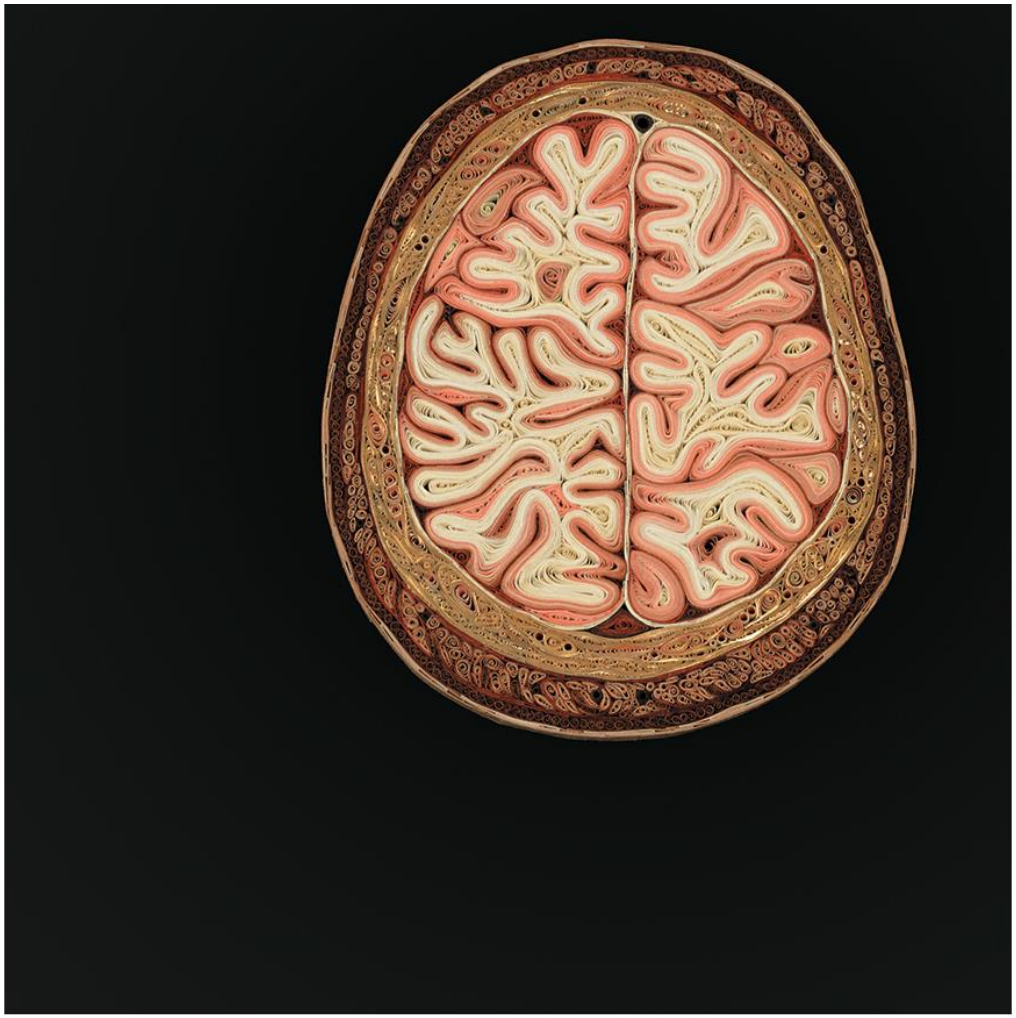
(4) Building Brain



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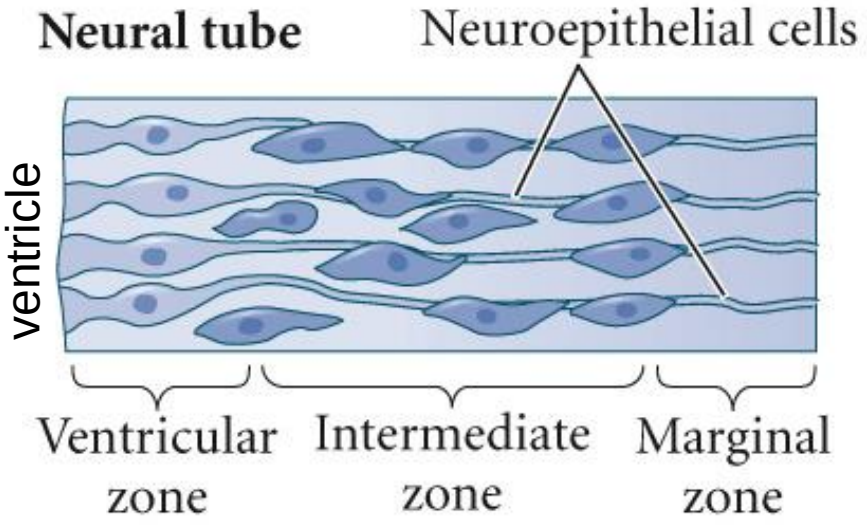
Gregor Eichele in 1992 (| Max Planck Institute for Biophysical Chemistry

WHAT IS PERHAPS THE MOST INTRIGUING QUESTION OF ALL is whether the brain is powerful enough to solve the problem of its own creation," Determining how the brain—an organ that perceives, thinks, loves, hates, remembers, changes, deceives itself, and coordinates all our conscious and unconscious bodily processes—is constructed is undoubtedly the most challenging of all developmental enigmas. A combination of genetic, cellular, and systems level approaches is now giving us a very preliminary understanding of how the basic anatomy of the brain becomes ordered.

CNS growth begins with expansion of the newly formed neural tube along the apicobasal axis within three regions:

1. ventricular zone of undifferentiated, proliferating stem cells, producing neuroblasts and glioblasts
2. mantle (intermediate) zone of differentiating neurons that will form the gray matter (spinal cord)
3. marginal layer that contains nerve fibers and will be the white matter.

- .



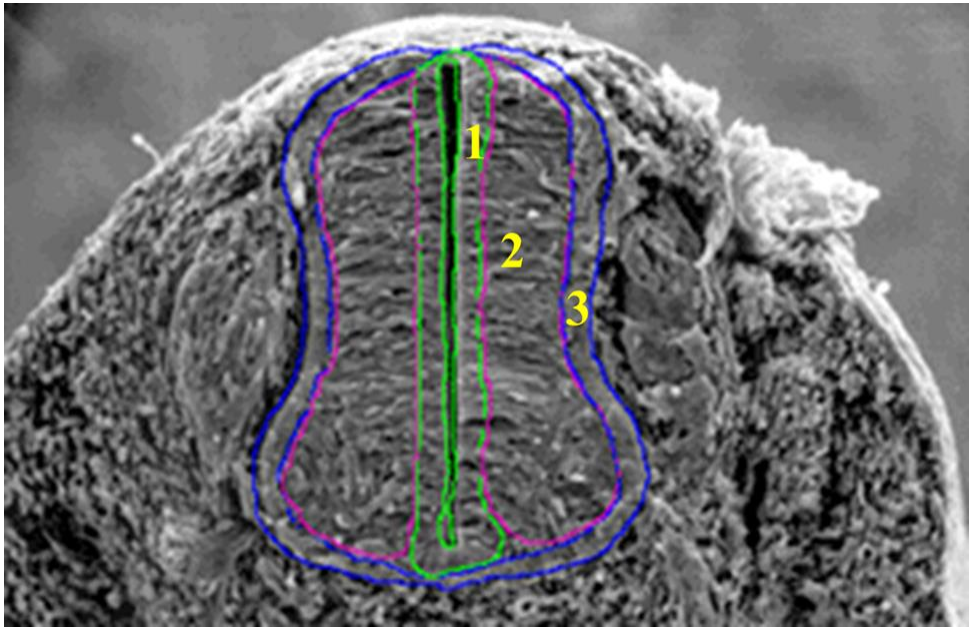
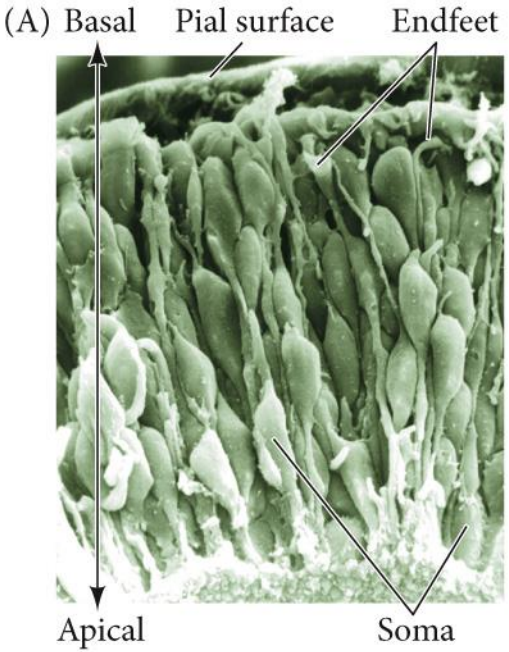
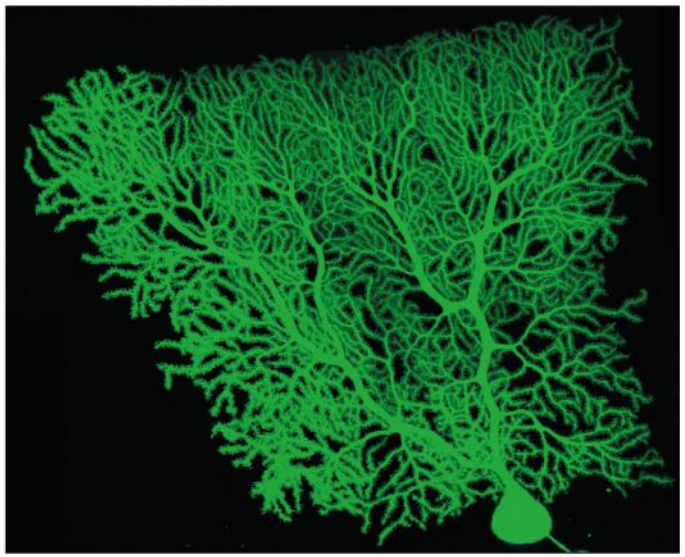


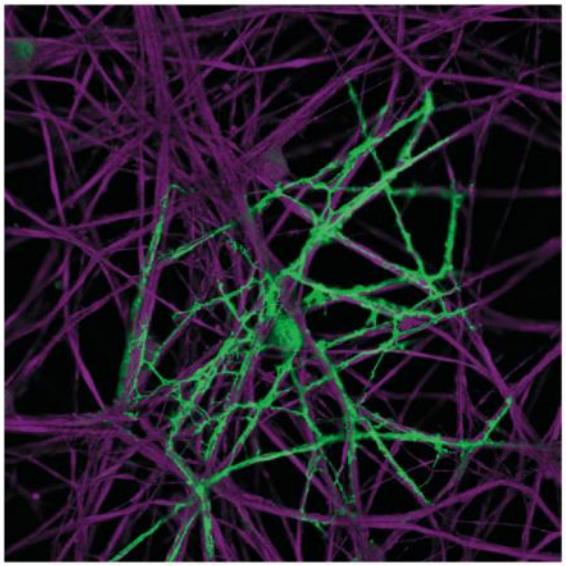
Figure 14.1 Cell types of the CNS

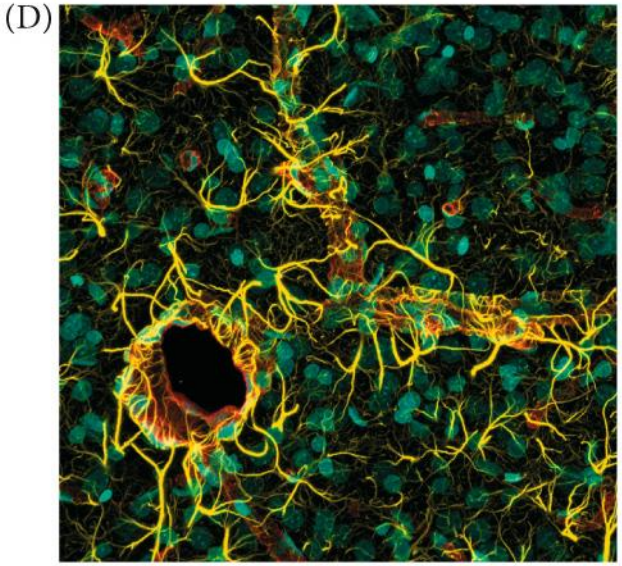




Purkinje neuron

Oligodendrocyte Processes wrap axons





Astrocytes end-feet on blood vessels

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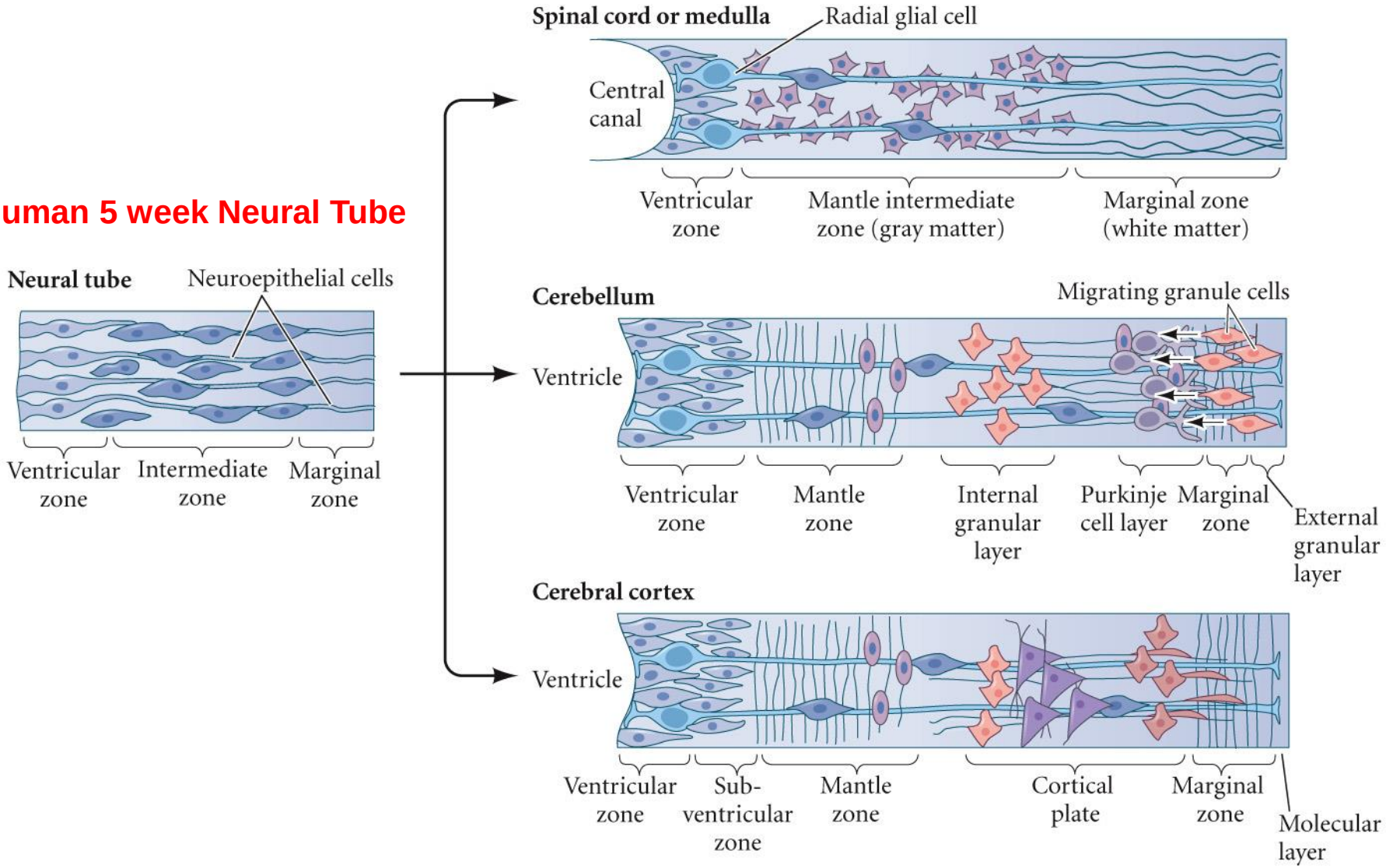
Figure 14.3 Differentiation of the walls of the neural tube

Human 5 week Neural Tube



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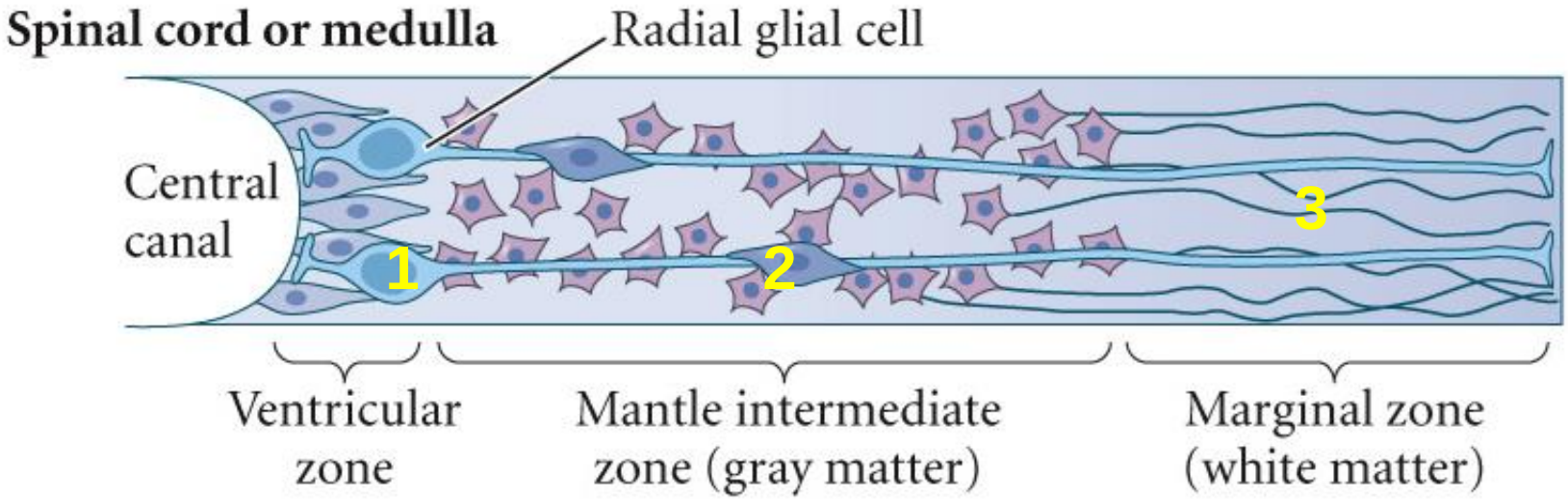
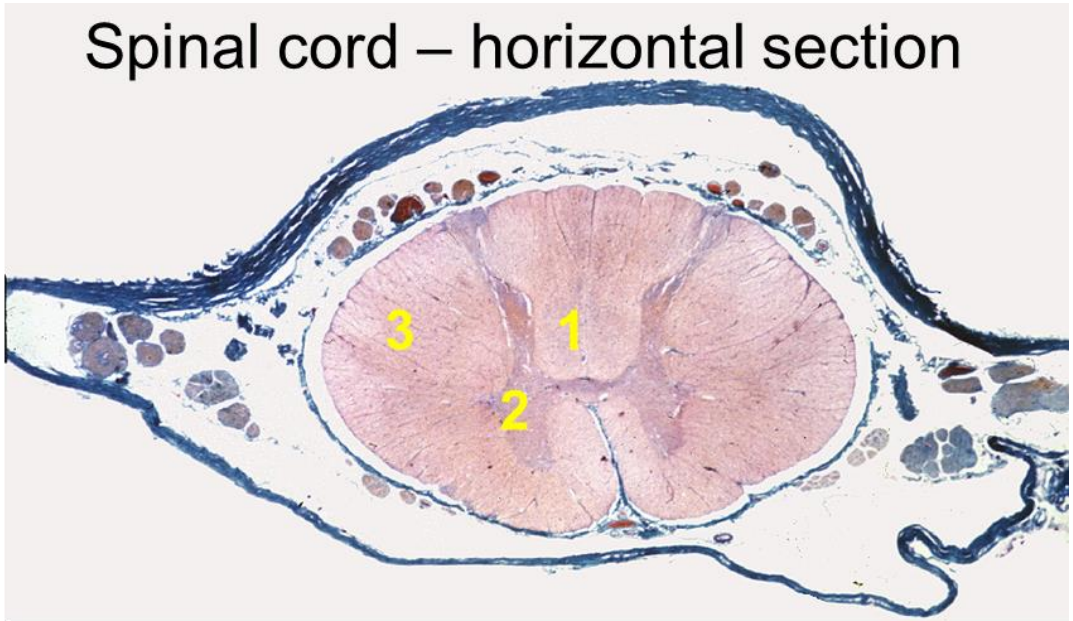


(germinal cells)



1- central canal (vestigial neural tube cannal with few/no germinal cells)
2 – neuronal zones (vestigial mantle, gray matter)
3- Processes axons (marginal layer)

Factors in Neurulation

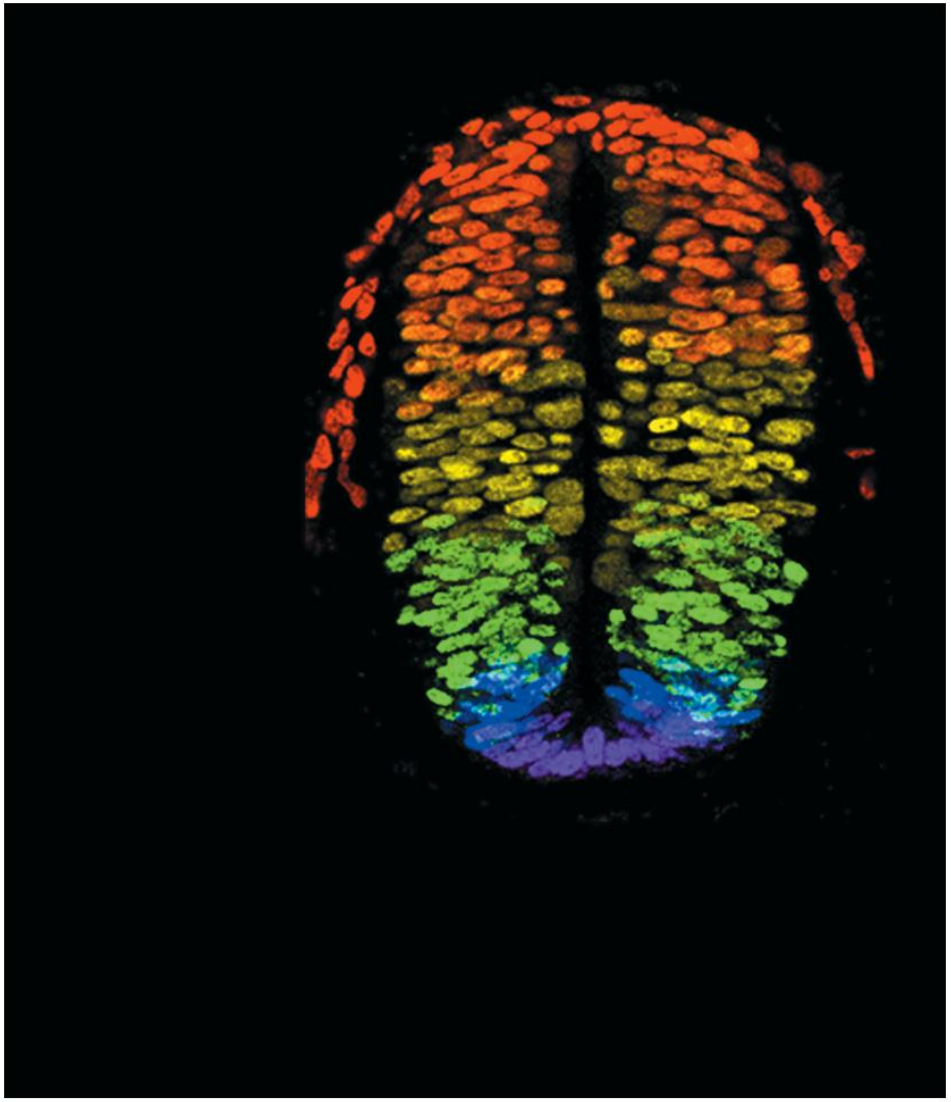


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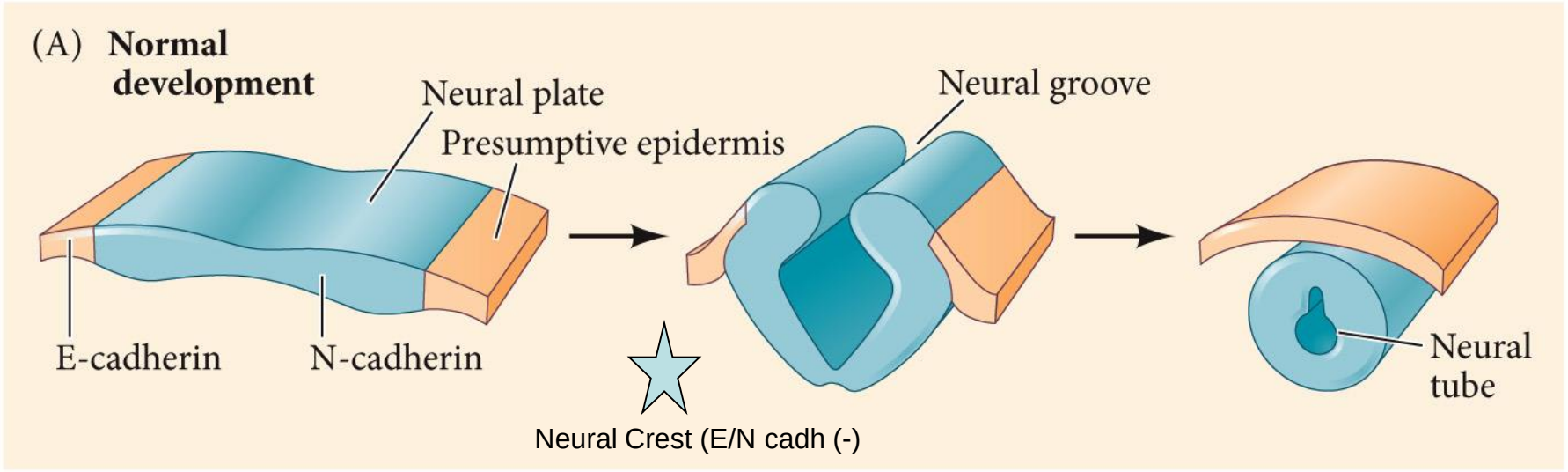
Figure 13.13 Expression of N- and E-cadherin adhesion proteins during neurulation in *Xenopus*



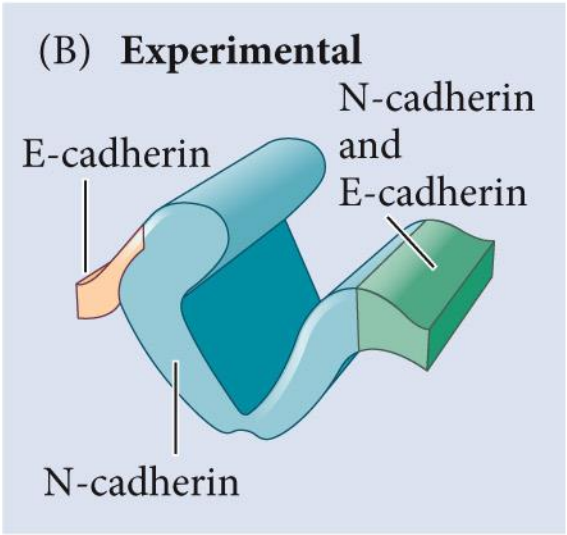


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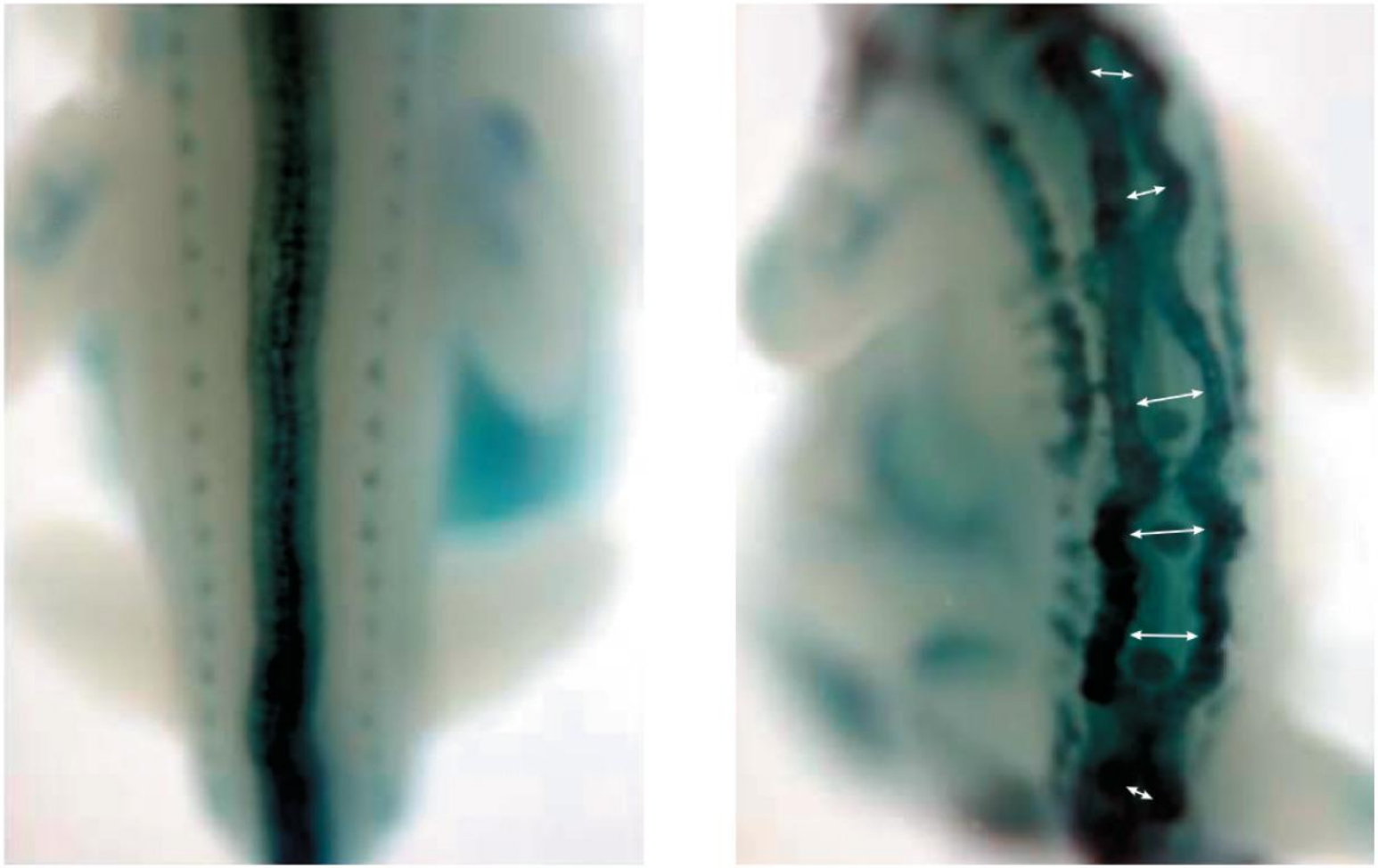
Figure 13.7 BMP-Nogin rivalry - activated BMP signaling leads to neural tube defects

(A) Wild-type

(B) *Noggin*$^{-/-}$



Noggin expressed;
neural tube closure

BMPs hyperactive,
neural tube fails to close

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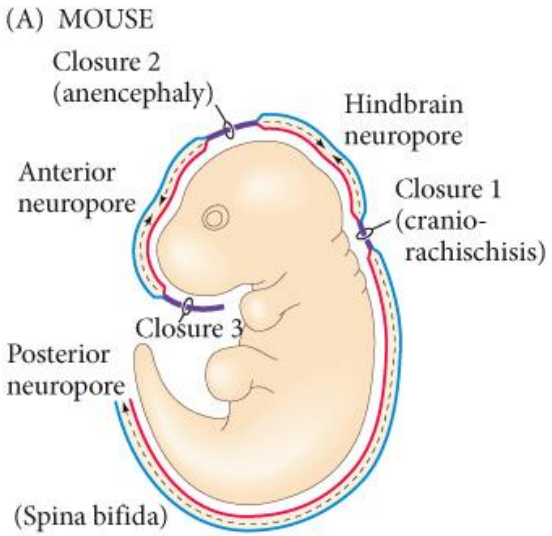
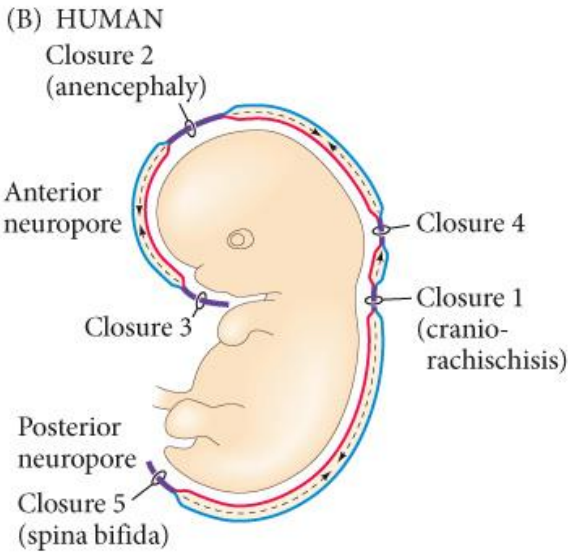
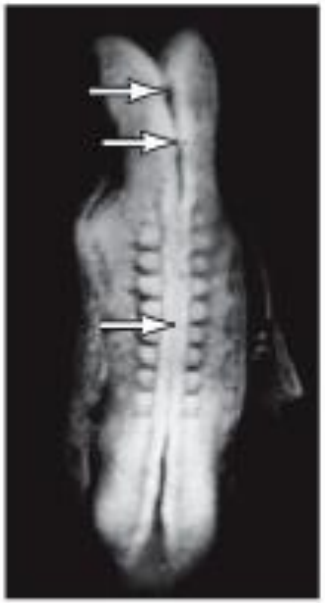
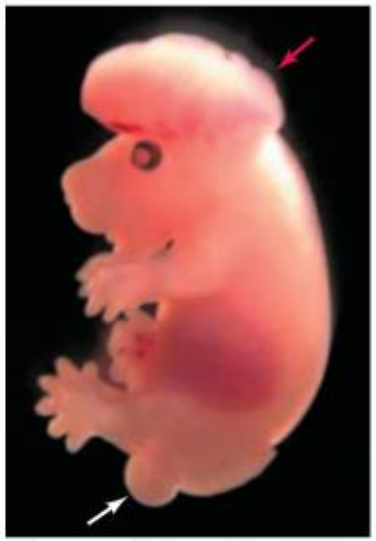
Figure 13.10 Neural tube closure in the mammalian embryo



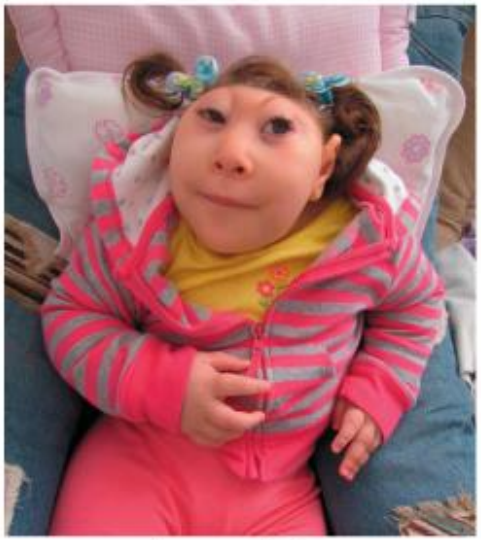






Exencephaly; spina bifida

curly tail mutation
(hSOM1



Anencephaly

DEVELOPMENTAL BIOLOGY 11e, Figure 13.10
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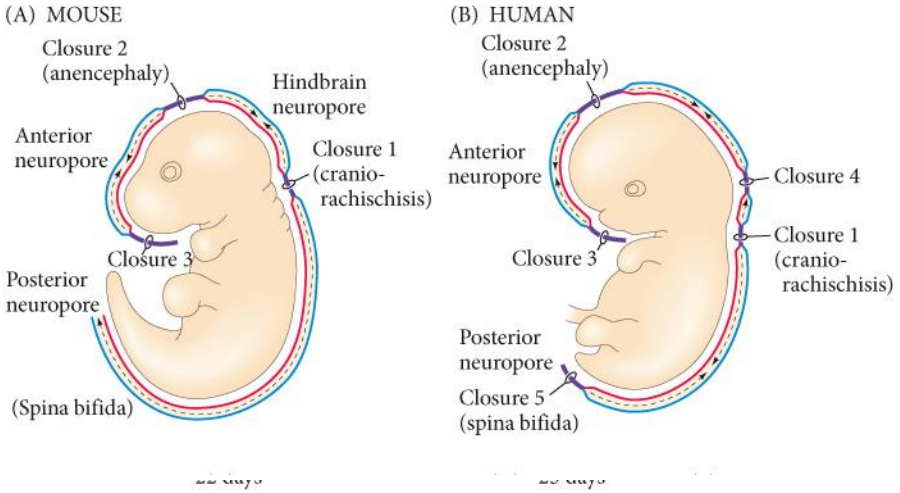
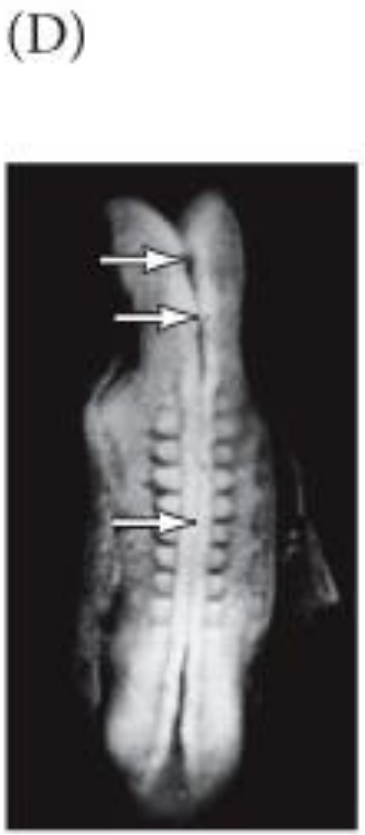
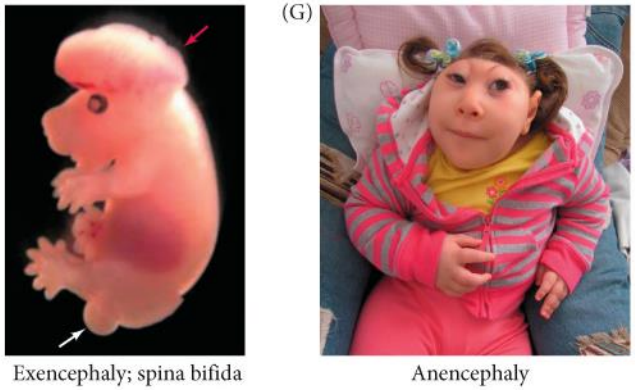
Figure 13.10 Neural tube closure in the mammalian embryo







Exencephaly; spina bifida

Anencephaly

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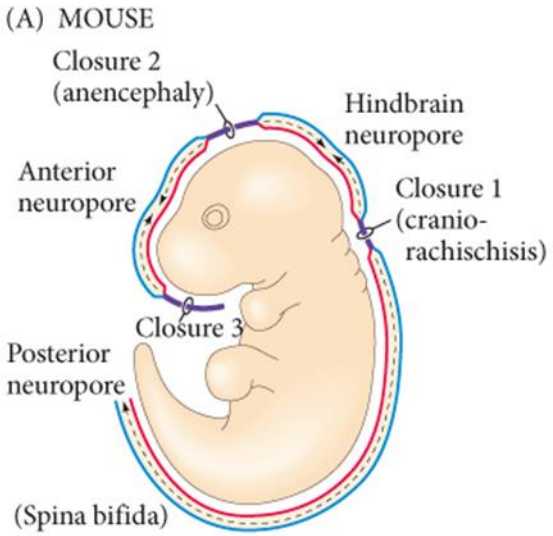

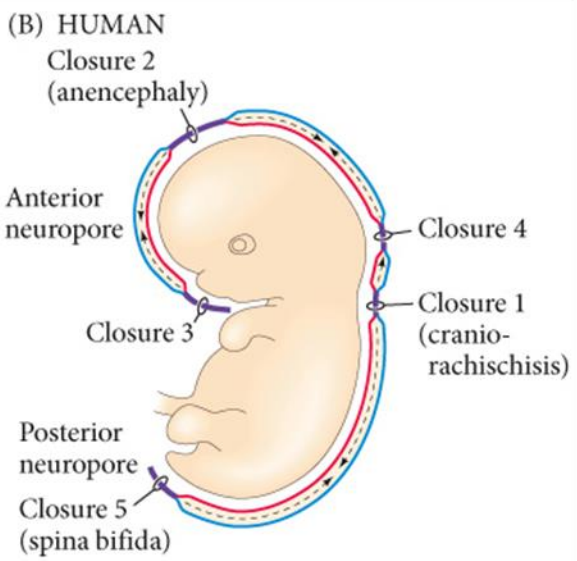

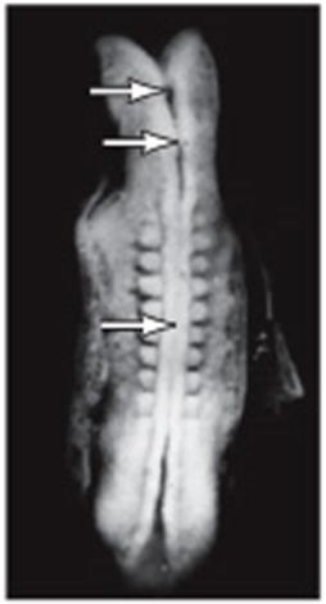

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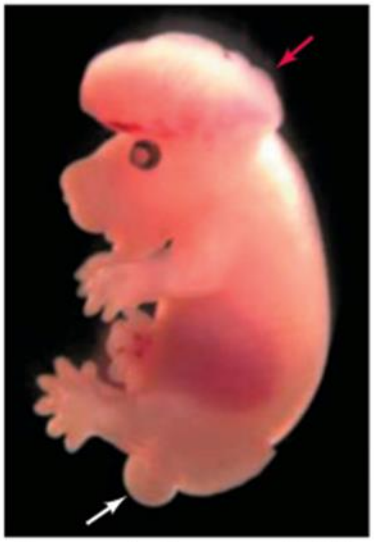
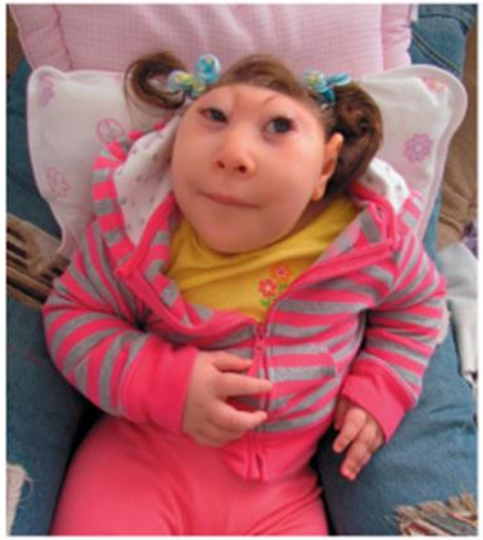


Exencephaly; spina bifida

(G)



Anencephaly

curly tail mutation
(hSOM1

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Figure 13.19 Dorsal-ventral specification of the neural tube (Part 1)

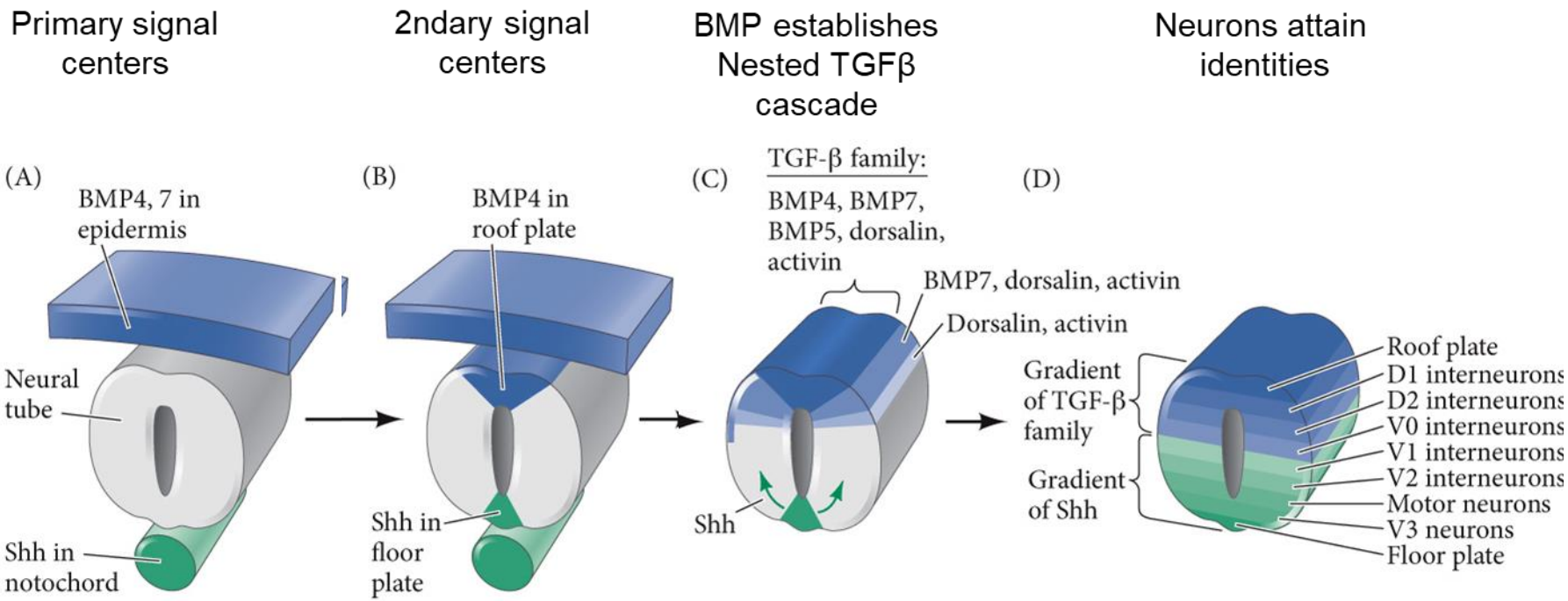

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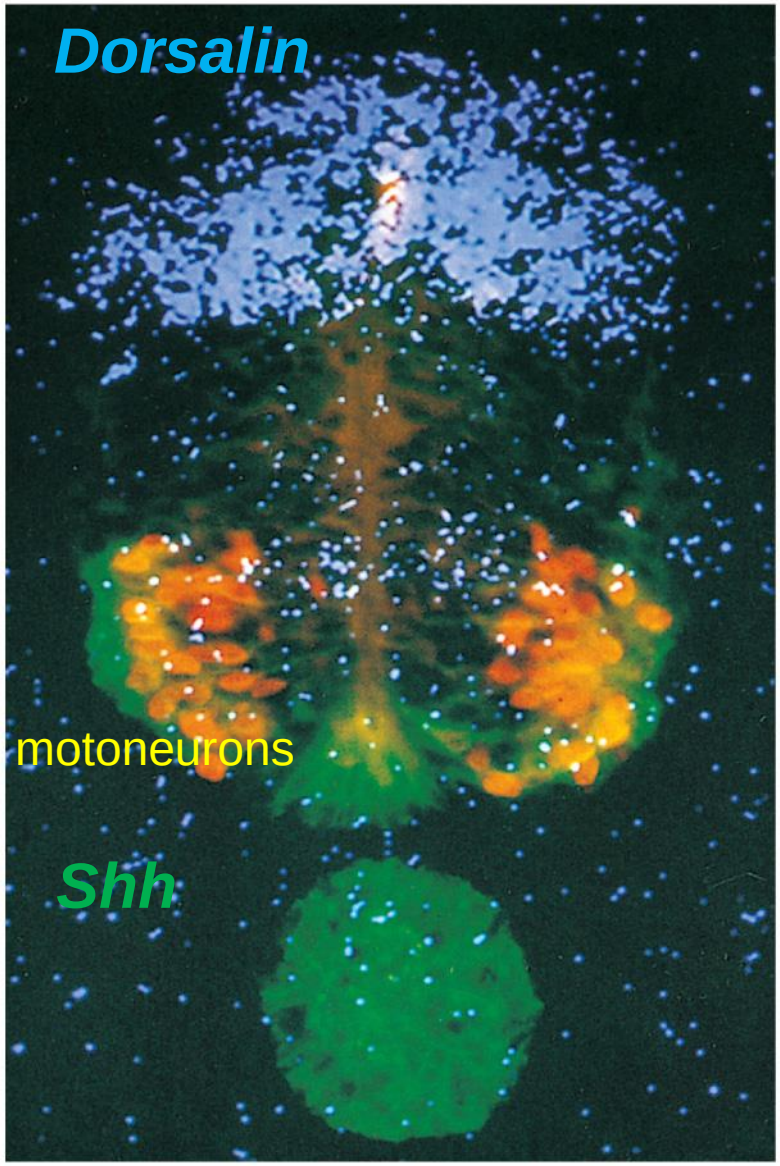
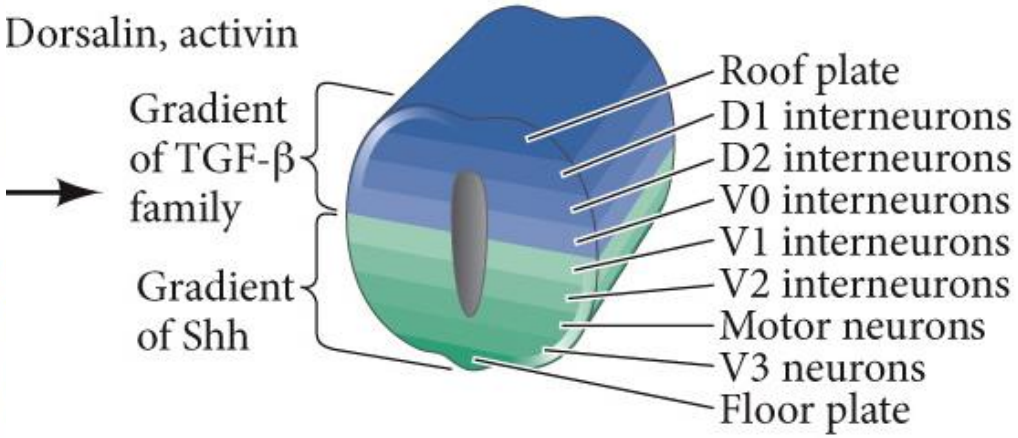
Figure 13.19 Dorsal-ventral specification of the neural tube (Part 2)

(E)





DEVELOPMENTAL BIOLOGY 11e, Figure 13.19 (Part 2)

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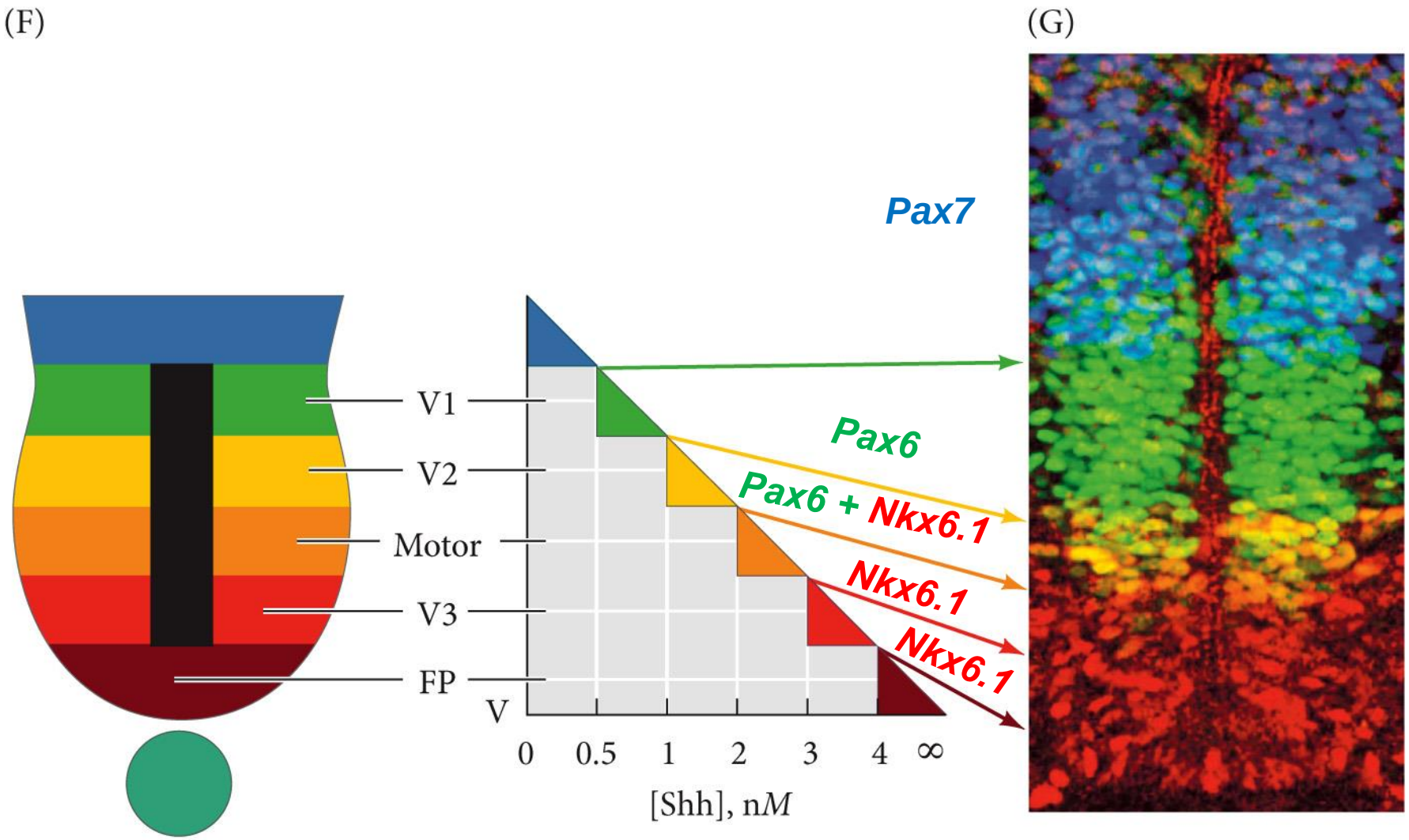
Figure 13.19 Dorsal-ventral specification of the neural tube (Part 3)



DEVELOPMENTAL BIOLOGY 11e, Figure 13.19 (Part 3)

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Figure 13.18 Differential expression of transcription factors define progenitor domains and derived cell types along the dorsoventral axis

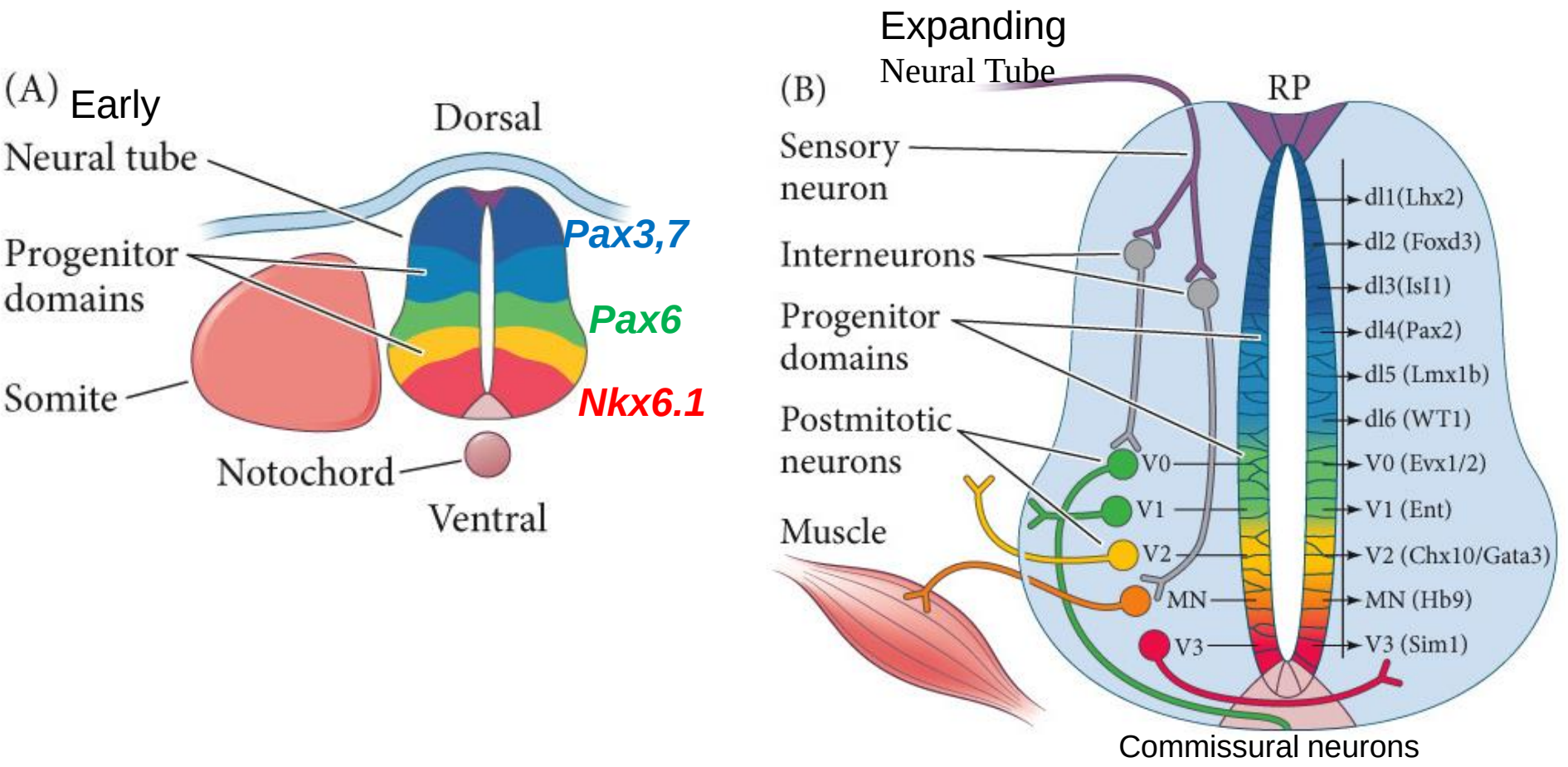

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Figure 13.24 Model for converging signals for maturation and specification of neural progenitors in the developing caudal region of the spinal cord

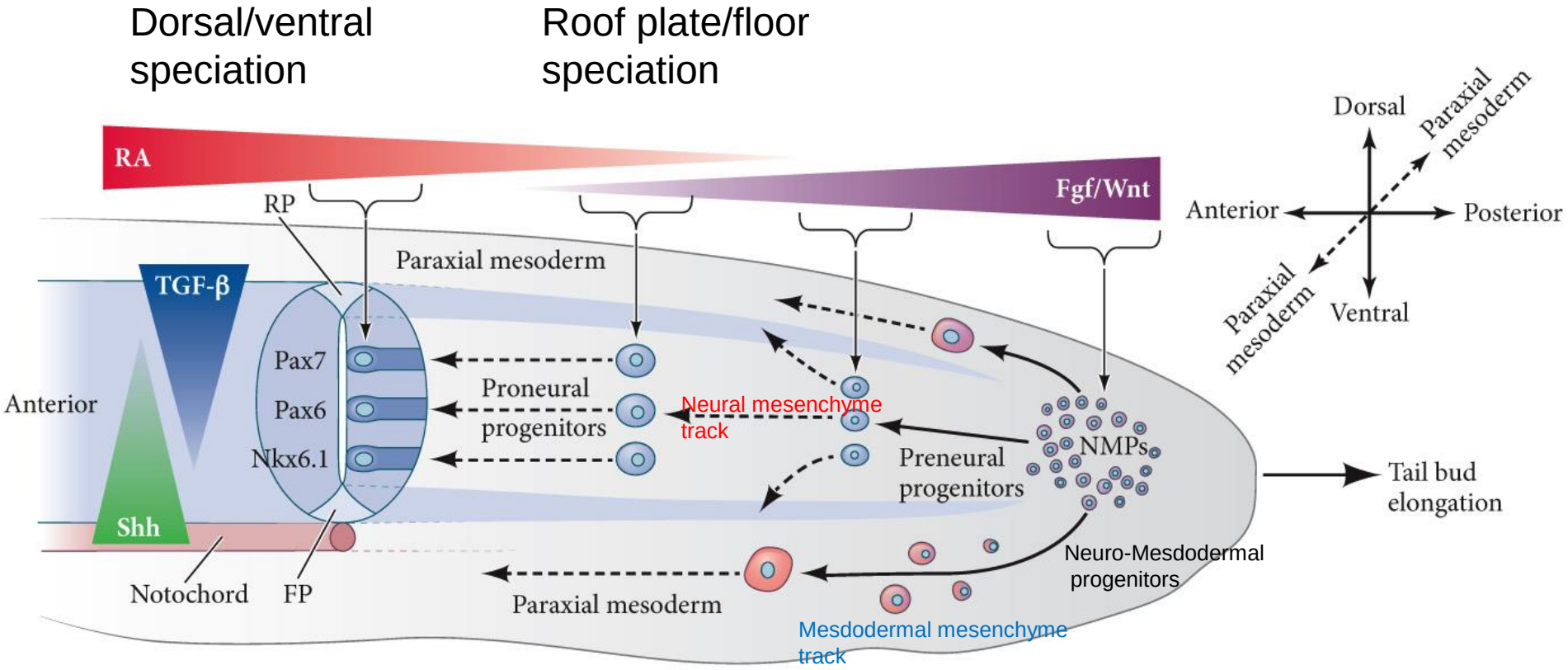

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Figure 14.3 Cerebellum Bergman Glia guidance

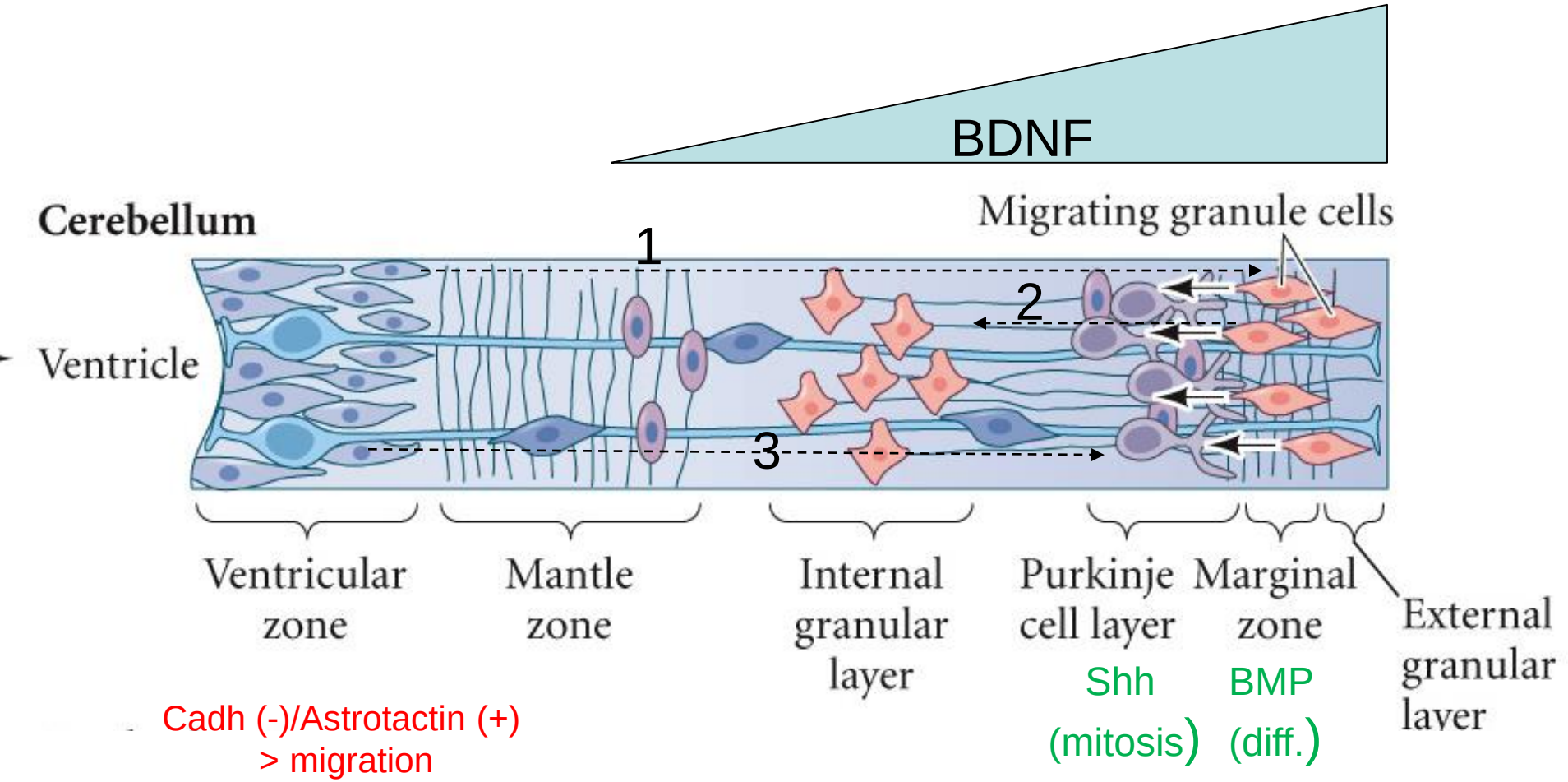

Figure 14.5 Cerebellar organization (Part 2)

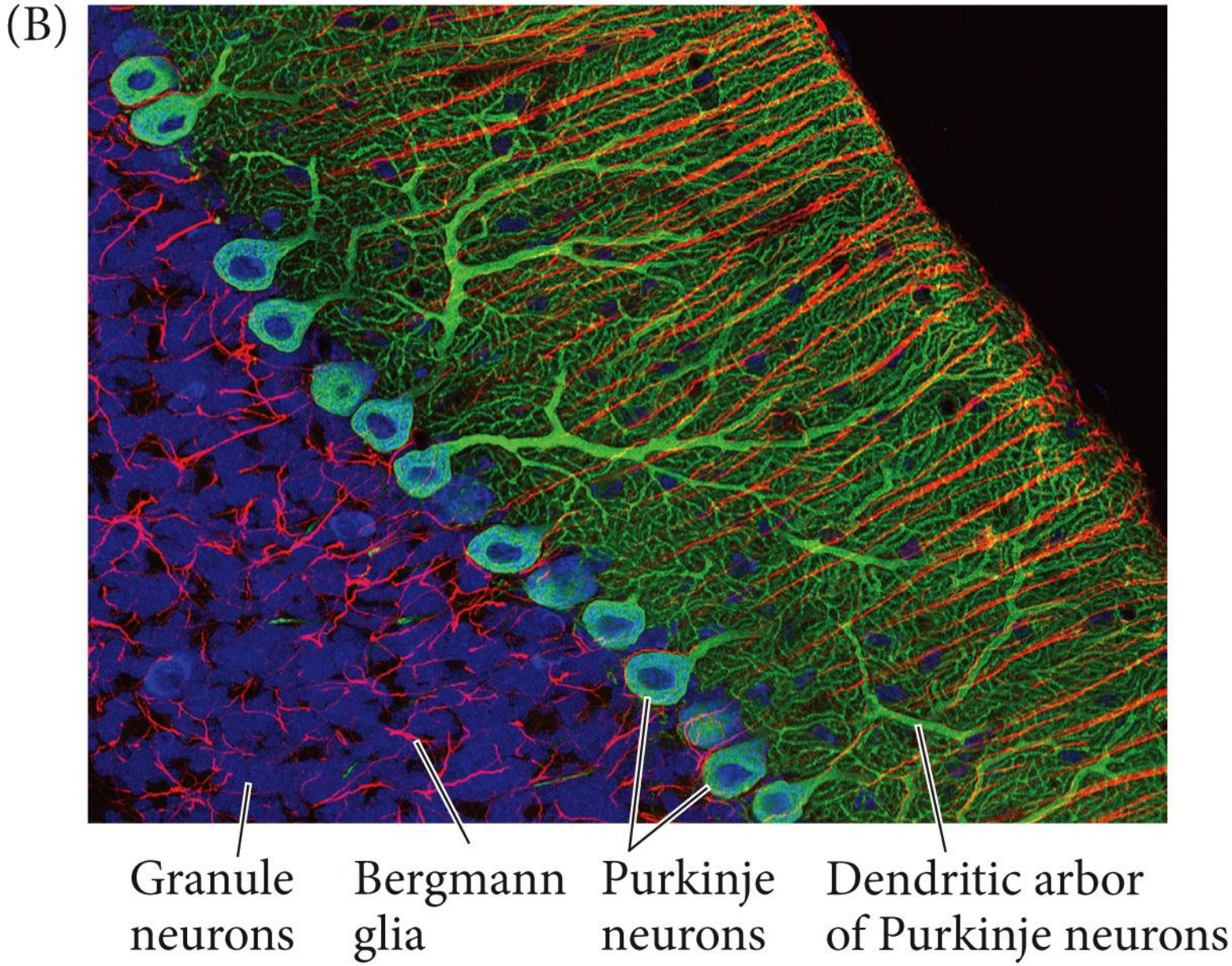

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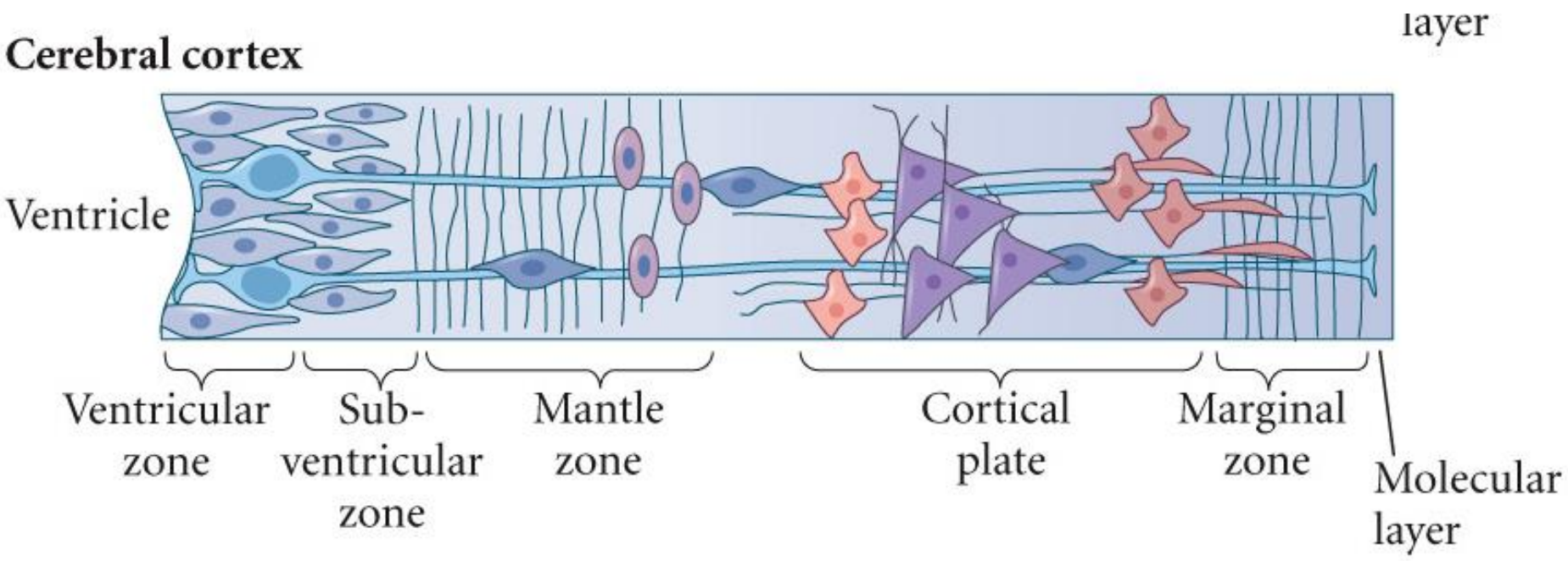
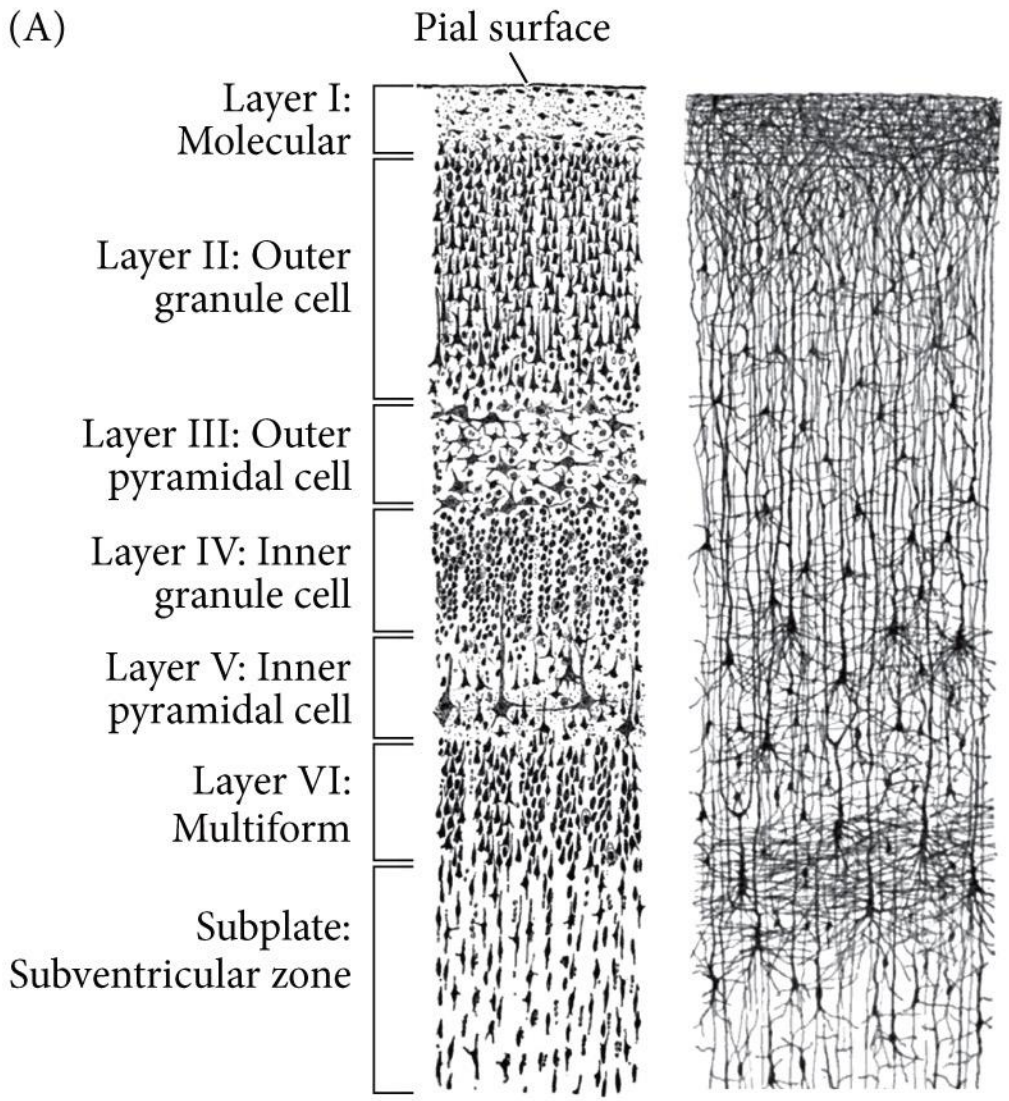
Figure 14.3 CORTEX: - a laminar structure. organized radially into 6 interacting layers

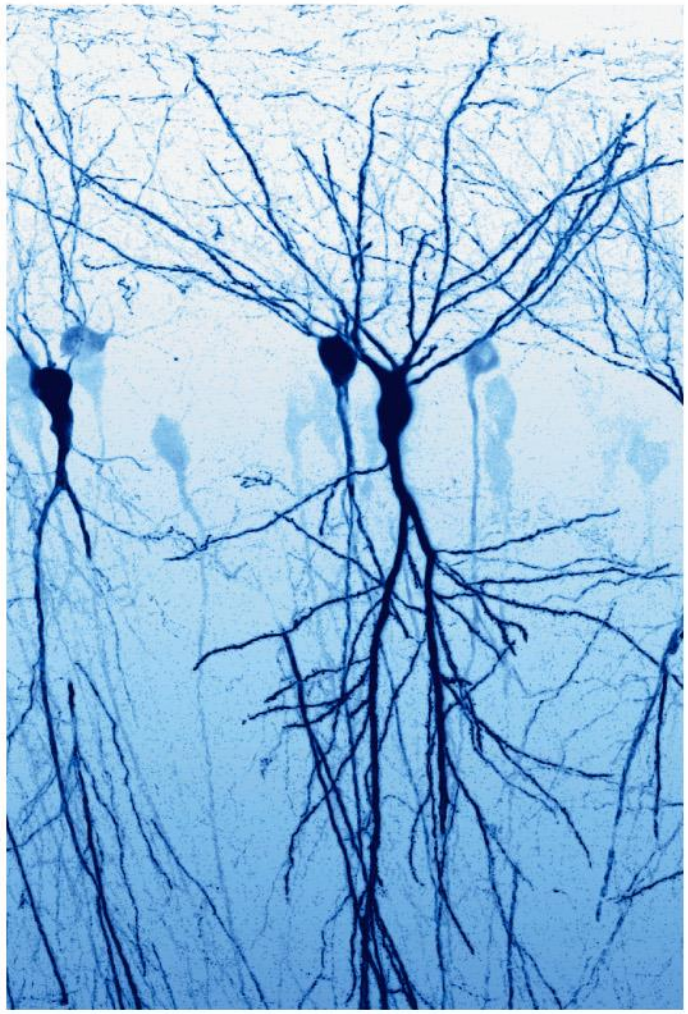


***Paracrine Regulators**: Notch, FGF, EGF, Reelin (Disabled), N-cadherins, Integrins, Notch, Shh, BMP)*

***Transcription factors**: Lhx2, ASPM, TBR1, Microcephalin, FOXP2, …*

Figure 14.7 Different neuronal cell types are organized into the six layers of the neocortex





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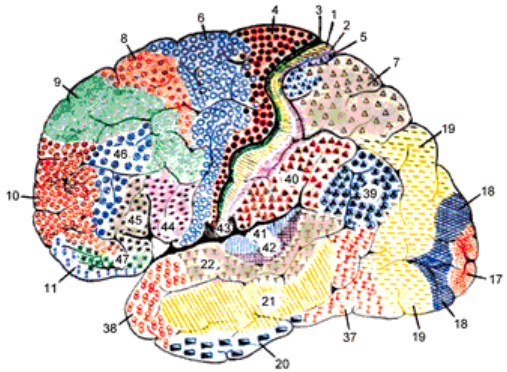
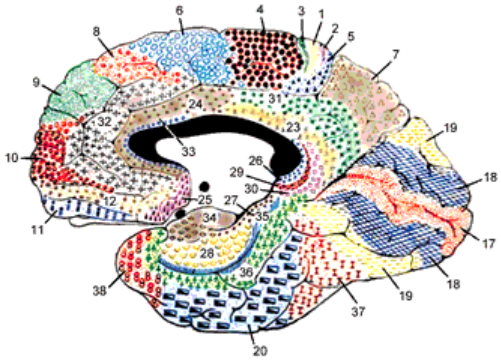
Brodmann divided cortex into 52 **structurally distinct** regions. These regions correspond well with **functional** anatomy, and so his numbering system has stayed popular.





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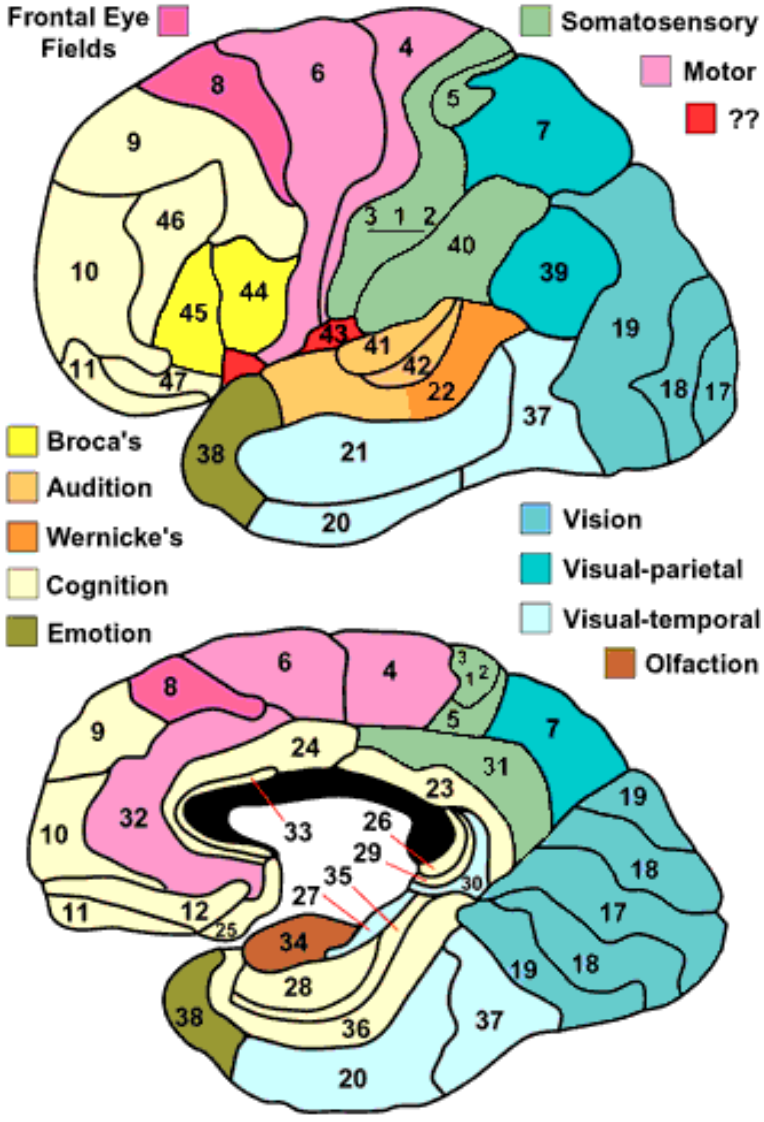
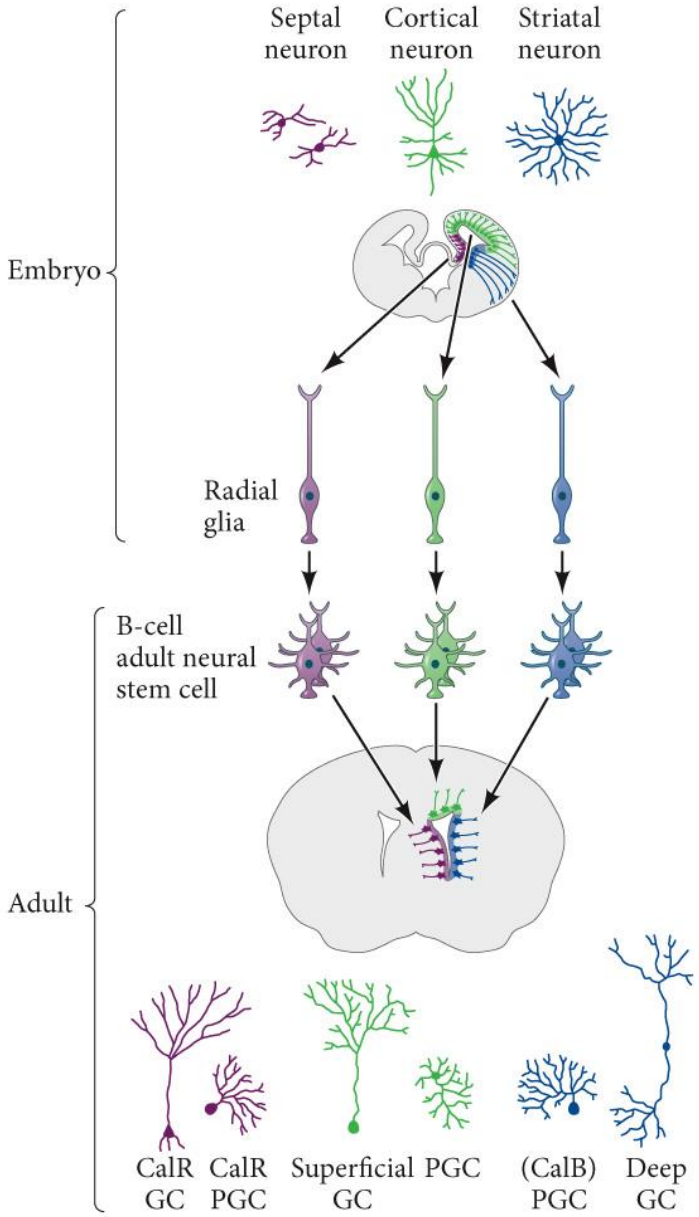


Figure 14.8 Early regional specification of embryonic radial glia translates into restricted progenitor derivation



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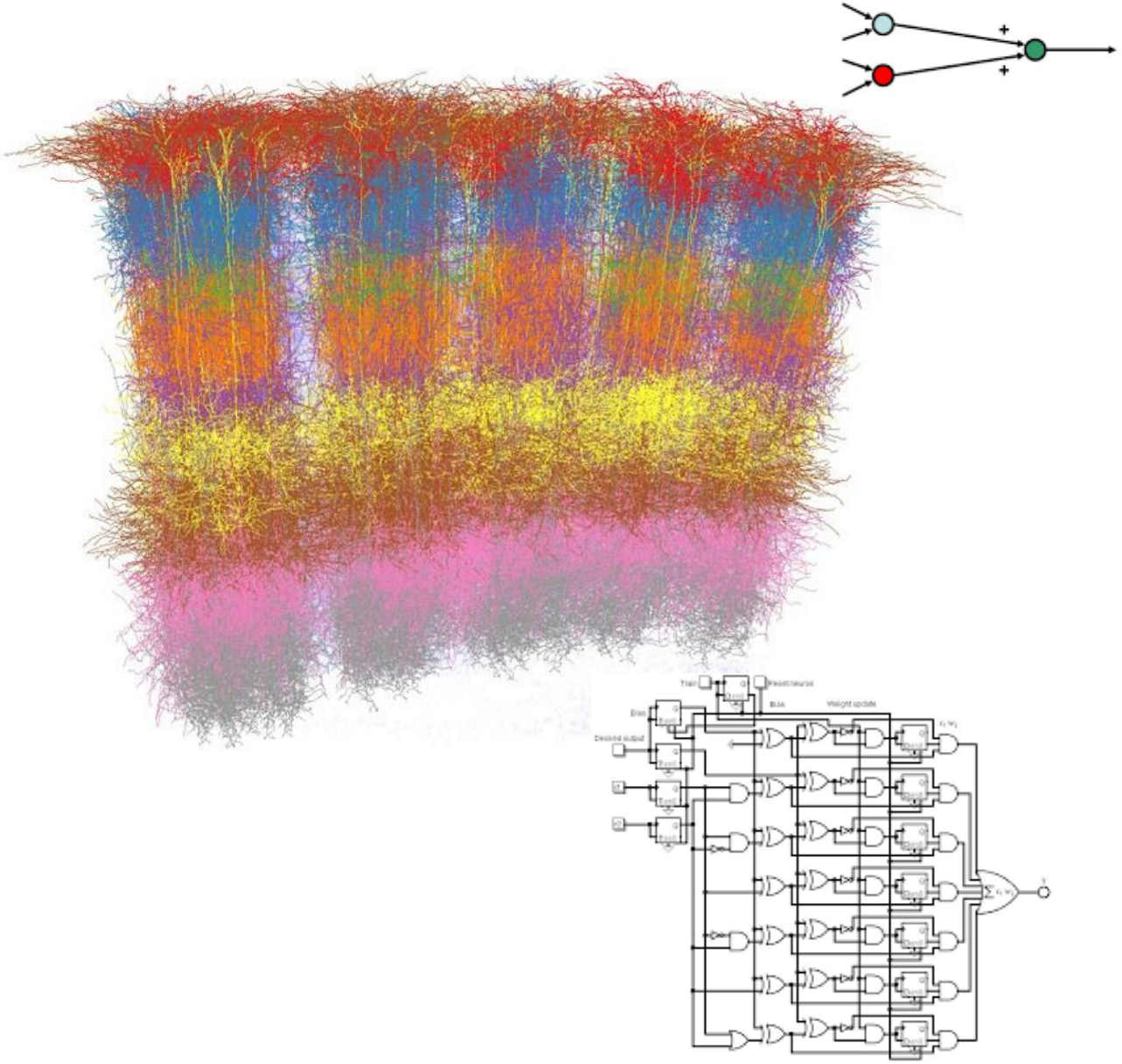
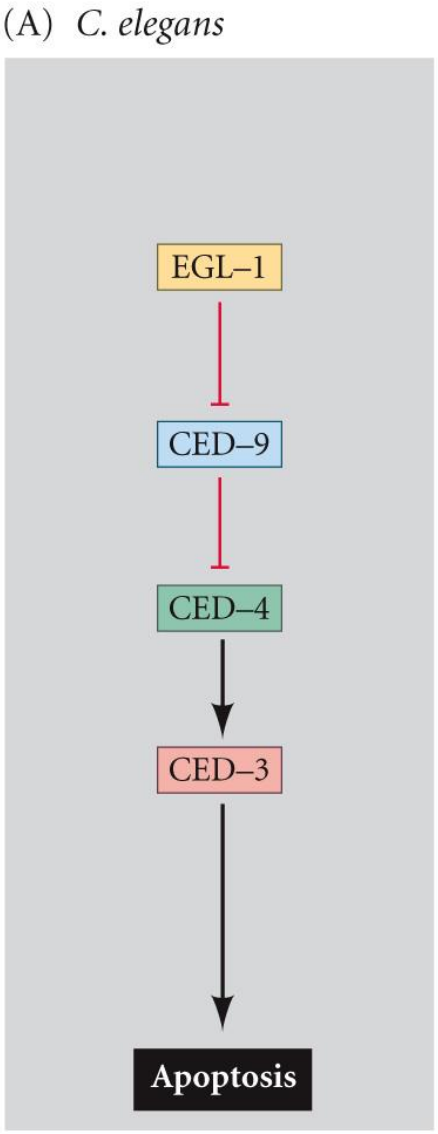
Cortical minicolumns – information processing units (importance of connecting calretinin interneurons)



Apoptosis – Programmed Cell Death

- A**poptosis** is a normal part of development and the existential dichotomy leave or die (exceptionally stark for embryonic cell)
- subject to evolutionary selection
- In an adult human, > **10^{11}** cells die each day & are replaced. (we lose a body weight of cells yearly).
- During embryonic development, we were constantly making and destroying cells
- We generate about **three times as many neurons** as we eventually ended up with when we **were born.**
- Species differ little conservation of apoptosis patterns;

Figure 15.41 The loss of apoptosis can disrupt normal brain development (Part 1)



Switch controlers

binary switch (tonic inhibition)

protease activator factor

proteases

DEVELOPMENTAL BIOLOGY 11e, Figure 15.41 (Part 1)
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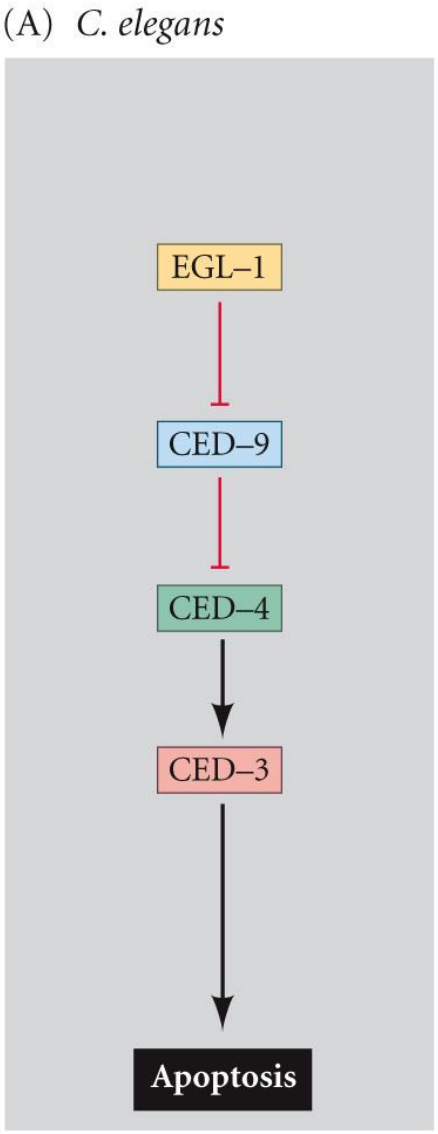
Nobel 2002: Sydney Brenner, H. Robert Horvitz, John E. Sulston in 2002.

Figure 15.41 The loss of apoptosis can disrupt normal brain development (Part 1)

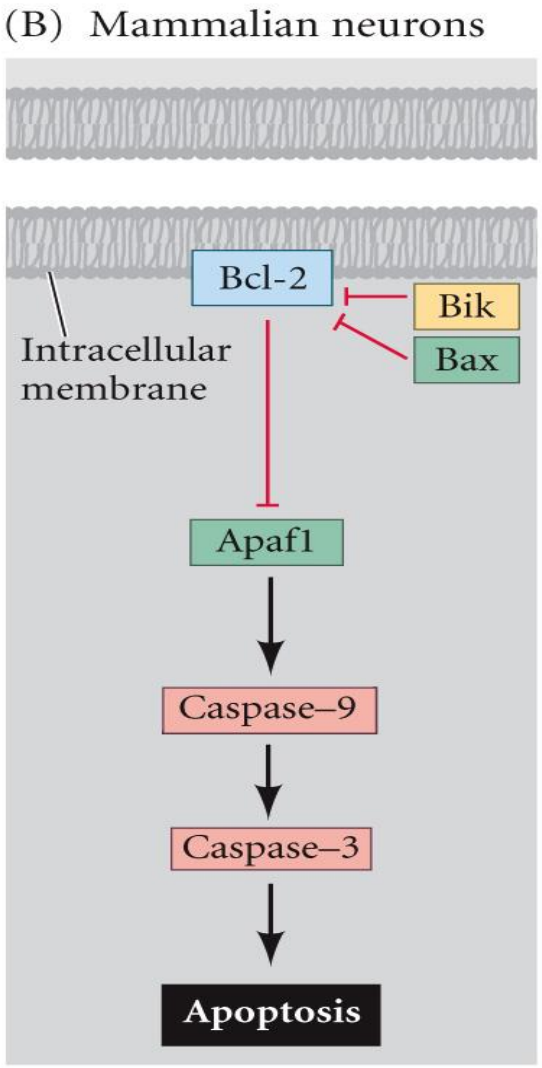


Switch controlers

binary switch (tonic inhibition)

protease activator factor

proteases



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DEVELOPMENTAL BIOLOGY 11e, Figure 15.41 (Part 2)
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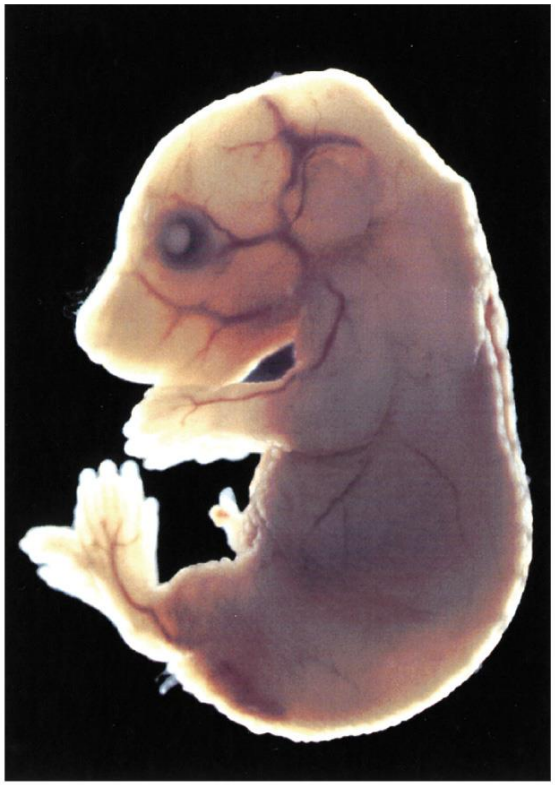
Nobel 2002: Sydney Brenner, H. Robert Horvitz, John E. Sulston in 2002.

Figure 15.41 The loss of apoptosis can disrupt normal brain development (Part 3)

(C) *caspase-9*$^{+/+}$ (wild-type)



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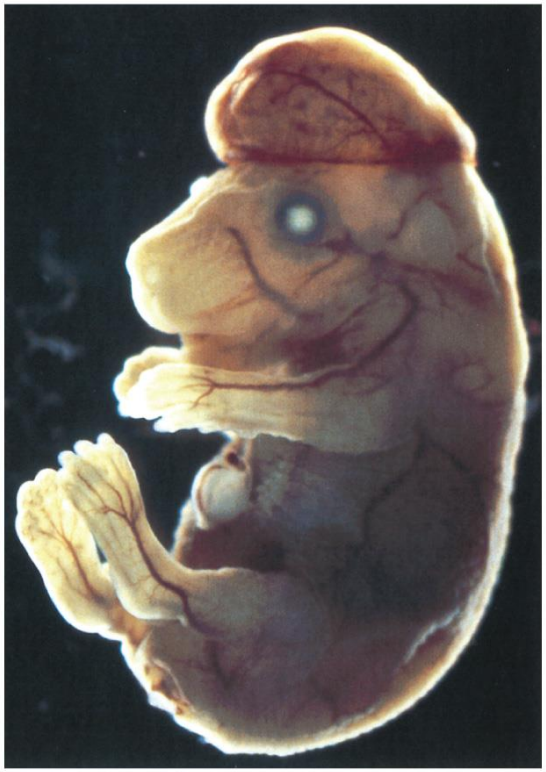
(D) *caspase-9*$^{-/-}$ (knockout)



DEVELOPMENTAL BIOLOGY 11e, Figure 15.41 (Part 4)
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Figure 15.41 The loss of apoptosis can disrupt normal brain development. © In mice in which the genes for caspase-9 have been knocked out, normal neural apoptosis fails to occur, The enlarged brain protrudes above the face, and the limbs are still webbed. (A,B after Adams and Cory 1998; C,D from Kuida et al. 1998.)

What is so different about human brain?

Figure 14.15 Humans continue neurogenesis and brain growth after birth

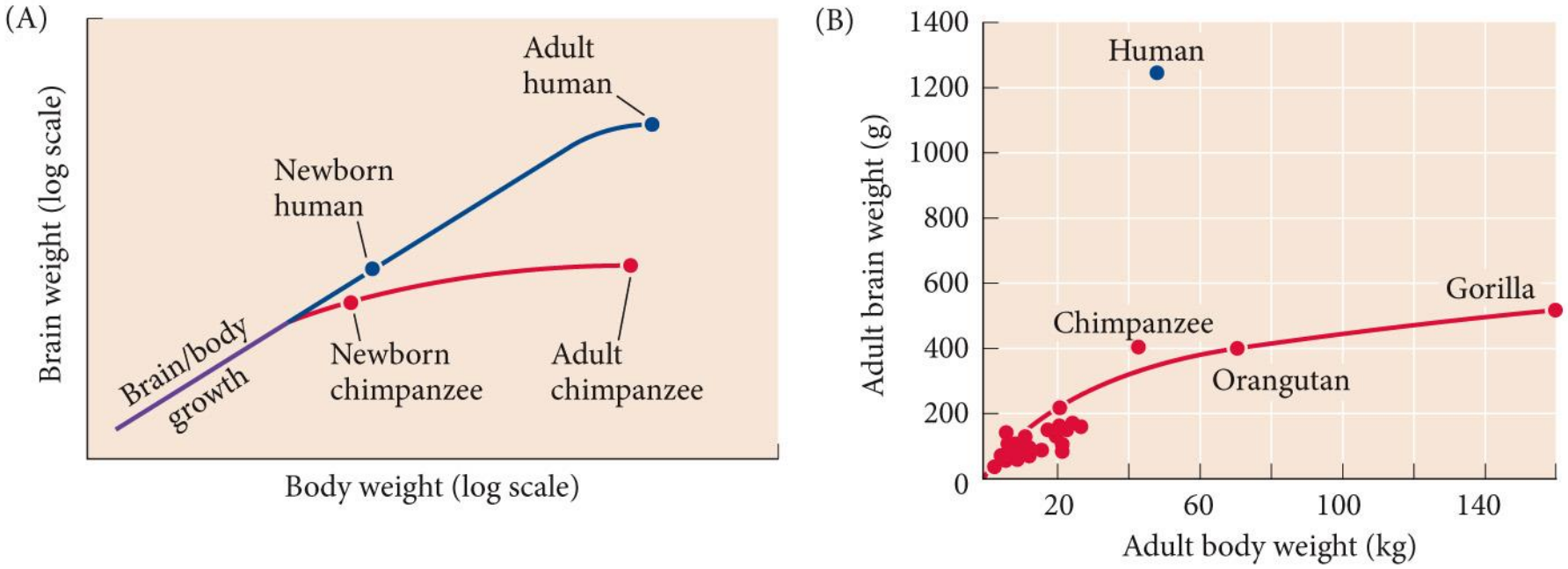

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Figure 14.16 Transverse sections of the human and mouse brain

gyrencephalic

lissencephalic)

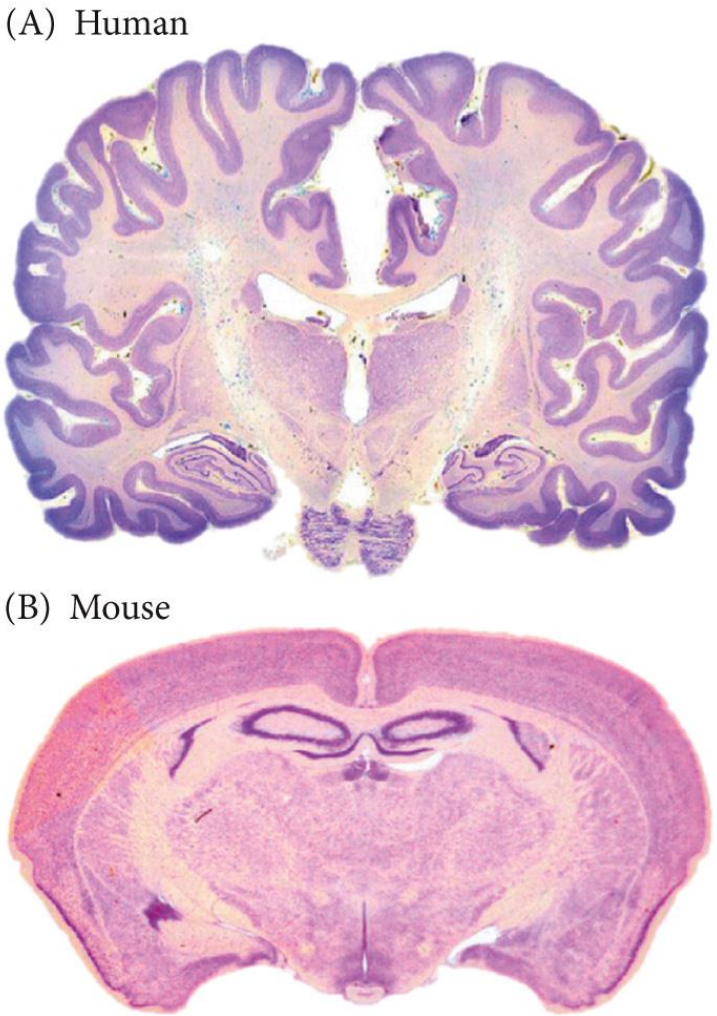

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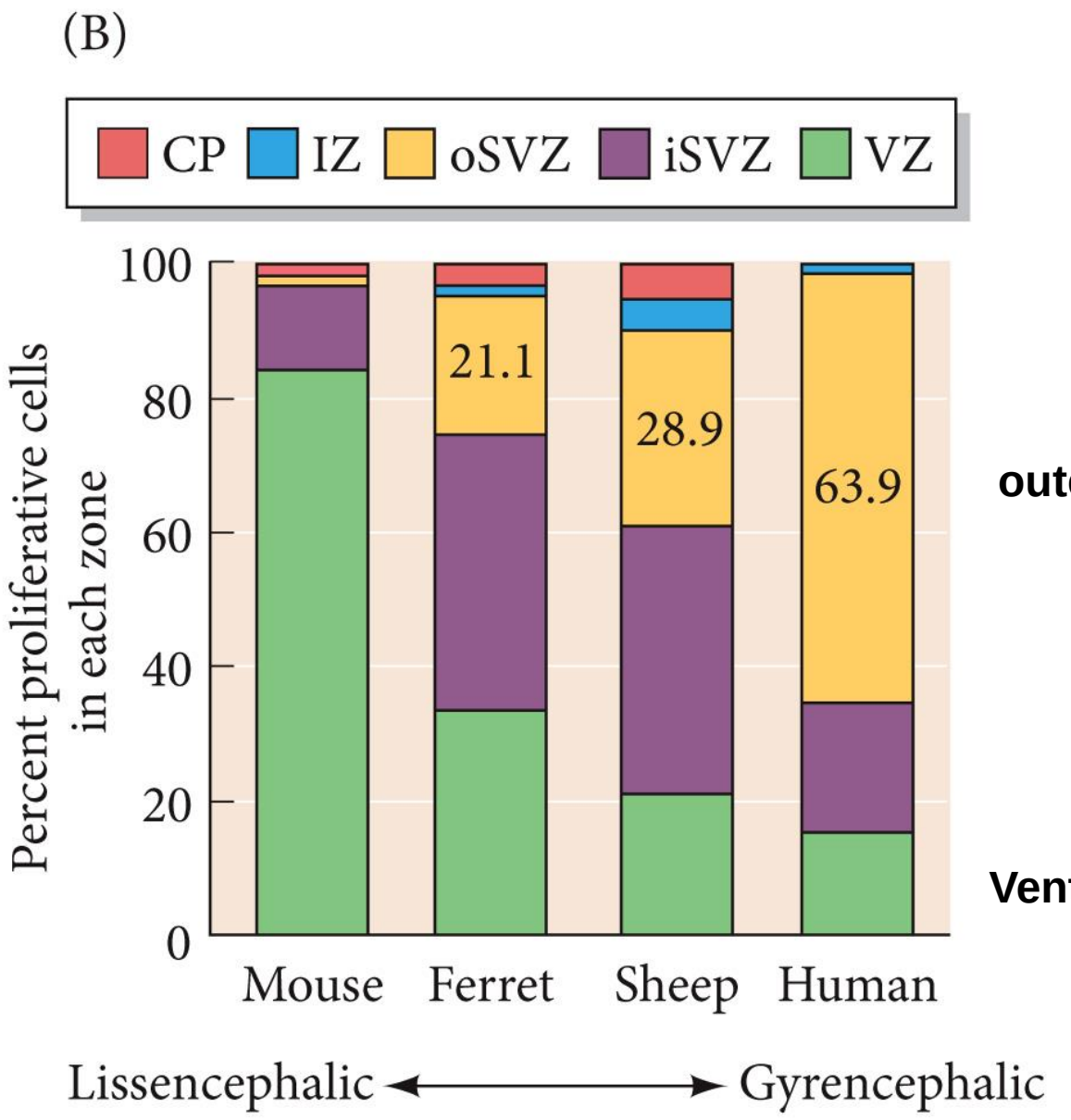
Figure 14.17 Radial glial proliferation and fanning creates during cortical folding



outer radial glial cells

Ventricle radial glial cells

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Figure 14.17 Characterization of radial glial fanning during cortical folding in the ferret neocortex (Part 3)

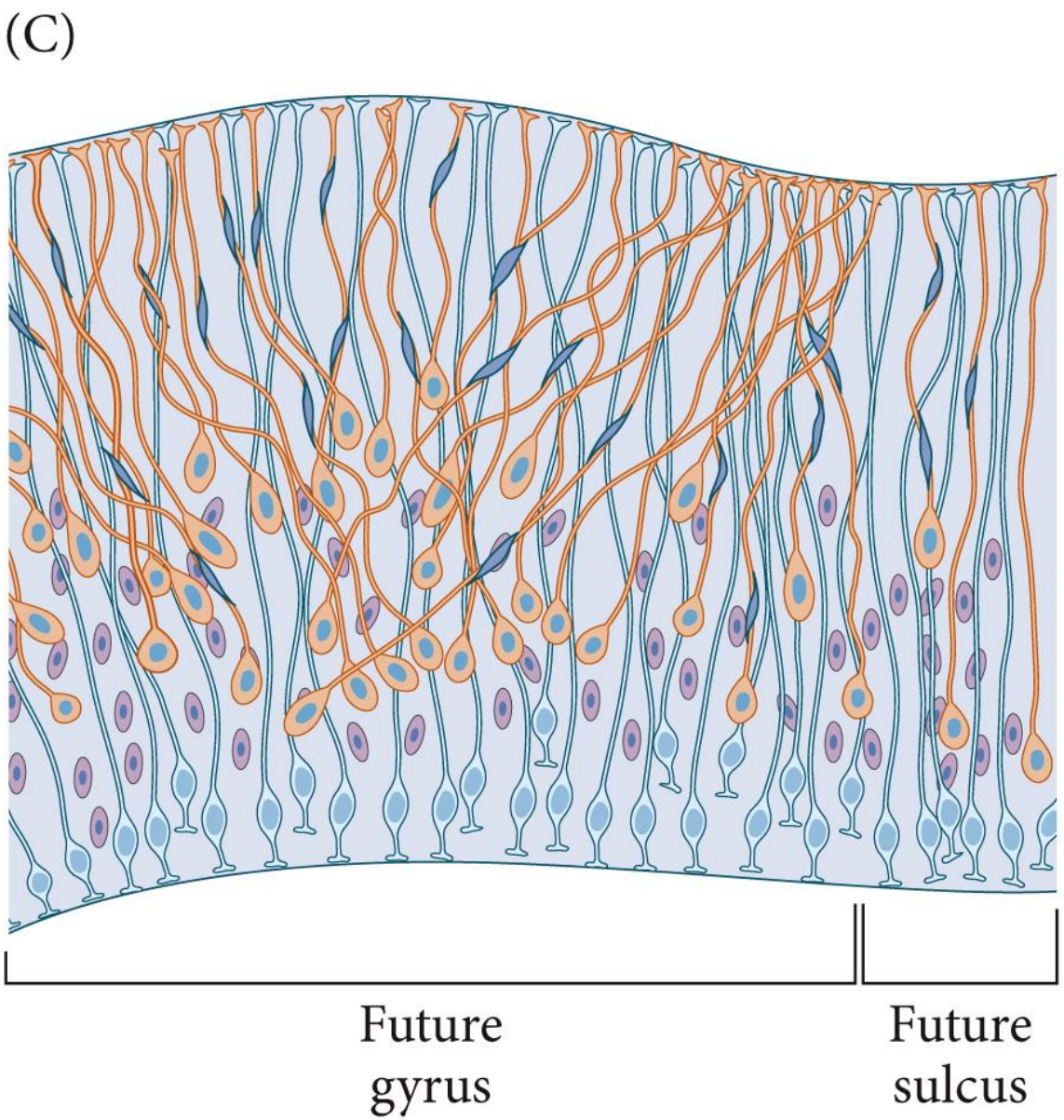

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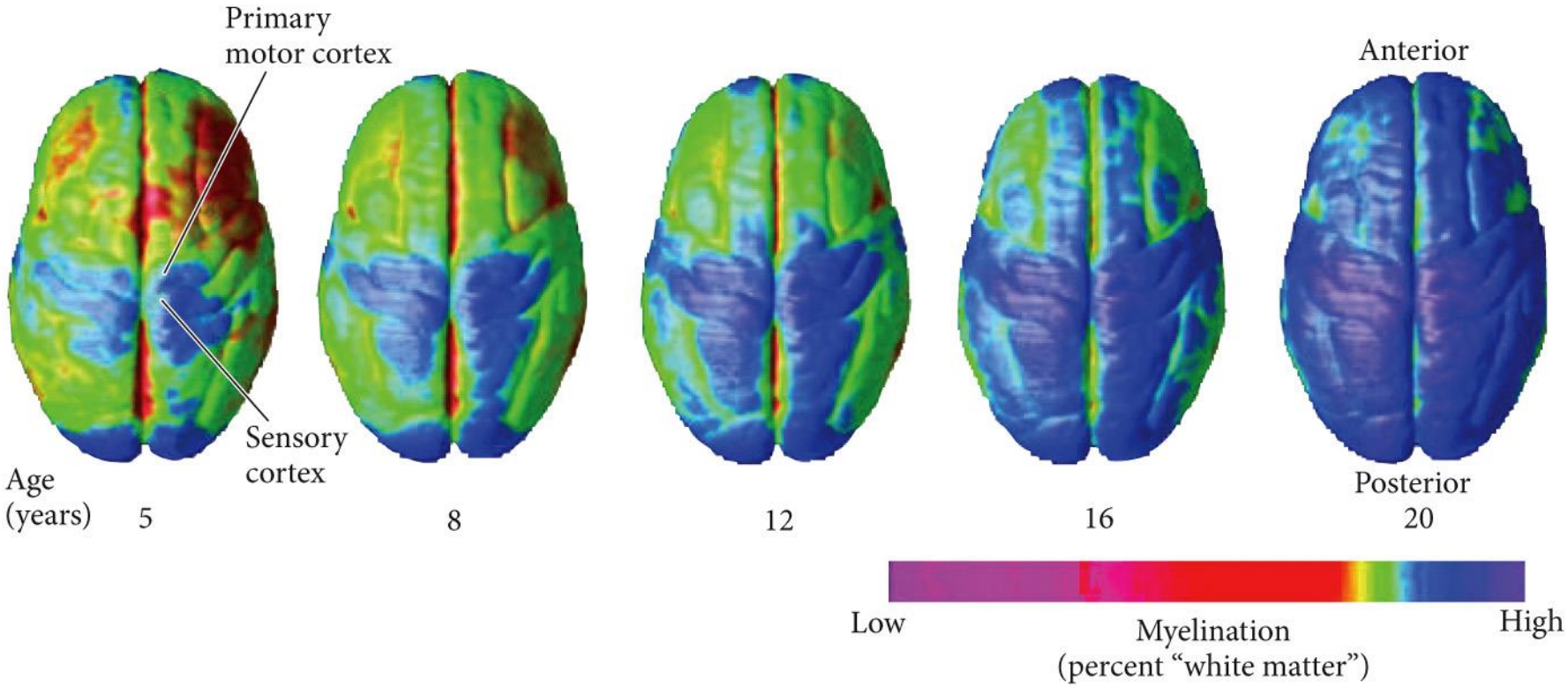
Figure 14.19 Dorsal view of the human brain showing the progression of myelination ("white matter") over the cortical surface during adolescence



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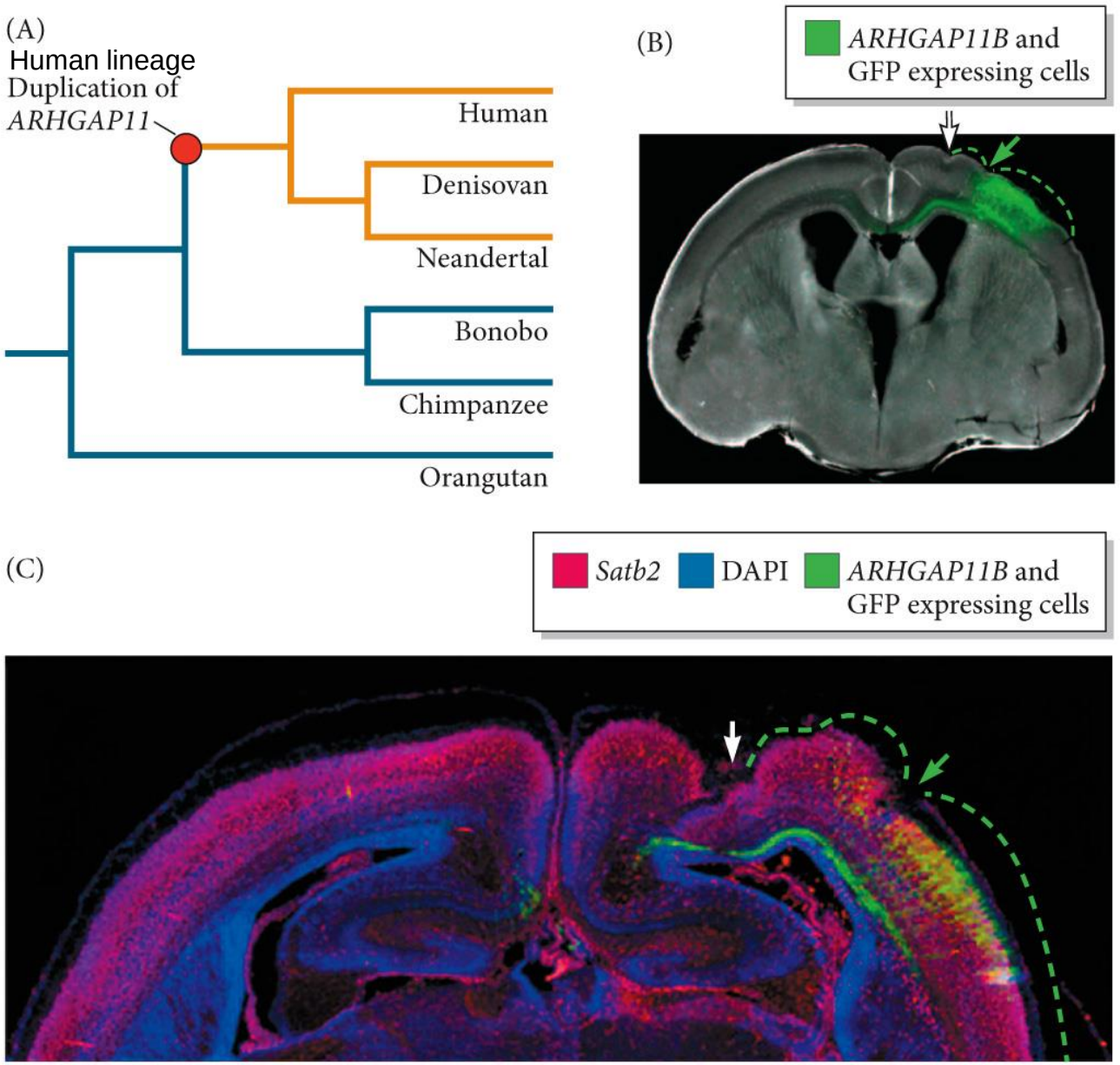
Genes important for cortical development

Lhx2, *ASPM*, *TBR1*, *Microcephalin*, *FOXP2*, *Satb2, SAtb2 as*, ***ARHGAP11B,*** *…*

Figure 14.18 *ARHGAP11B* is an evolutionarily novel human gene that can induce the formation of gyri in mouse neocortex



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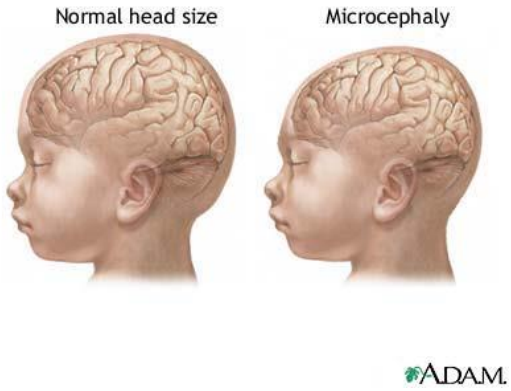
From Florio et al., 2015

Diseases reveal genes important for cortical development

Genes involved in Brain Development have undergone recent evolution.



Pathological Mutations in MCPH1 (Microcephalin) gene are associated with smaller brain size.

Recent history of this gene:

***Microcephalin*, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans**

Patrick D. Evans,[1,2] Sandra L. Gilbert,[1] Nitzan Mekel-Bobrov,[1,2] Eric J. Vallender,[1,2] Jeffrey R. Anderson,[1] Leila M. Vaez-Azizi,[1] Sarah A. Tishkoff,[4] Richard R. Hudson,[3] Bruce T. Lahn[1]**Science* 9 September 2005:Vol. 309. no. 5741, pp. 1717 - 1720DOI: 10.1126/science.1113722

The gene ***Microcephalin* (*MCPH1*)** regulates brain size and has evolved under strong positive selection in the human evolutionary lineage. We show that one **genetic variant** of *Microcephalin* in modern humans, which **arose 37,000 years ago**, increased in frequency too rapidly to be compatible with neutral drift. This indicates that it has spread under strong positive selection, although the exact nature of the selection is unknown. The finding that an important brain gene has continued to evolve adaptively in anatomically modern humans suggests the **ongoing evolutionary plasticity of the human brain.** It also makes *Microcephalin* an attractive candidate locus for studying the genetics of human variation in brain-related phenotypes.

Abnormal Spindle-like Microcephaly associated (*ASPM*) gene

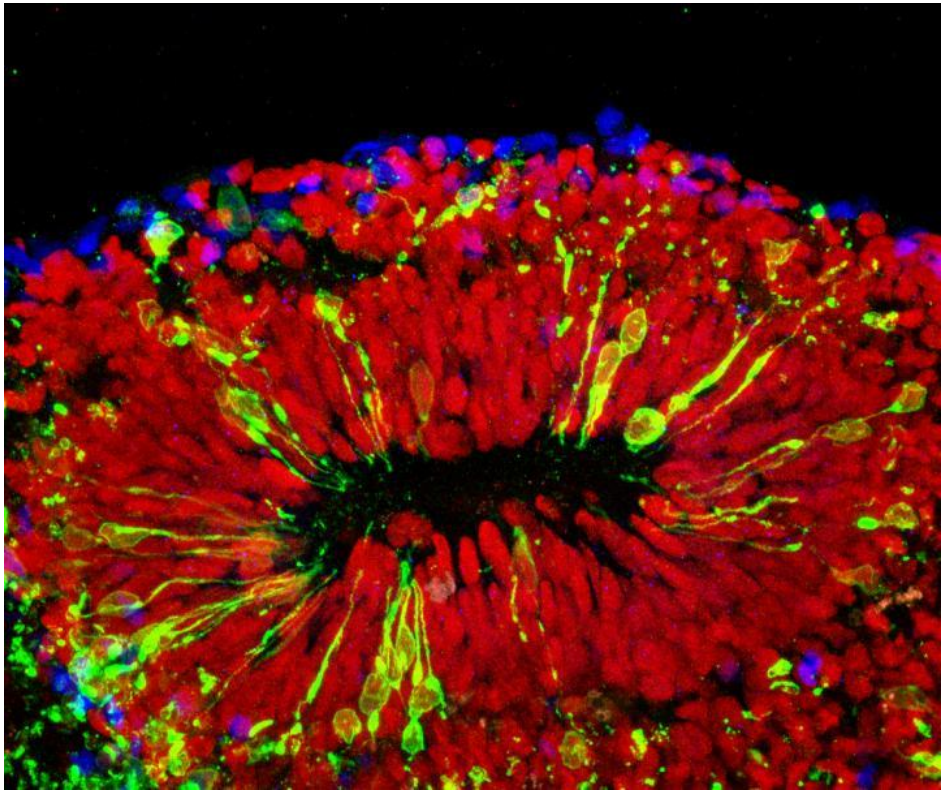
Mutation in *ASPM* cause a drastic reduction in the size of the brain's cerebral cortex, the region responsible for such higher brain functions as **abstract thought and planning.**

Lahn and his colleagues - Recent ASPM allele (variant) appeared with a mean estimate of 5,800 years ago and roughly correlates with the development of atonal language, written language, spread of agriculture and development of cities.

Forkhead box protein P2 (FOXP2) transcriptional factor (7q31)

Developmental verbal dyspraxia (KE family)

Cell Stem Cell Brief Report Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth Hengli Tang,1,11, * Christy Hammack,1,11 Sarah C. Ogden,1,11 Zhexing Wen,2,3,11 Xuyu Qian,2,4,11 Yujing Li,9 Bing Yao,9 Jaehoon Shin,2,5 Feiran Zhang,9 Emily M. Lee,1 Kimberly M. Christian,2,3 Ruth A. Didier,10 Peng Jin,9 Hongjun Song,2,3,5,6,7, * and Guo-li Ming2,3,5,6,7,8, *

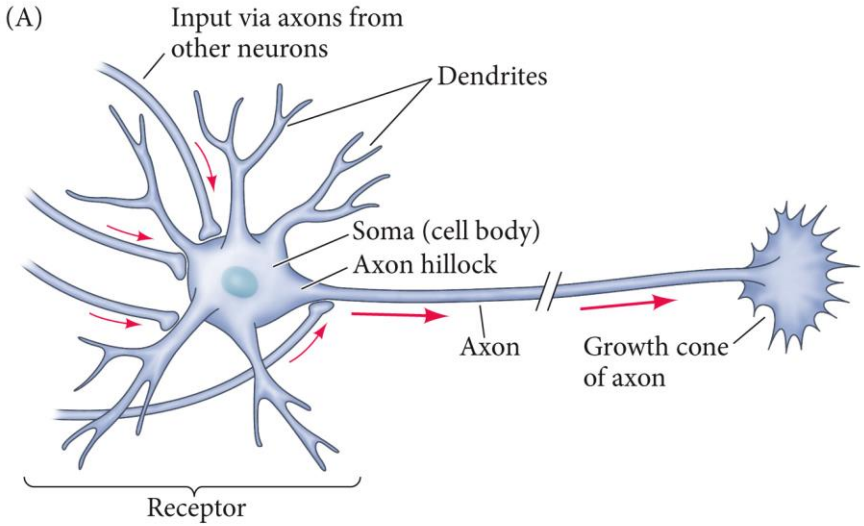


This is a mini-brain infected with Zika virus. The virus is shown in green, vulnerable neural progenitor cells are shown in red, and neurons are shown in blue

(5) Axonal growth & Specificity

Ch. 15, part 2

Figure 15.42 Analysis of motor neuron axon stalling and cell death in *Frizzled-3* knockout mice (Part 2)



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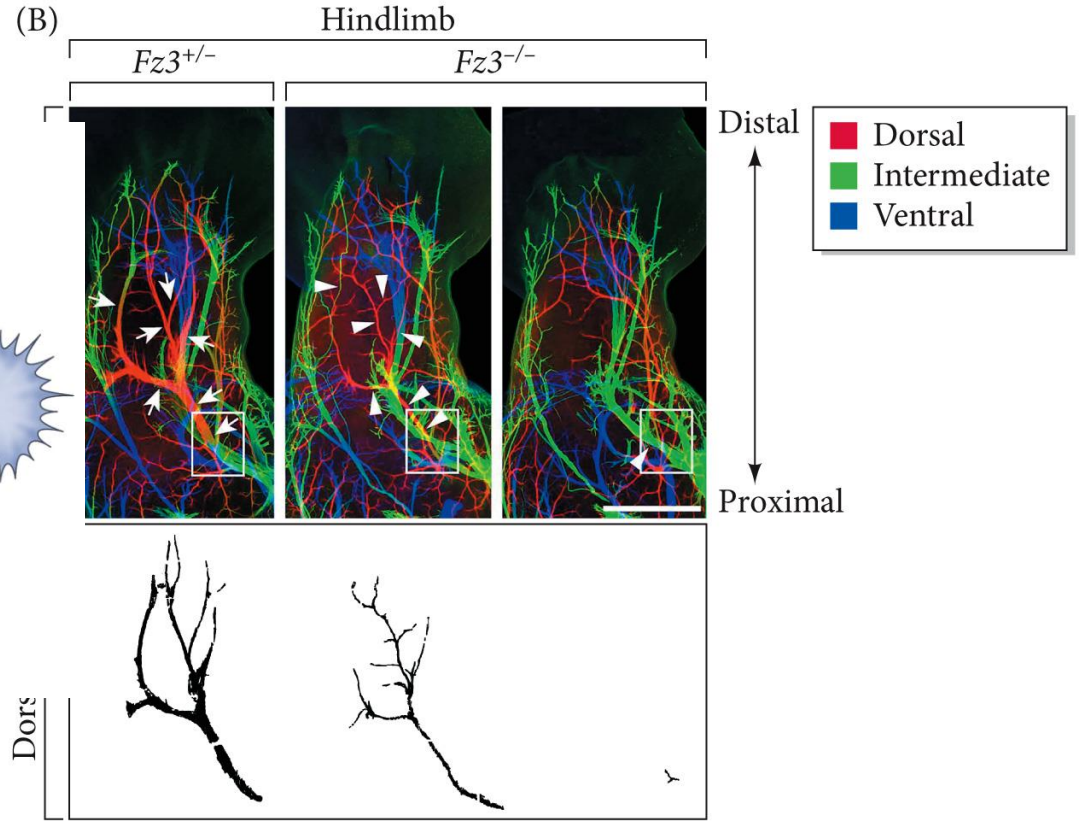

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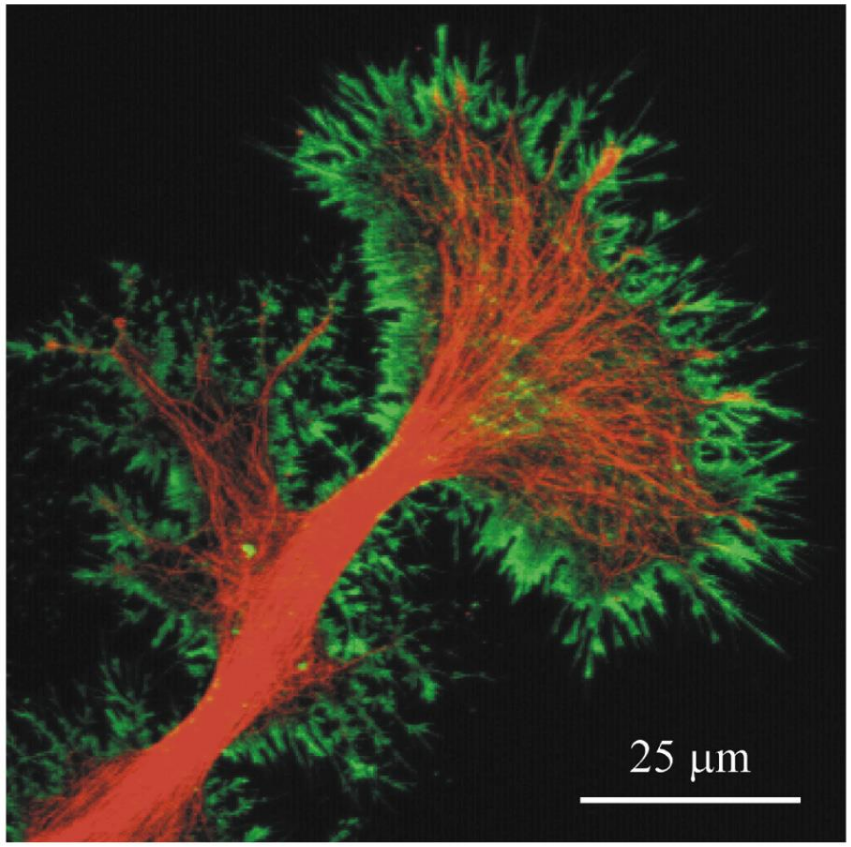
Establishing Axonal Pathways in the Nervous System

At the beginning of the twentieth century, there were many competing theories on how axons formed.

- Theodor Schwann - numerous neurons linked themselves together in a chain to form an axon.
- Viktor Hensen - axons formed around preexisting cytoplasmic threads between the cells.
- Wilhelm His (1886) and Santiago Ramón y Cajal (1890)- axon is an outgrowth (albeit an extremely large one) of the neuron's soma.

1907 – Harrison grows from nerve cells by 'hanging drop' technique

Figure 15.24 Axon growth cones (Part 1)



DEVELOPMENTAL BIOLOGY 11e, Figure 15.24 (Part 1)
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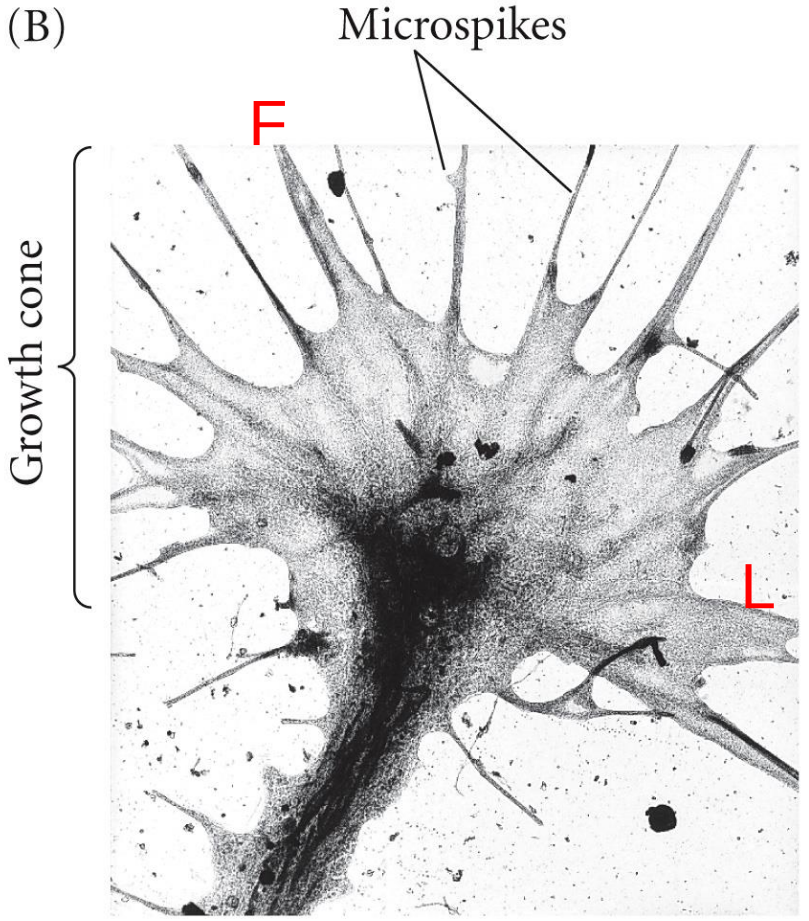

DEVELOPMENTAL BIOLOGY 11e, Figure 15.24 (Part 2)
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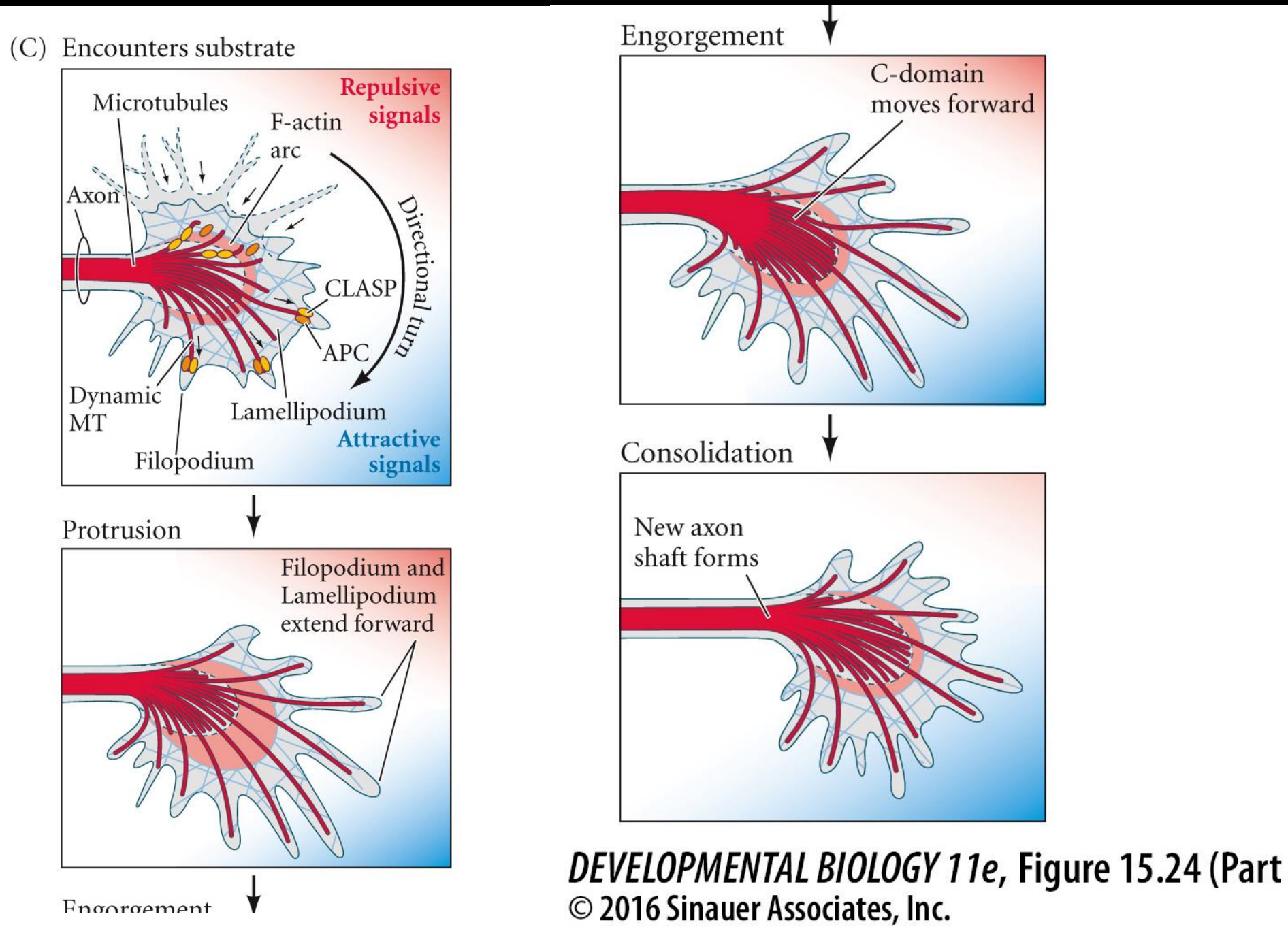
Figure 15.24 (A) Growth cone of the hawkmoth *Manduca sexta*. The actin imicrospikes in the filopodia is stained green with phalloidin, and the microtubules red with a fluorescent antibody to tubulin. (B) Actin microspikes in sensory filopodia (F) and f-actin in lammelipodia (L) - transmission electron microscopy. (

Figure 15.24 Axon growth cones (Part 3)



DEVELOPMENTAL BIOLOGY 11e, Figure 15.24 (Part

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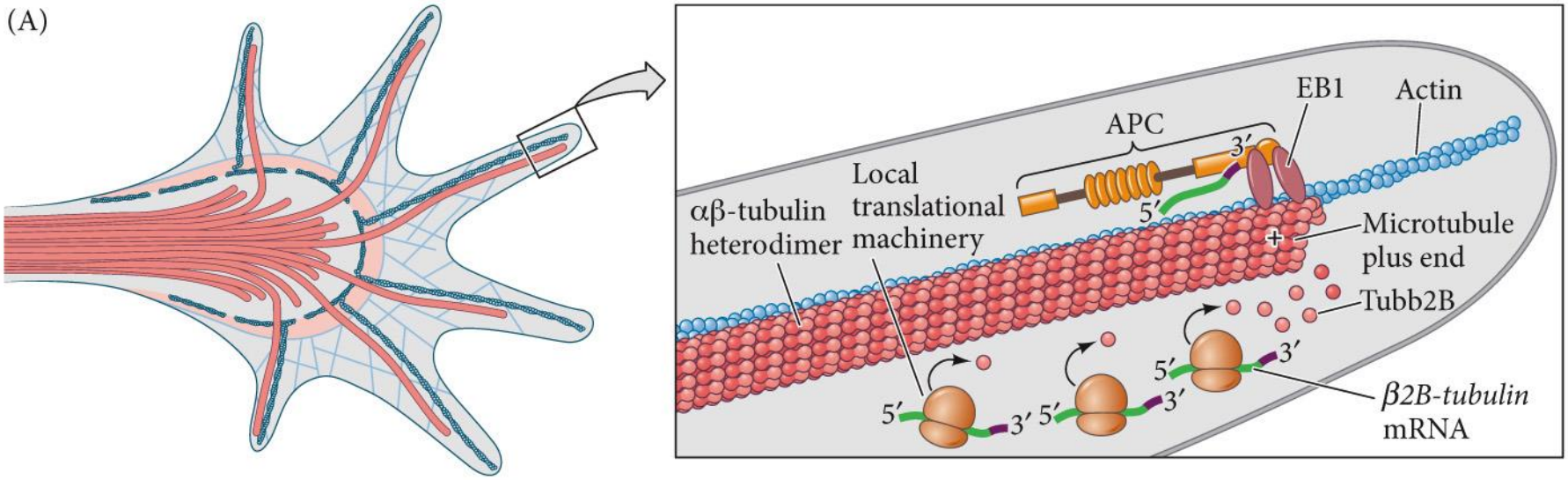
Figure 15.25 APC localizes tubulin mRNA at the plus end of microtubules for spatially targeted translation to fuel growth cone expansion (Part 1)

Tubulin turnover:



DEVELOPMENTAL BIOLOGY 11e, Figure 15.25 (Part 1)

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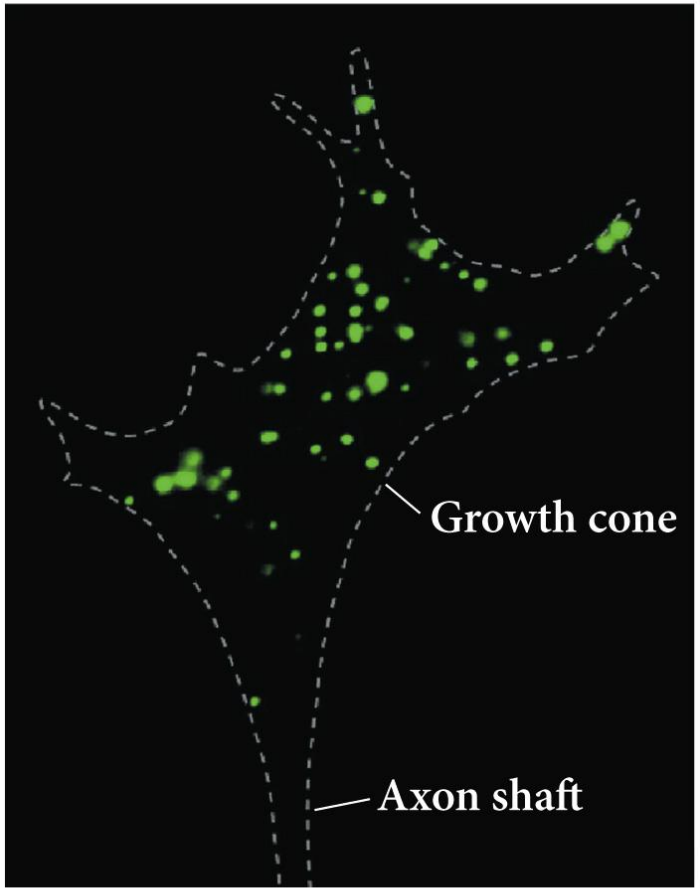
Figure 15.25 APC co-localizes tubulin at the plus end of microtubules

(B) *Tubb2b* mRNA



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Colocalization of Tub protein and APC

(C)

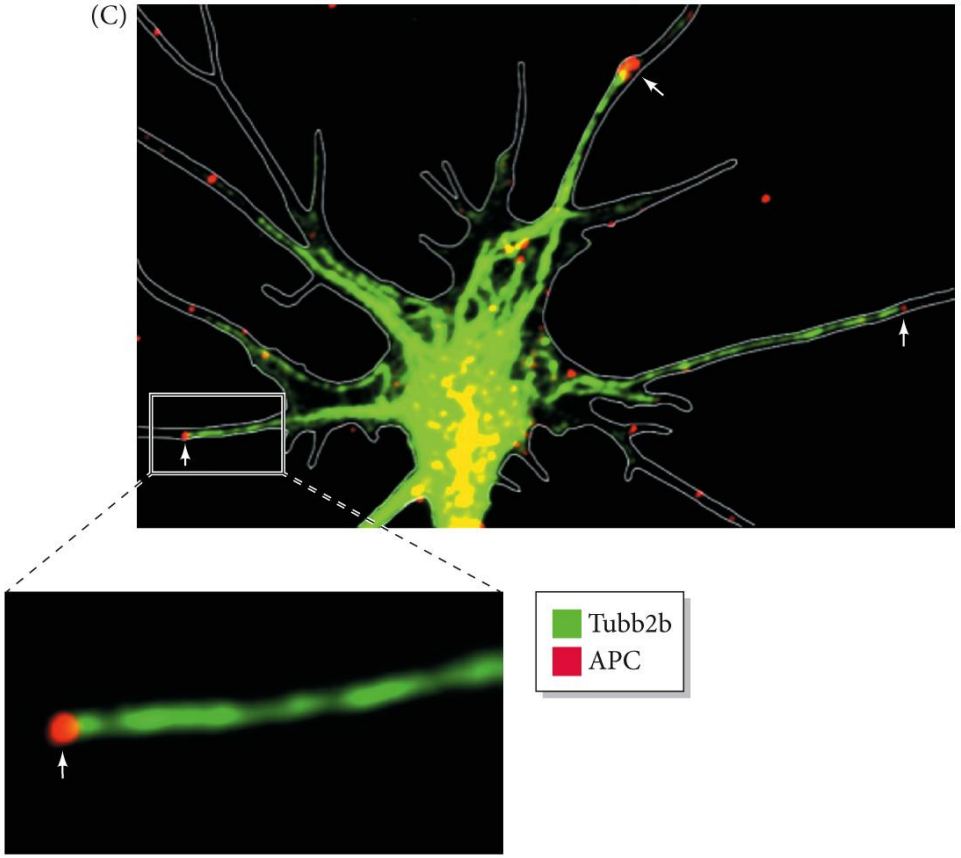

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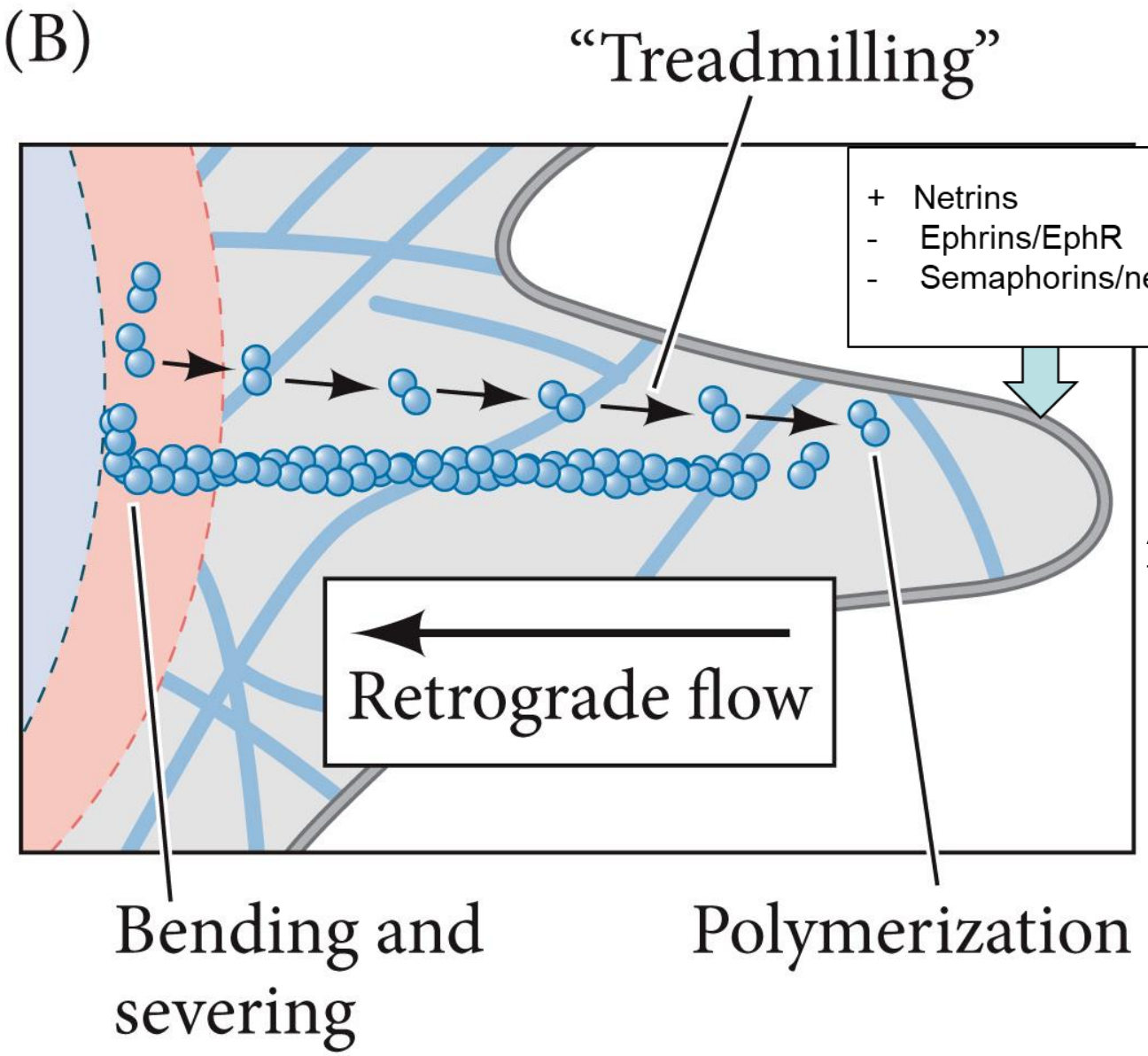
Figure 15.26 Rho GTPases interpret and relay external guidance signals to the actin cytoskeleton (Part 2)



Focal Adhesions (transient): Actin connected to **Cadherins, Integrins** to ECM (regulated by FAK)

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Figure 15.29 Repulsion of dorsal root ganglion growth cones

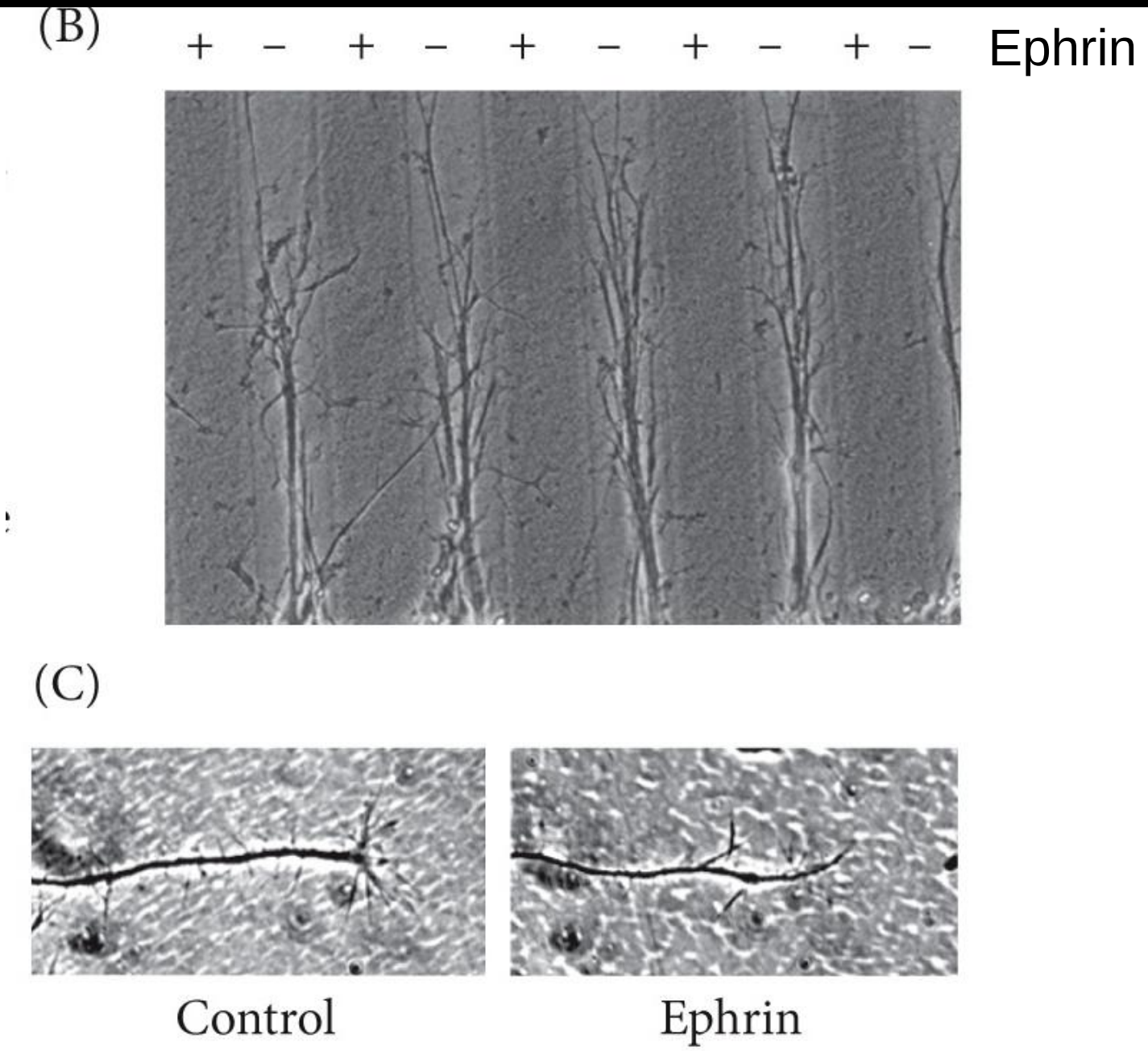
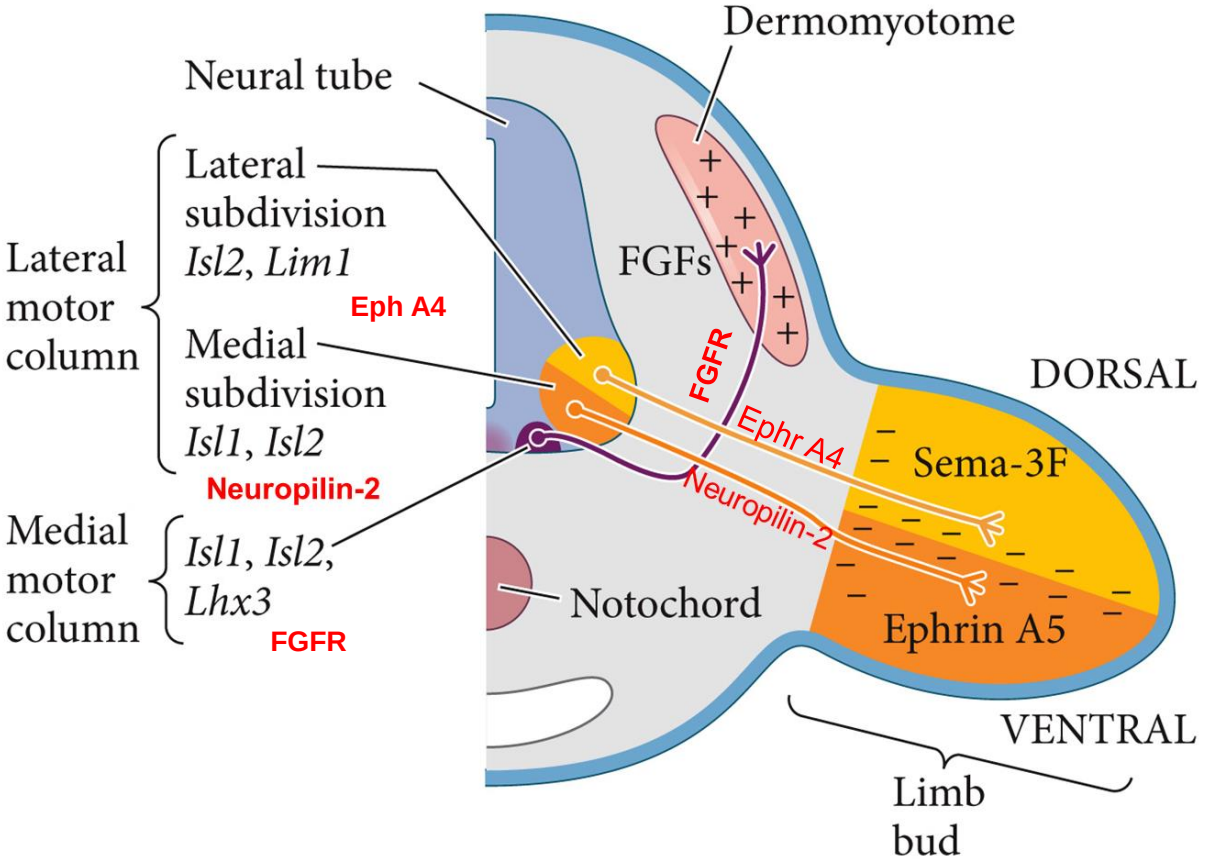


Figure 15.28 Motor neuron organization and Lim specification in the spinal cord innervating the chick hindlimb Transcription factors Lim determine growth factor receptor expressed and GF target selection.



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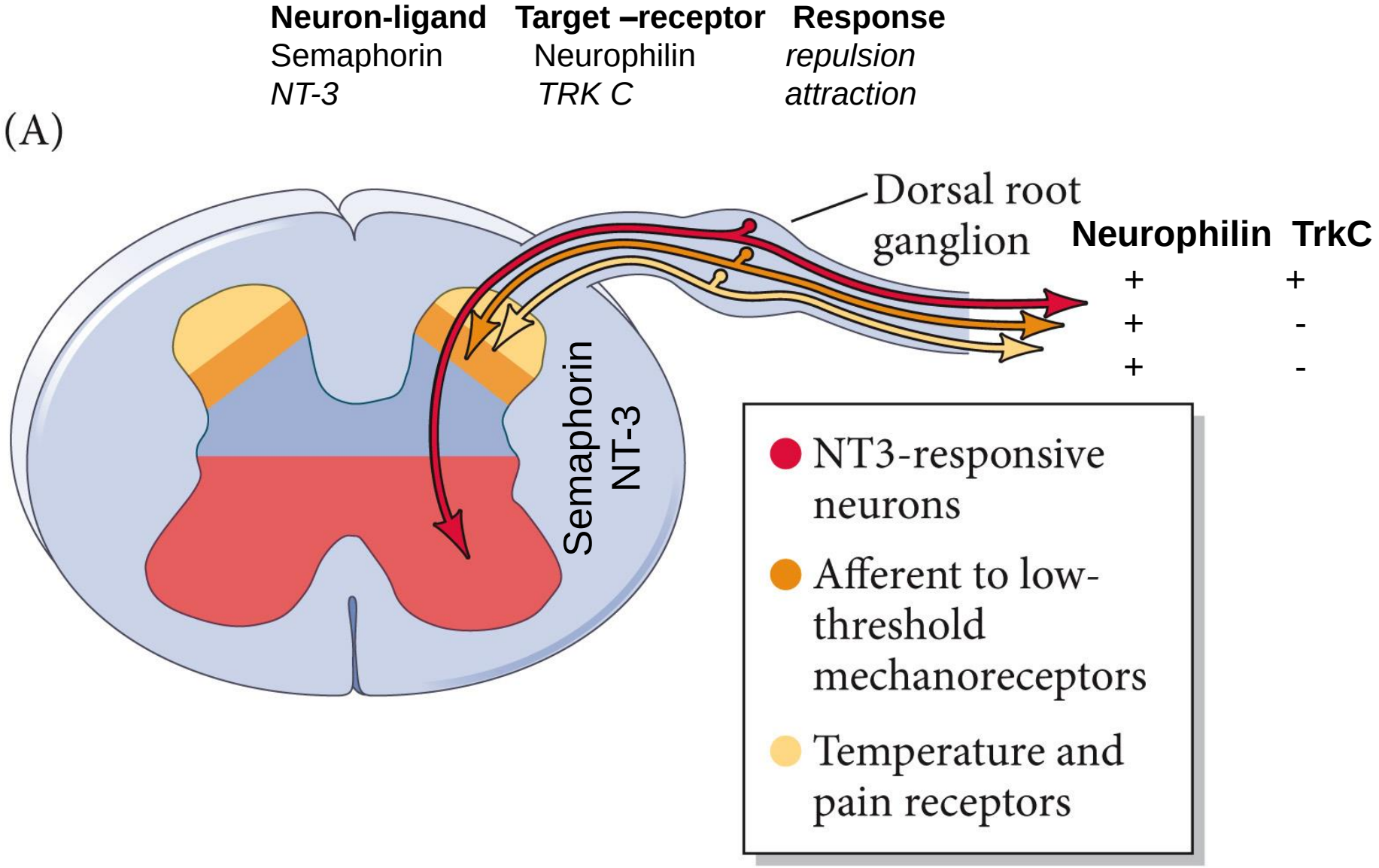
Neuron-ligand	**Target –receptor**	**Response**
Semaphorin	Neurophilin	*repulsion*
Eph A4	*Ephrin A5*	*repulsion*
FGF	*FGFR*	*attraction*

Figure 15.31 Semaphorin-3 as a selective inhibitor of axonal projections into the ventral spinal cord (Part 1)



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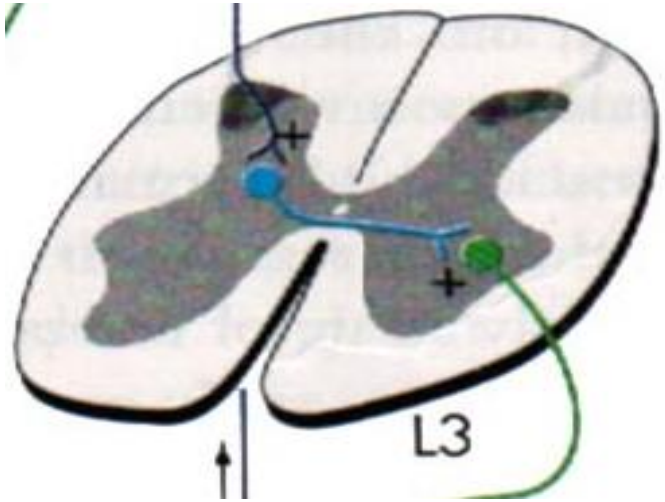
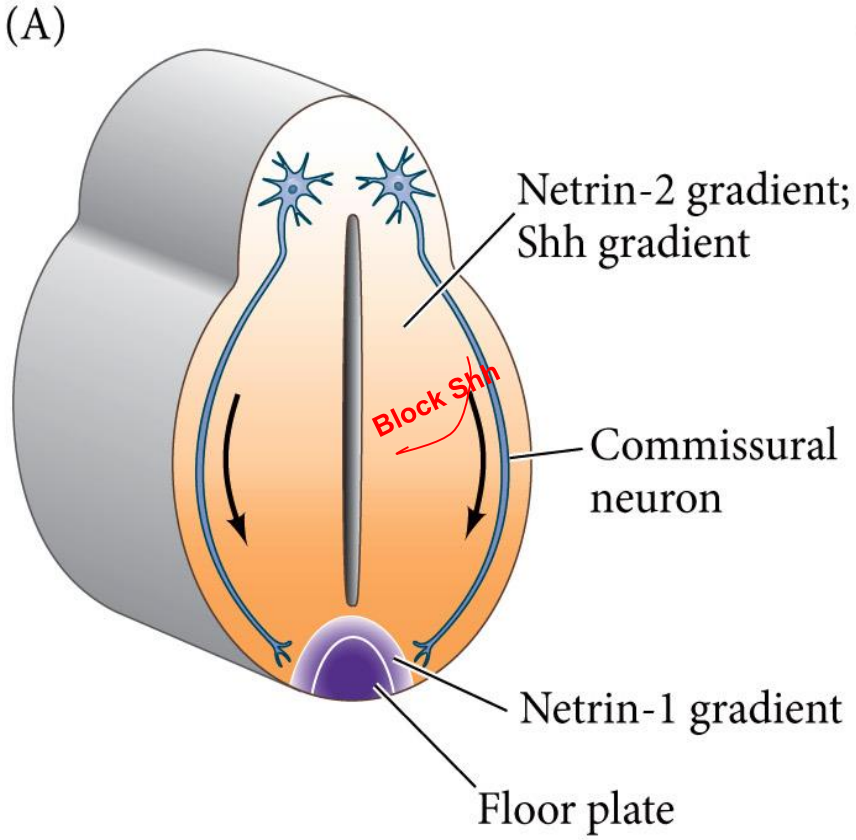
HOW DID THE AXON CROSS THE ROAD?

Commissural neurons



Santiago Ramón y Cajal (1892)
-" diffusible molecules might signal the commissural neurons of the spinal cord to send axons from their dorsal positions in the neural tube to the ventral floor plate"
and to cross….

Figure 15.32 Trajectory of commissural axons in the rat spinal cord



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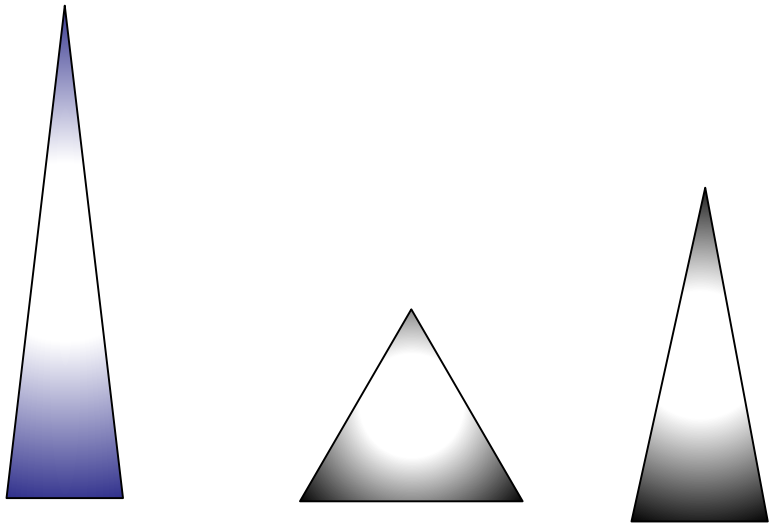

Shh Netrin Vegf

Neuron-ligand	**Target –receptor**	**Response**
Shh	Patched/smoothened	attraction
Netrin	*DCC*	*attraction*
Vegf	*VEGFR*	*attraction*

Legend: DCC-deleted in colon Cancer; VEGF Vascular Endothelial GF.

Figure 15.35 Model of axon guidance of commissural neurons crossing the midline in the fly and the mouse (Part 1)

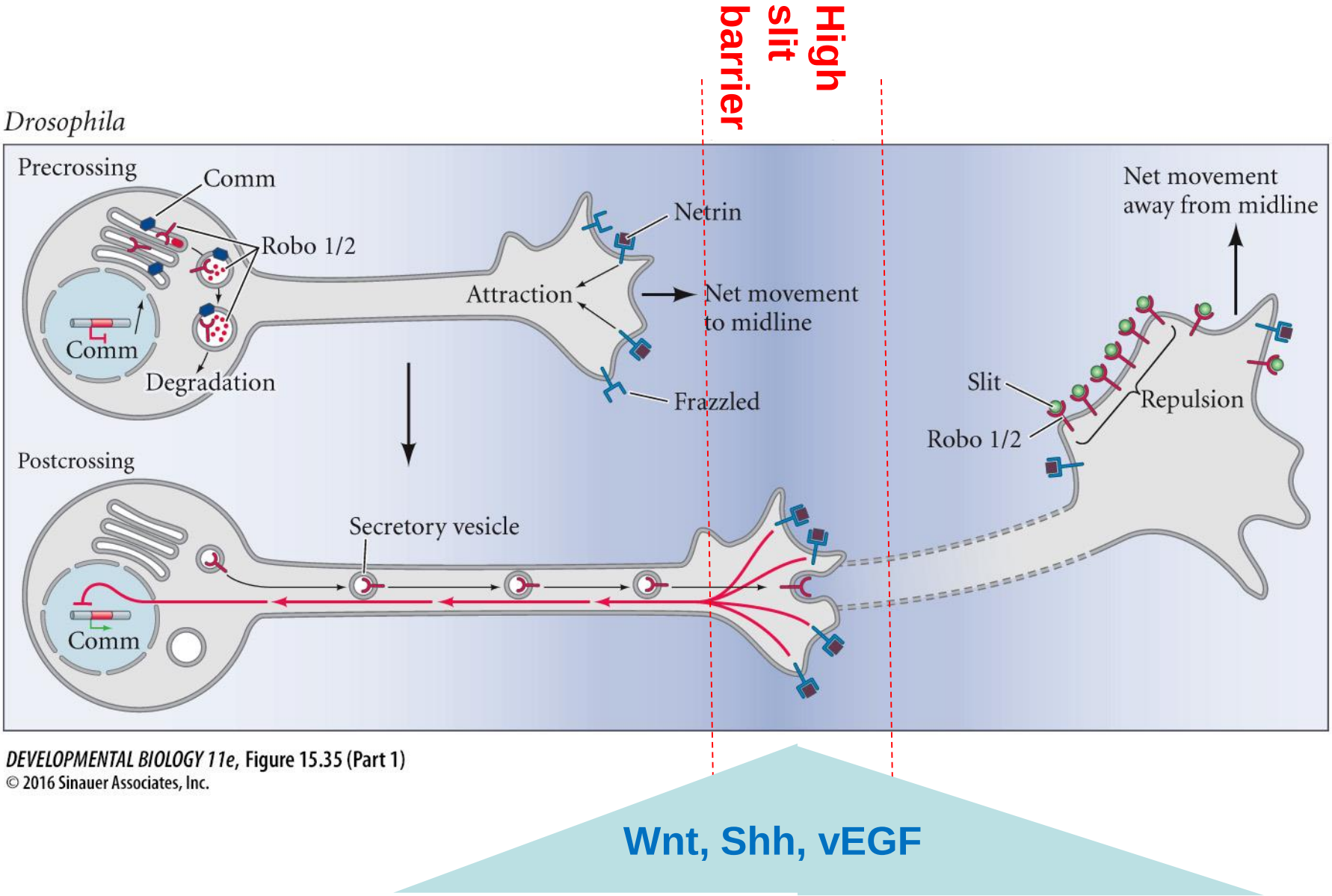

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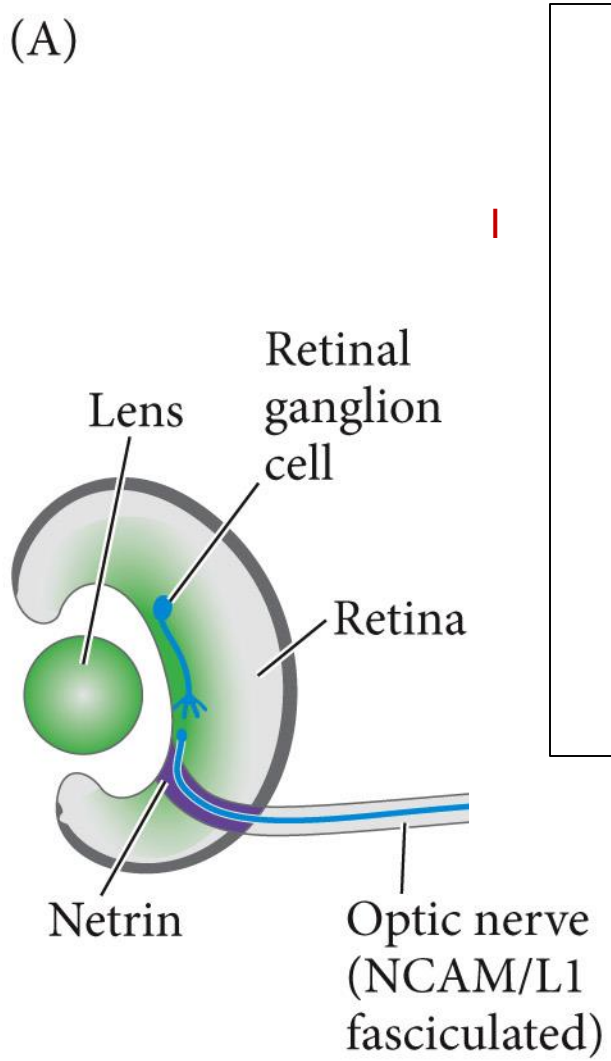
Figure 15.36 Leaving Retina



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Receptor on RGC	Ligand in Retina
RGC Retinal repellants:	
Integrins	Chondroitin sulfate
Robo	Slit
RGC retinal attractants:	
DCC	Netrin (optic disc)
RGC axonal fasciculators:	
FGFR, NCAM	NCAM,L1

Figure 15.36 Multiple guidance cues direct the movement of retinal ganglion cell (RGC) axons to the optic tectum (Part 2)

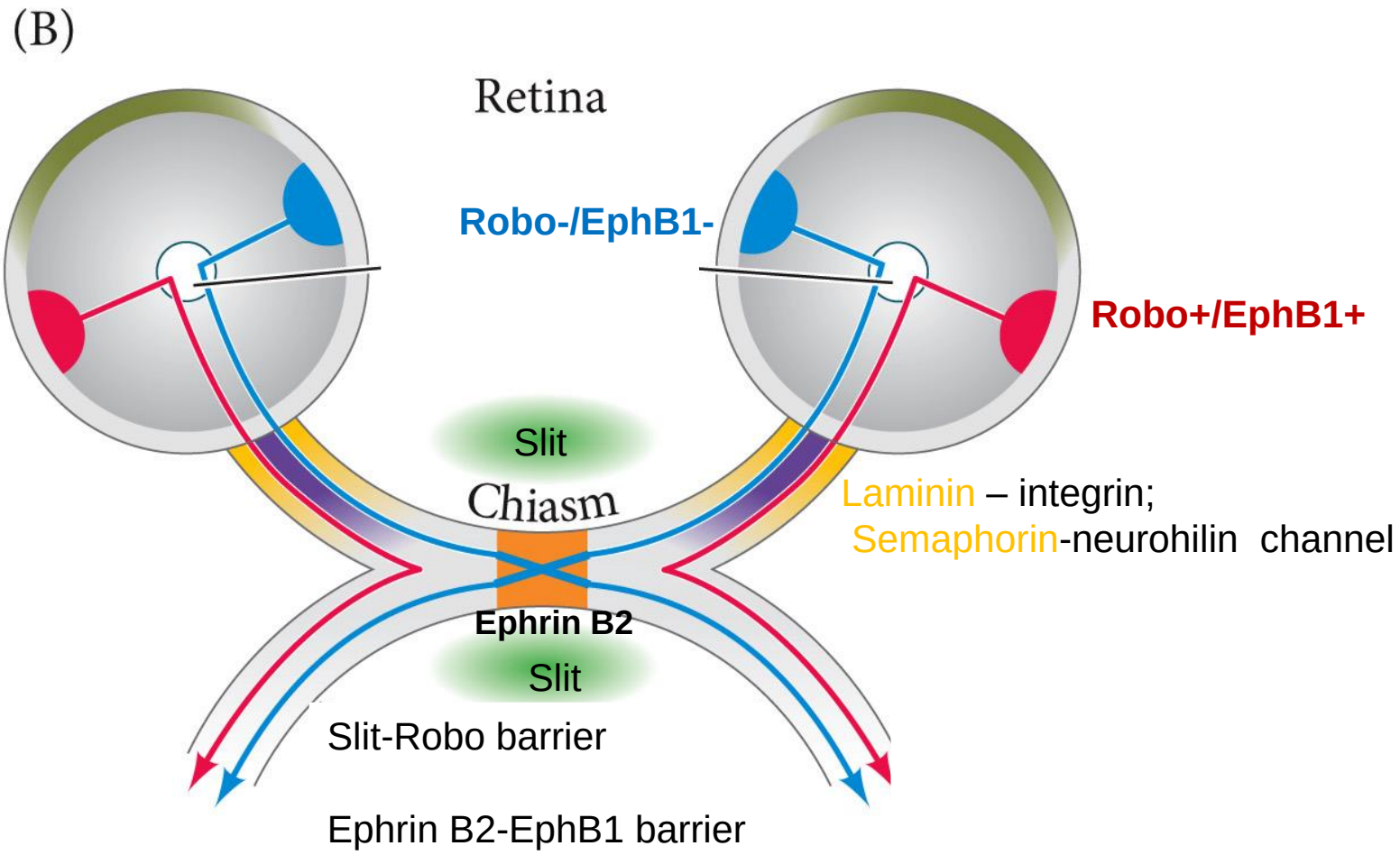

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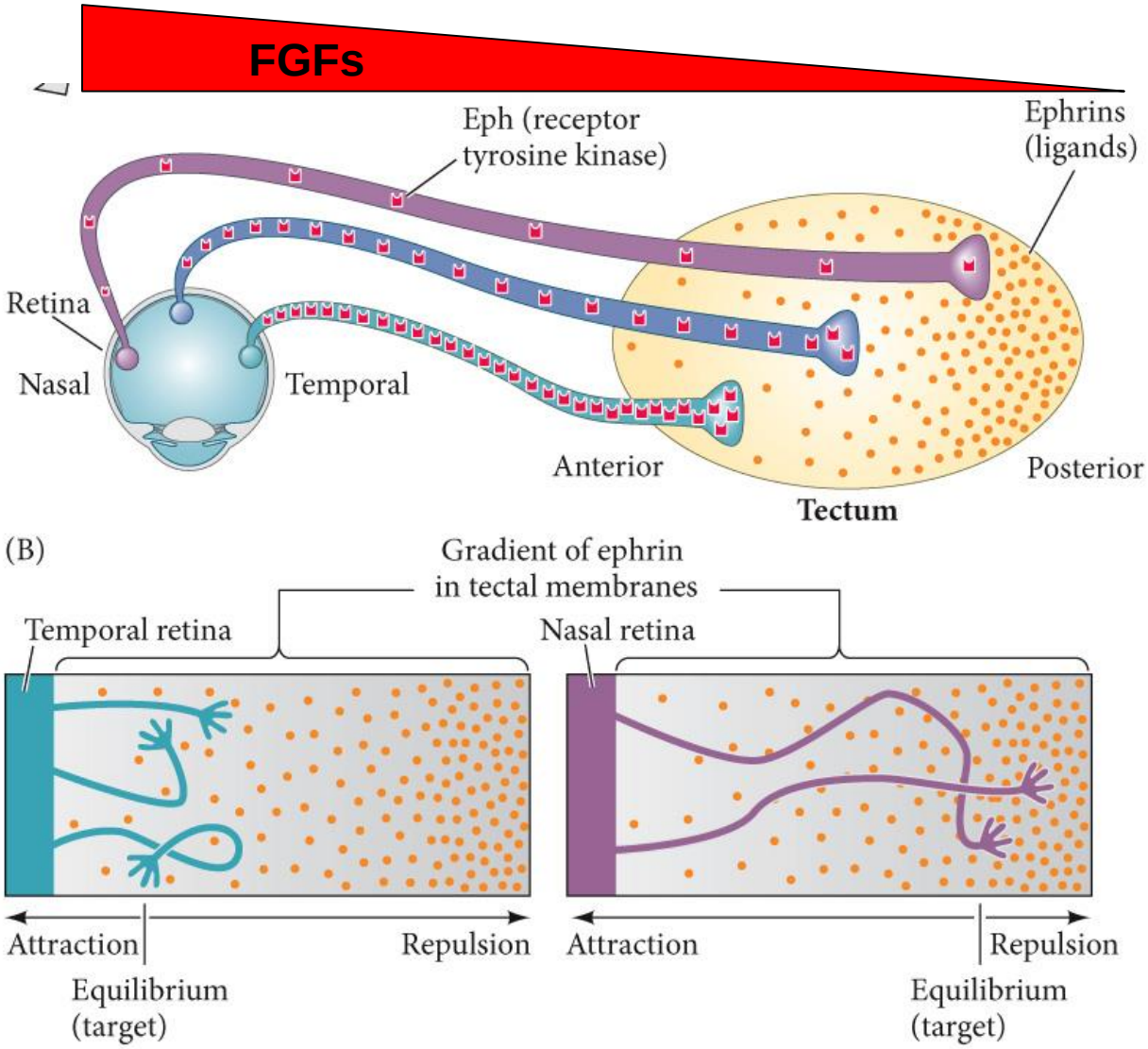
Figure 15.39 Topographic maps - Differential retinotectal adhesion is guided by gradients of Eph receptors and their ligands



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