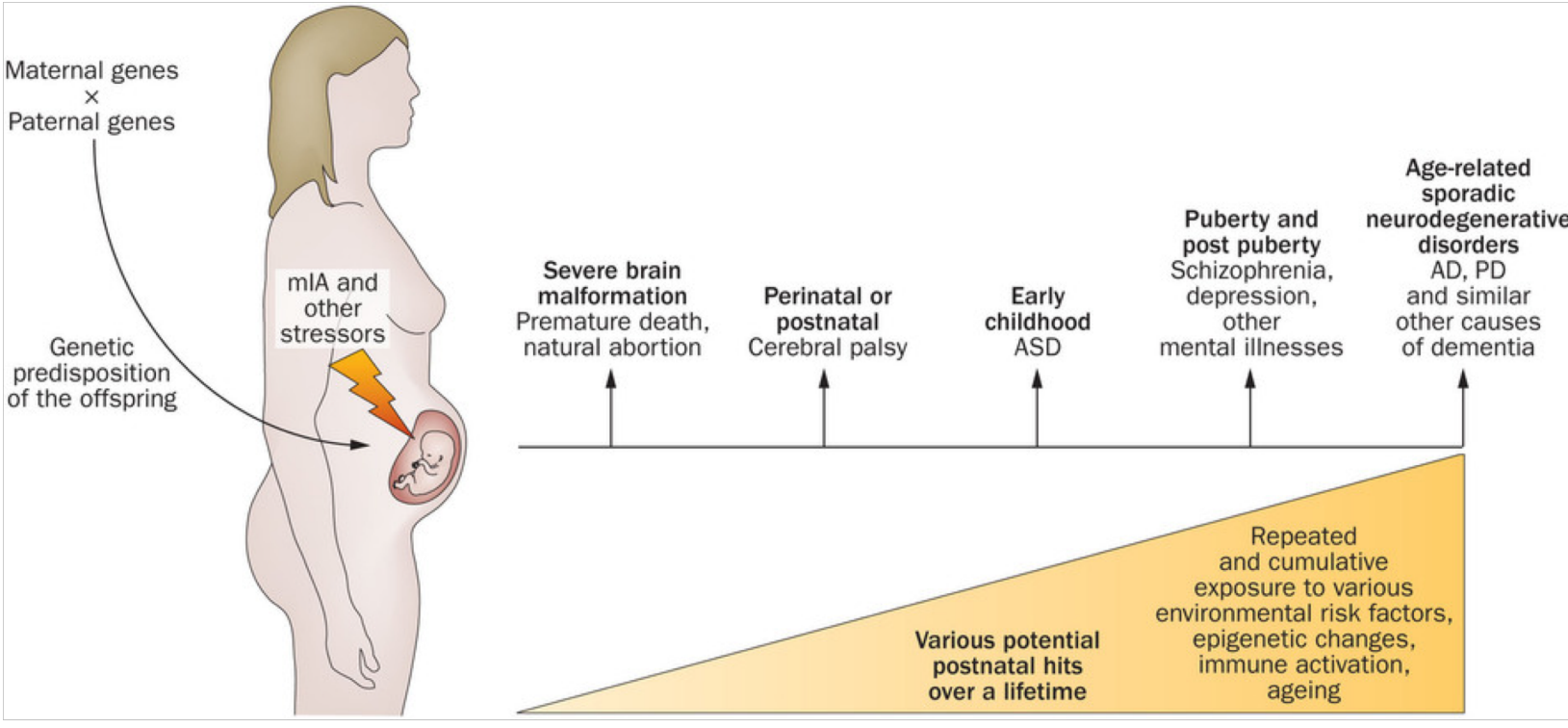
2. Be able to explain how a cell's response to the repeated exposure to the same signaling molecule depends on the cell's developmental history.

3. Know how chemical signaling is critical for early induction and patterning of the nervous system and for the guidance of extending axons.

4. Understand that activity ("wire together fire together") is the final step in forming correct synaptic connections.

Use these examples to learn overarching themes that govern neural development

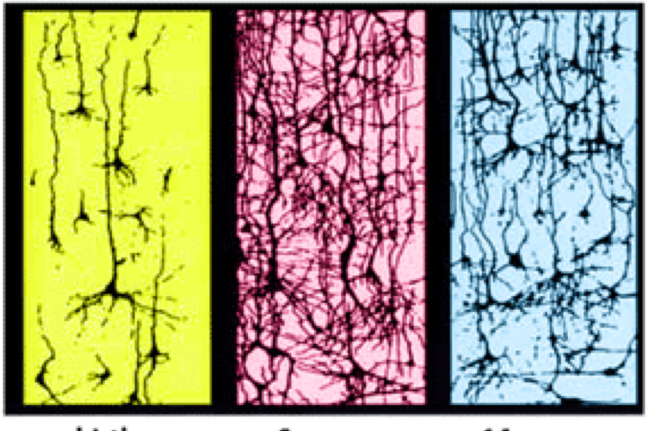
The study of neural development is overwhelmingly important in treating human disease



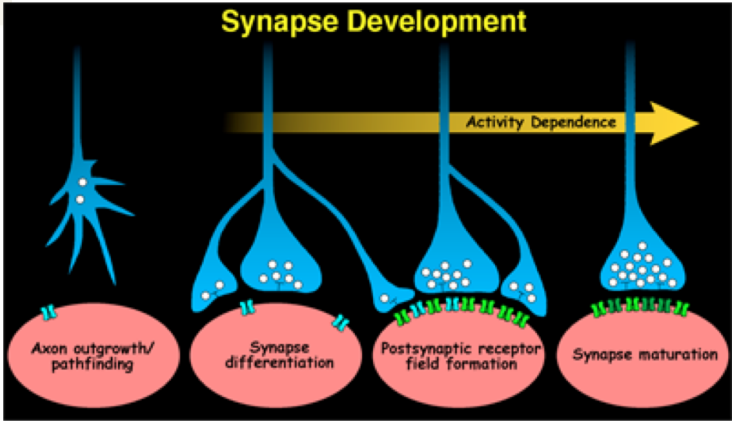
The study of neural development is also closely related to the study of learning

Experience Shapes Brain Architecture by Over-Production Followed by Pruning

Center on the Developing Child HARVARD UNIVERSITY



Source: Shonkoff, J. P. (2008) **



How do cells find their way to forming a nervous system?

1. How do cell bodies assume the correct neural identity?

2. How do the cell bodies send out axons that travel in the right direction?

3. How do the axons make the correct precise synaptic connections?

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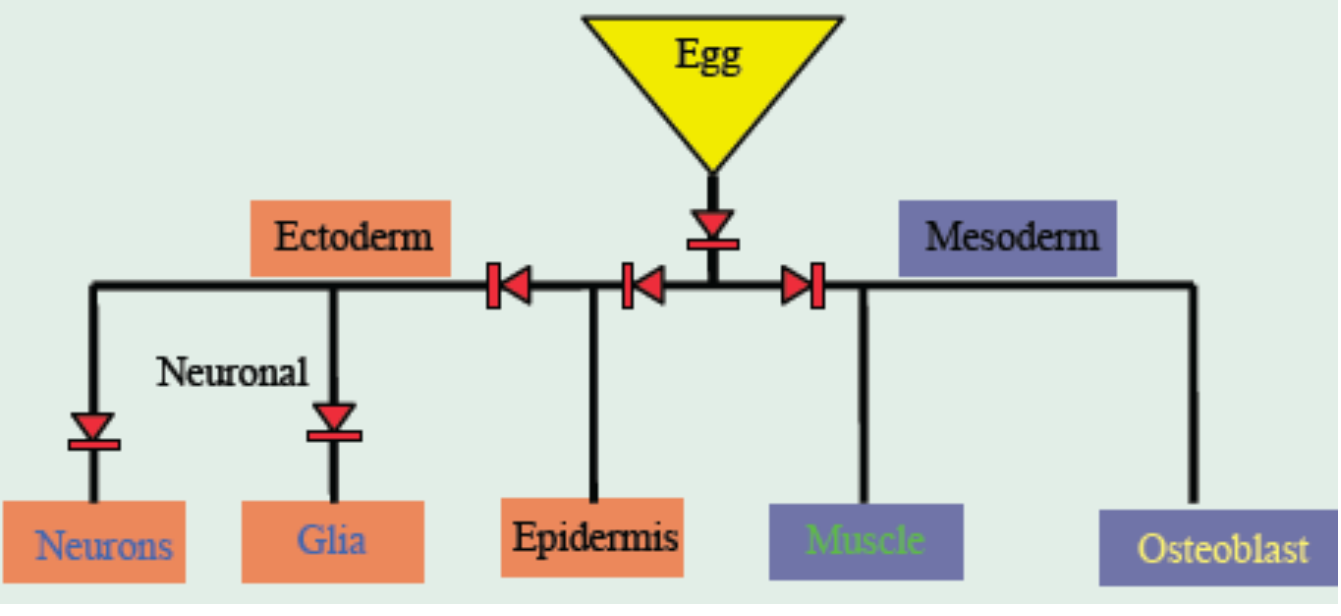
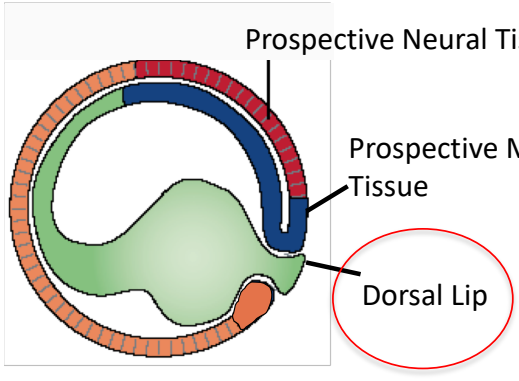
Cells start pluripotent, then their fates become determined



Arrow represents a critical decision point, cell fate is determined = not reversible

when is the fate if the cell determined?
what is the molecular basis of cellular determination? GENE EXPRESSION

Recap: after gastrulation, only the ectoderm can become neural tissue



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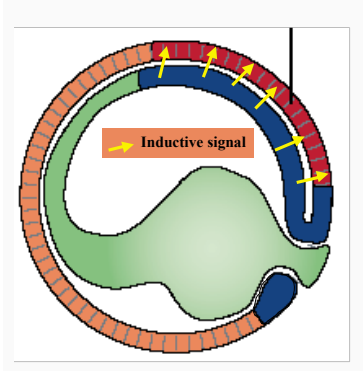
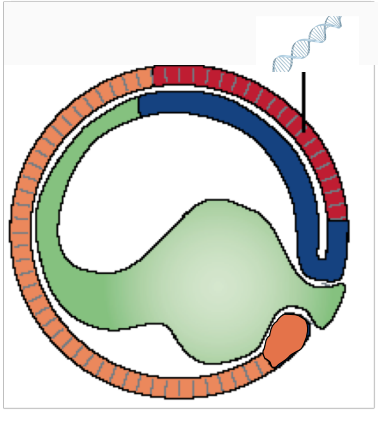




Are the cells' genes determining their fate, or is there some factor, something produced by nearby cells, that programs them?

Is there a chemical telling these cells what to do … a neural inducer?

Clicker question

If the dorsal lip was removed or damaged at the gastrulation stage, what do you think would happen to the eventual embryo?

A. No neural tissue would develop

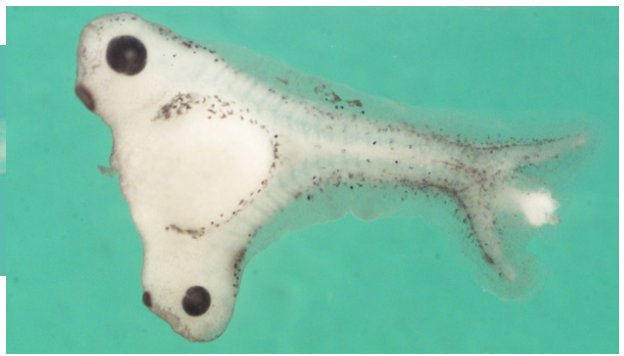
B. Only neural tissue would develop

C. All the cells in the embryo would cease to divide

D. All the cells in the embryo would divide and proliferate uncontrollably

Damaged/removed lip

Normal



Transplanted lip

Cues that influence developmental fates can be intrinsic or extrinsic

Intrinsic cues/factors

-- genes
-- DNA modification
-- cell lineage/inherited factors

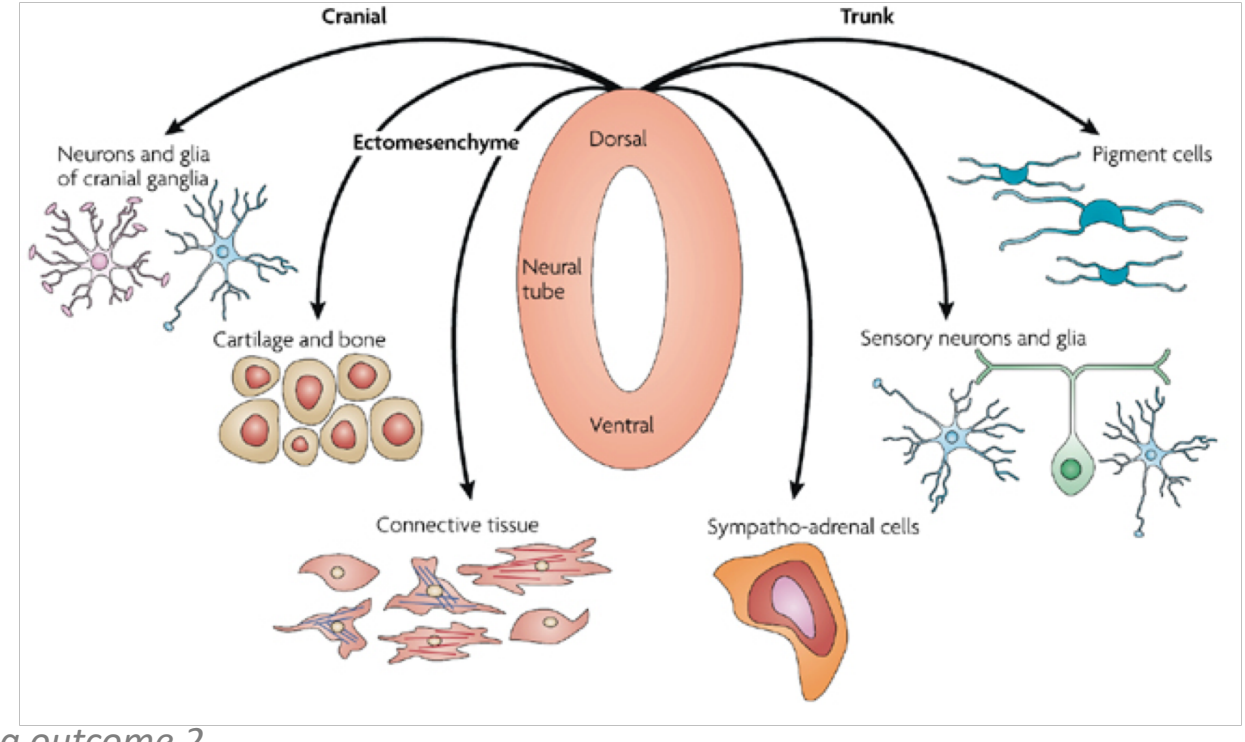
Extrinsic cues/factors

-- cell-cell interaction
-- trophic factors
-- hormones
-- patterns of neural activity

Learning outcome 1

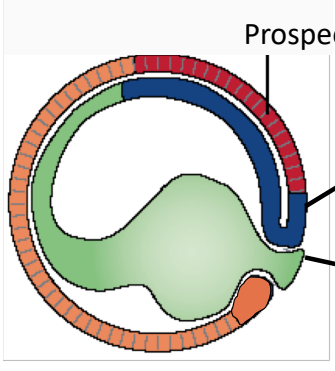
The major principle of development you need to remember: **sequential signals build on each other**

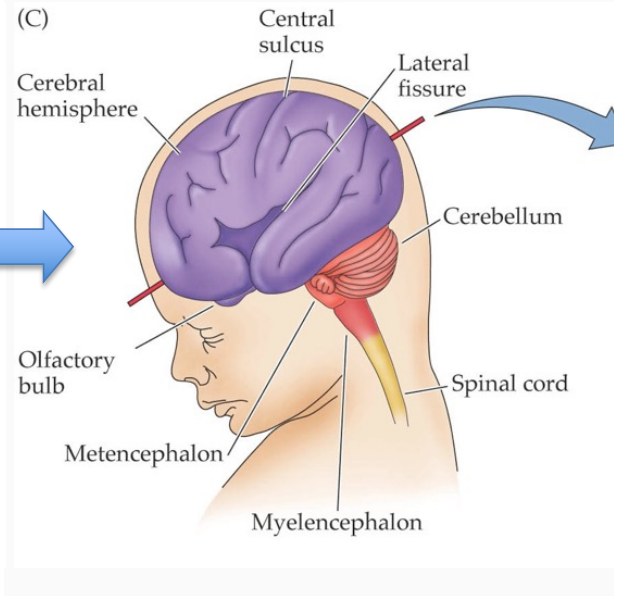
Original signal → gene expression → express new receptors → can respond to next signal



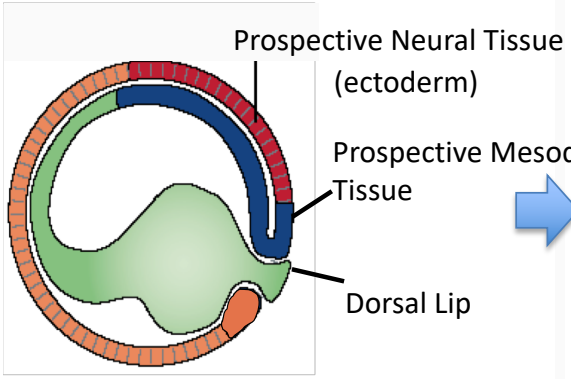
Learning outcome 2

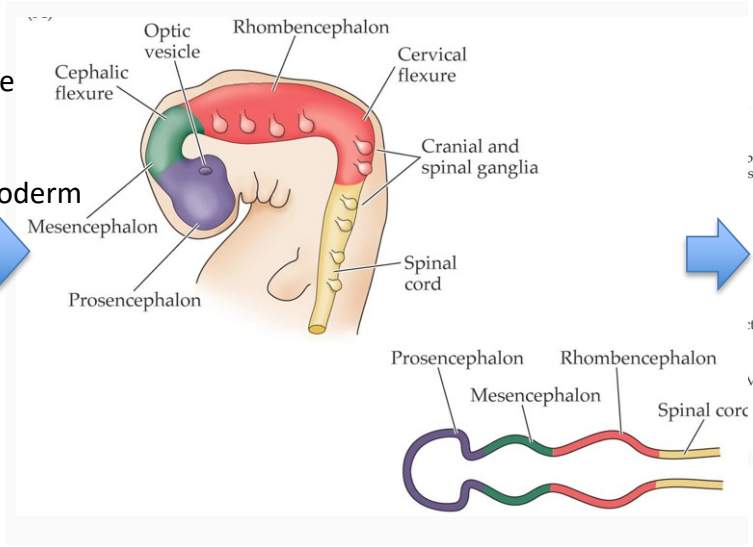
How do we get from a ball of cells to a CNS?

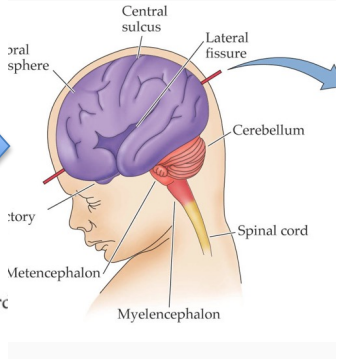




How do we get from a ball of cells to a CNS?
Through patterning: turning a ball into a tube.



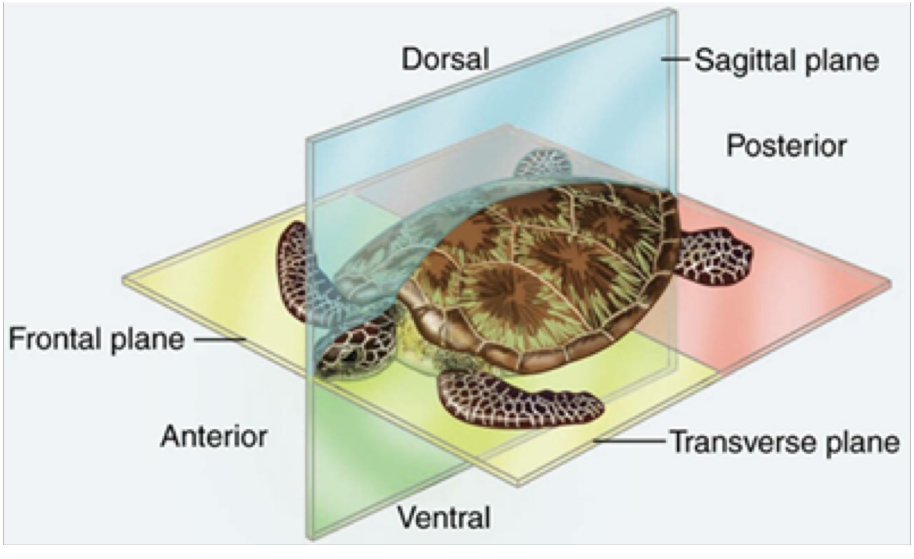




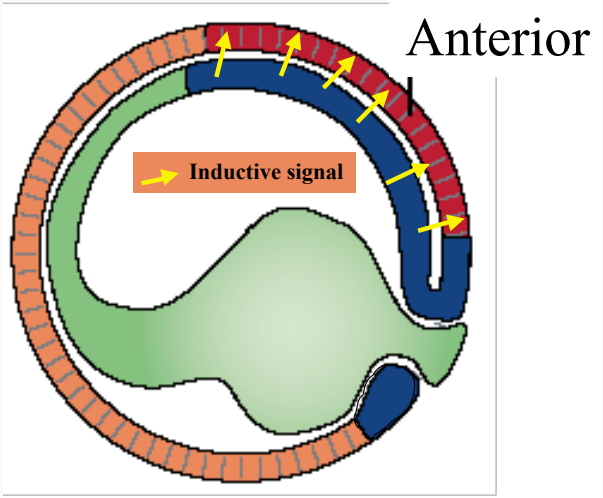
Neural patterning: process by which cells in the developing nervous system acquire distinct identities according to their specific spatial positions

Continuing theme: Cells turn on particular genes in response to extrinsic cues

Two major decisions: anterior-posterior (A-P) axis and dorsal-ventral (D-V) axis



At the end of the induction process, all neural tissue has an anterior identity

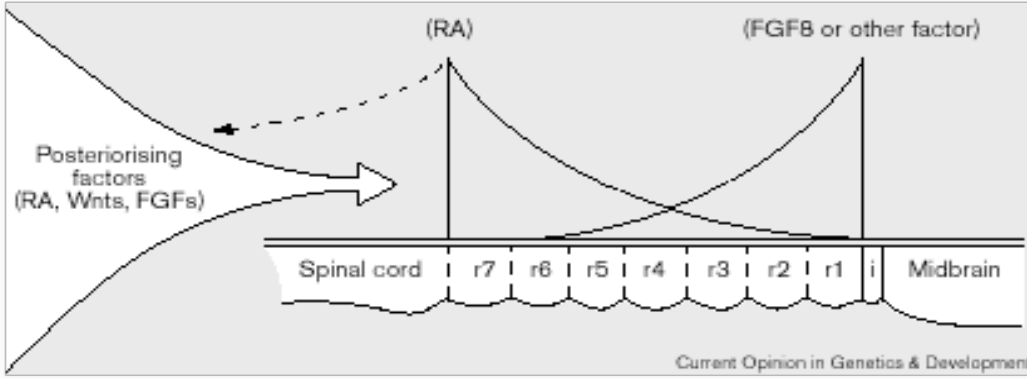


At first, all neural cells have the anterior gene expression pattern … but we will eventually need posterior neural cells, too.

A-P axis determined in two steps: inducer (anterior) and transformer (posterior)

- Step 1. Primary inducers induce anterior neural tissue

- Step 2. Transformer signals act on the anterior neural tissue to specify posterior neural tissue (hindbrain, spinal cord)



Transformer Signals:

Fibroblast Growth Factor (FGF)

Retinoic Acid (RA)

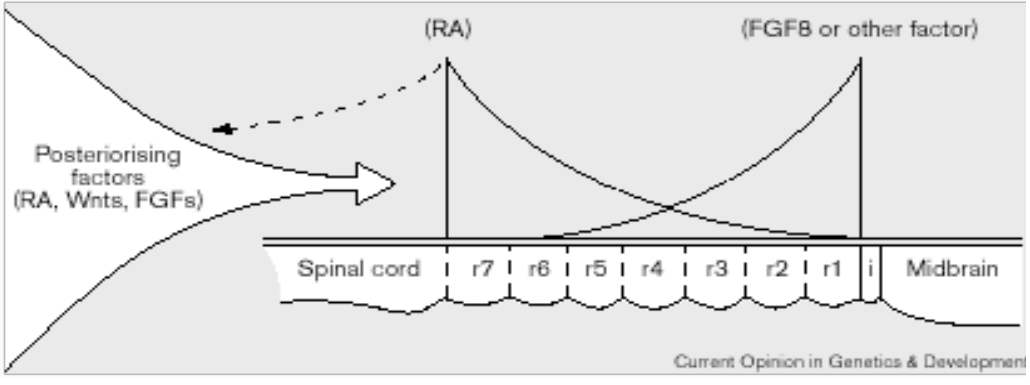
Wnts

} Drive gene expression

*Continuing theme: a **gradient** of chemical signals tells cells where they are along an axis*

Learning outcome 3

Clicker question

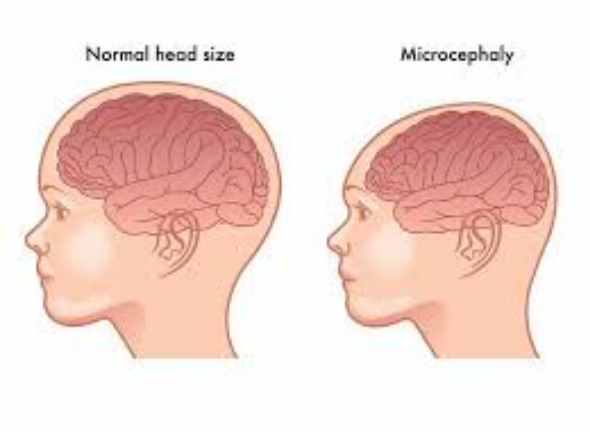


What would be the effect of exposing a developing embryo to drug that mimicked RA?

A. Too little spinal cord tissue

B. Too little frontal cortex tissue

C. Too little total neural tissue



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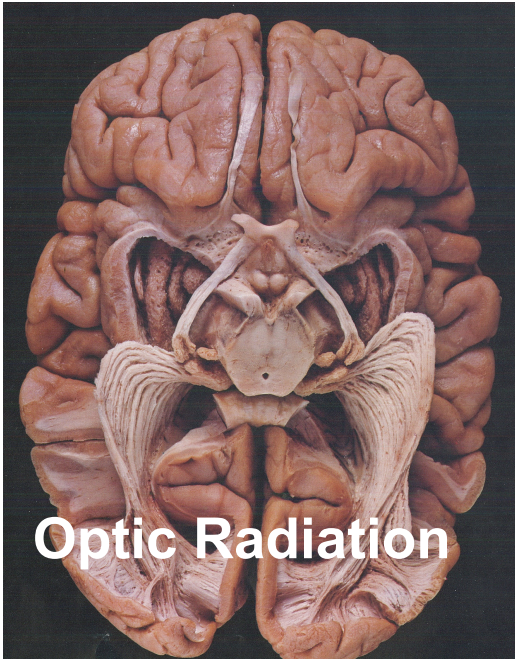
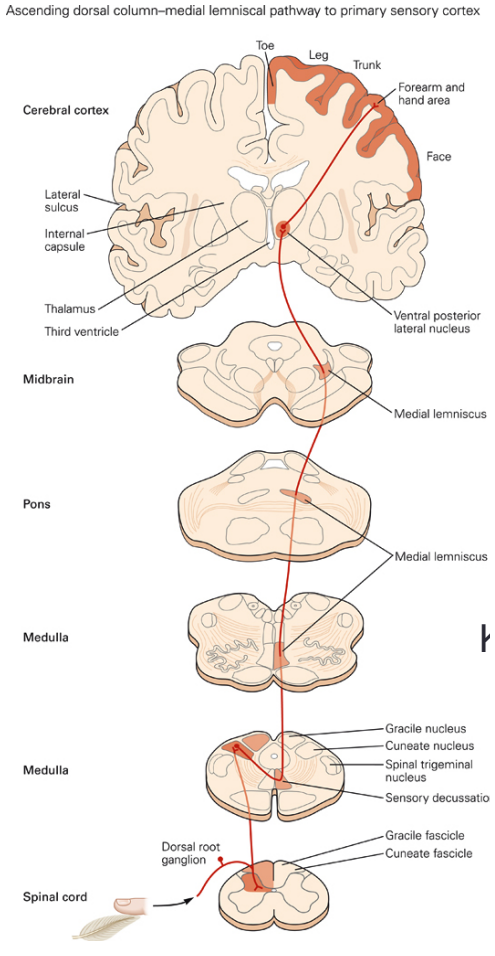
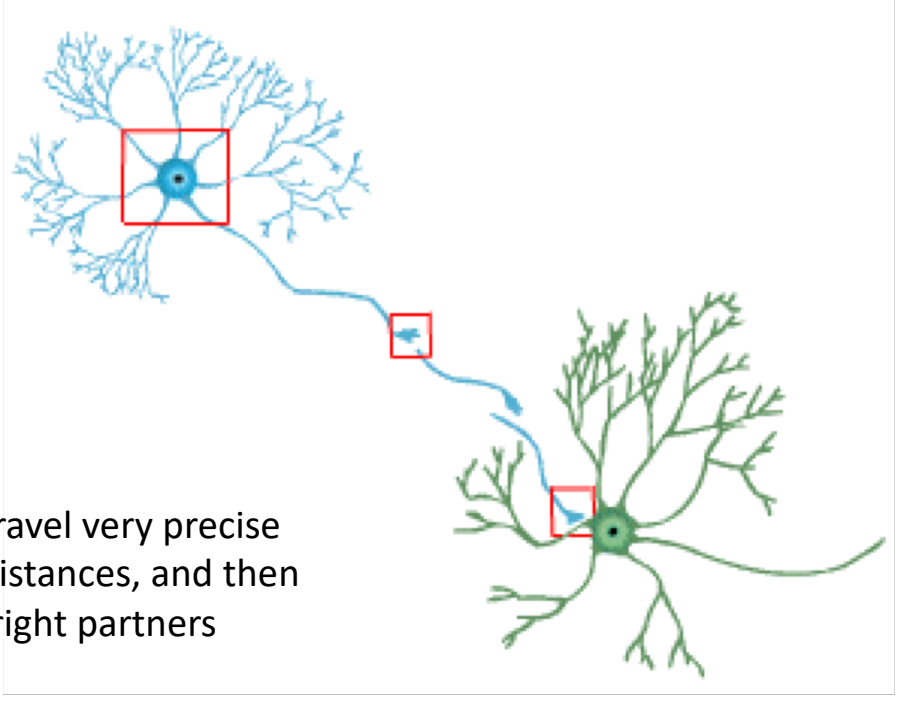
Cell fate is only the beginning of the development challenge …

Information highways need to traverse long distances perfectly





Correct axon guidance is critical for development

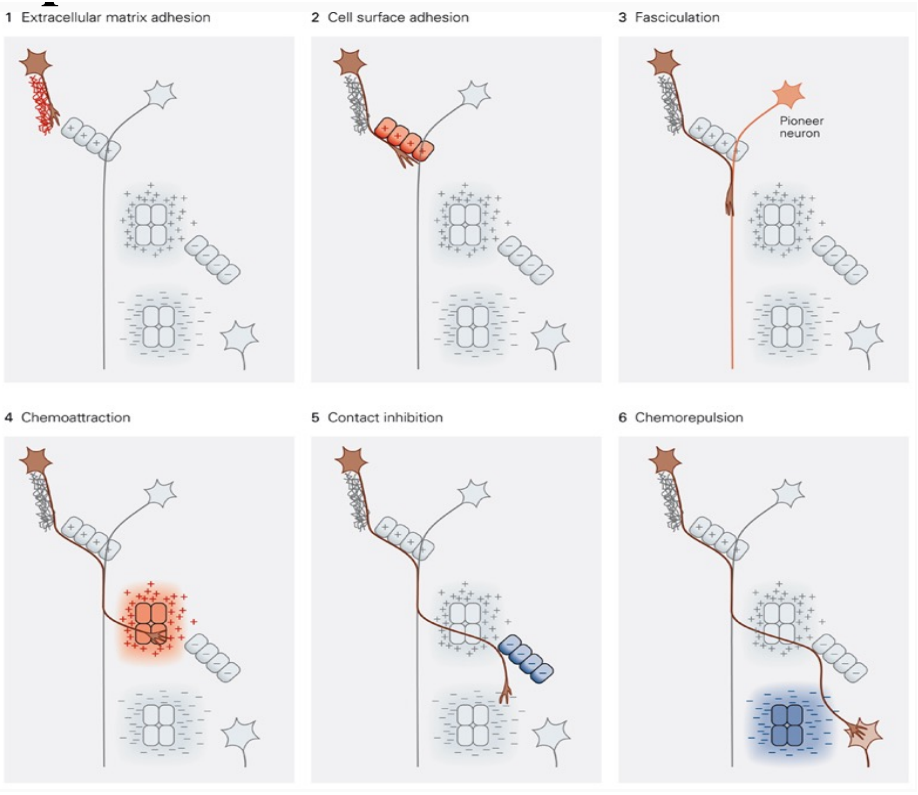


Axons have to travel very precise paths for long distances, and then connect to the right partners

How do axons find their way?

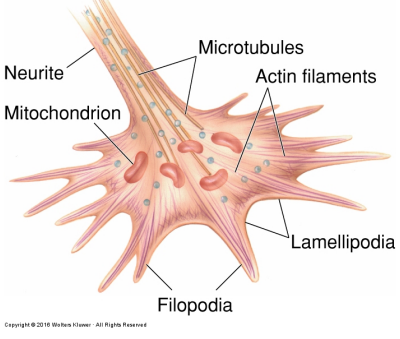
Continuing theme: oriented growth in response to chemical signals.

Migrating neurons and outgrowing axons use both chemical and contact cues to navigate



– Chemical cues are ligands for receptors

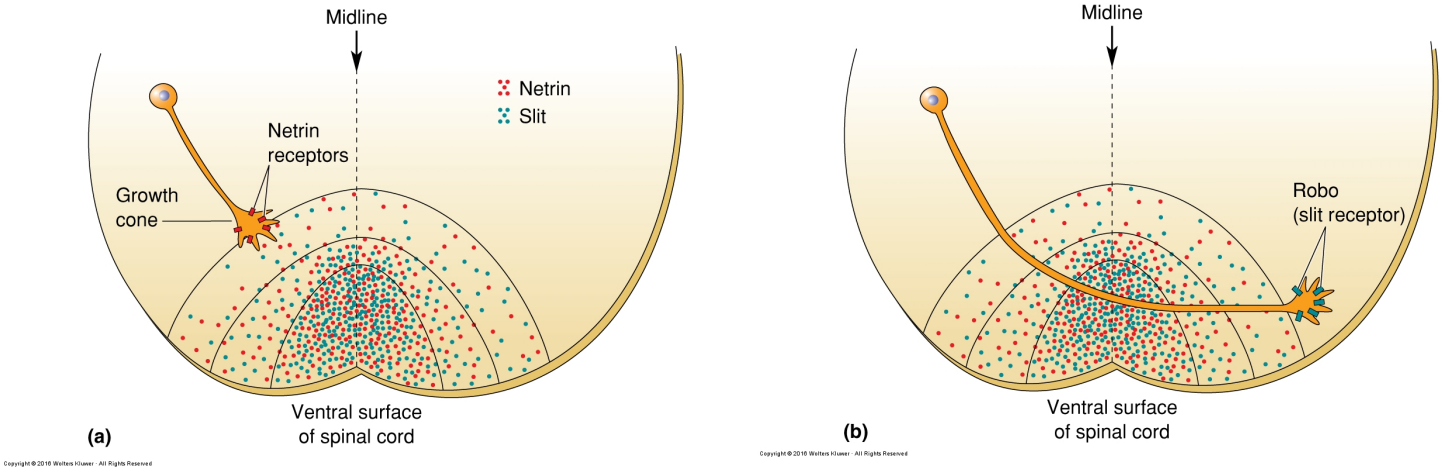
– Receptors mediate attraction or repulsion



Growth cones direct outgrowth of axons

Learning outcome 3

Developmental history determines response to new signal



1. Growth cone expresses netrin receptors, attracted by netrin

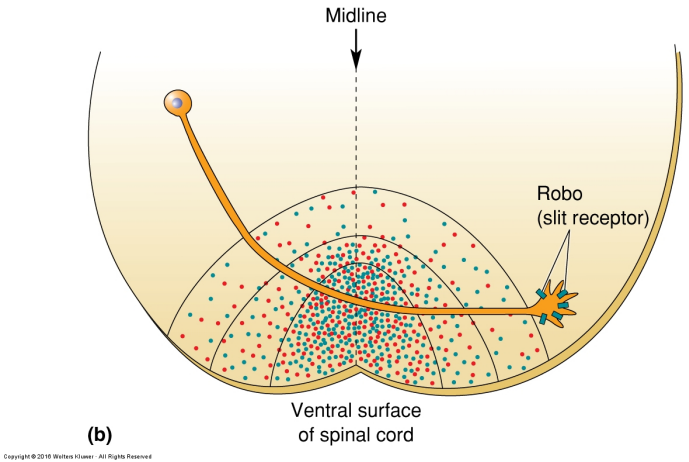
2. Midline crossing *induces* expression of slit receptors

3. Growth cone expresses slit receptors, repelled by slit

Continuing theme: sequential signals build on each other

Clicker question

What would most likely happen to a mutant cell that expressed the slit receptor prematurely?



A. It would stop short of the midline

B. It would continue growing past its usual target on the contralateral side

C. It would reach its target on the contralateral side, but faster than usual

D. There would be no change in its development

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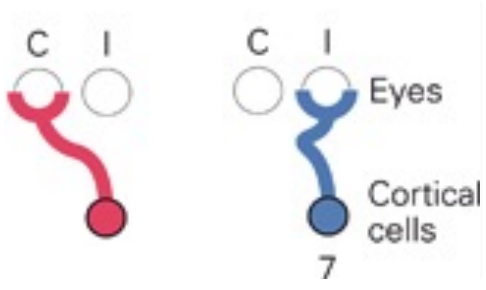
How can specific patterns of neuronal contacts be implemented?

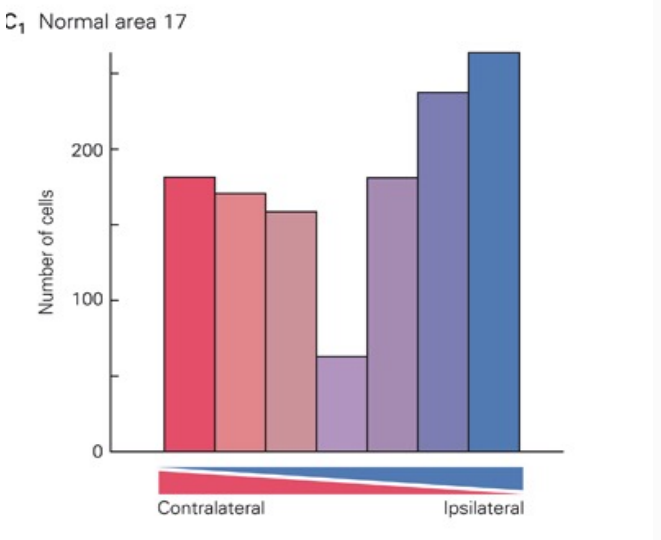
Chemical gradients guide axons to the general location, but ultimately are too coarse …

-- In layer 4 of the visual cortex the inputs are segregated by eye

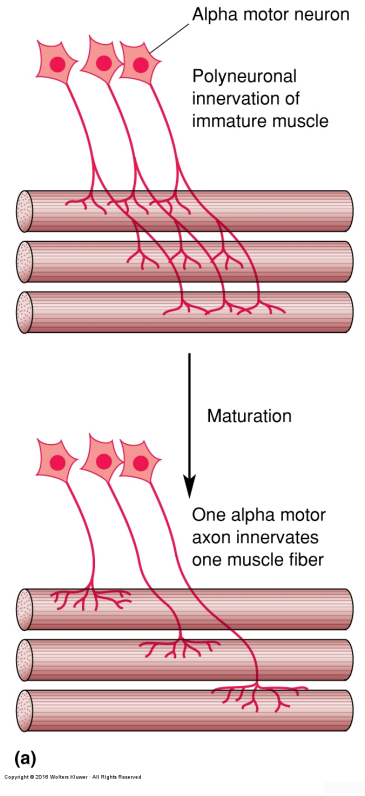
-- The response of most cells in the visual cortex is dominated by inputs from the contralateral or ipsilateral eye

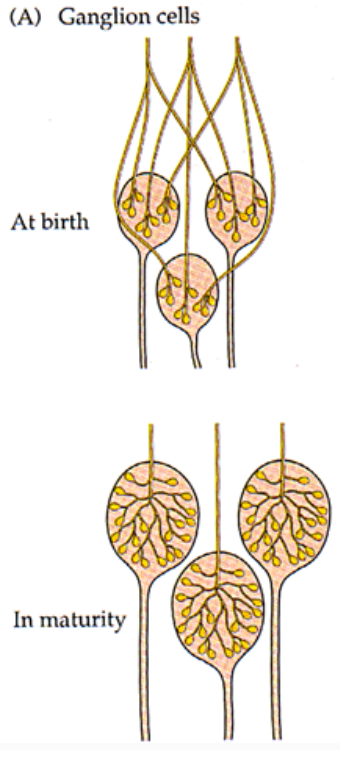
-- Few cortical neurons respond equally to visual stimuli presented in in both eyes





In many systems, axons first make broad connections, then prune them back

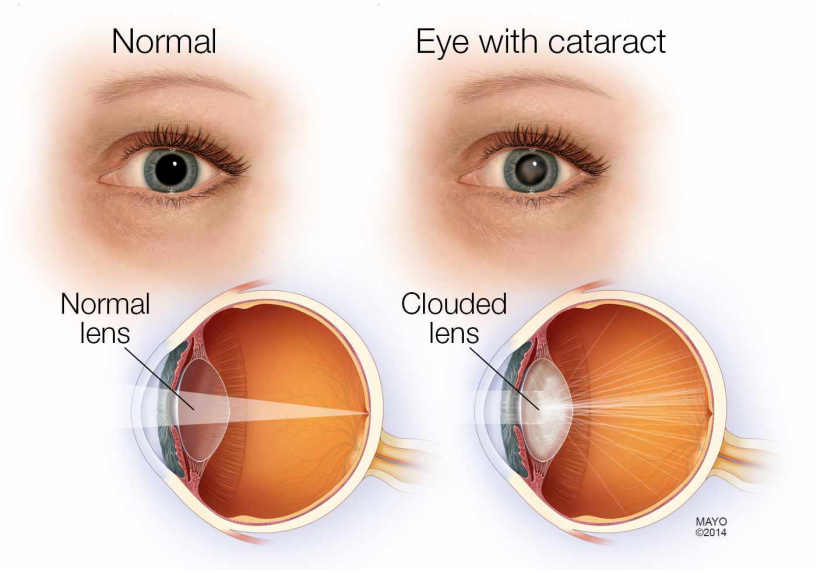




The broad connections come from the genetically directed chemical signals … but where does the pruning come from? ACTIVITY.

The nervous system of a newborn is a rough draft that is modified and refined by experience

There are critical periods for activity-dependent refinement



Develop cataract as adult

Children who develop cataract before age 10

Surgery

Normal vision immediately restored

Permanent vision deficit

Repair after critical period, too late to form correct cortical connections

Hebbian rule: synapses that fire together, wire together

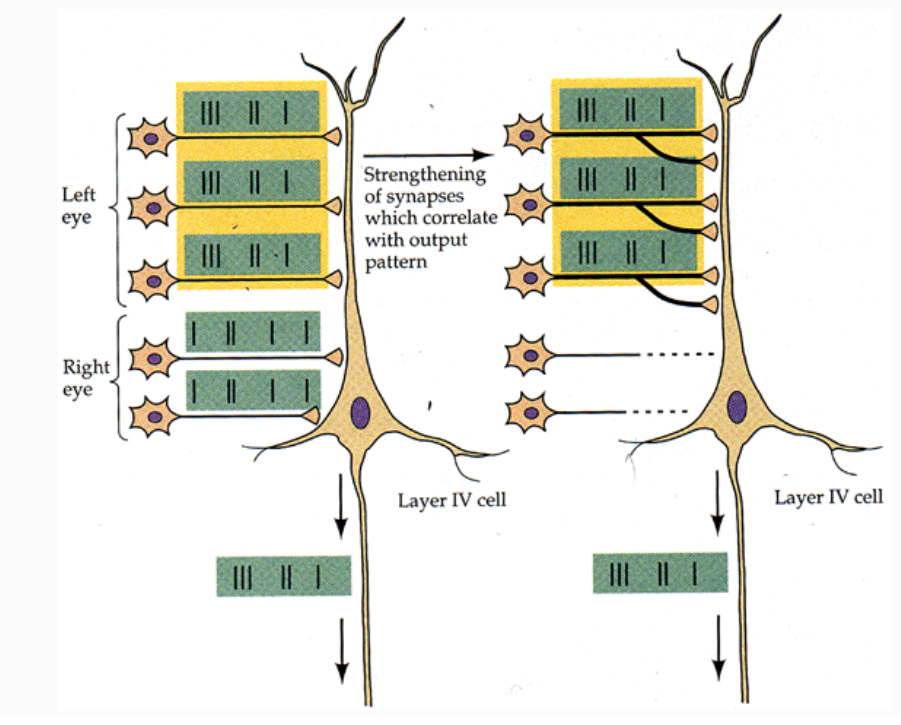
- A combination of **competition** and **cooperation** is involved in the formation of the ODCs

- Synapses from neighboring neurons tend to fire synchronously (cooperate)

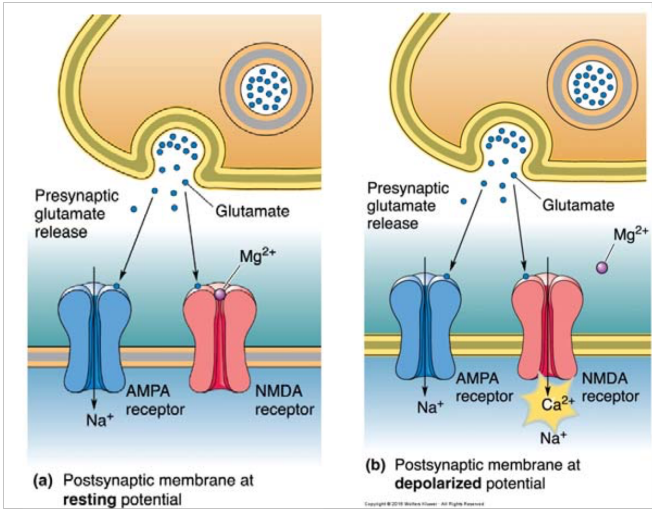
- One cooperating team wins, and the target neuron fires synchronously with the winning team

All synapses that were active synchronously with the target cell firing are strengthened

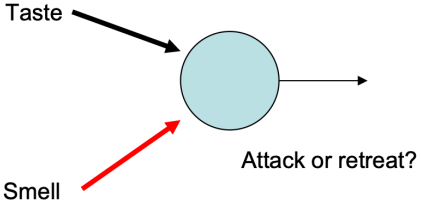
The losing, asynchronous team's synapses are weakened

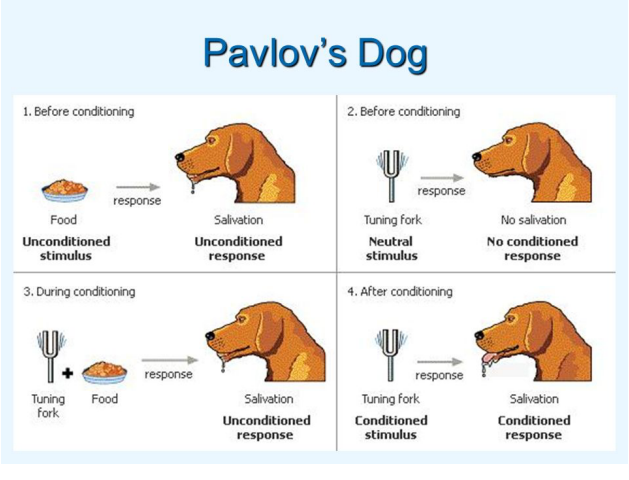


Fire together, wire together mechanism is LTP



Friday: LTP triggered by paired pre- and post-synaptic activity





Hebbian rule is also a cornerstone of the theory of associative memory formation

Learning outcome 4

Why do critical periods end?

Trade flexibility for stability

Multiple physiological changes contribute to reduced capacity to grow and change:

-- very little neurogenesis

-- loss of axonal growth capability

-- change in properties of plasticity

-- glial and extracellular matrix changes