

Specificity of Synaptic Connections II (i.e. Target Selection by Axons)

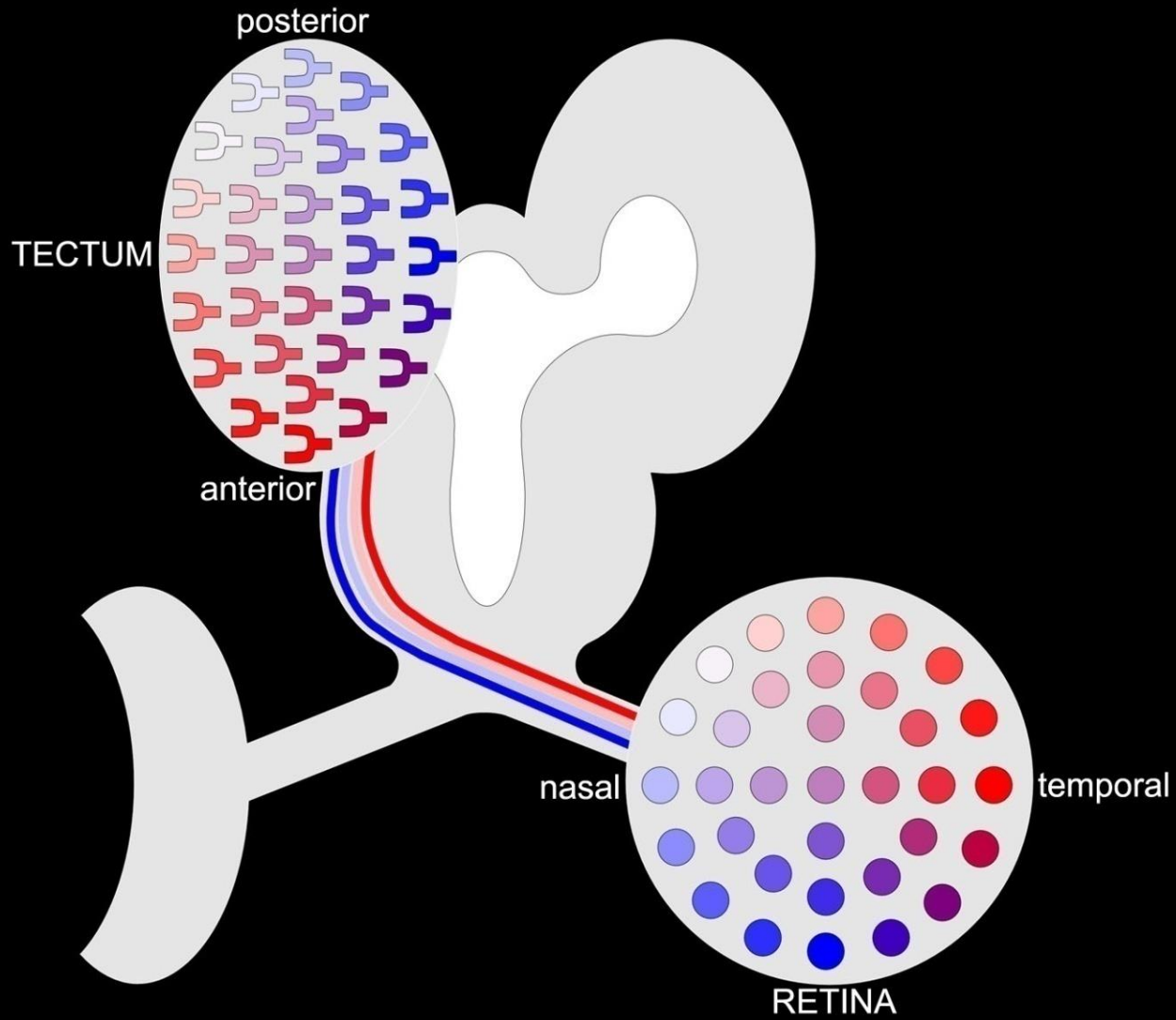
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Specificity of Synaptic Connections

Axons form synaptic connections with ...

- a specific side of the body.
- specific cell populations.
- cells in a specific location within a population.
- specific cell types in a location.
- a specific part or region of a cell.

Topographic Specificity

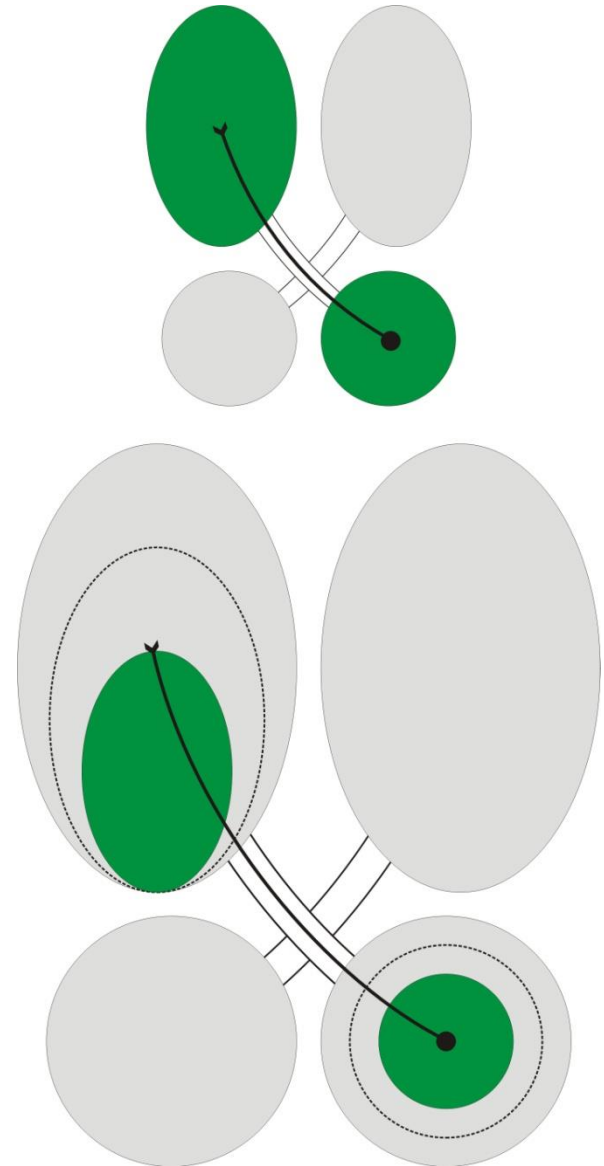


Possible Mechanisms Involved in Topographic Specificity

- Timing of axon growth into the target.
- Organized growth of axons into the target.
- Chemospecificity:
 - Axon-target cell affinity
 - Axon-non target cell aversion
- Selective retention based on functional validation.

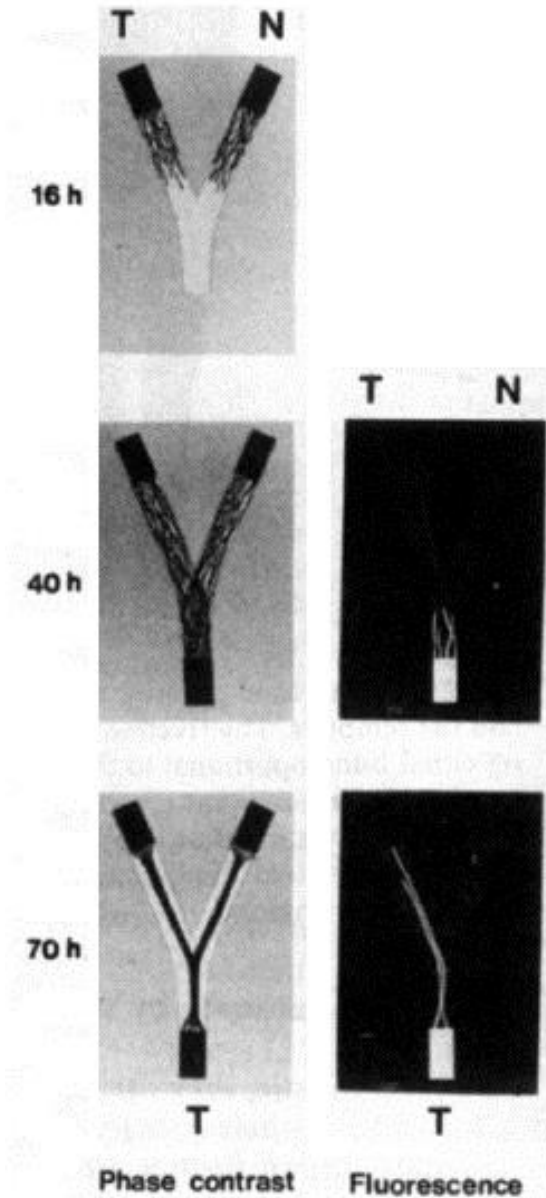
Timing of growth of axons into target could establish topography.

- Axons could grow into a structure just as their appropriate target cells are ready to receive synapses.
- Axons that are experimentally induced to enter their target too early, 'wander aimlessly'.
- However, in the retinotectal system, there is a topographic mismatch in the timing of development of the retina and tectum. (i.e sliding connections)



Orderly growth of axons into the target could establish topography.

- Axons grow into the target in topographic order. (Not known how.)
- Axons from double half eyes grow only in the correct half of the pathway.
- Retinal axons recognize other retinal axons based on position. (Bonhoeffer's Y maze)



Orderly growth of axons into the target could establish topography.

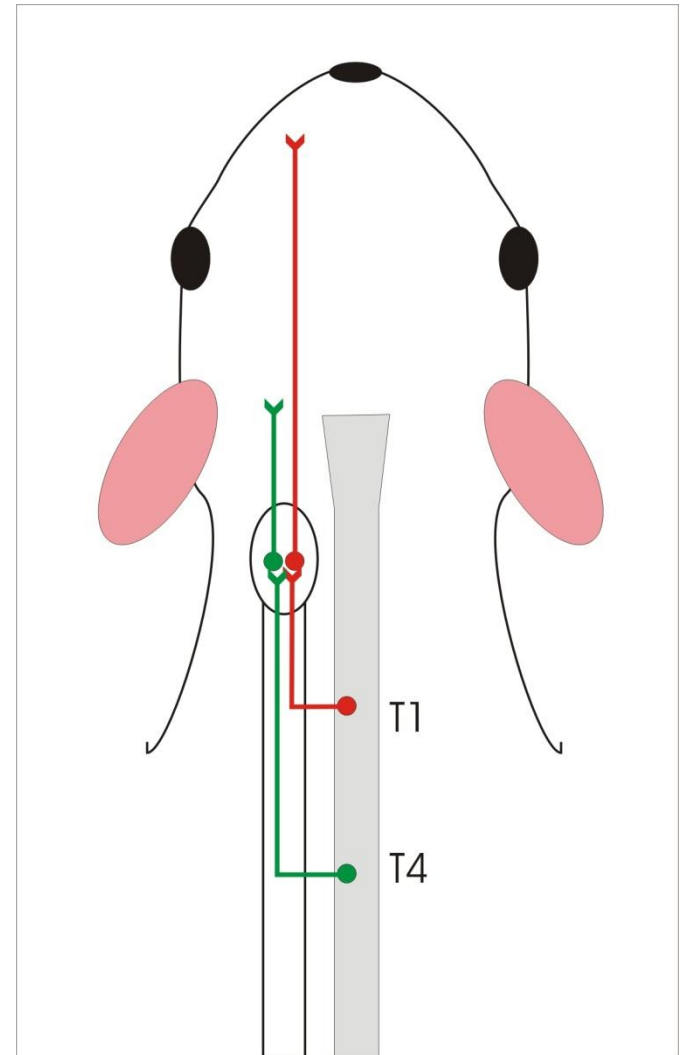
- However, scrambled axons still find their correct target.

Chemospecificity could establish topography .

- Cajal (1892) proposed that orderly neuronal interconnections are the result of chemical recognition between axons and the cells to which they connect.

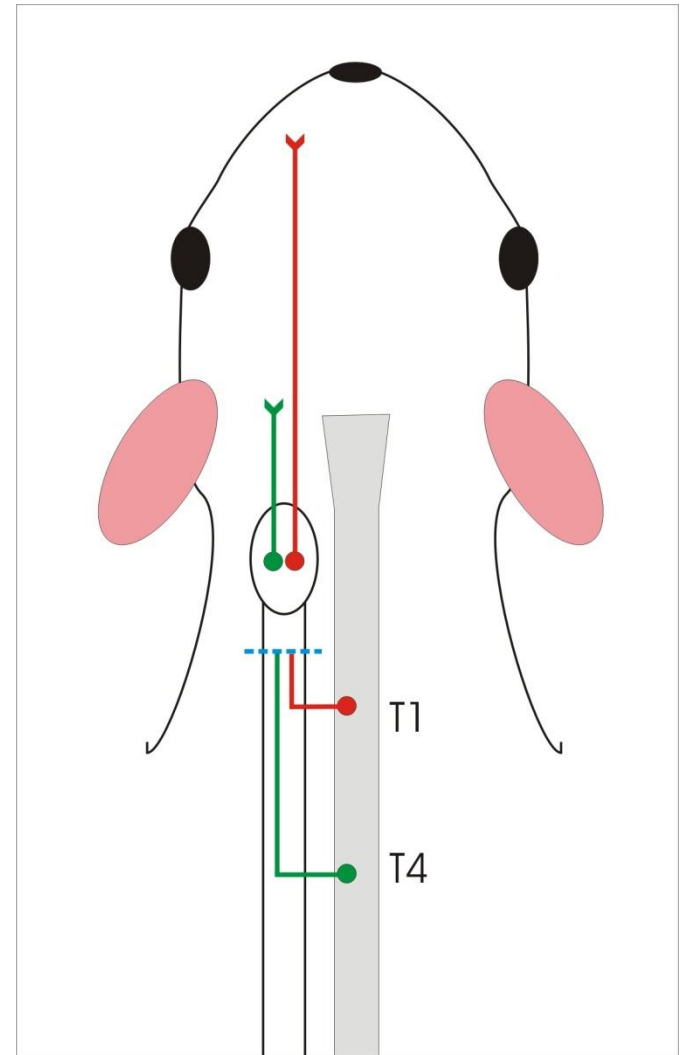
Chemospecificity could establish topography .

- Langley (1895) provided the first experimental evidence for axon-target cell recognition by cutting preganglionic axons to SCSG, allowing axons to regenerate and finding correct topography by electrical stimulation.

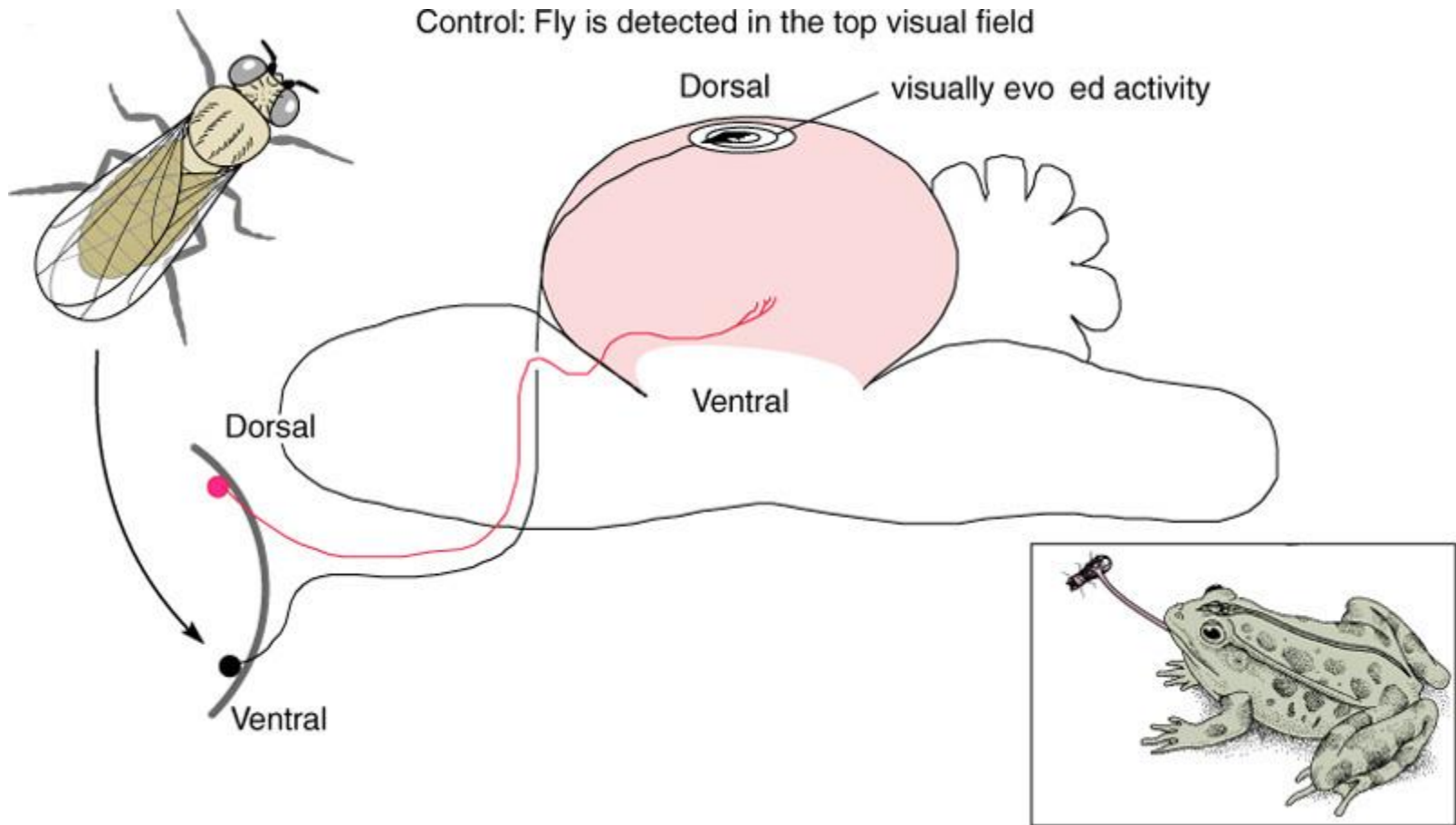


Chemospecificity could establish topography .

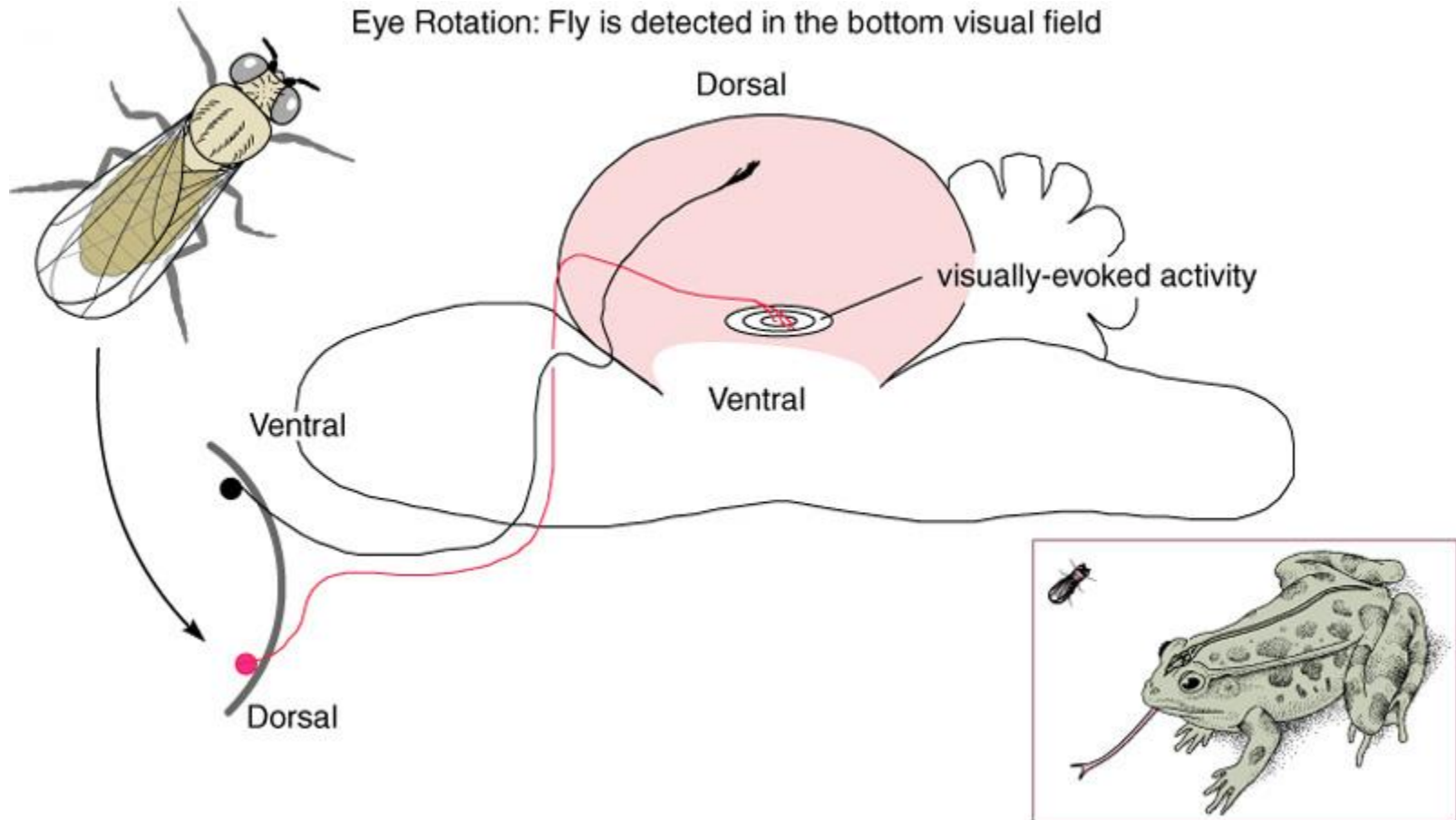
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Sperry (1943)



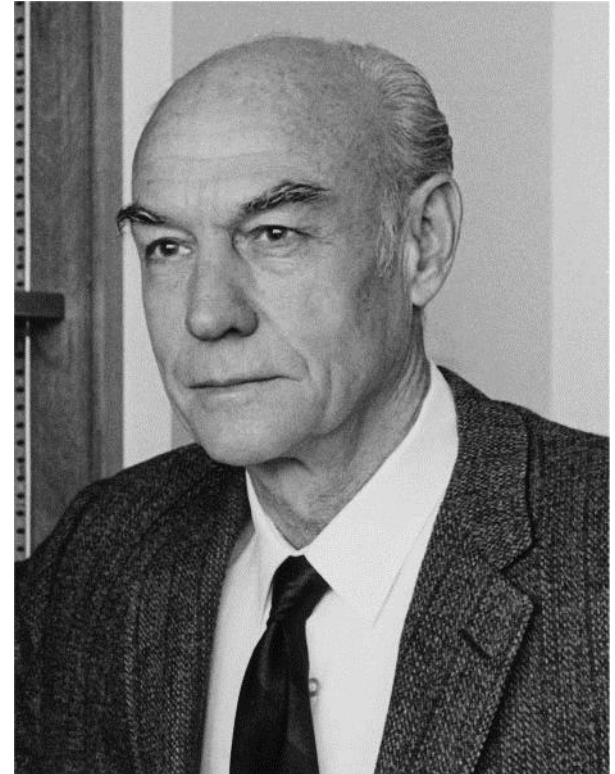
Sperry (1943)



Chemospecificity could establish topography .

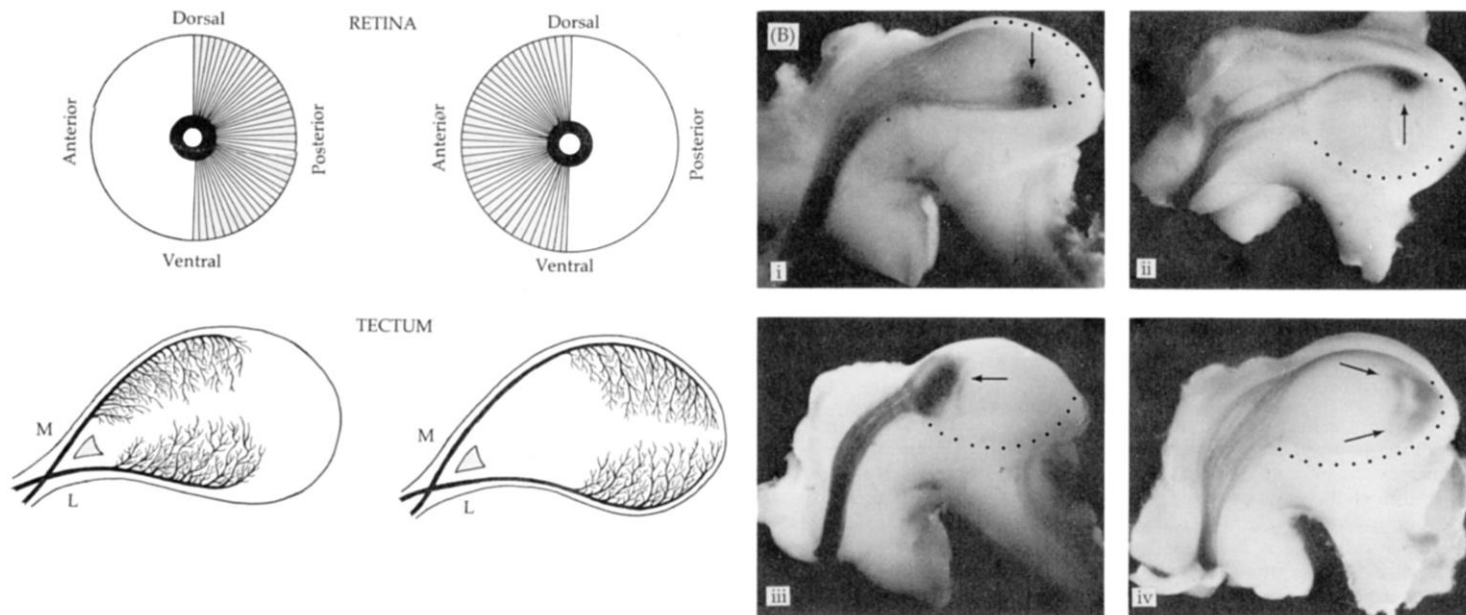
Sperry (1943) showed that regeneration of optic axons after 180° eye rotation in frog resulted in inverted perception of the world based on behavior.

He was awarded a Nobel Prize in 1981 for his work on split brain people.



Chemospecificity could establish topography .

- Sperry (1963) showed regenerating axons from nasal half retina in goldfish grew over empty rostral tectum to reconnect to posterior tectum, central retina reconnected selectively to central tectum and temporal retina reconnected to anterior tectum.

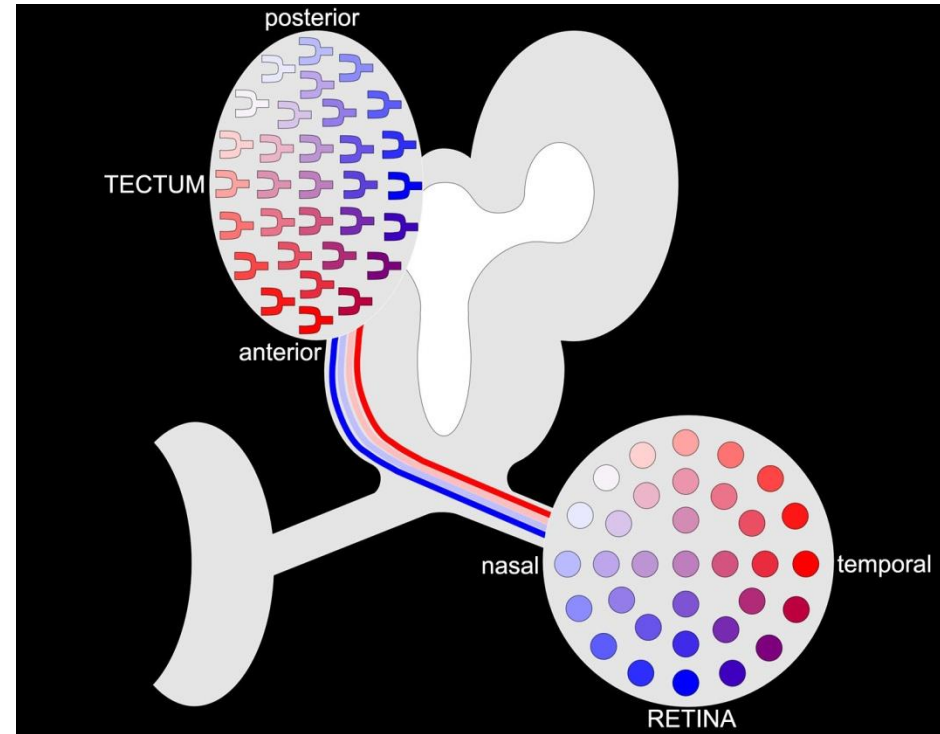


Chemospecificity Hypothesis (Sperry)

- Neurons within a population are intrinsically different from one another.
- Differences are position dependent.
- Differences are acquired early in development.
- Differences are biochemical in nature.
- Presynaptic and postsynaptic cells with complimentary biochemical labels connect with one another selectively.

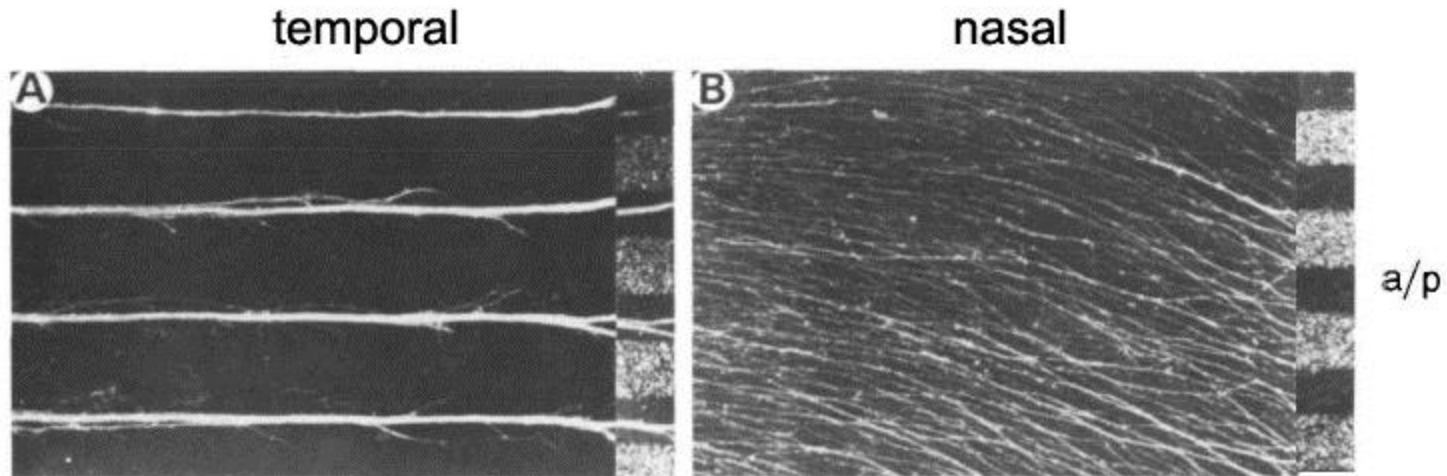
Molecular Basis for Chemospecificity

- Axons from the temporal side of the retina normally synapse on cells in anterior tectum. Axons from the nasal side of the retina normally grow through anterior tectum and synapse on cells in posterior tectum.



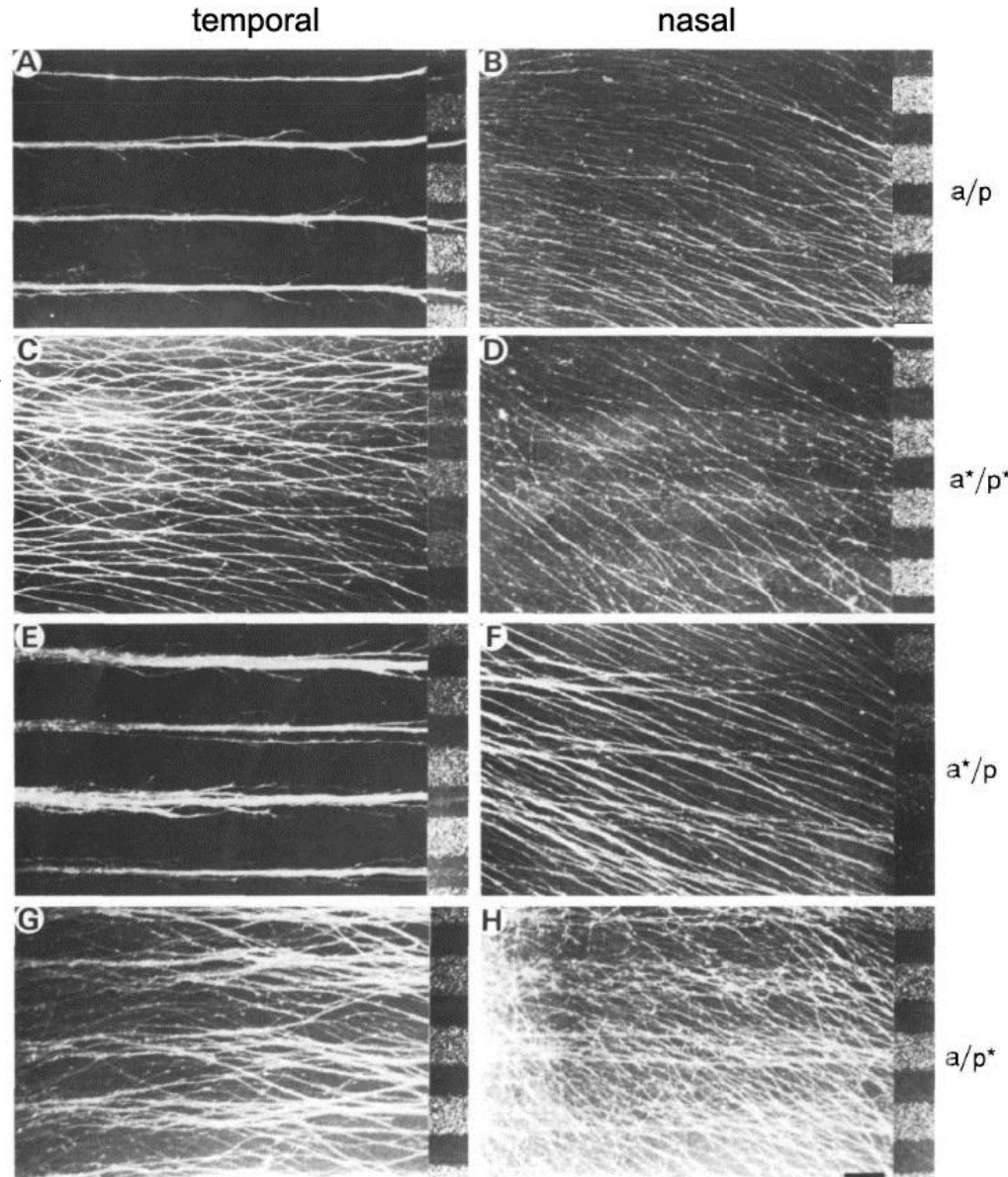
Molecular Basis for Chemospecificity

- Axons from the temporal side of the retina grew preferentially on stripes of cell membranes prepared from the anterior third of the tectum while avoiding the alternating stripes of membranes prepared from the posterior third of the tectum. Axons from the nasal side showed no preference.



Molecular Basis for Chemospecificity

- Heat treating the cell membranes from posterior tectum resulted in axons from the temporal and nasal sides of the retina preferring heat treated posterior tectal cell membranes over untreated anterior tectal membranes.

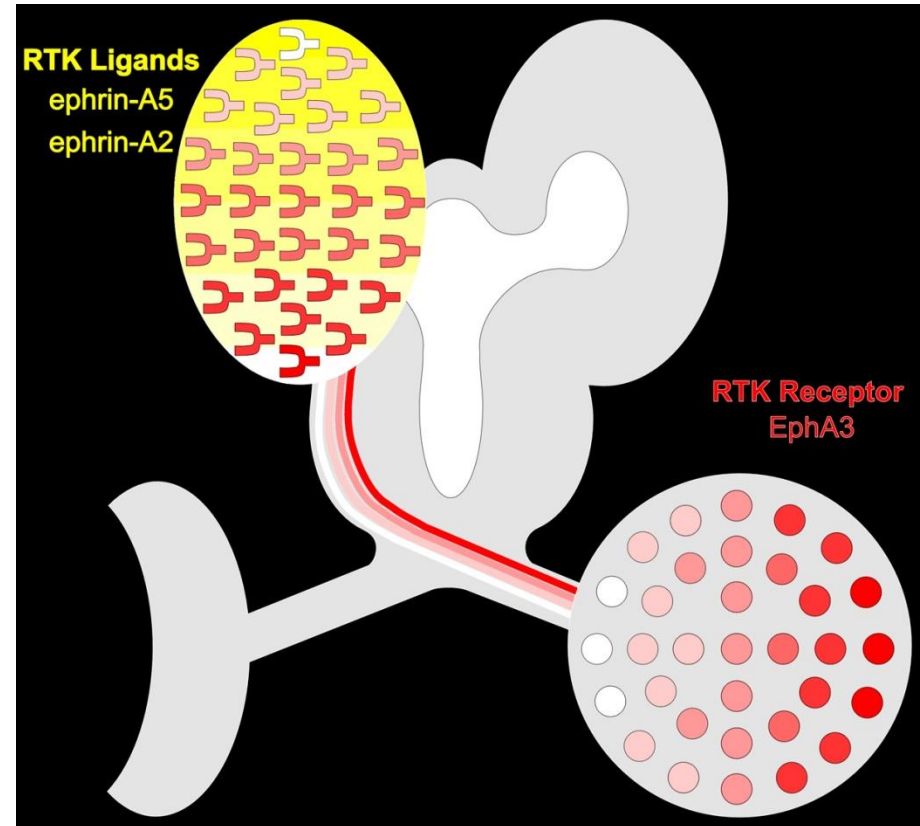


Molecular Basis for Chemospecificity

- The aversive activity in the tectum is in an anterior-posterior gradient.
- The response of retinal axons to the aversive factor is graded in the nasal-temporal axis.

Molecular Basis for Chemospecificity

- Eph/ephrin signaling establishes topography of the nasal-temporal axis of the retinotectal projection:
 - Ephrin-A2, ephrin-A3 and ephrin-A5 were identified as repulsive factors for growing retinal axons expressed in anterior-posterior, low-to-high gradients in the tectum.
 - The ephrin receptor, EphA3 (chick) or EphA5 (mouse), is expressed by retinal ganglion cells in a nasal-temporal, low-high gradient.

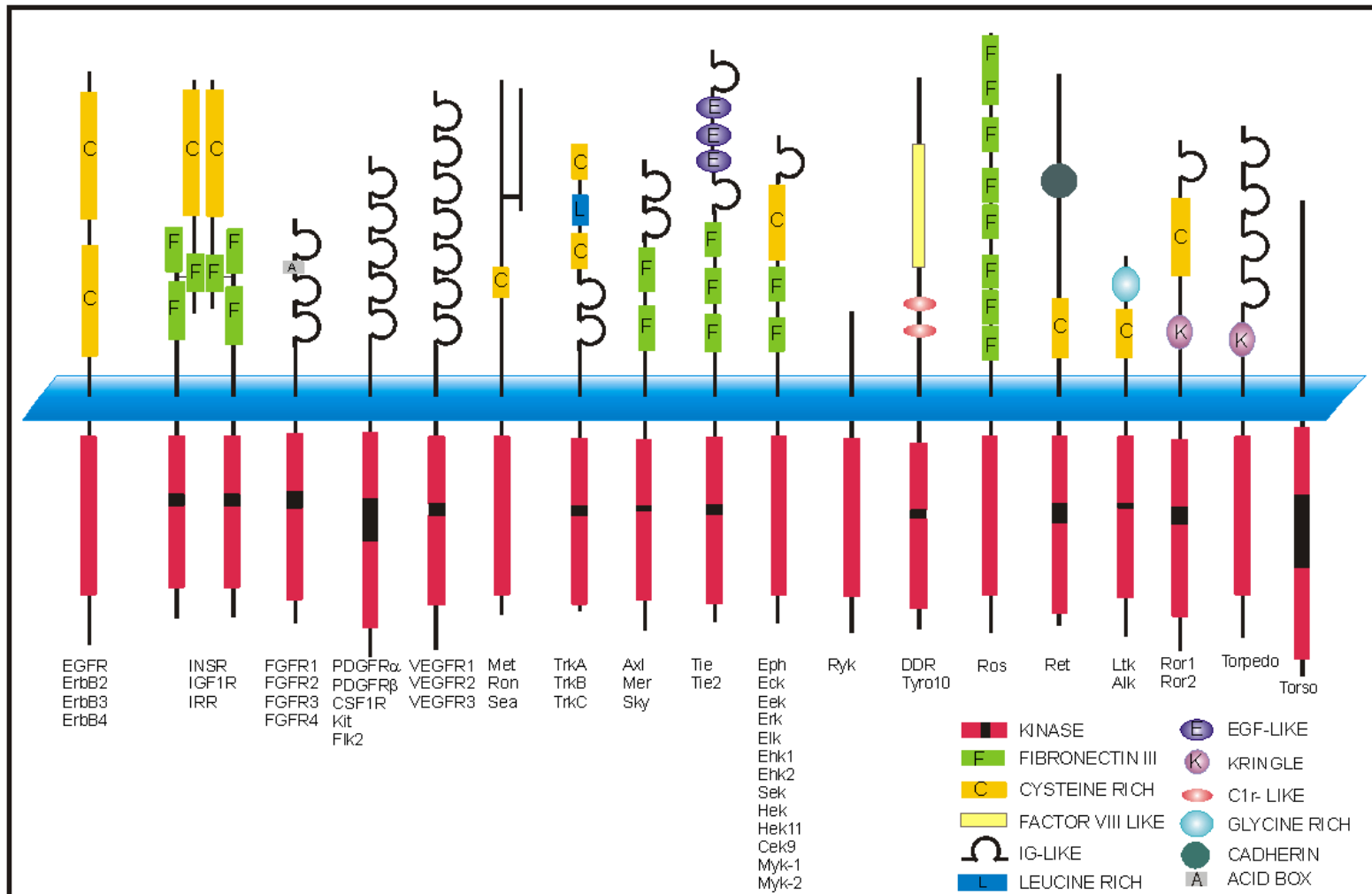


Molecular Basis for Chemospecificity

- Eph/ephrin signaling establishes topography of the nasal-temporal axis of the retinotectal projection:
 - Knockout of the genes for the ephrins or Eph resulted in loss of normal topography in the retinal projection.
 - Misexpression of ephrin-A2 in high concentration across the entire tectum prevented retinal axons from invading the tectum.

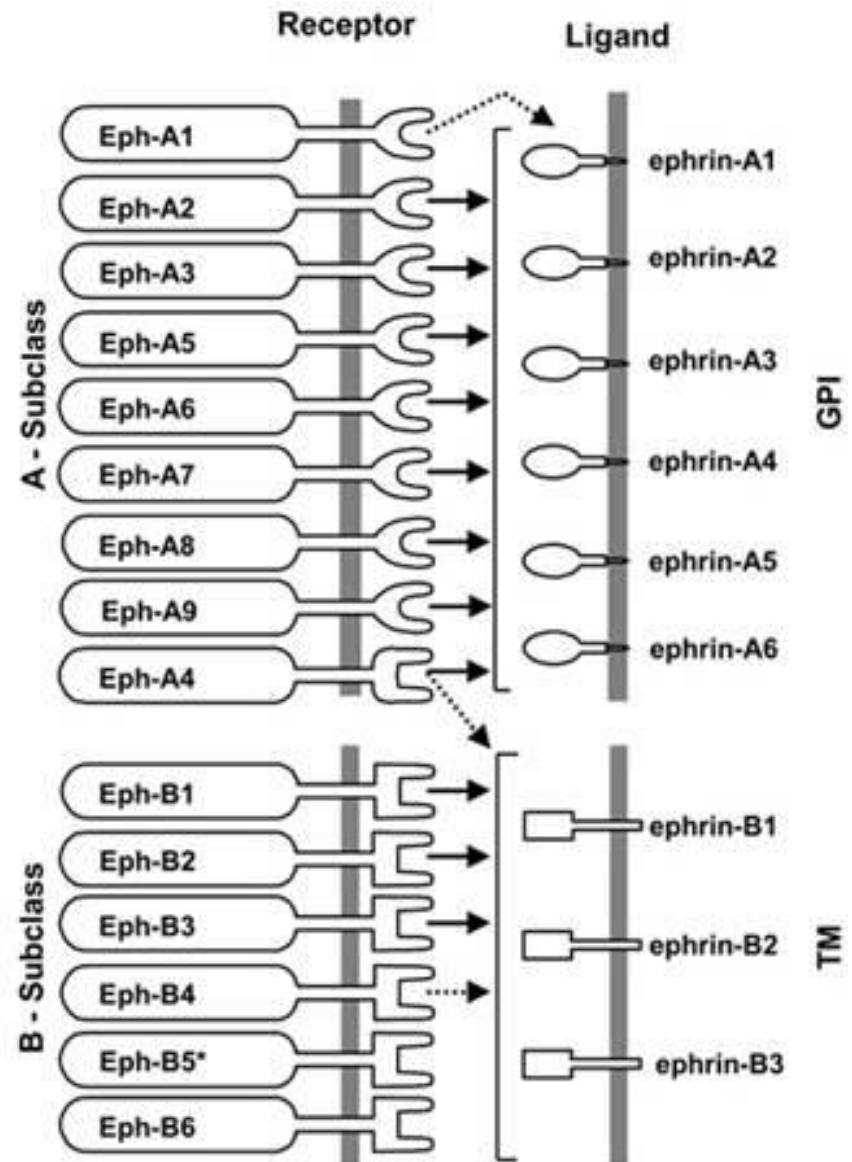
Eph / Ephrin Signaling

- Eph's are receptor tyrosine kinases.



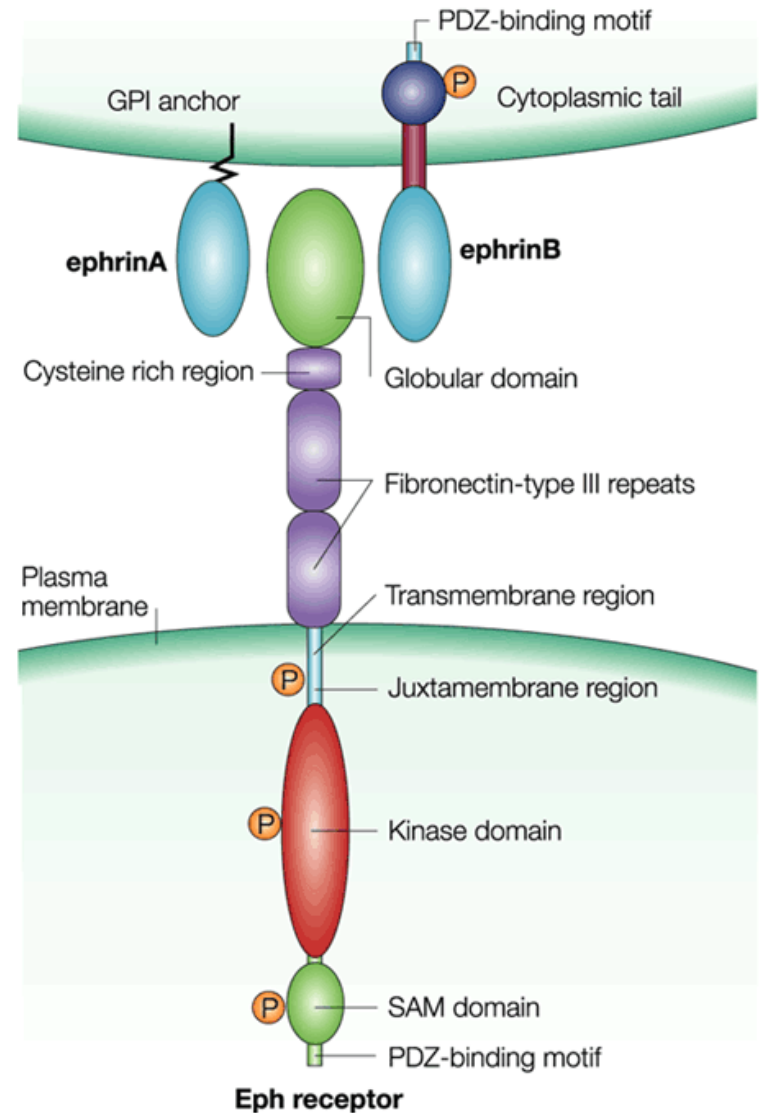
Eph / Ephrin Signaling

- Eph's and Ephrins are in two subfamilies, A and B. Receptor-ligand recognition within a subfamily is promiscuous.
- Eph's and ephrins are diverse families, expressed most abundantly in nervous system.



Eph / Ephrin Signaling

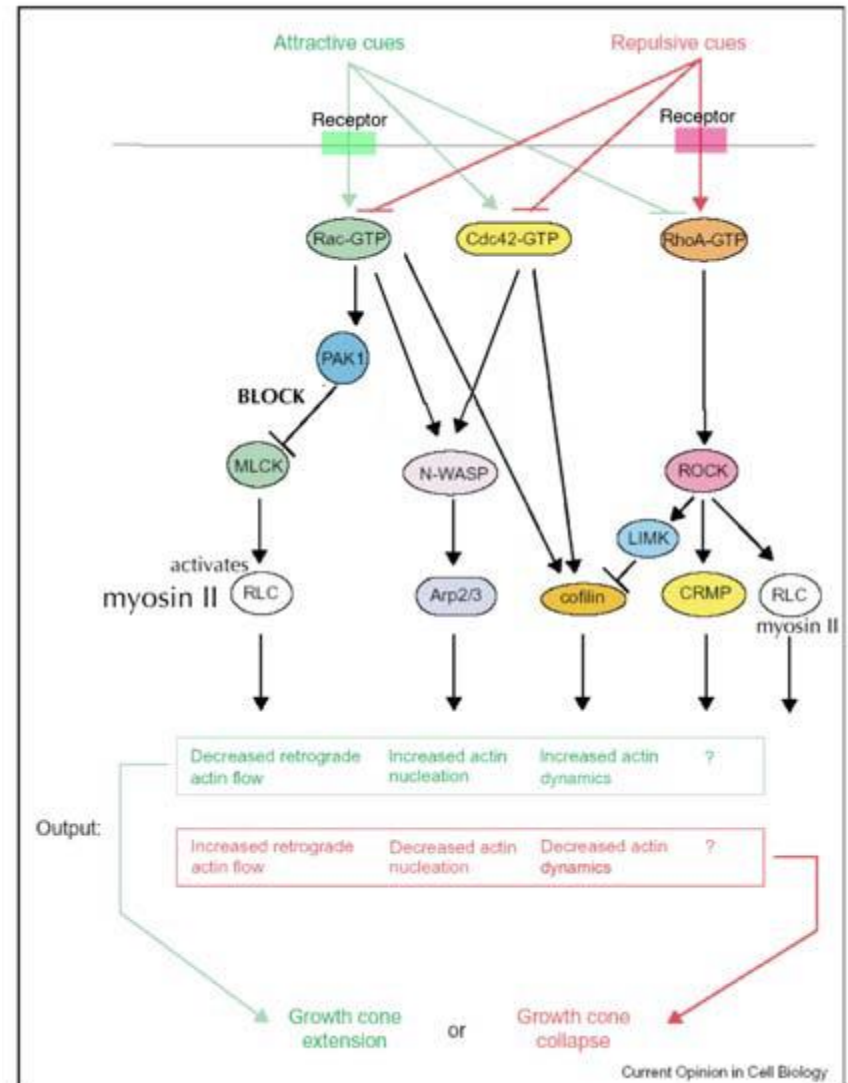
- EphrinA's are GPI-linked to the cell surface. EphrinB's are transmembrane.
- EphB/EphrinB signaling can be bidirectional.
- EphA/EphrinA signaling can activate Rho-GTPases.



Eph / Ephrin Signaling

Activation of RhoA in growth cones induces growth cone collapse and axon retraction.

-Paul Letourneau

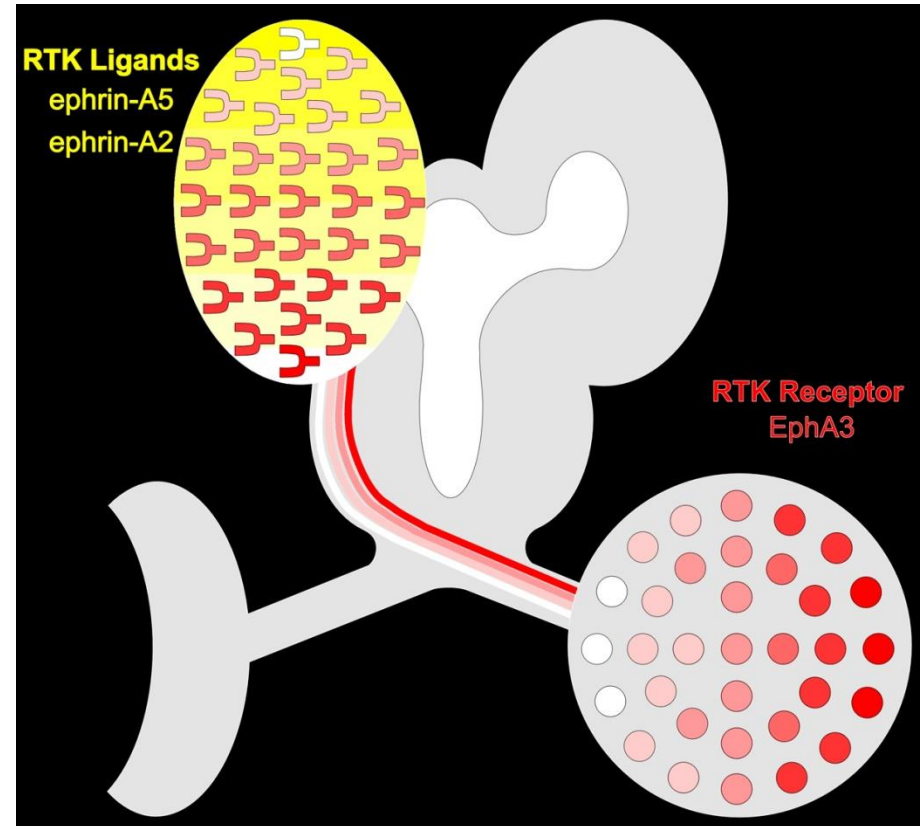


Molecular Basis for Chemospecificity

- Eph / Ephrin signaling has been implicated in patterning many topographic projections including:
 - Auditory: spiral ganglion > cochlear nucleus
 - Somatosensory: ventral posterior thalamus > S1 cortex
 - Motor: spinal motor neurons > limb muscles

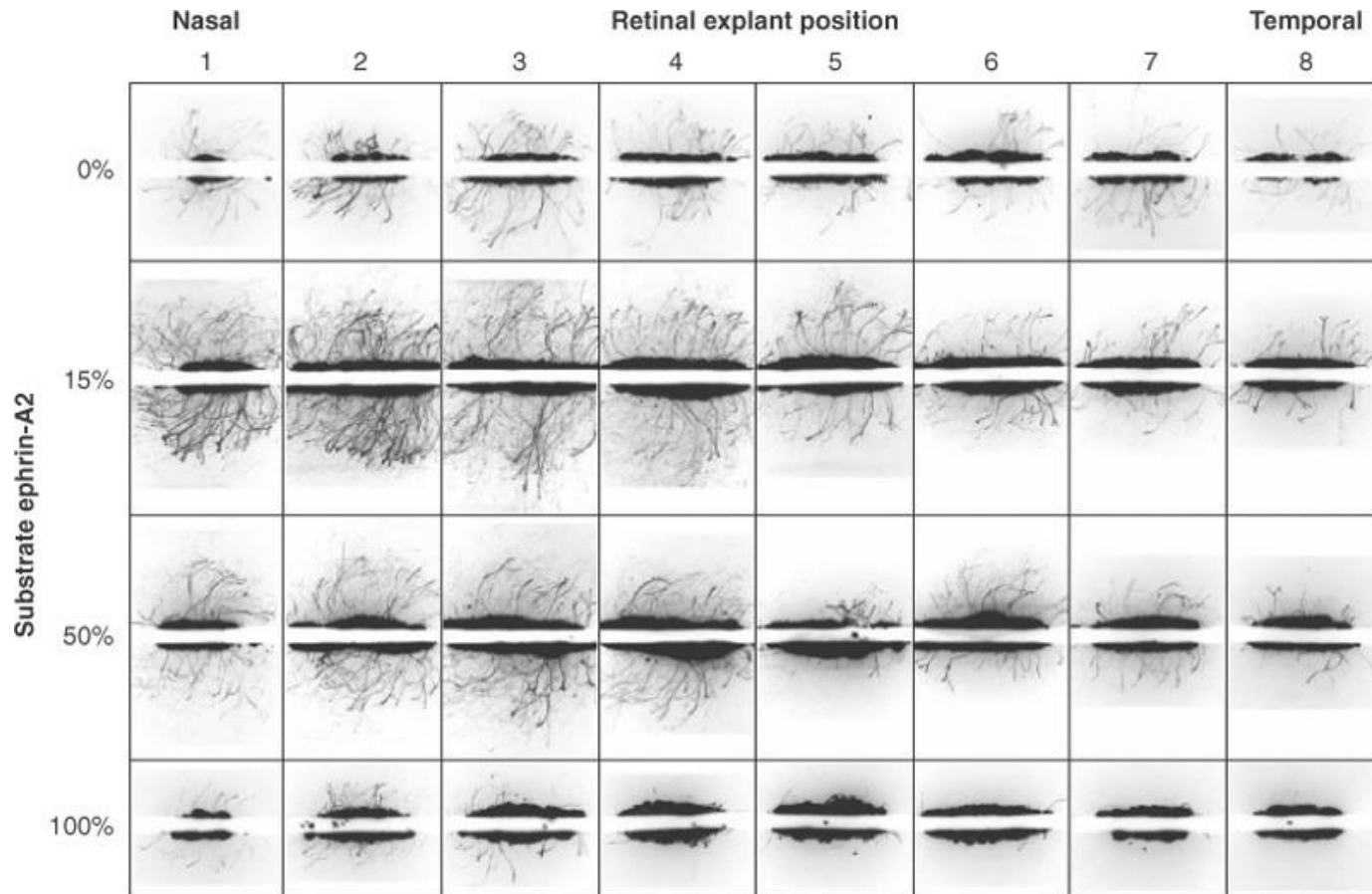
Molecular Basis for Chemospecificity

- EphA / EphrinA signaling patterns the nasal-temporal pattern of retinotectal connections by axon repulsion.
- Two big questions remain to address in development of retinotectal topography:
 - Why do retinal axons invade the tectum given the presence of a repulsive signal?
 - What accounts for the other two dimensions of the three dimensional retinotectal projection?



Molecular Basis for Chemospecificity

- Why do retinal axons invade the tectum given the presence of a repulsive signal?
 - At low concentrations, ephrin-A can promote retinal axon growth.
 - This effect is concentration / position dependent.



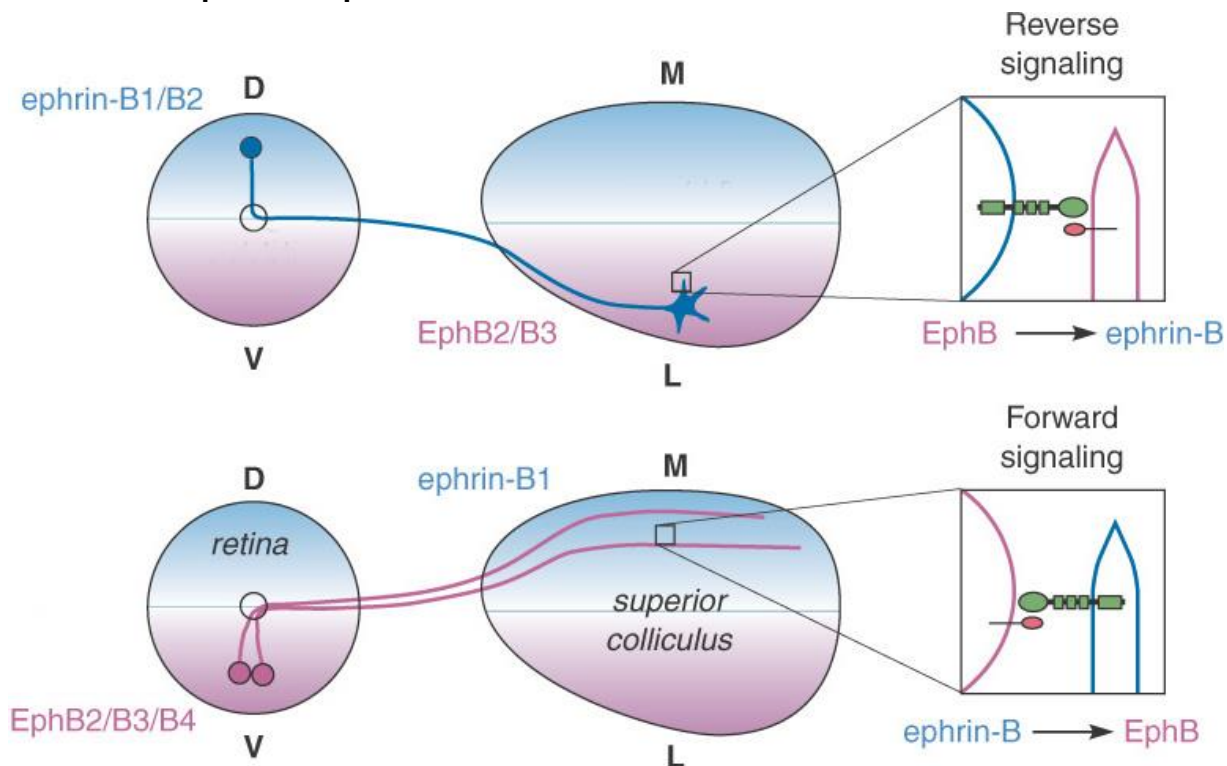
(After Hansen et al., 2004)

Molecular Basis for Chemospecificity

- At least three signaling systems have been implicated in development of the dorsal-ventral axis of the retinotopic map.
 - EphrinB / EphB
 - Wnt3 / Ryk and Frizzled
 - Slit1 and Slit2 / Robo

Molecular Basis for Chemospecificity

- EphB's and EphrinB's are expressed in reverse gradients in both the retina and tectum.
- Forward and reverse EphB/EphrinB affinity as been suggested to establish the dorsal-ventral axis of the retinotopic map.

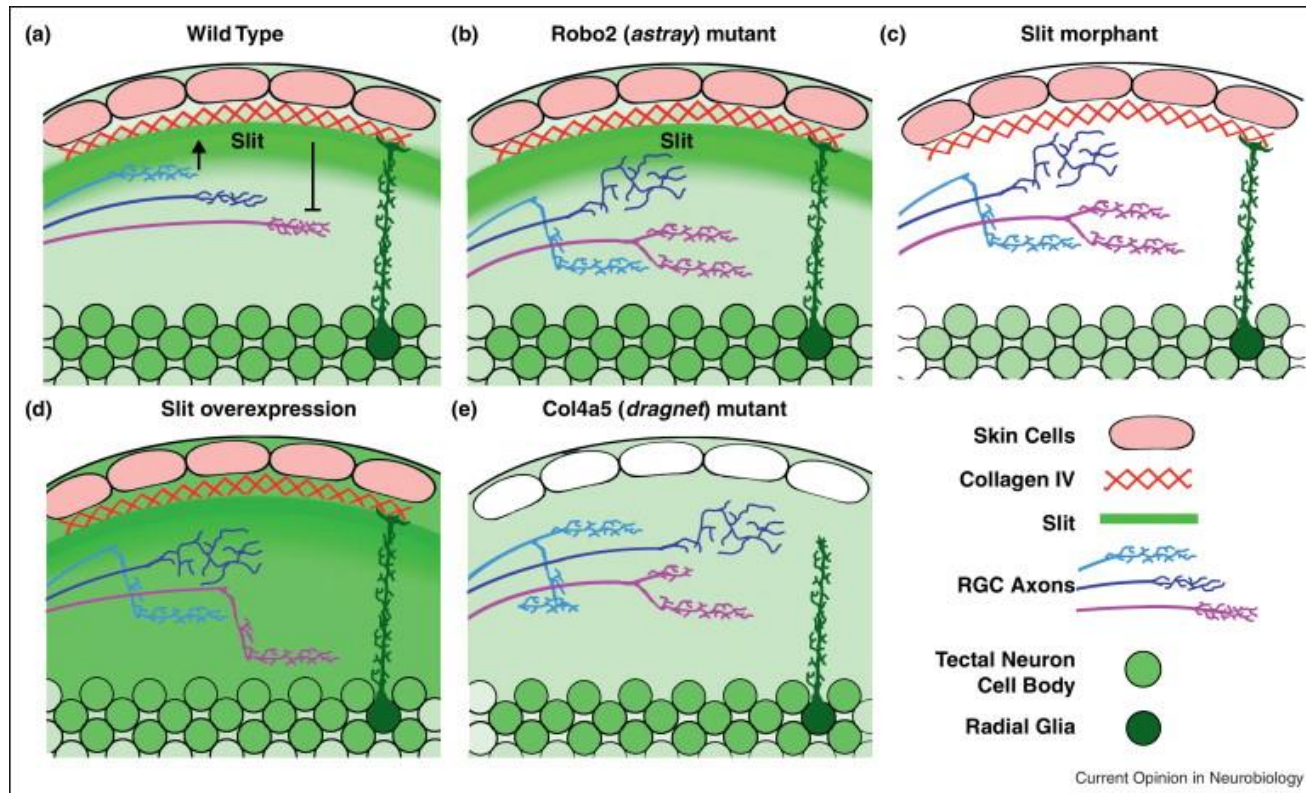


Molecular Basis for Chemospecificity

- Laminar specificity in the retinotectal projection:
 - Homophilic interactions involving several classes of cell adhesion molecules (Cadherins, Sidekicks and Dscams) determine the particular tectal layer in which retinal axons synapse. [multiple papers from Sanes and others]

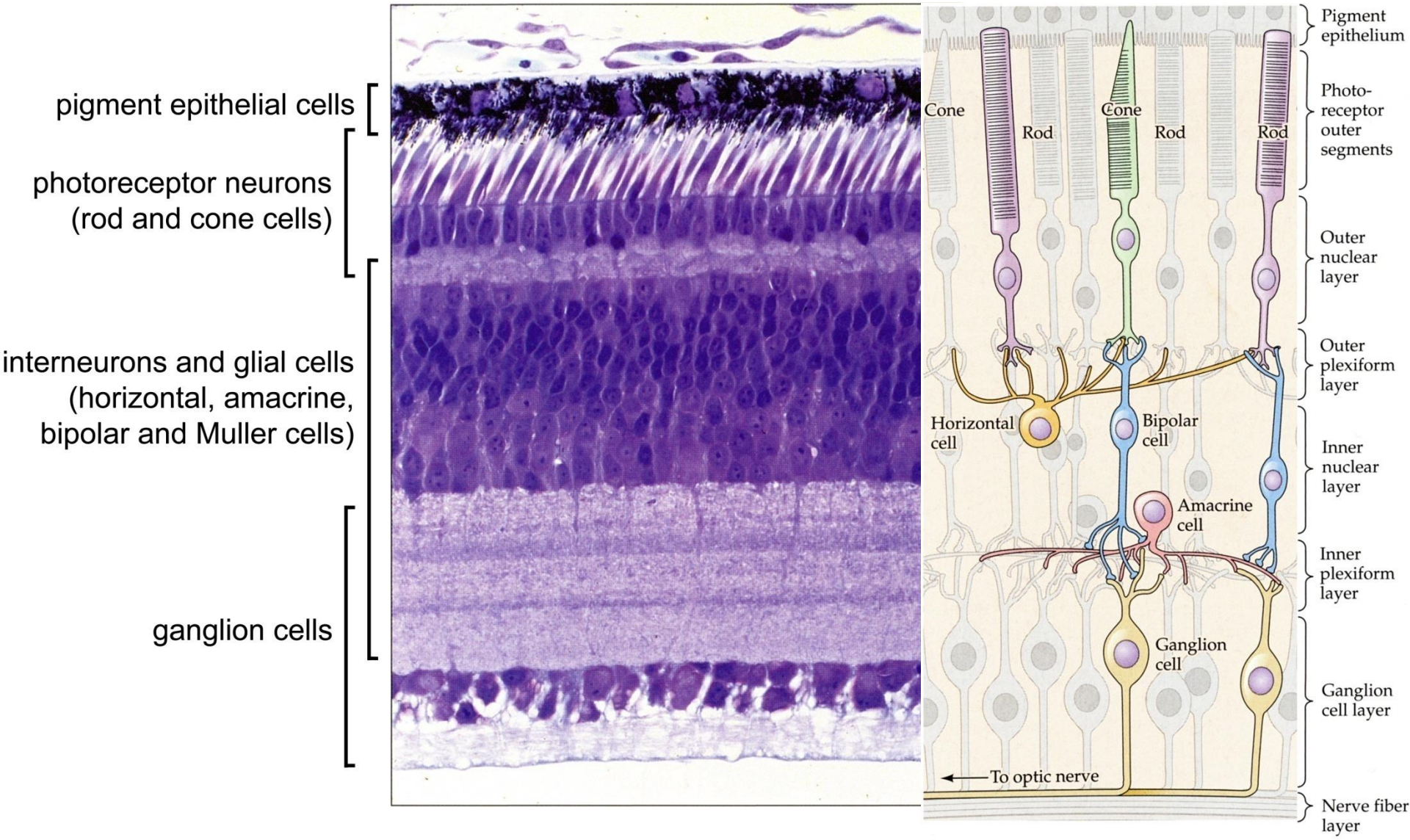
Molecular Basis for Chemospecificity

- Laminar specificity in the retinotectal projection also is mediated by Slit-Robo signaling:



(Robles & Baier, 2012)

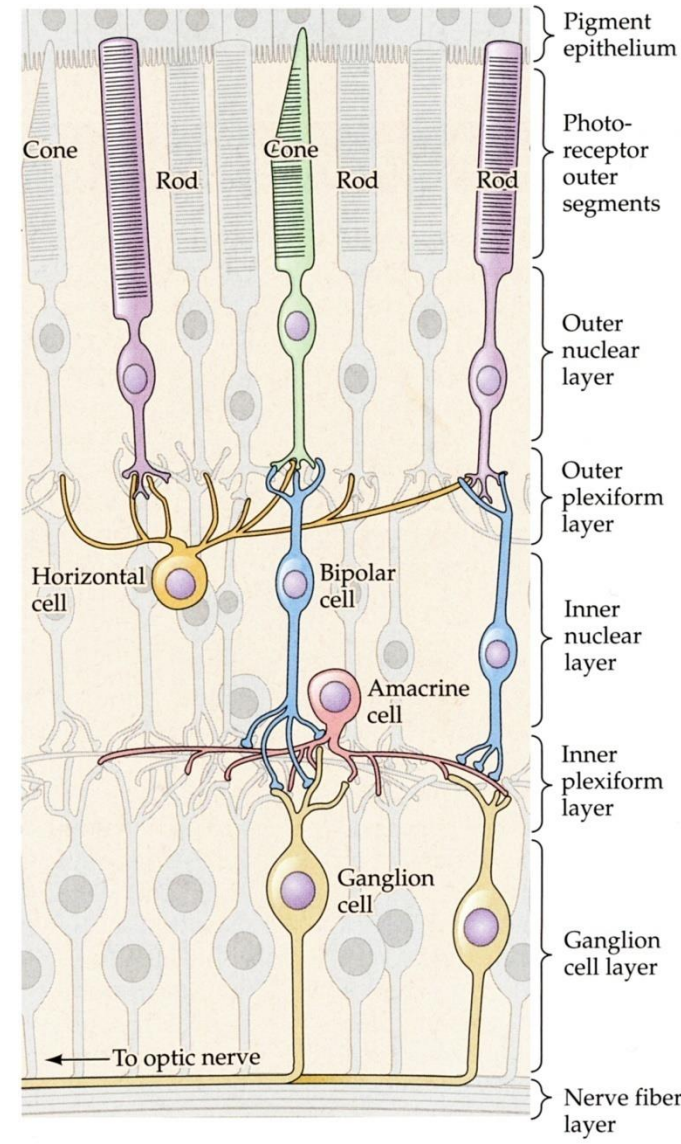
Mechanisms Involved in Cell Type Specificity



Mechanisms Involved in Cell Type Specificity

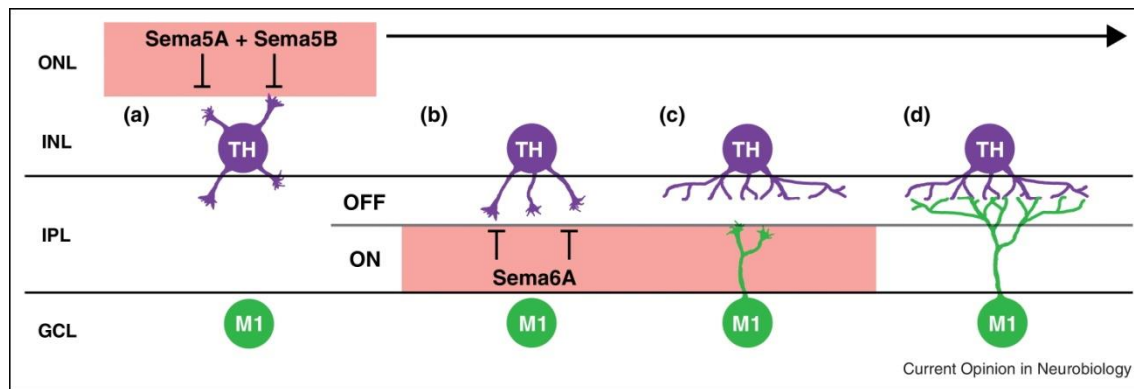
Bipolar cells and amacrine cells synapse with retinal ganglion cells in the inner plexiform layer (IPL) of the retina.

Different types of bipolar and amacrine cells synapse with different types of ganglion cells in different sublaminae of the IPL.



Mechanisms Involved in Cell Type Specificity

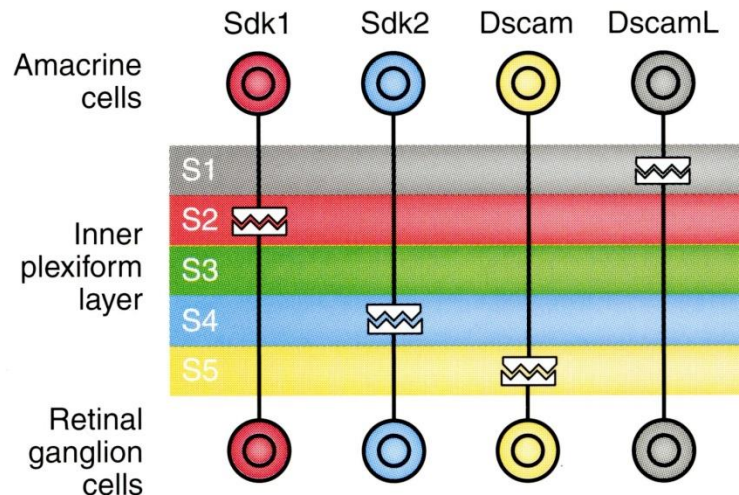
- Guidance molecules direct axons and dendrites to the appropriate lamina of the IPL:
 - Transmembrane repellent semaphorins, Sema5A & Sema5B, drive amacrine cell axons into the IPL.
 - Sema6A restricts dopaminergic amacrine cell processes to off-sublaminae.



(Robles and Baier, 2012)

Mechanisms Involved in Cell Type Specificity

- Homophilic binding between Ig-like CAMs mediates synapse formation between specific cell types in the IPL:
 - Sidekick1 (Sdk1), Sdk2, Dscam and DscamL function with different cell types.
 - e.g. DscamL is required for synapse formation between dopaminergic amacrine cells and M1-ipRGCs.

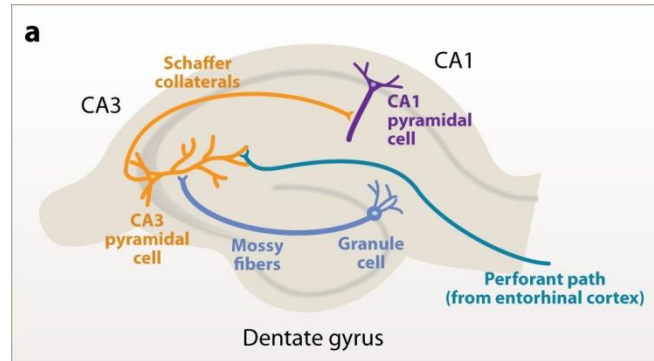


(Burgess, 2009)

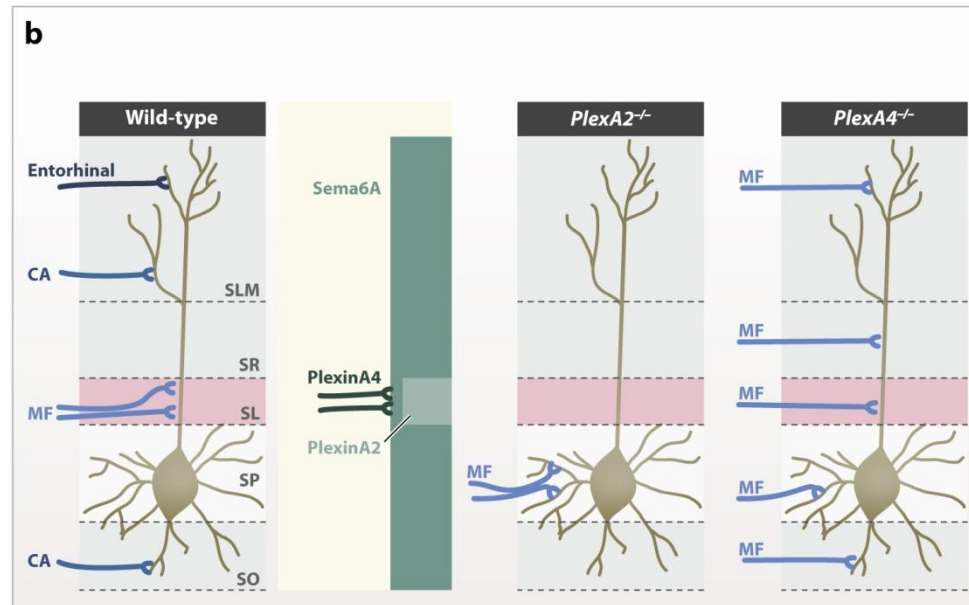
Mechanisms Involved in Cell Type Specificity

- Thus, the pattern of connections between cell types is specified by a combination of repellant and attractive interactions.
- Multiple molecular signaling systems are needed to specify the connections between any two cell populations.

Mechanisms that Determine Subcellular Specificity of Synaptic Connections



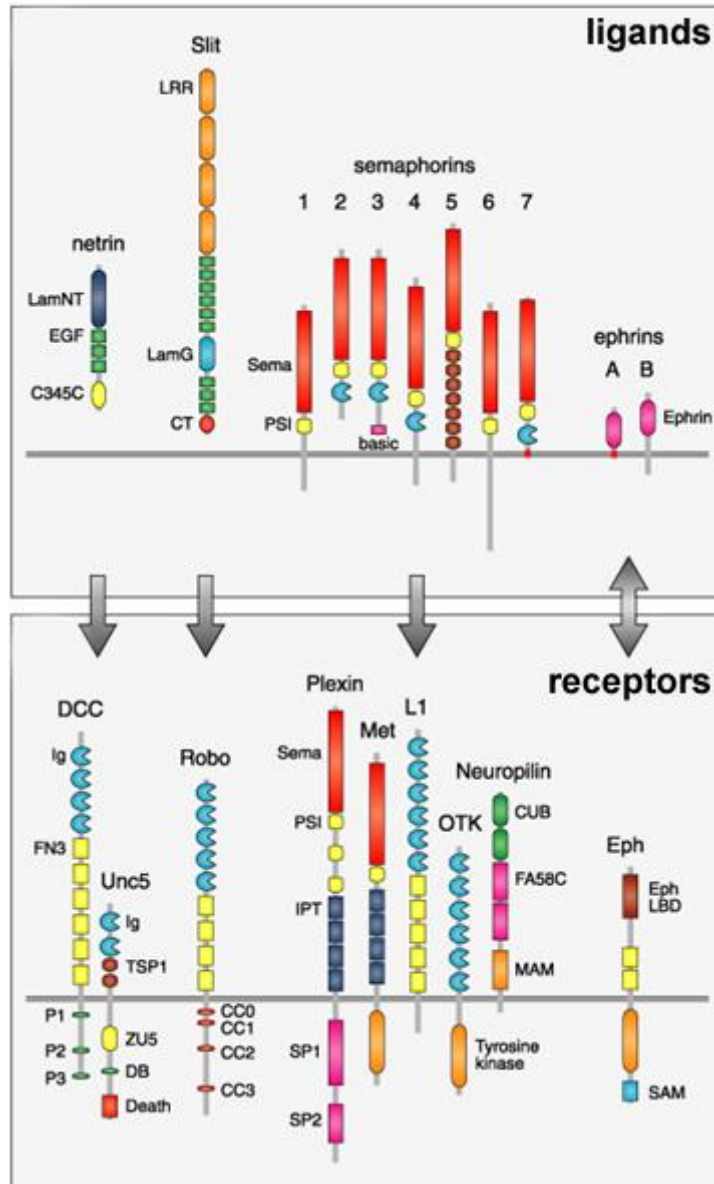
PlexinA4+ mossy fibers synapse on the Sema6A-region of CA3 pyramidal cells in the hippocampus.



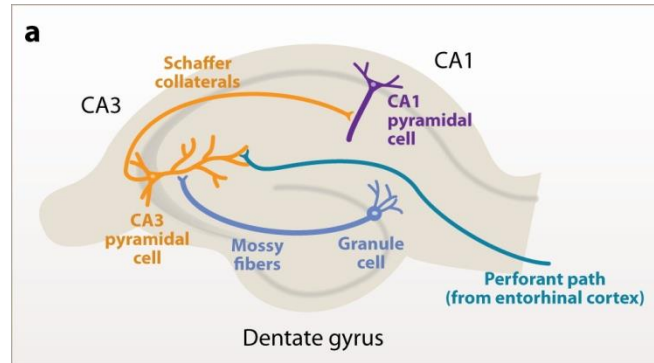
AR Sanes JR, Yamagata M. 2009.
Annu. Rev. Cell Dev. Biol. 25:161–95

Guidance Molecule Families (ligands & receptors)

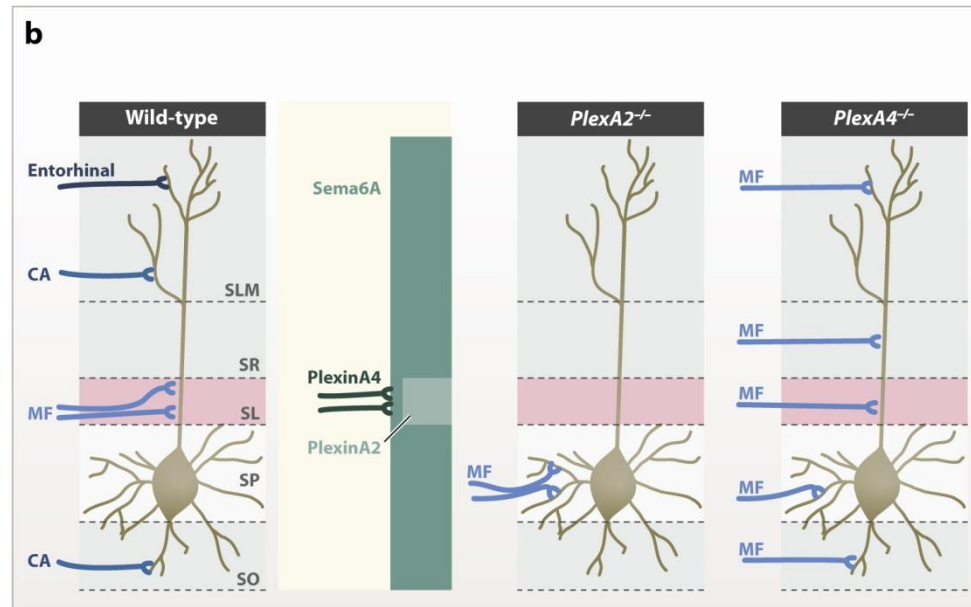
(can attract or repel)



Mechanisms that Determine Subcellular Specificity of Synaptic Connections



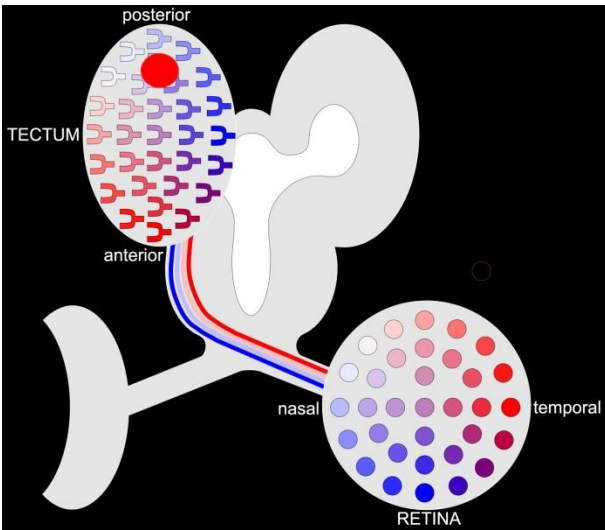
PlexinA4+ mossy fibers synapse on the PlexinA2+/Sema6A- region of CA3 pyramidal cells in the hippocampus.



AR Sanes JR, Yamagata M. 2009. Annu. Rev. Cell Dev. Biol. 25:161–95

Refinement in the Pattern of Connections

(i.e. selective retention based on functional validation)

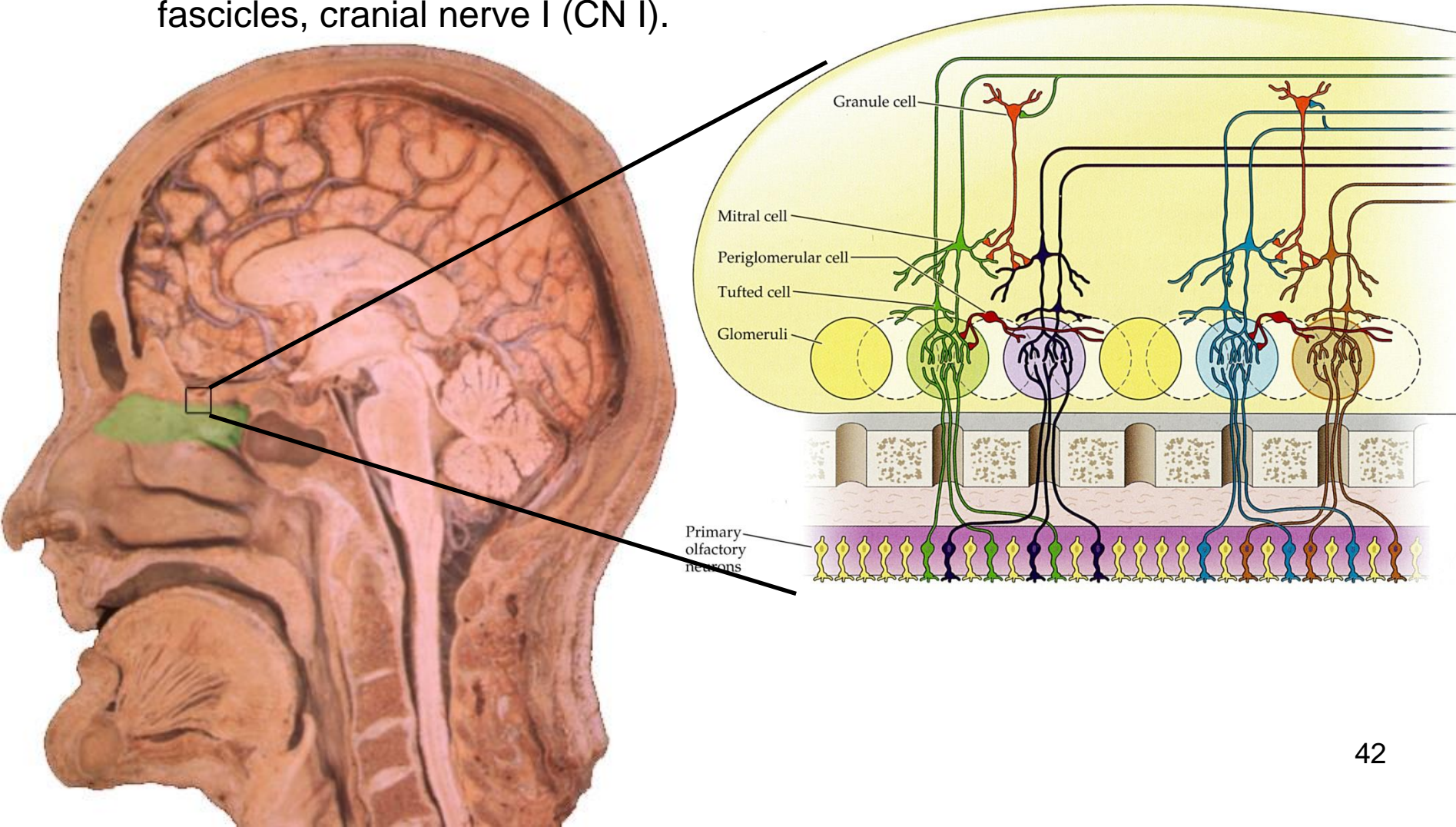


- Chemospecificity establishes a rough topographic map. The precision of the map is poor, and there are many 'errors'.
- Activity dependent mechanisms refine the pattern of connections.

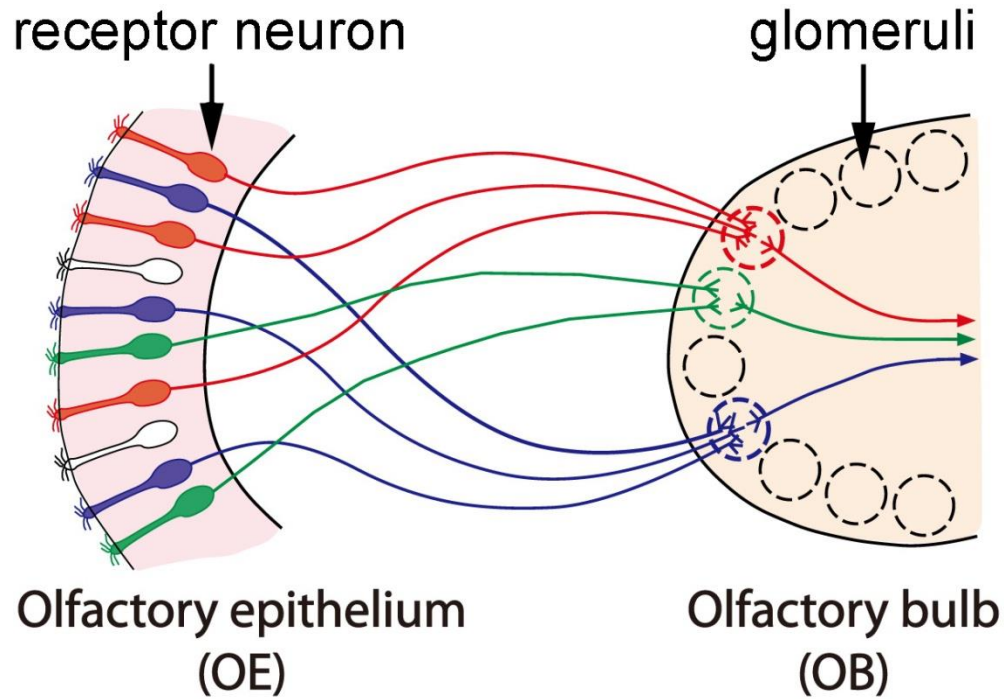


Topography in the Primary Olfactory Projection

- Olfactory axons pass through the bone into the cranium in multiple fascicles, cranial nerve I (CN I).



Topography in the Primary Olfactory Projection



Topography in the Primary Olfactory Projection

- Knockout of a receptor caused the cells that normally express that receptor to wander in the bulb, and they did not connect.
- Replacement of one receptor gene with another caused the cells misexpressing the new gene to connect to different glomeruli.
- Receptor proteins are expressed on the axonal growth cones.
- Receptor proteins appear to function in homophilic cell-cell interactions.