

Late Embryonic and Fetal Development of the Nervous System

Prof. Ken Ashwell

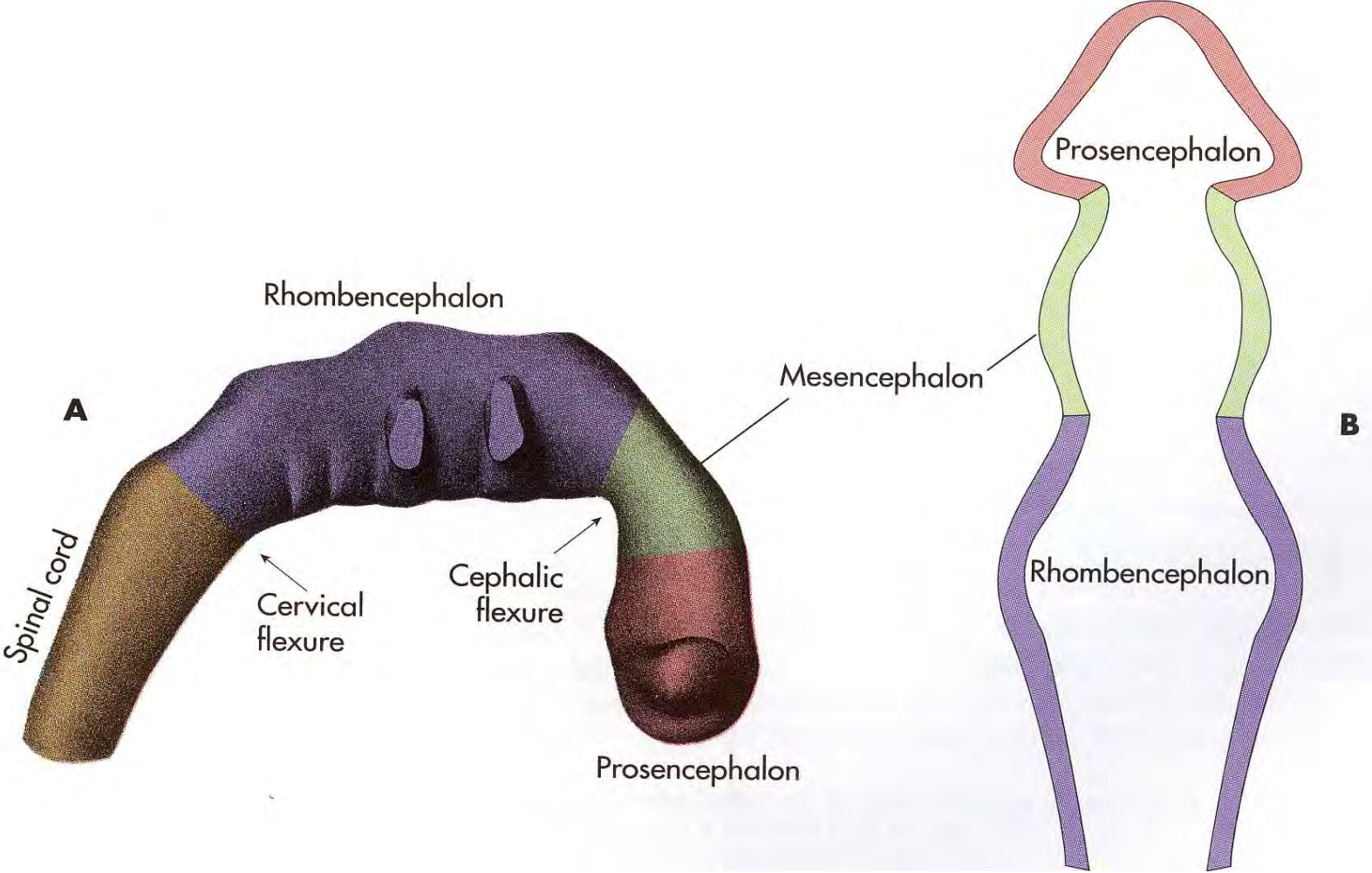
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School of Medical Sciences



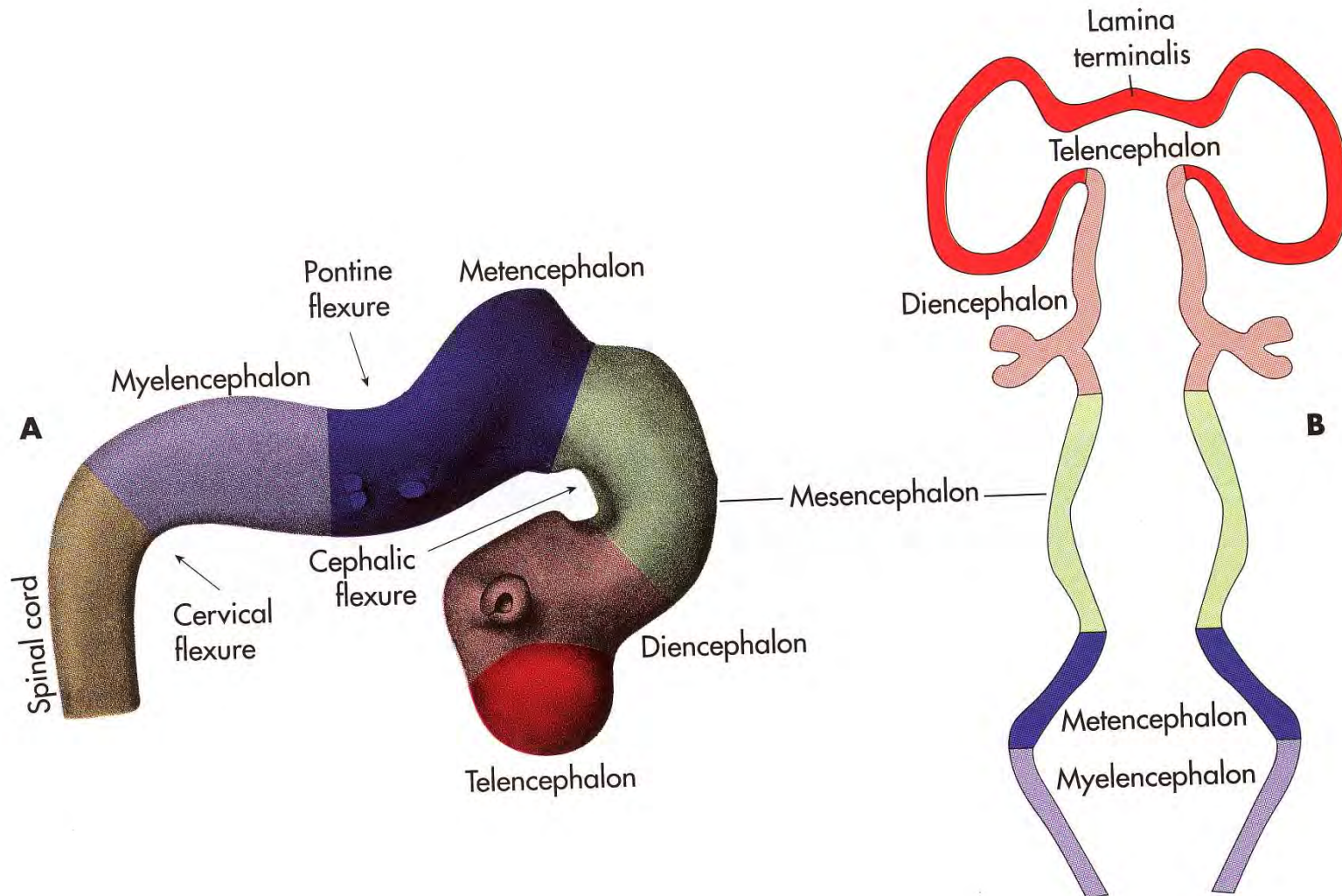
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The Developing Brain Vesicles 1

(The Traditional View)



The Developing Brain Vesicles 2 (The Traditional View)



Neuromeric Organization

Fig. 12 - 8

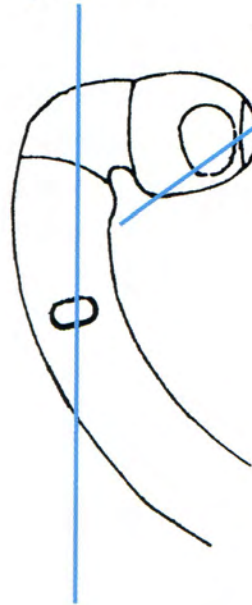
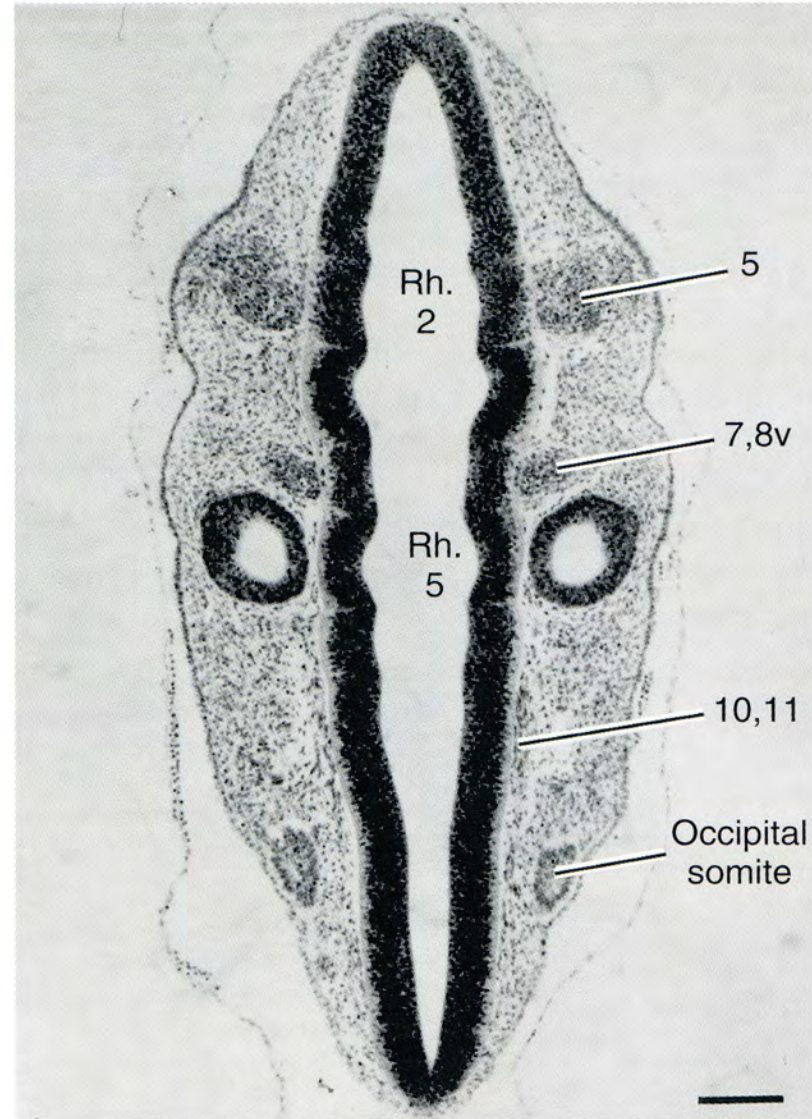
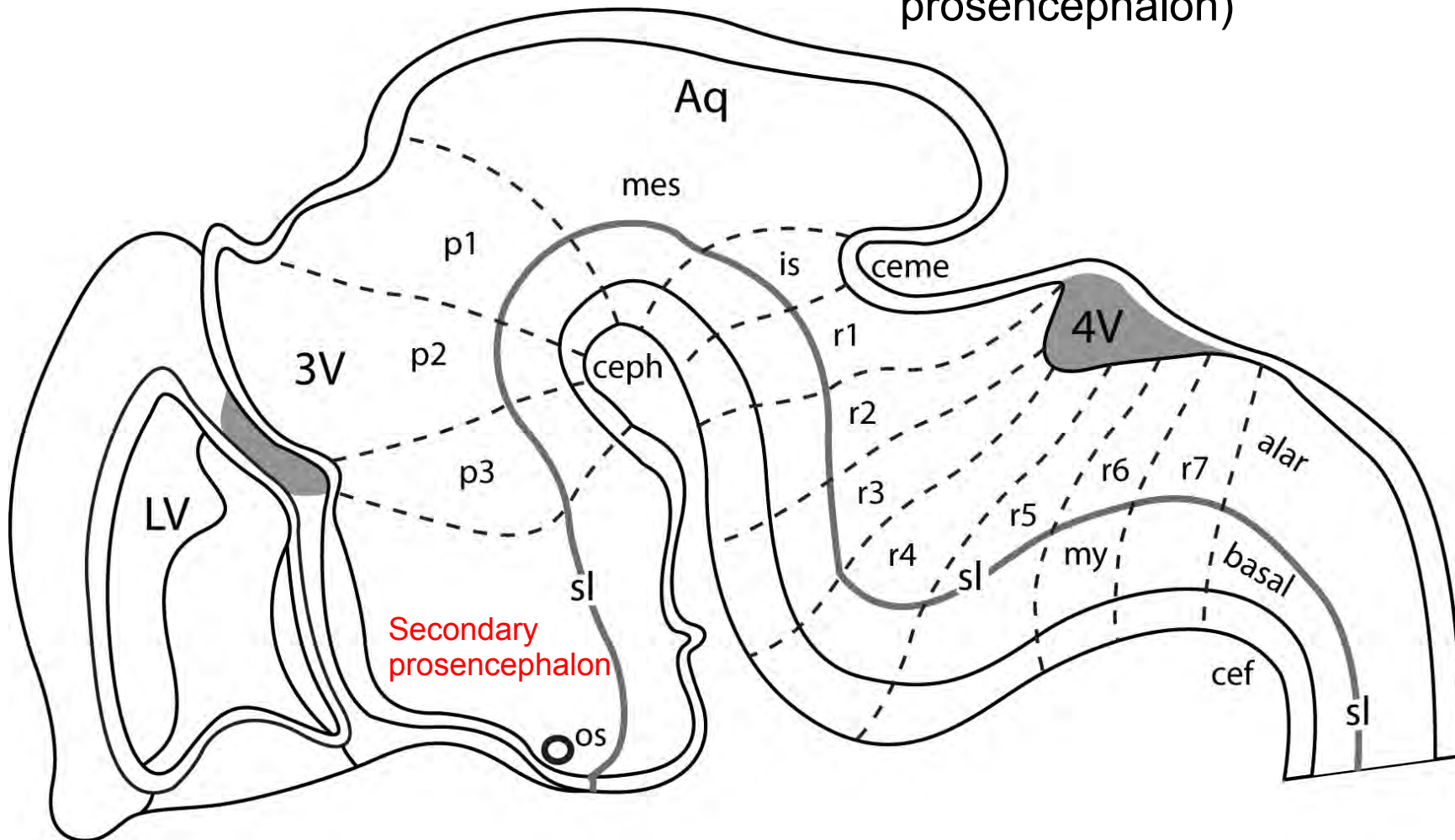


Fig. 12 - 7

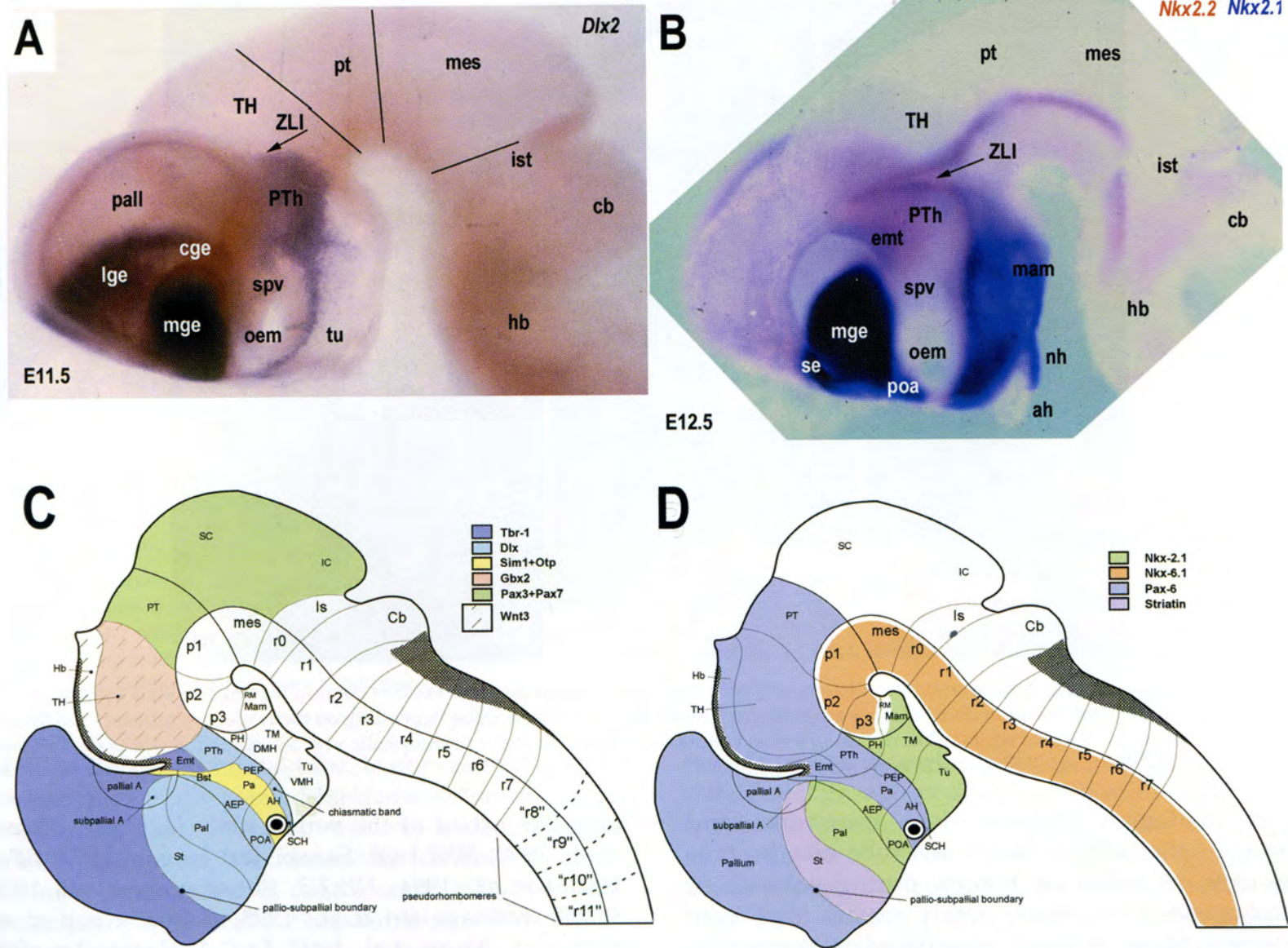


Neuromeres

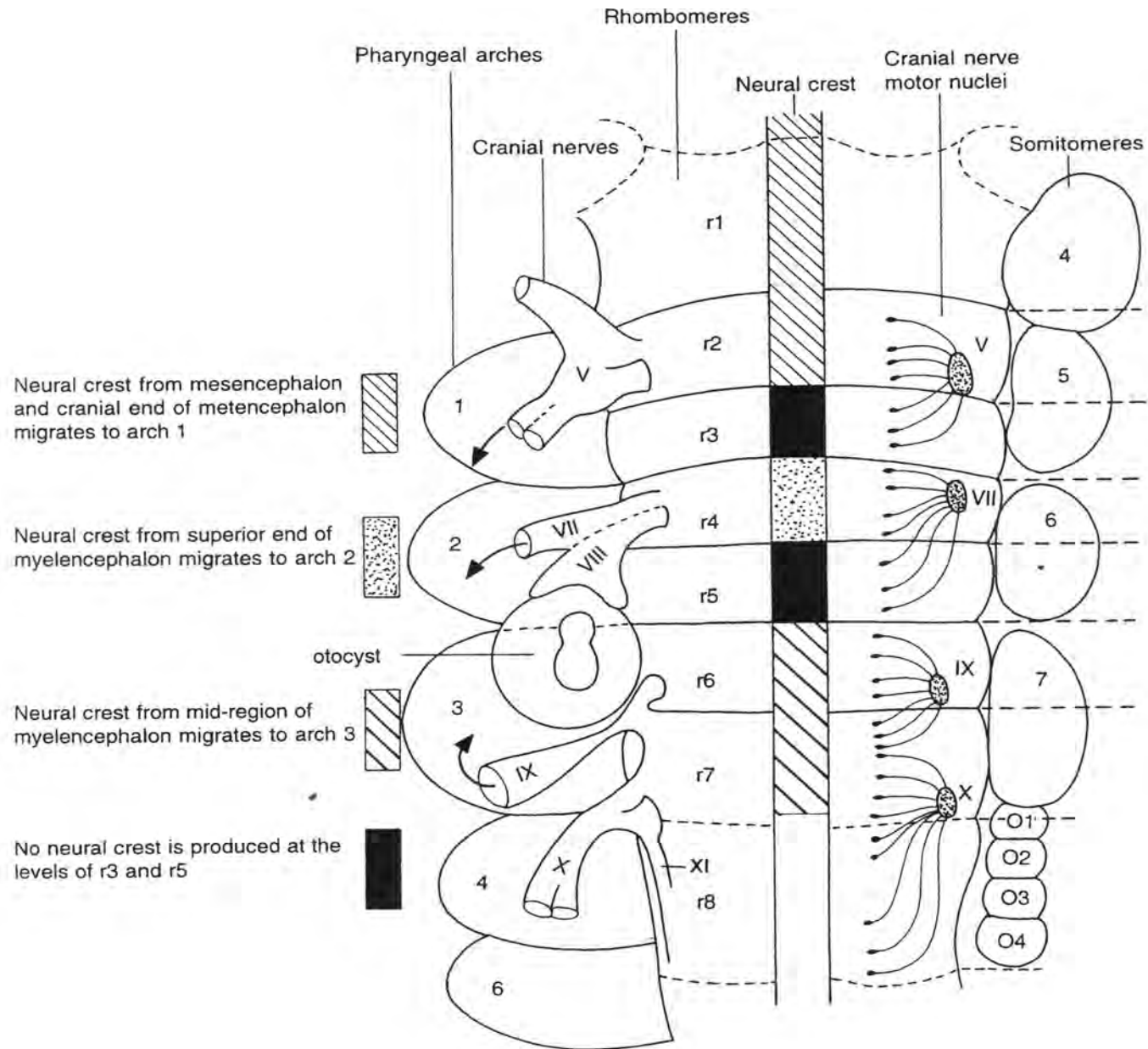
- Rhombomeres: r1 to r7 (8)
- Isthmic neuromere: is
- Mesencephalic neuromere: mes
- Prosomeres: p1 to p3
- Proneuromere zone (secondary prosencephalon)



Gene Expression and Neuromeric Organization of the Brain



Derivatives of the Rhombomeres



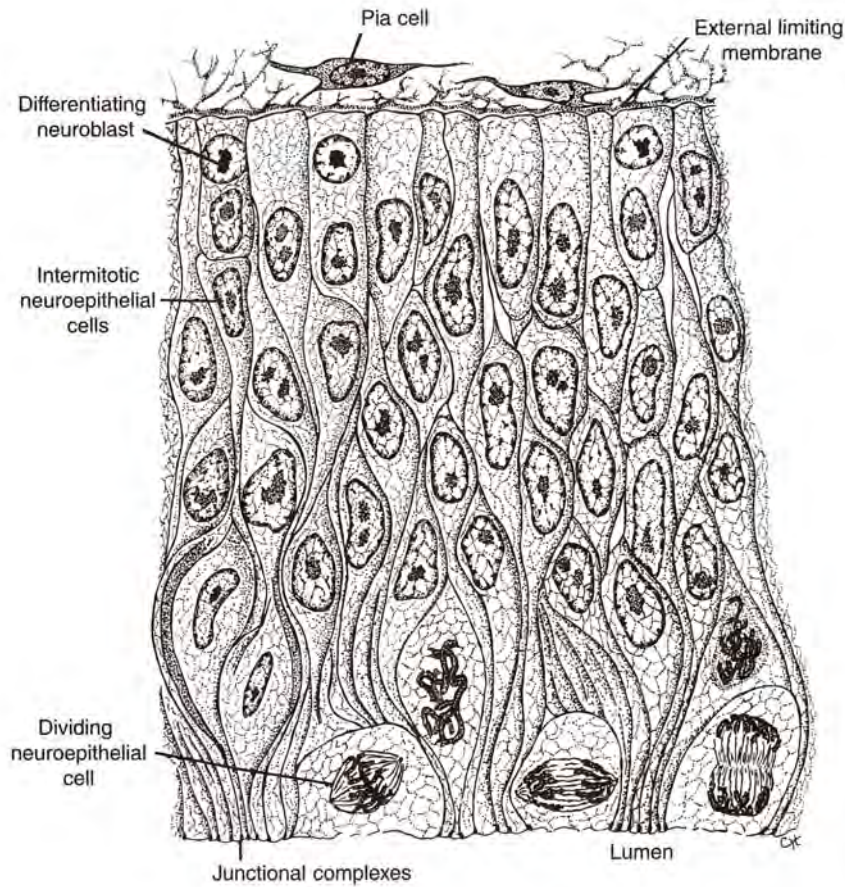
Derivatives of the Prosomeres

- p1 → pretectum
- p2 → dorsal thalamus (motor and sensory relay nuclei)
- p3 → ventral thalamus (reticular thalamic nucleus, zona incerta, subthalamus)

Derivatives of the Proneuromere Zone

- Telencephalic vesicle (cortex, striatum, pallidum, septal nuclei)
- Hypothalamus (including preoptic area)
- Retina

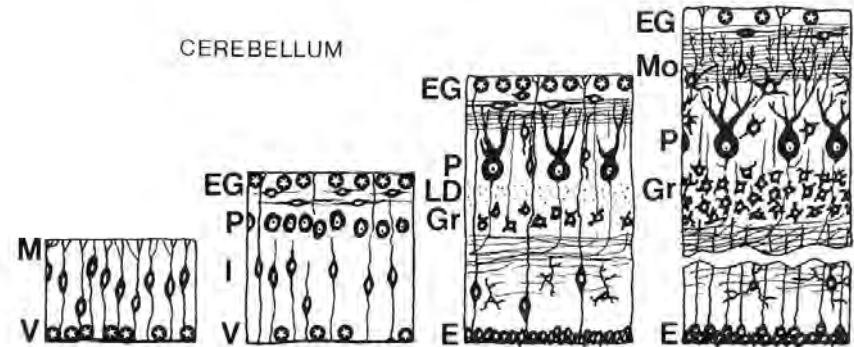
Primary and Secondary Proliferative Zones



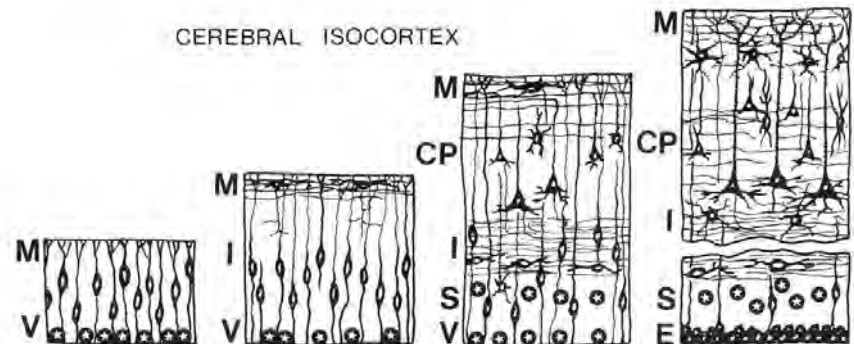
SPINAL CORD



CEREBELLUM



CEREBRAL ISOCORTEX



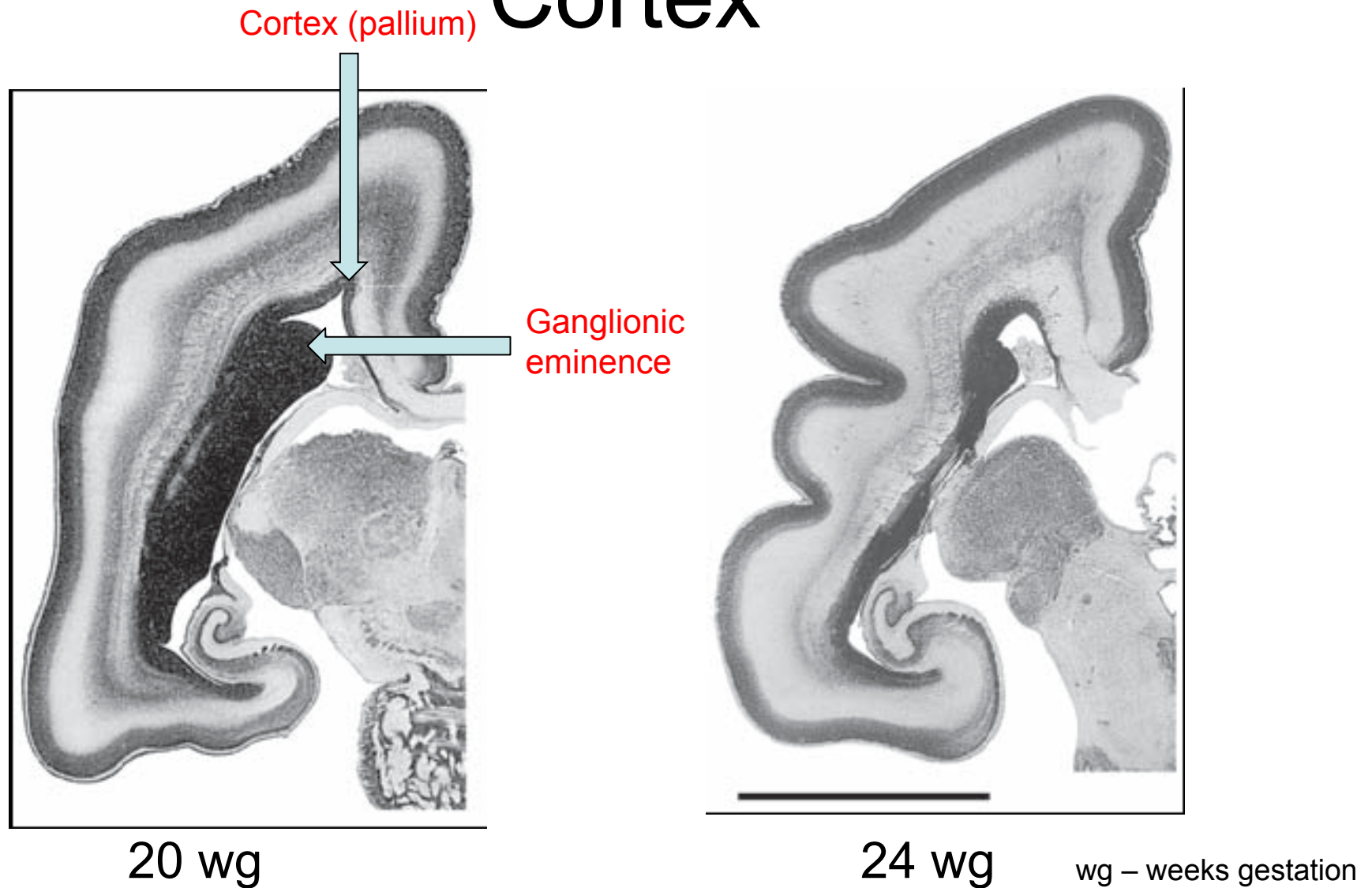
Wall of early neural tube

Proliferative Zones of the Developing Forebrain

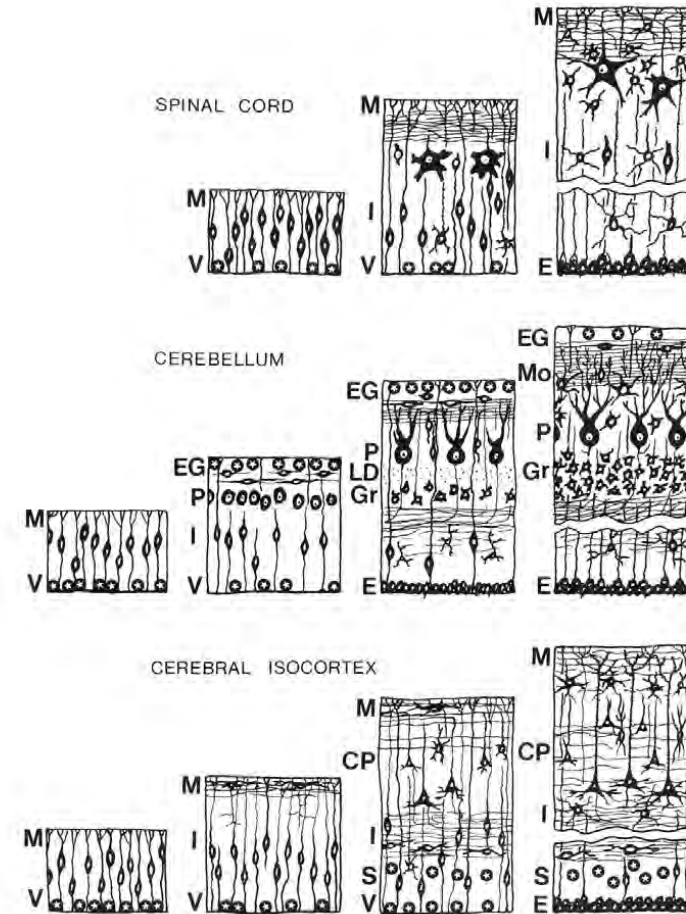
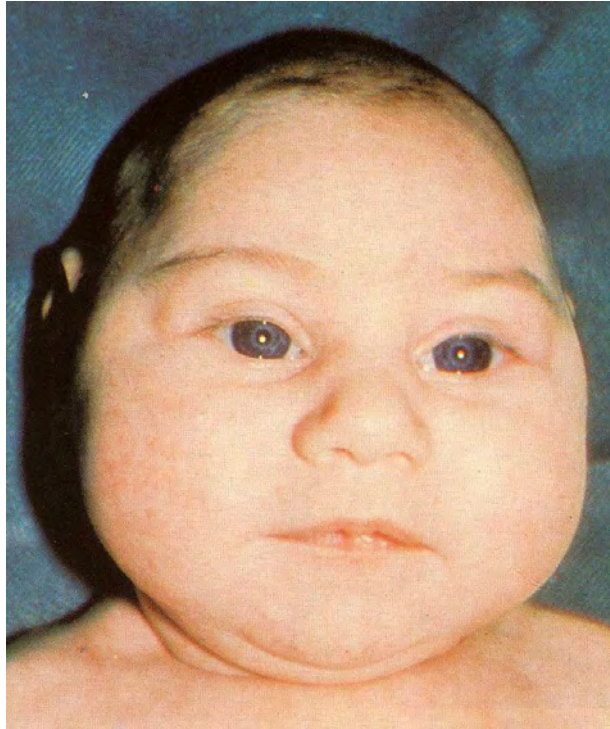
- **Ventricular Germinal Zone (VGZ)** –
 - mitosis at the ventricular luminal surface
 - produces early-generated macroneurons
- **Subventricular Zone (SVZ)** –
 - mitosis away from the ventricular surface
 - produces later-generated microneurons and glia

The SVZ is found beneath developing cortex and in developing basal ganglia (ganglionic eminences).

Layers of Developing Human Cortex

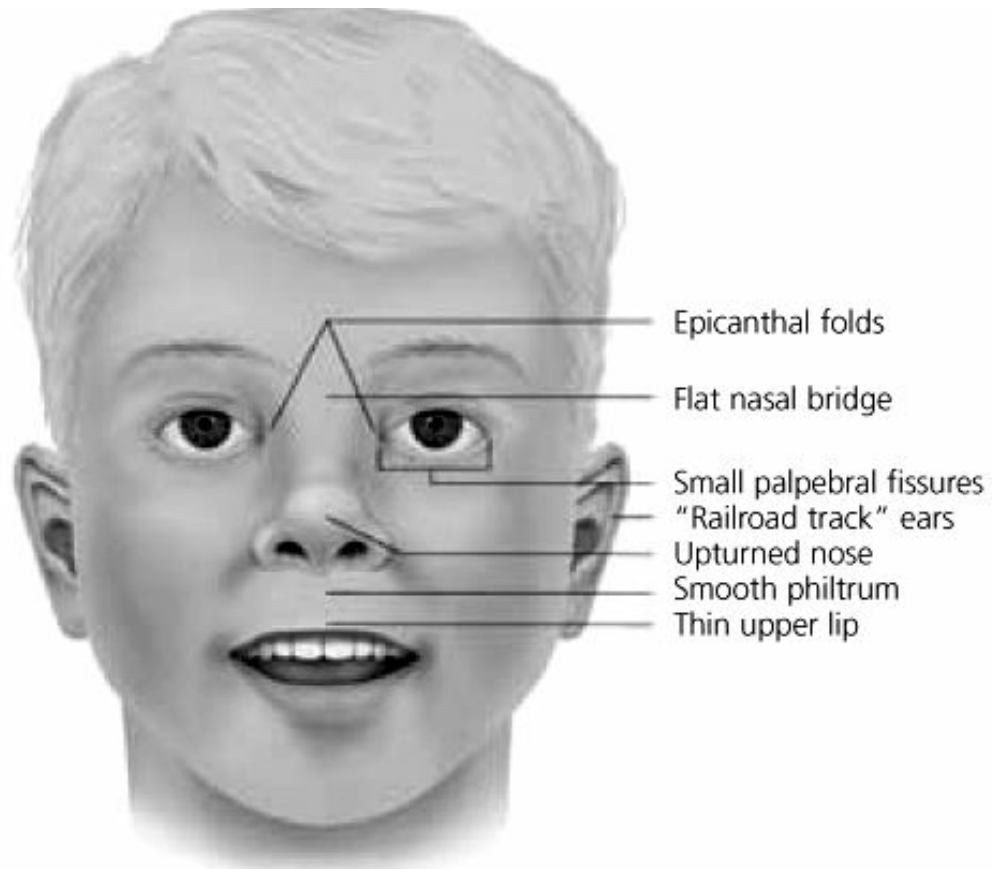


Microcephaly



- Neurons and most glia of the brain are produced by proliferation of cells in the ventricular germinal zone
- Some physical (ionizing radiation, elevated maternal temperature), chemical (anticancer drugs) and biological (rubella, cytomegalovirus, herpes simplex virus, **zika**) agents kill those dividing cells and lead to a reduction in the ultimate size of the brain

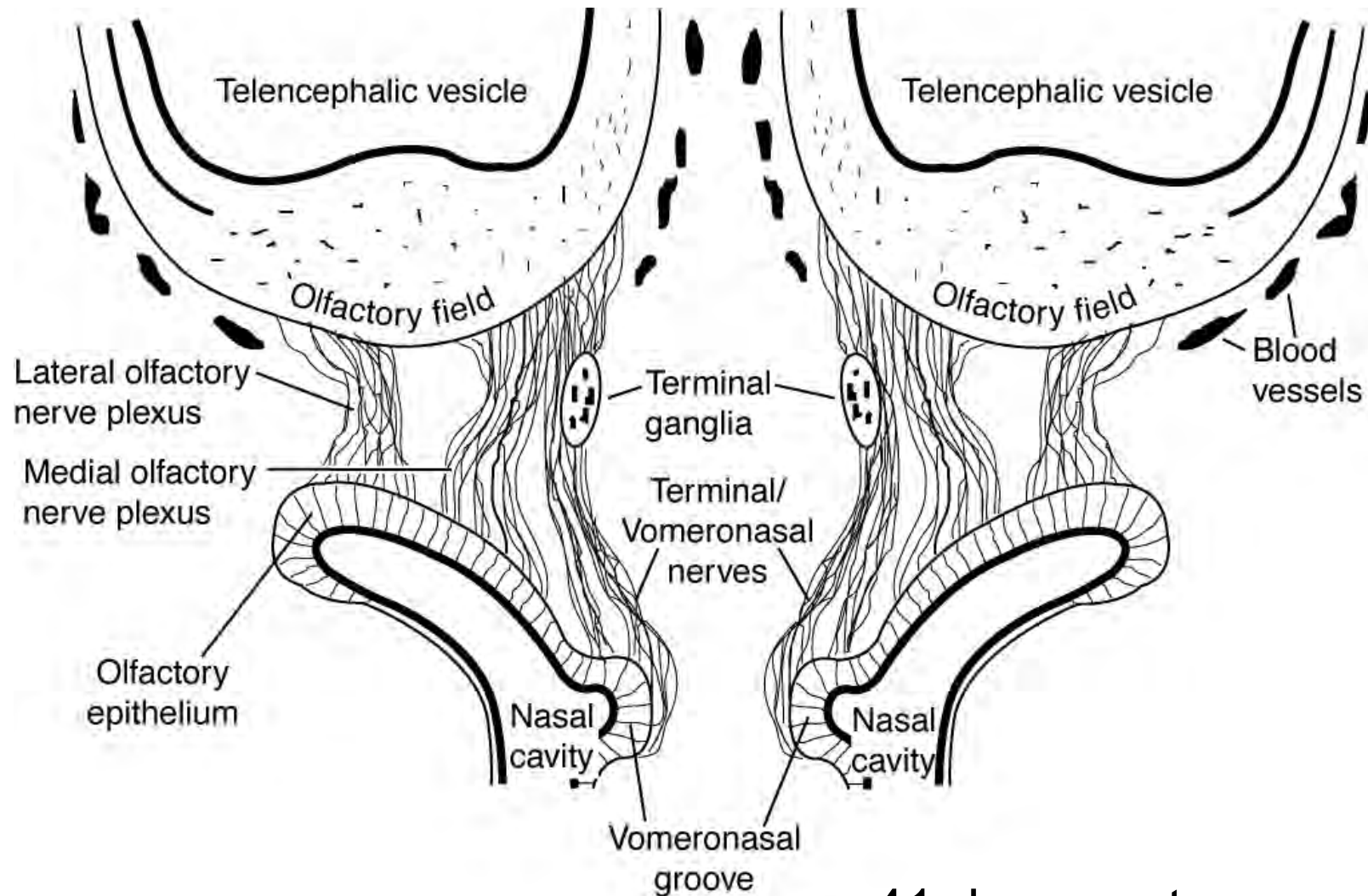
Fetal Alcohol Spectrum Disorder



Binge drinking at critical stages of development (i.e. just after neural tube closure) can cause fetal alcohol syndrome

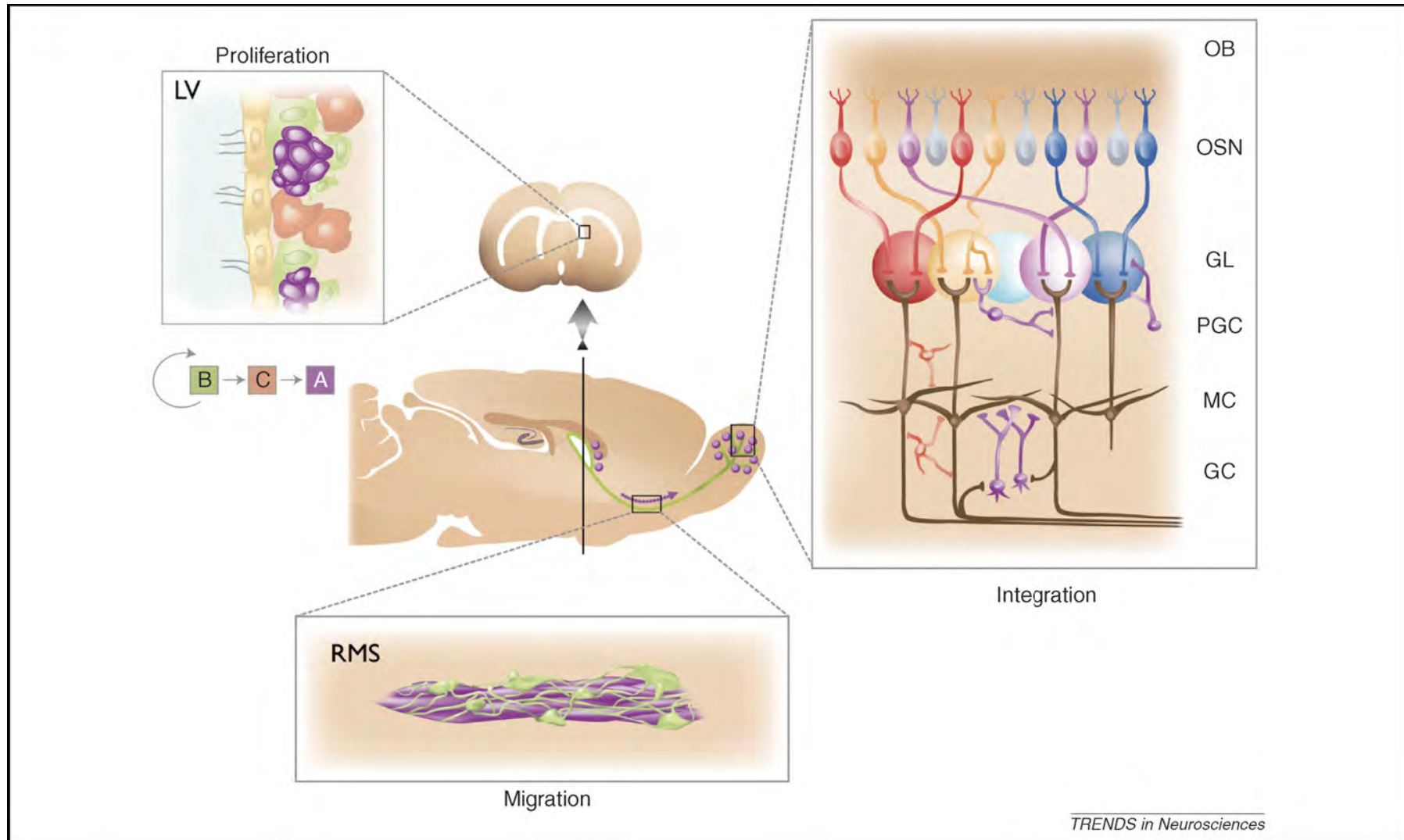


Olfactory Development

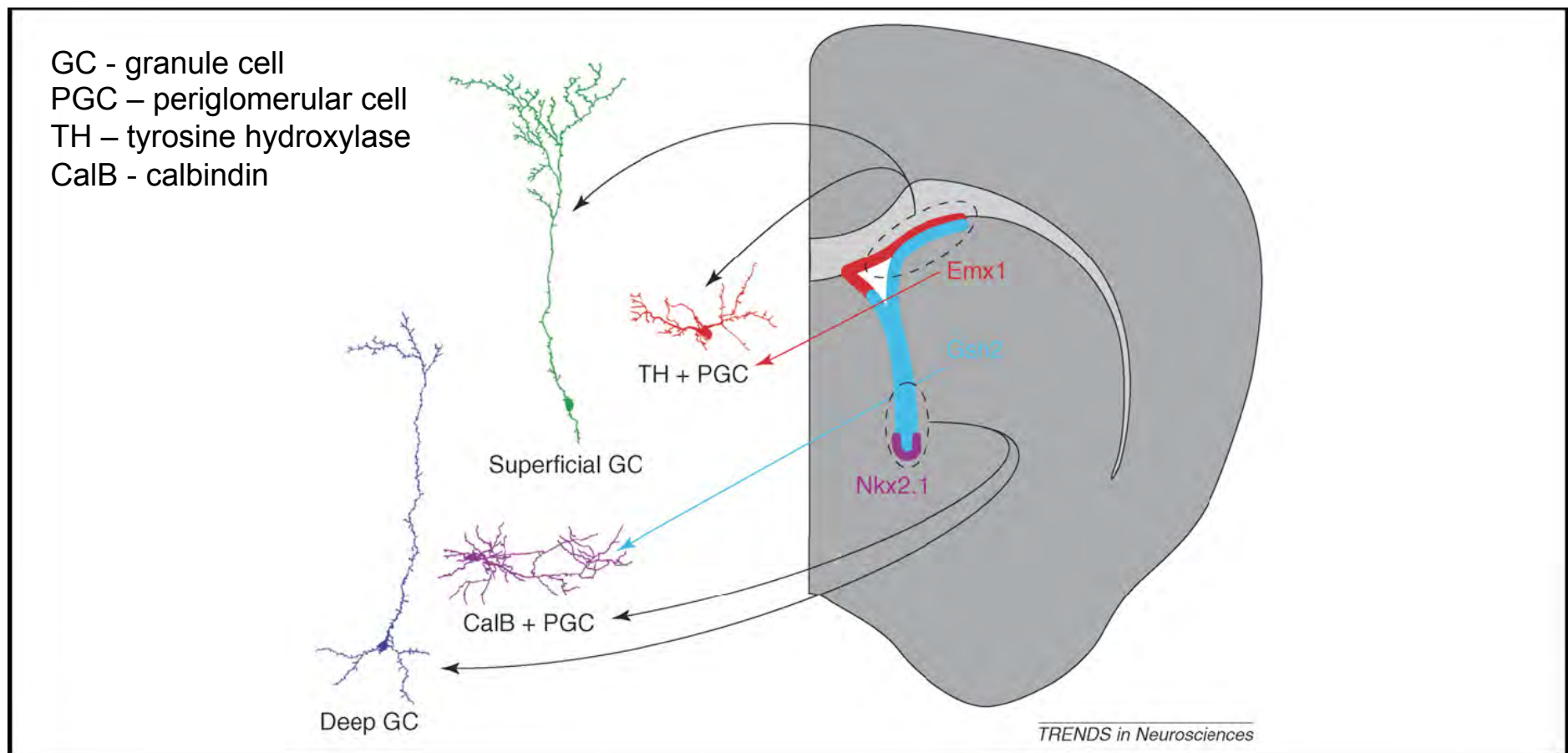


41 days post conception (pc)

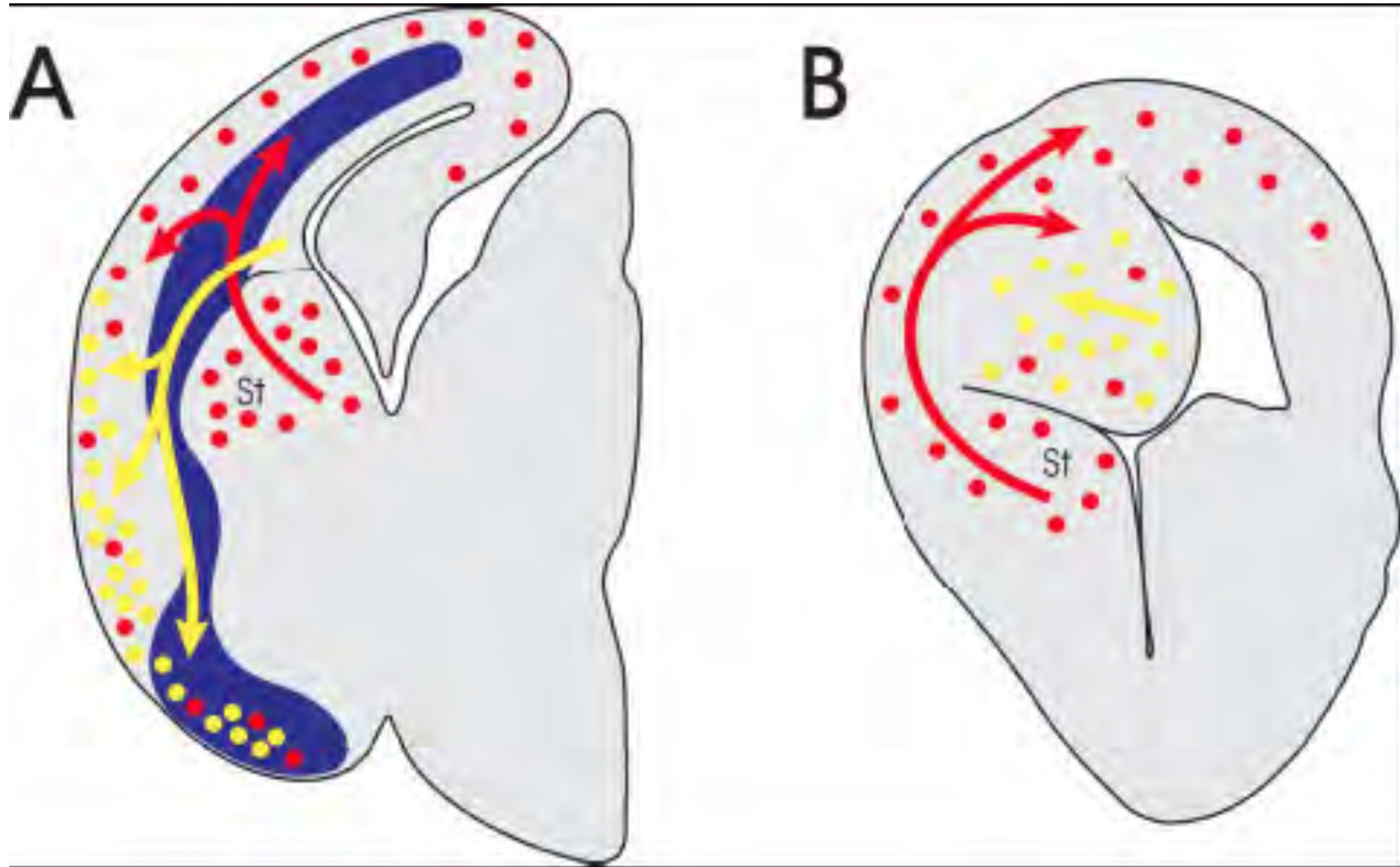
Many Small Olfactory Neurons are Derived from SVZ of Forebrain



Specific Neuron Types in the Olfactory Bulb come from Specific Regions of SVZ






Origins of Cortical Neurons



Mammal

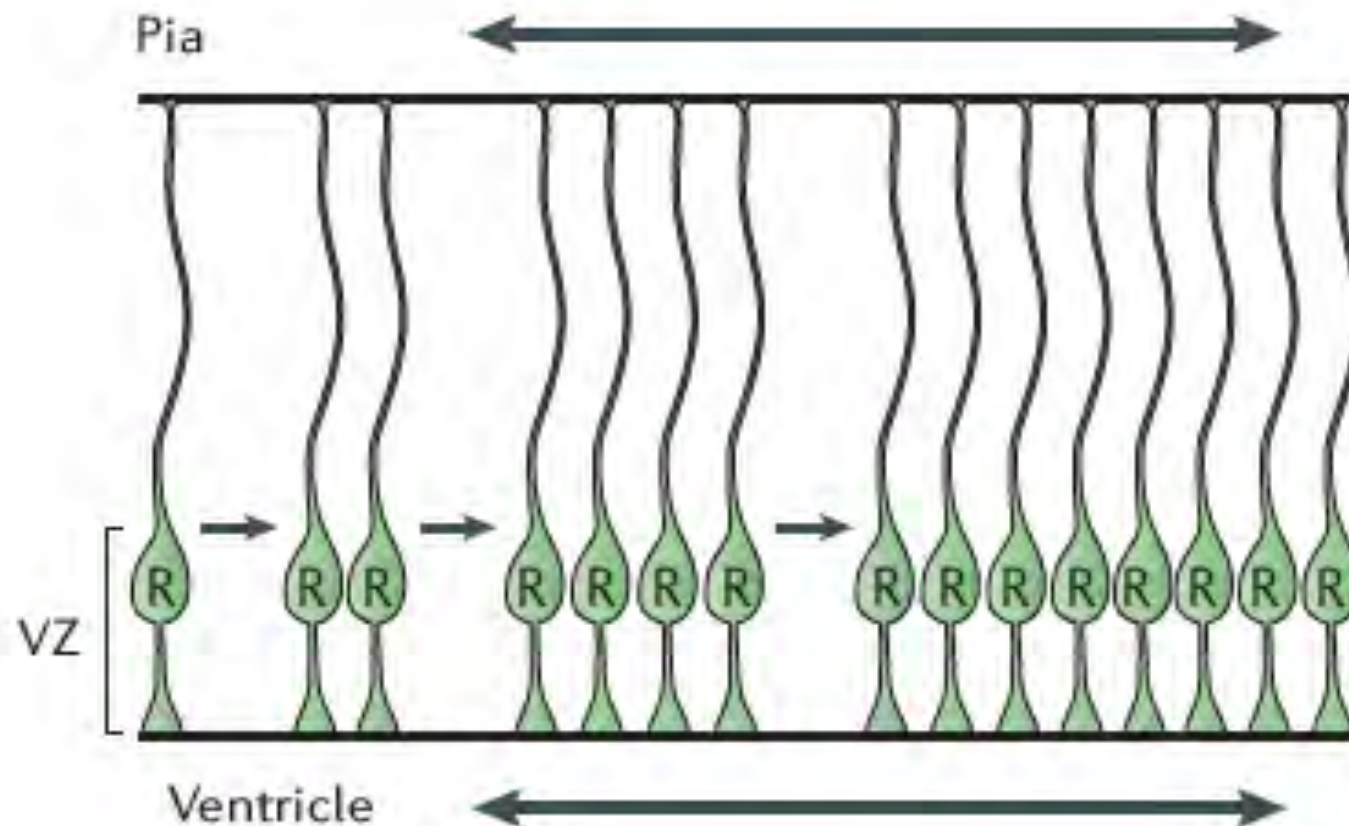
Bird

Cortical neurons come from several distinct sources

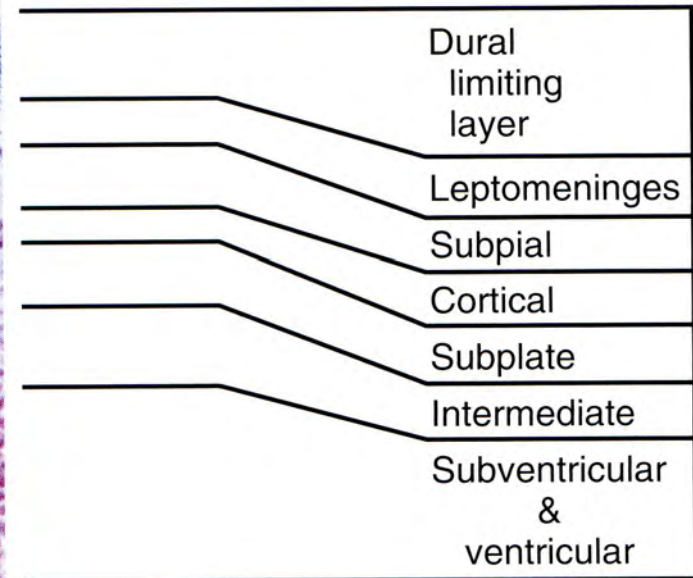
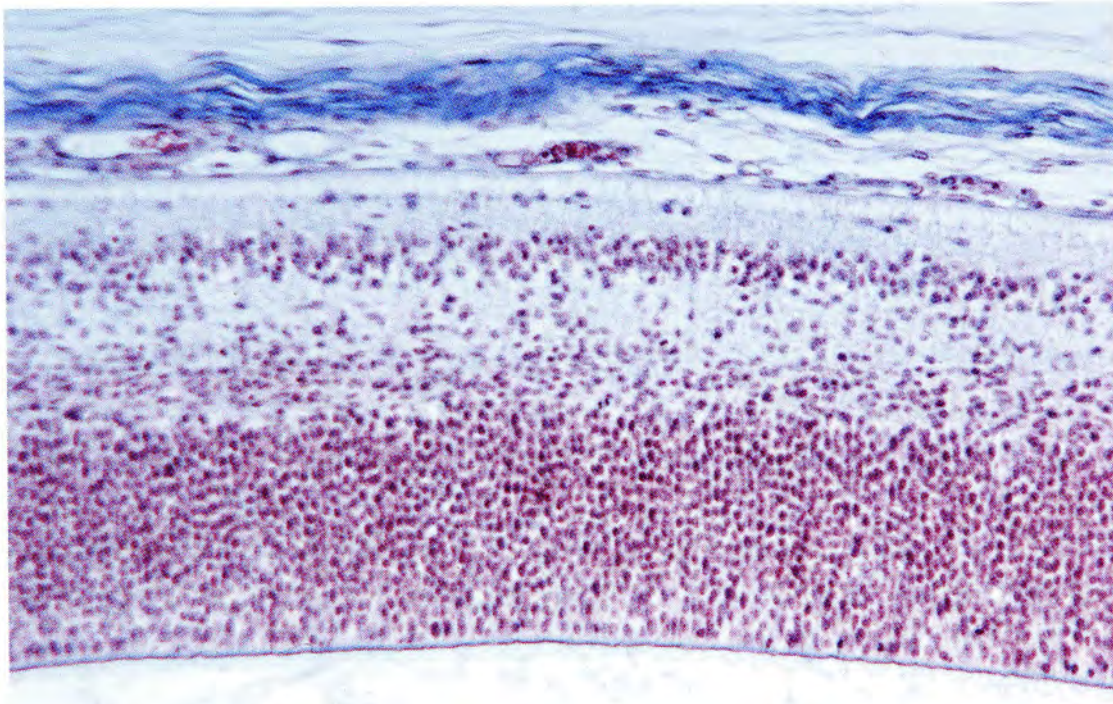
- 1 Local (pallial) ventricular zone  early generated glutamatergic neurons.
- 2 Local (pallial) subventricular zone, which may itself be derived from precursor cells migrating out of the nearby ventricular zone  late generated glutamatergic neurons.
- 3 Subventricular zone of the lateral and medial ganglionic eminences of the ventral telencephalon  GABAergic neurons.

Expansion of the Cortical Surface

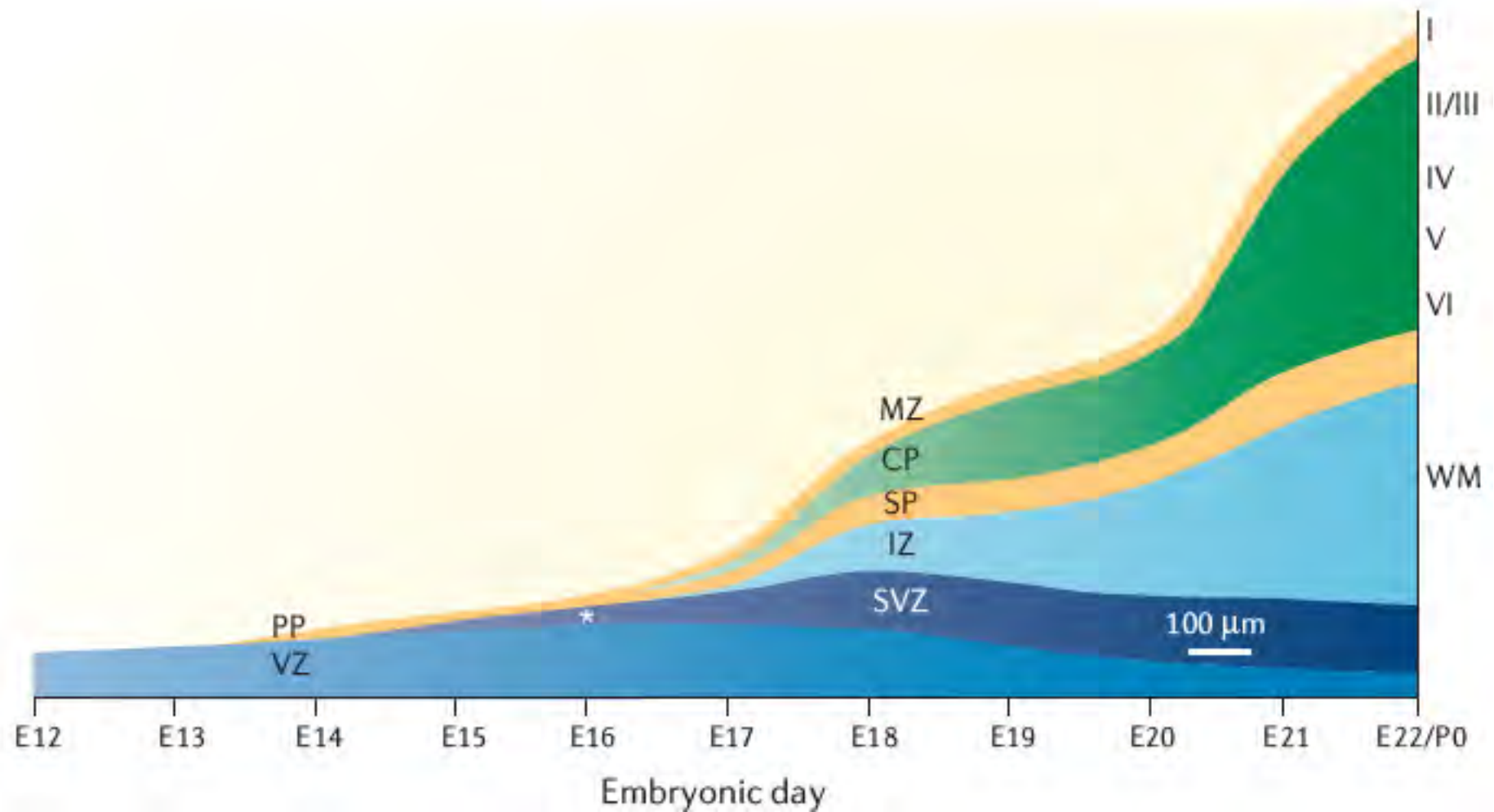
a Symmetric progenitor divisions



Layers of Developing Cortex



Development of Cortex

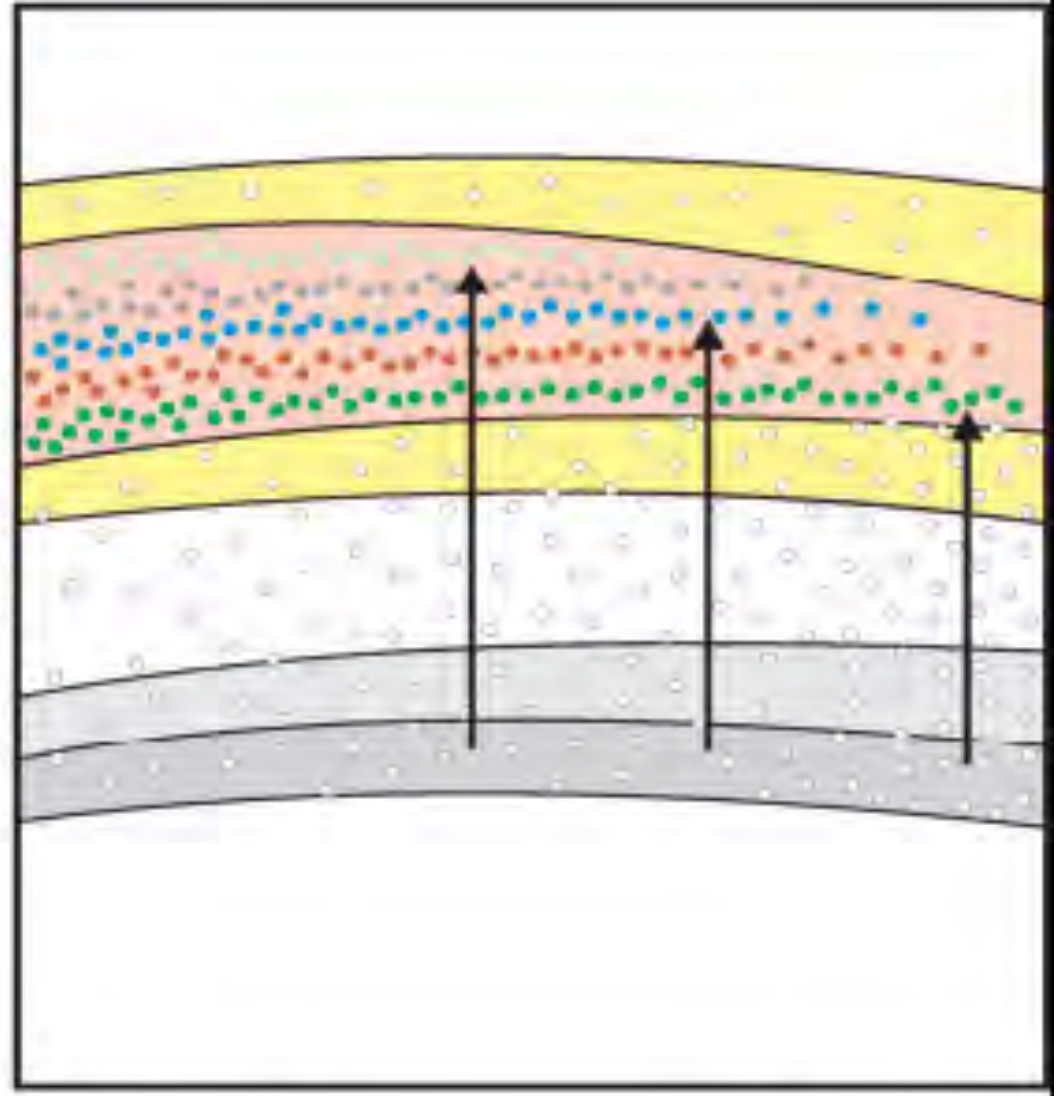


A



B

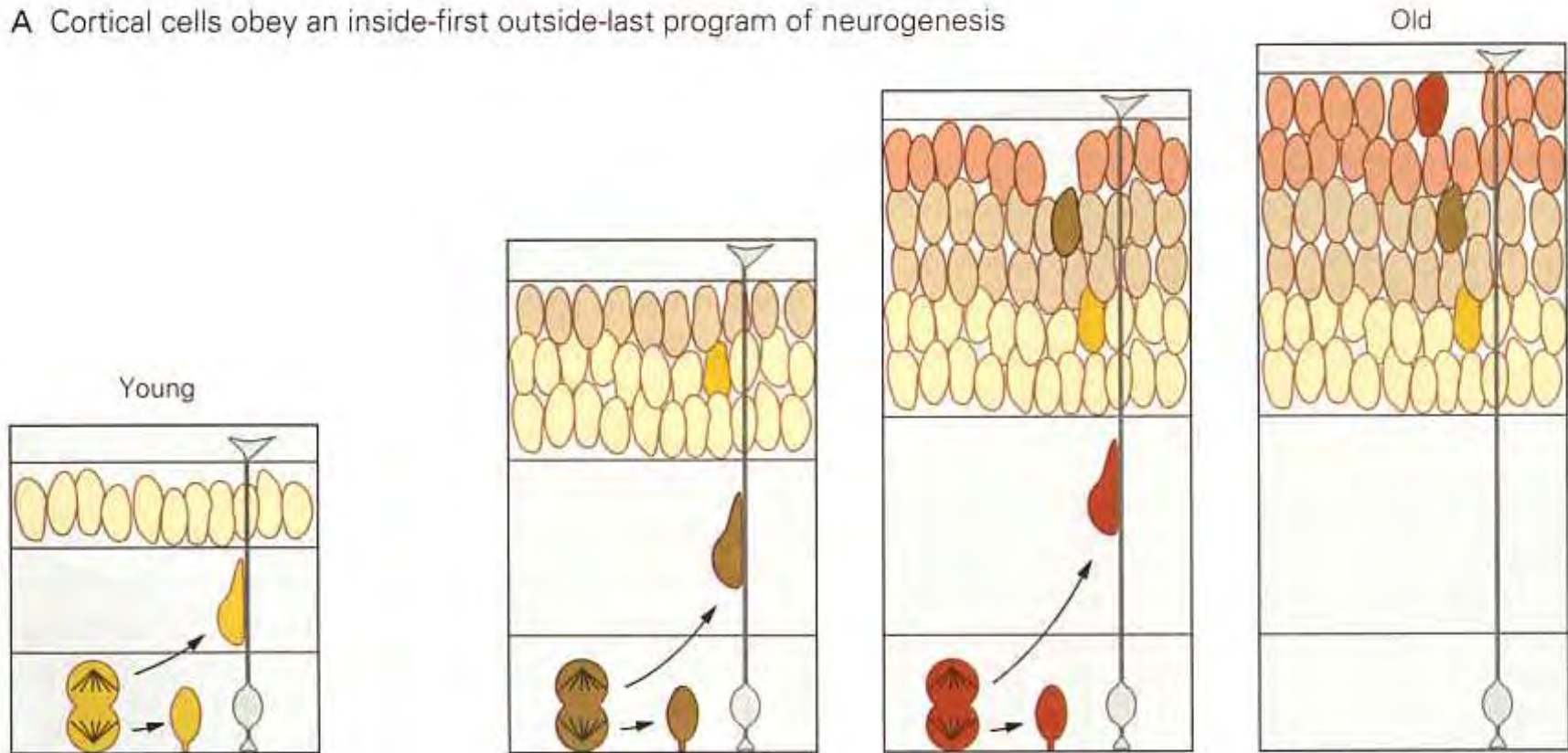
Marginal Zone
Cortical Plate
Subplate
Intermediate Zone
Subventricular Zone
Ventricular Zone



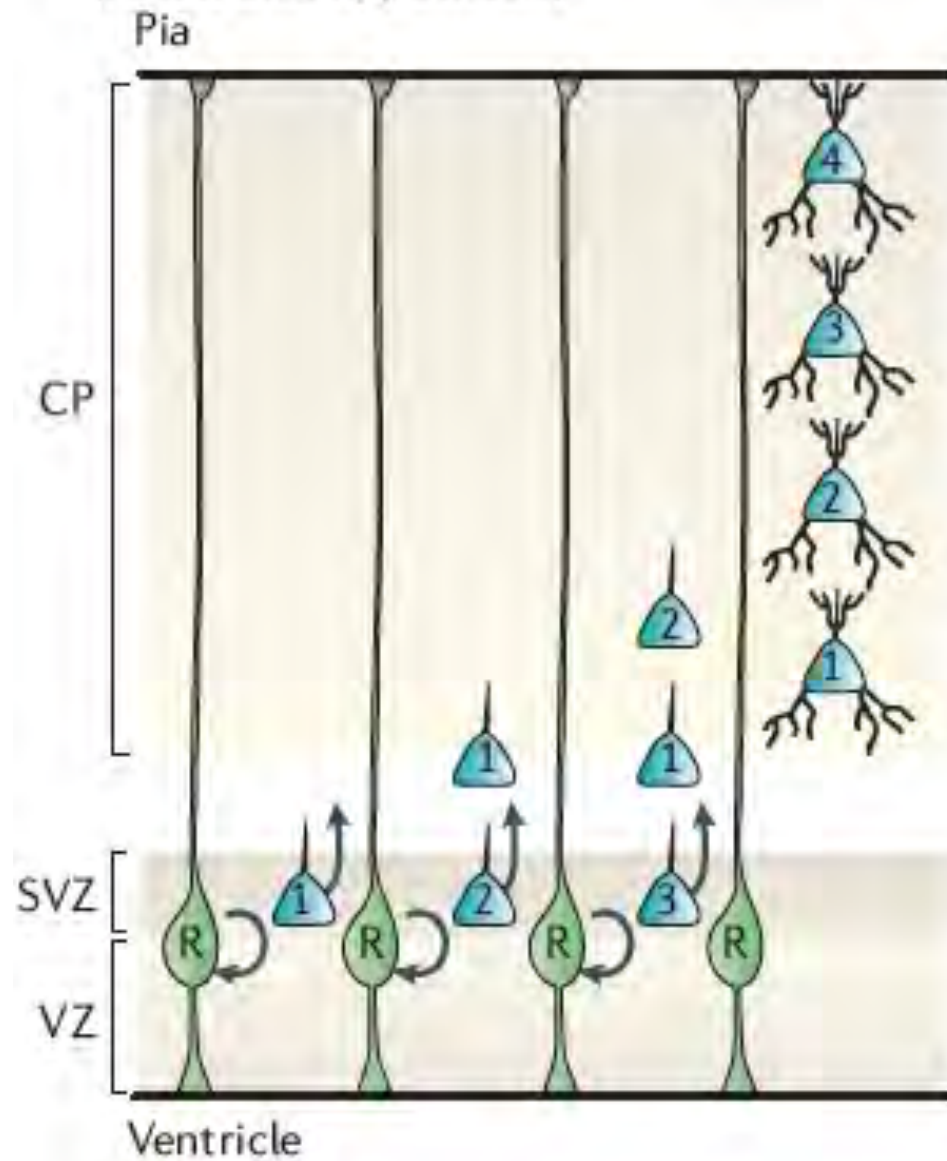
Ventrolateral → Dorsomedial

The Developing Cerebral Cortex

A Cortical cells obey an inside-first outside-last program of neurogenesis

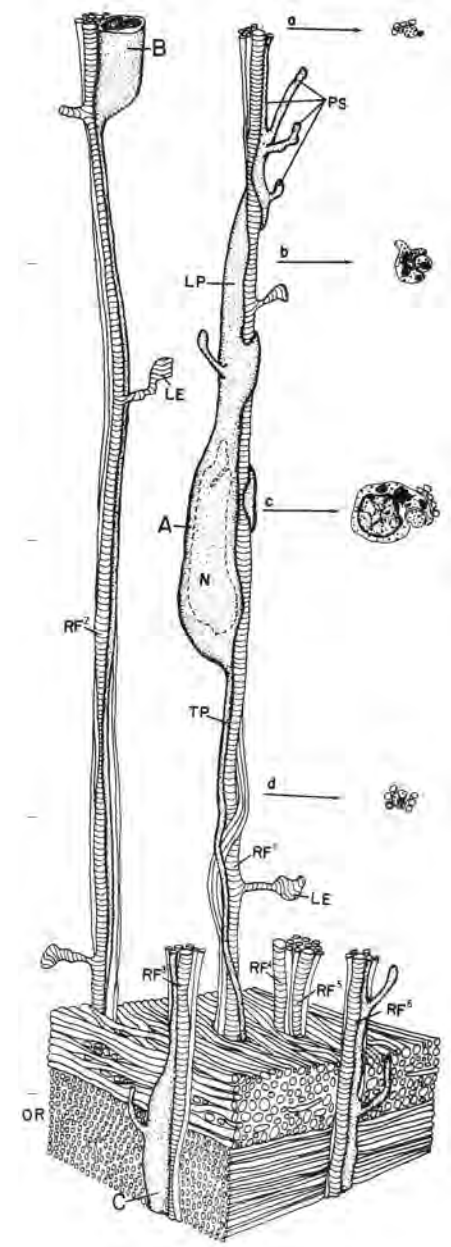
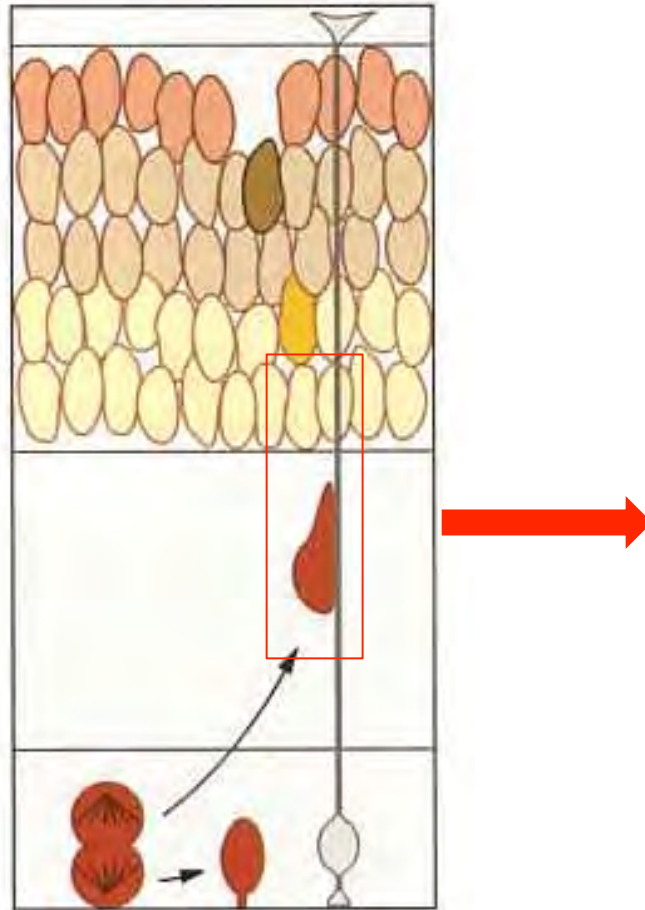


**b Asymmetric neurogenesis
(radial unit hypothesis)**



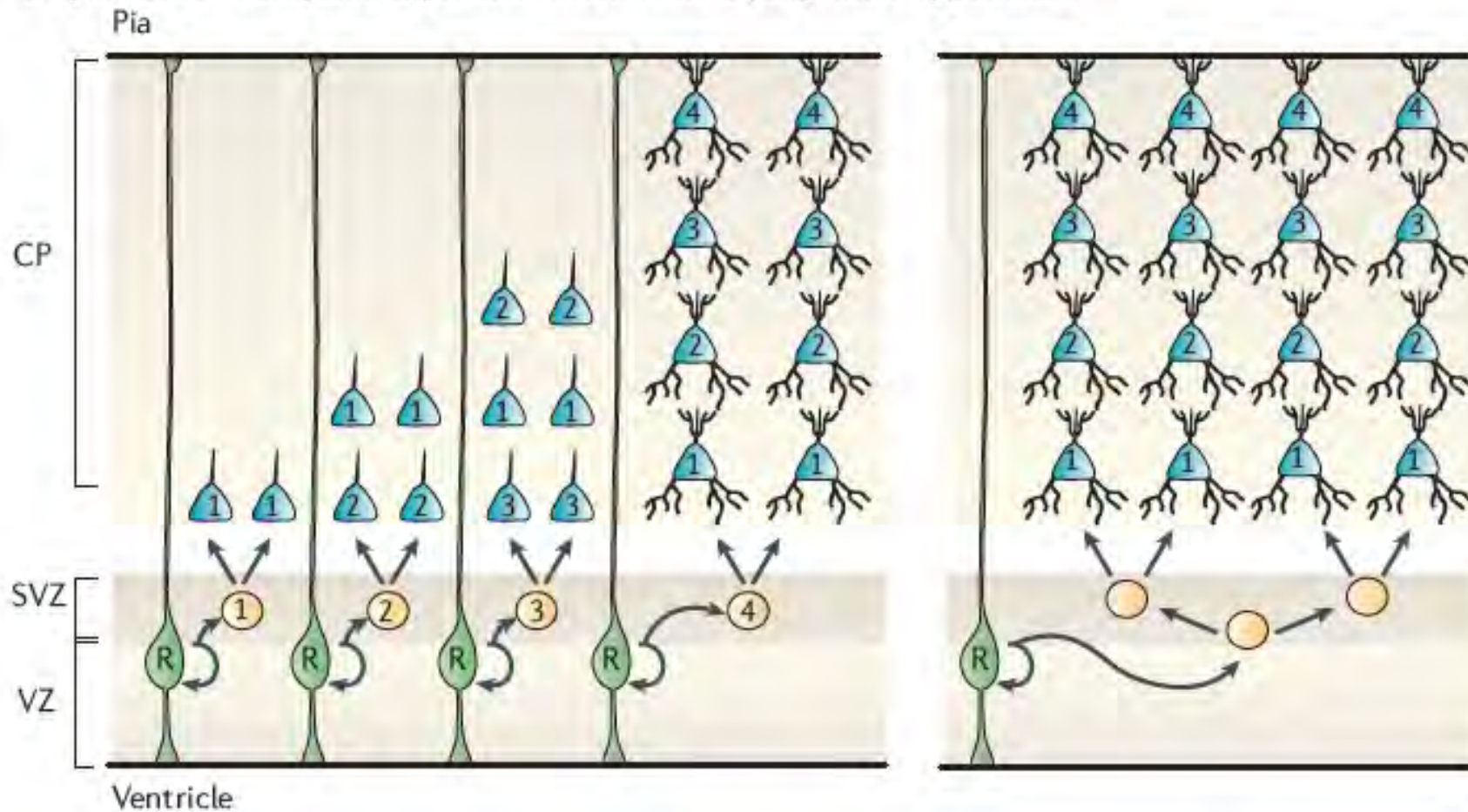
How Do Neurons Migrate?

Young neurons migrate from the ventricular germinal zone by using a radial glial scaffold

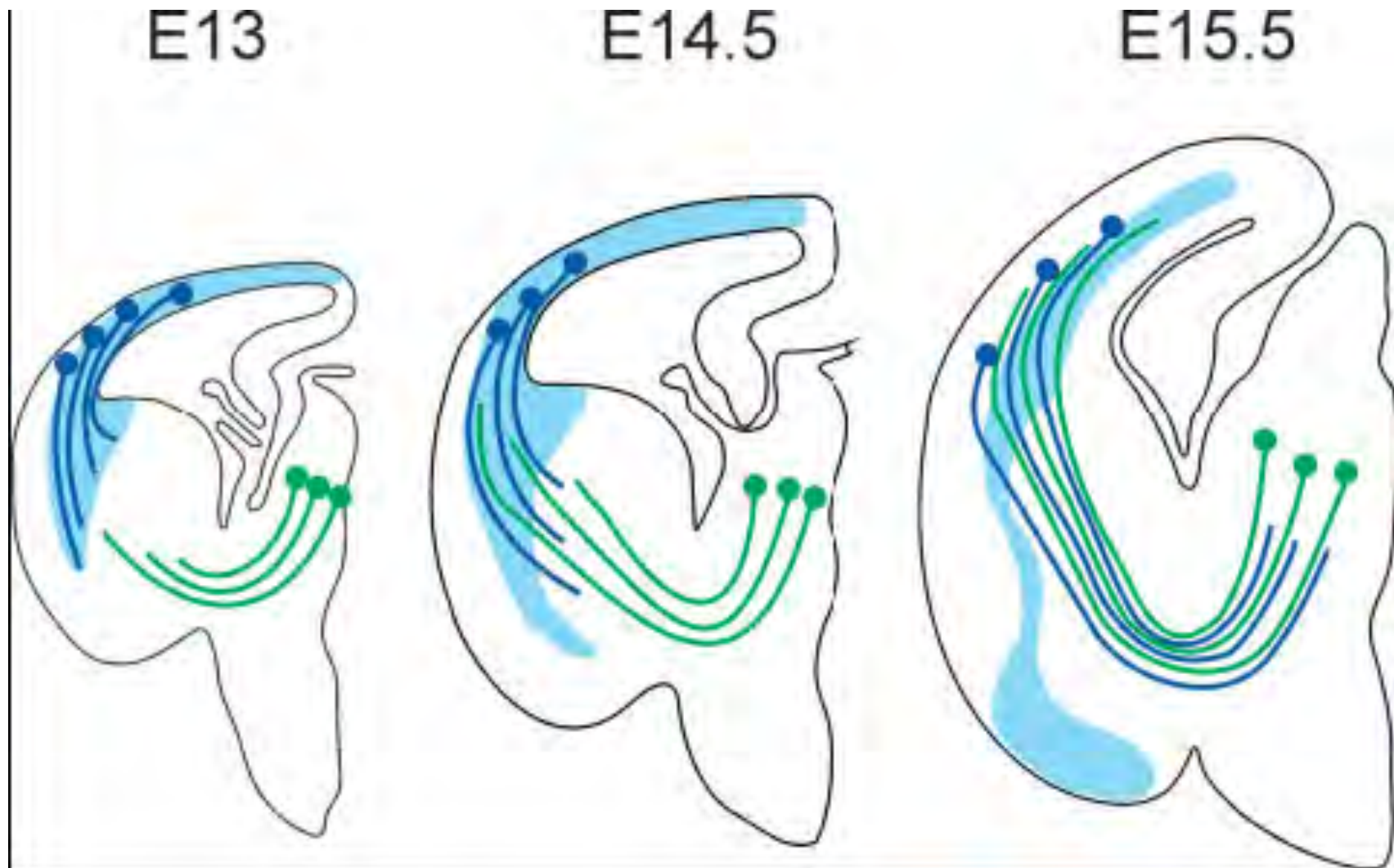


Intermediate Progenitors in SVZ

C Symmetric neurogenic expansion (intermediate progenitor hypothesis)



Formation of Cortical Connections (Rat)



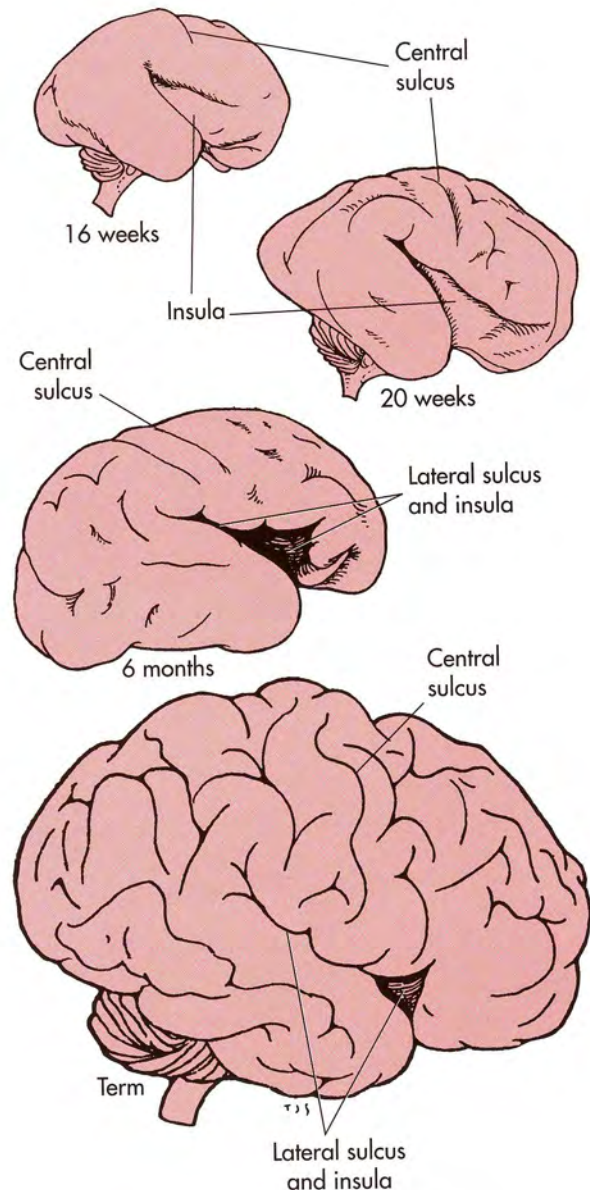
The Role of the Cortical Subplate

- The cortical subplate provides an initial waiting and termination site for thalamocortical afferents destined for the cortex
- It also provides the first corticofugal projections which may serve as guidance pathways for afferents to the cortex.

Collateralization of Developing Axons and Subsequent Error Correction

- Corticofugal axons project to diverse targets during development (e.g. corticospinal axons may also have collaterals to pontine nuclei, superior colliculus)
- Inappropriate connections are corrected by removal of excess and incorrect collaterals during fetal and early postnatal life (humans) or early postnatal life (rodents).

Development of Gyri

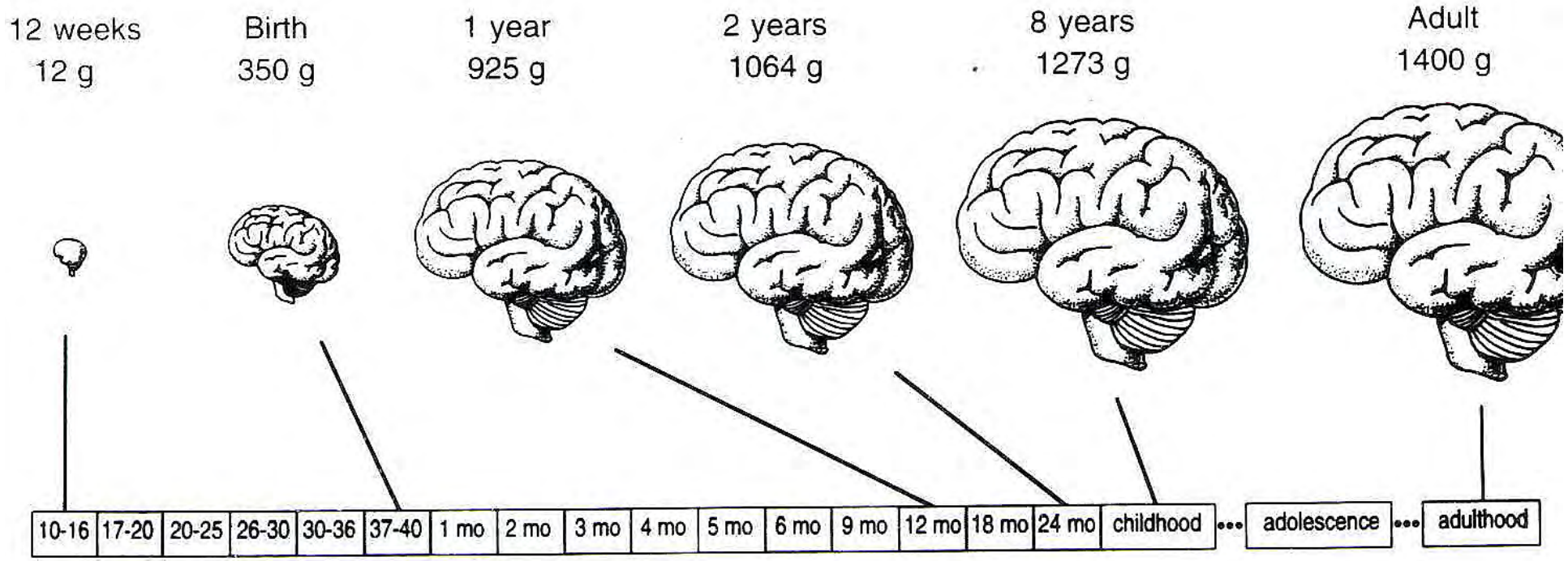


Most of the brain growth after birth is in the cerebral cortex.

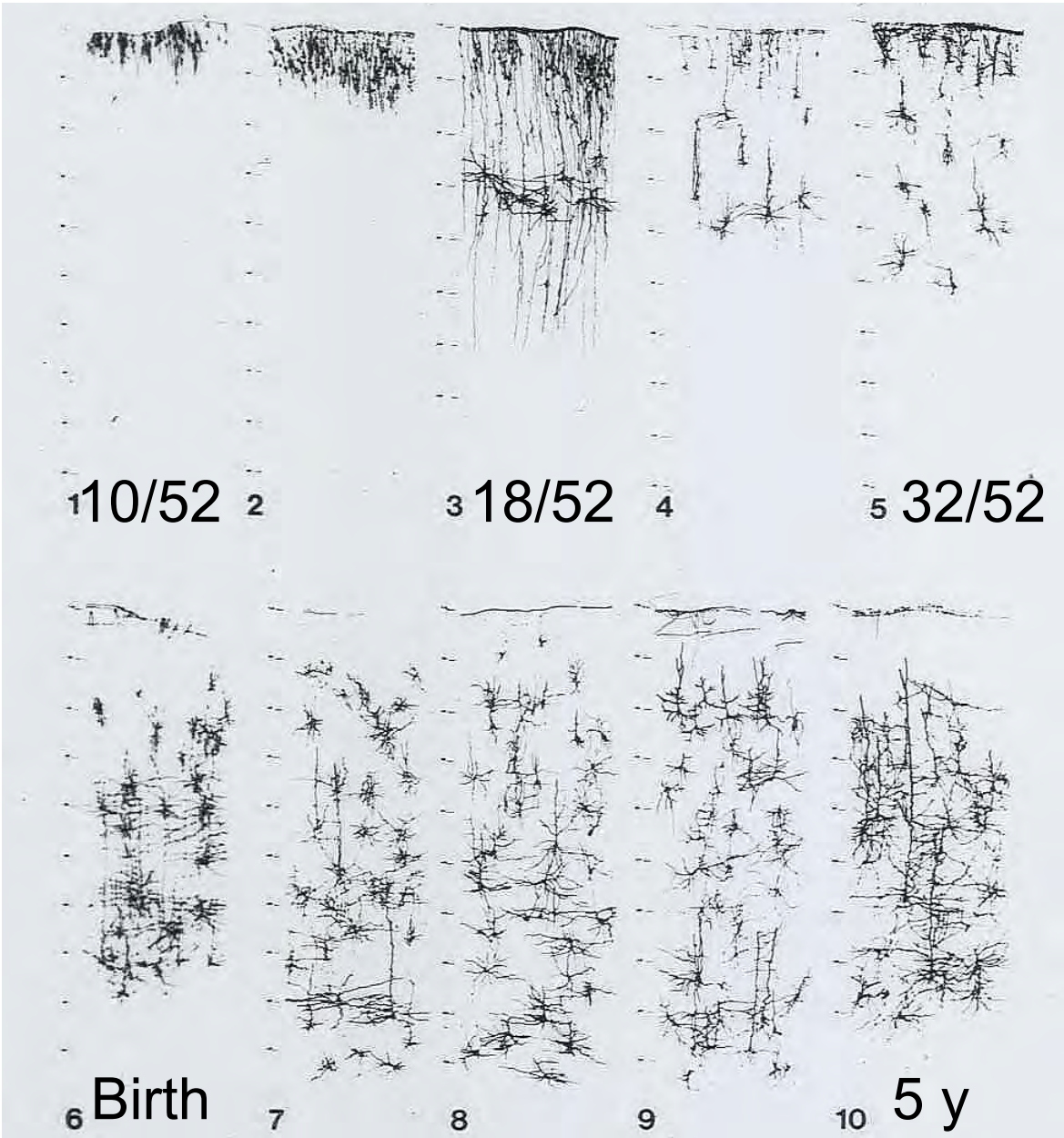
Brain growth continues until 5 to 7 years of age.

Cerebral cortex growth involves increased folding (gyrification) and elaboration of nerve cell processes.

Brain Growth

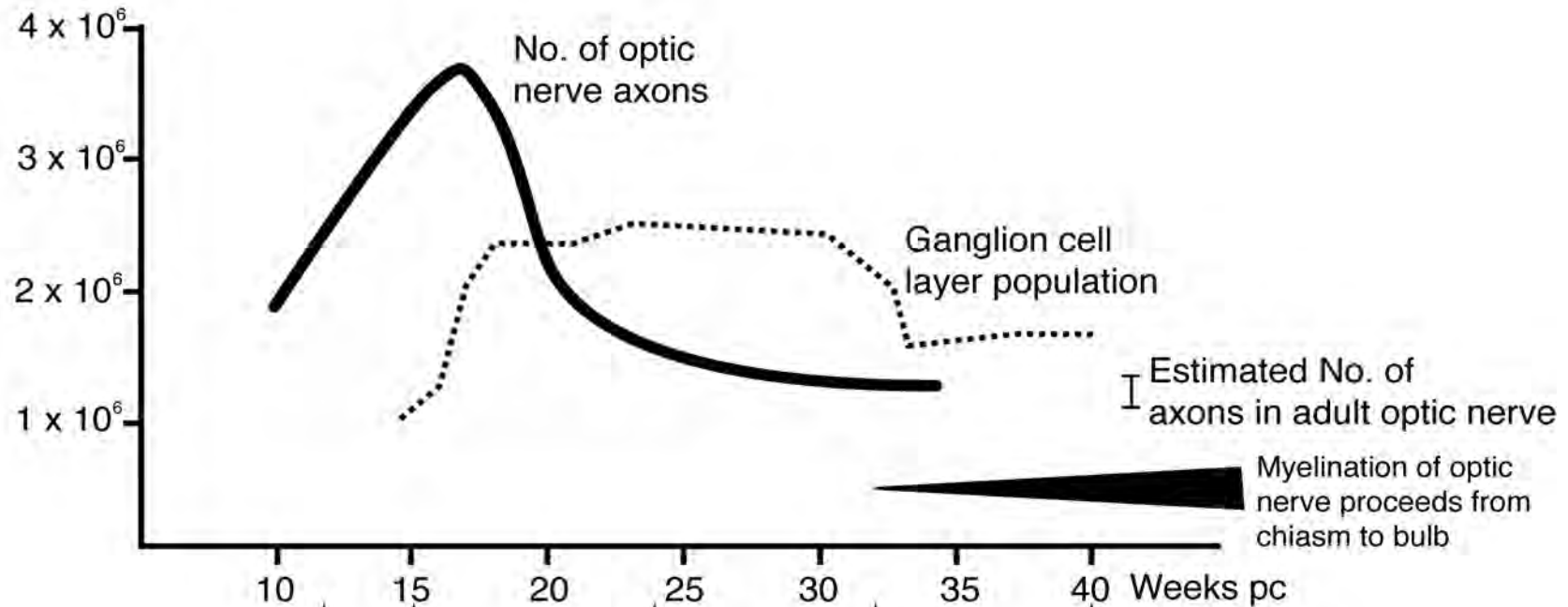


Growth of Nerve Cell Processes



Developmental Neuronal Death

No. of cells/axons



Rapid optic nerve vascularisation occurs from 12 to 14 weeks pc.

Dura mater first appears around optic nerve.

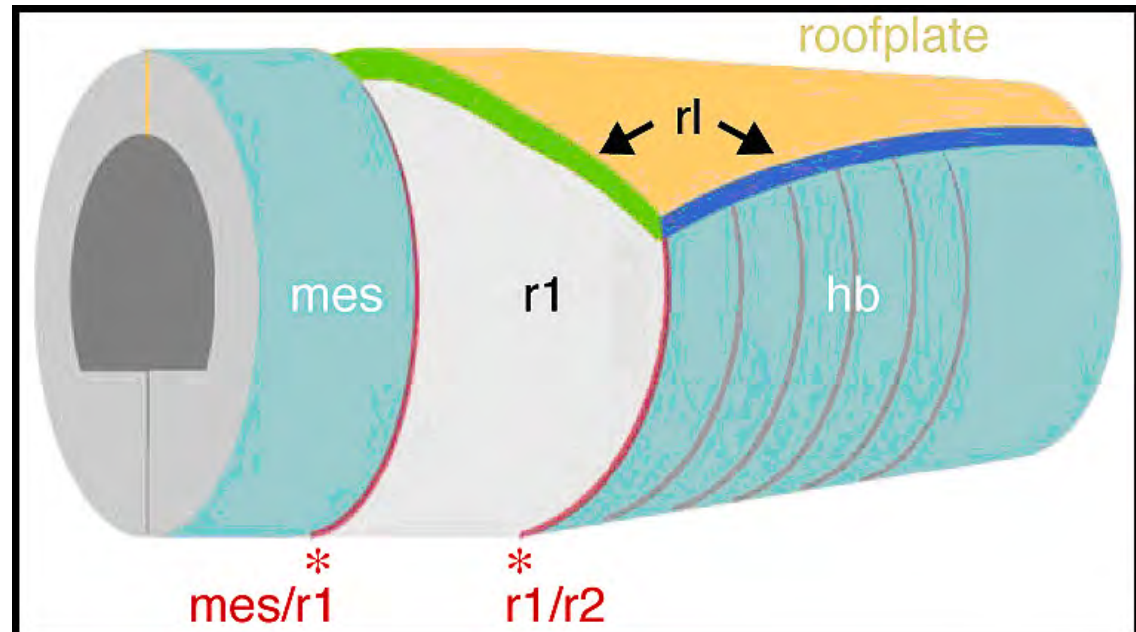
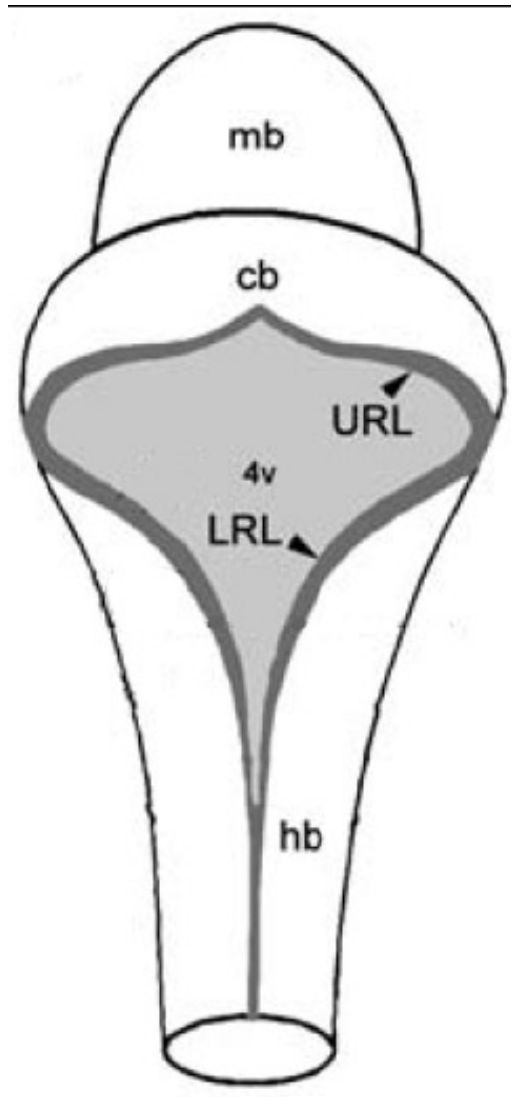
Immunoreactivity for glial fibrillary acidic protein first appears in optic nerve.

First myelinated fibres seen in intracranial part of optic nerve. Immunoreactivity for myelin basic protein appears in optic nerve.

First myelinated fibres seen in retrobulbar optic nerve.

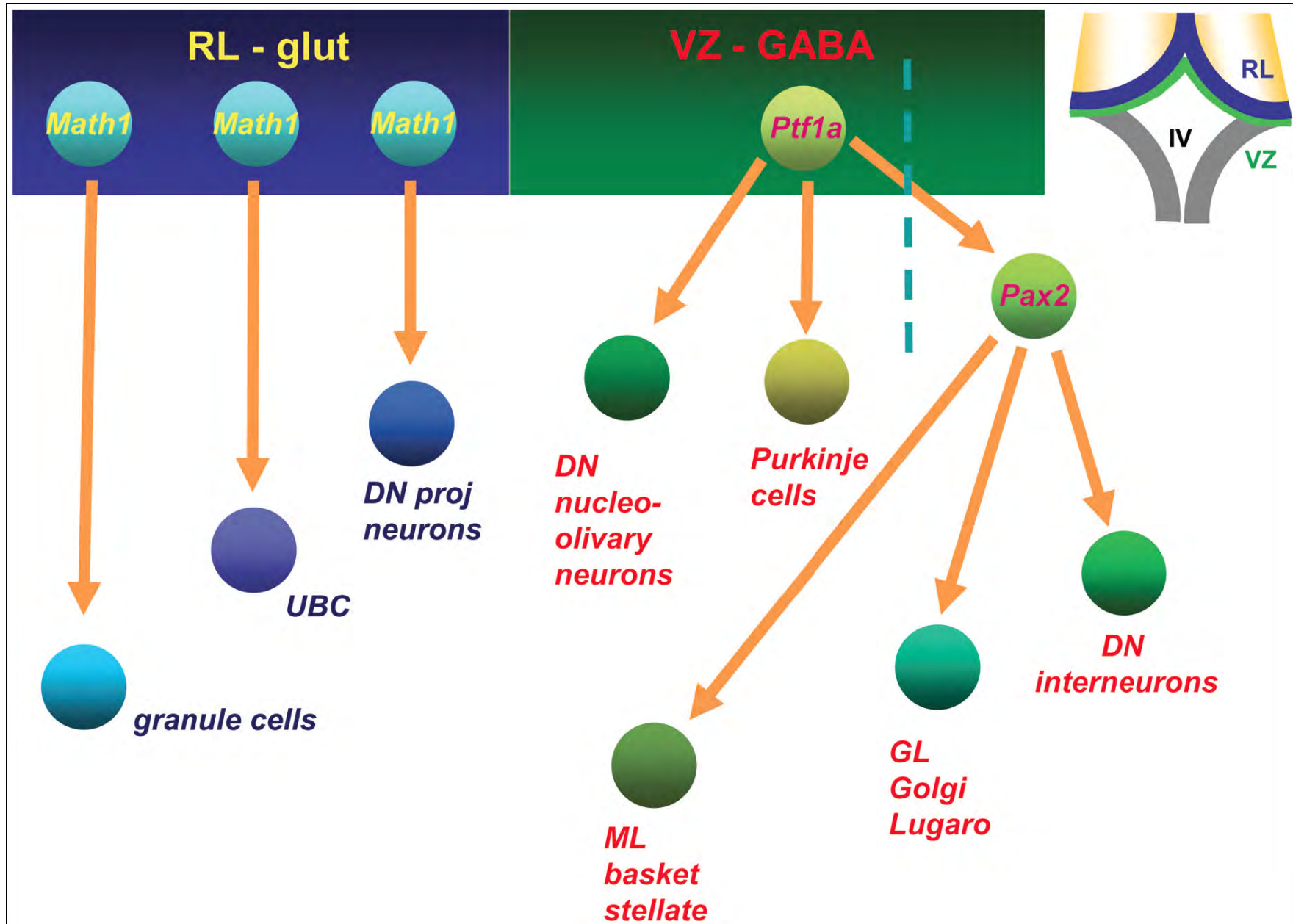
The Rhombic Lip

A dorsal view of the neural tube illustrating the rhombic lip (in dark grey). Abbreviations: mb, midbrain; cb, cerebellum; 4v, fourth ventricle; hb, hindbrain; URL, upper rhombic lip; LRL, lower rhombic lip. Adapted from Landsberg et al., 2005.

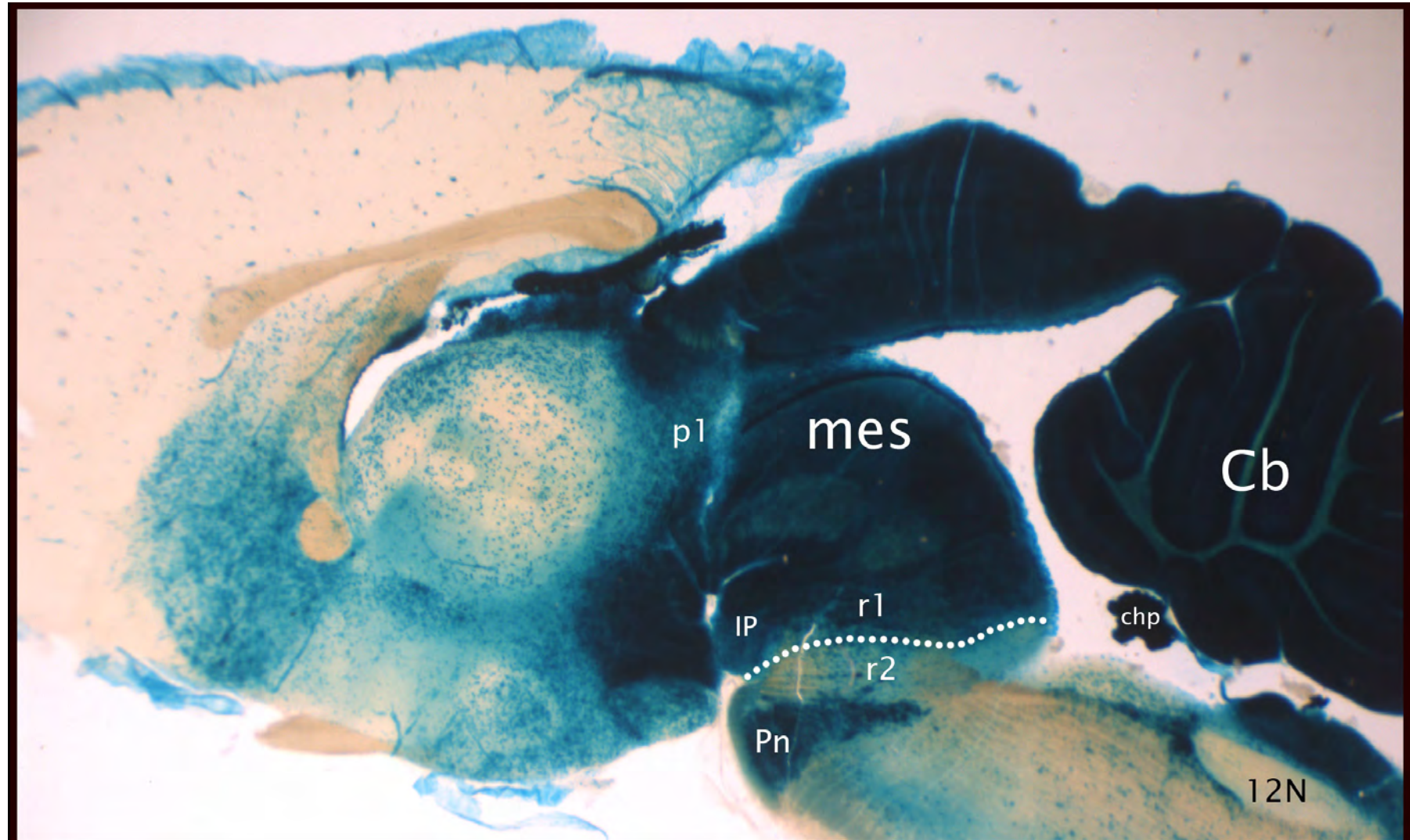


Development of the Cerebellum

- Two distinct progenitor zones:
 - **Cerebellar ventricular zone** (*Ptf1a*+) gives rise to **GABAergic** (inhibitory) deep cerebellar projection neurons (i.e. nucleo-olivary neurons), basket, stellate, Golgi and Lugaro cerebellar interneurons, and Purkinje cells.
 - **Rhombic lip** (*Wnt1*, *Math1*+) gives rise to **glutamatergic** (excitatory) derivatives (precerebellar nuclei - pontine and inferior olivary nuclei), glutamatergic deep cerebellar nuclei projection neurons, external granular layer (to produce granule cells).

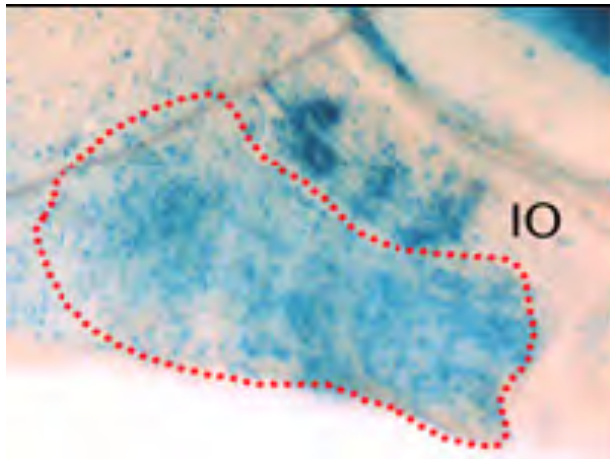


Derivatives of the Rhombic Lip

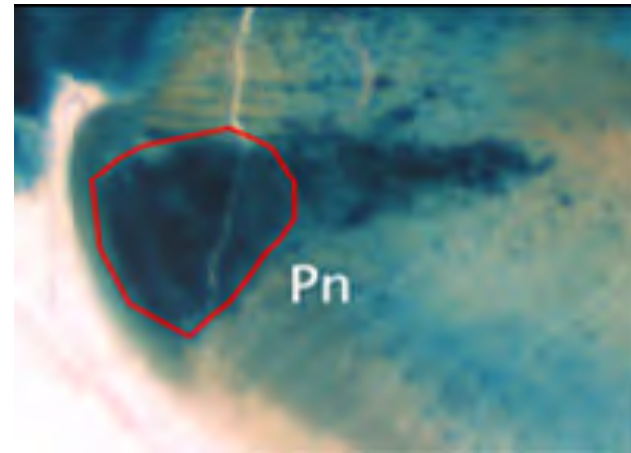


Wnt1 expression reveals rhombic lip derivatives

Precerebellar Nuclei are Rhombic Lip Derivatives



Inferior olive (climbing fibre projection)

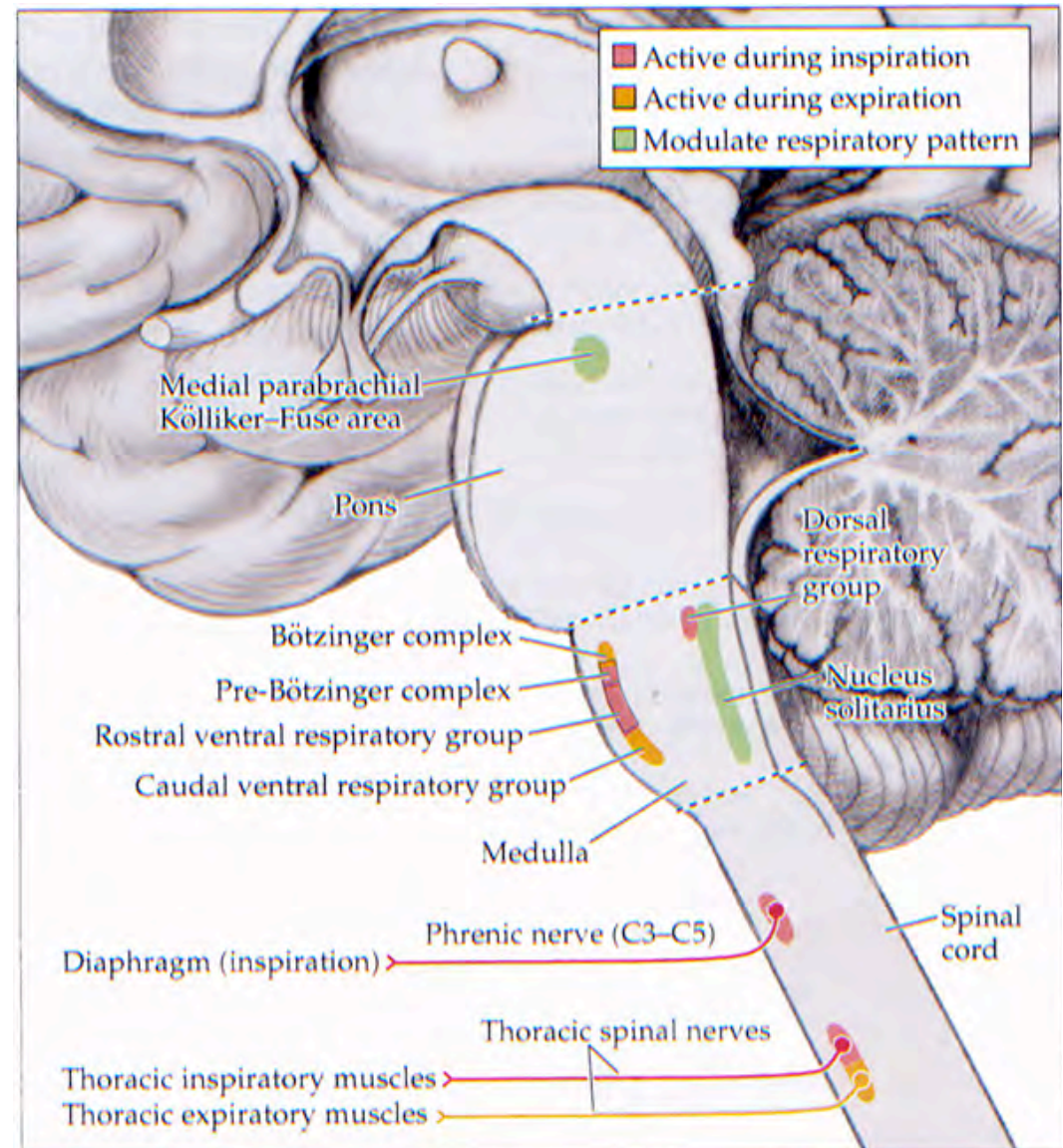


Pontine nuclei (mossy fibre projection)

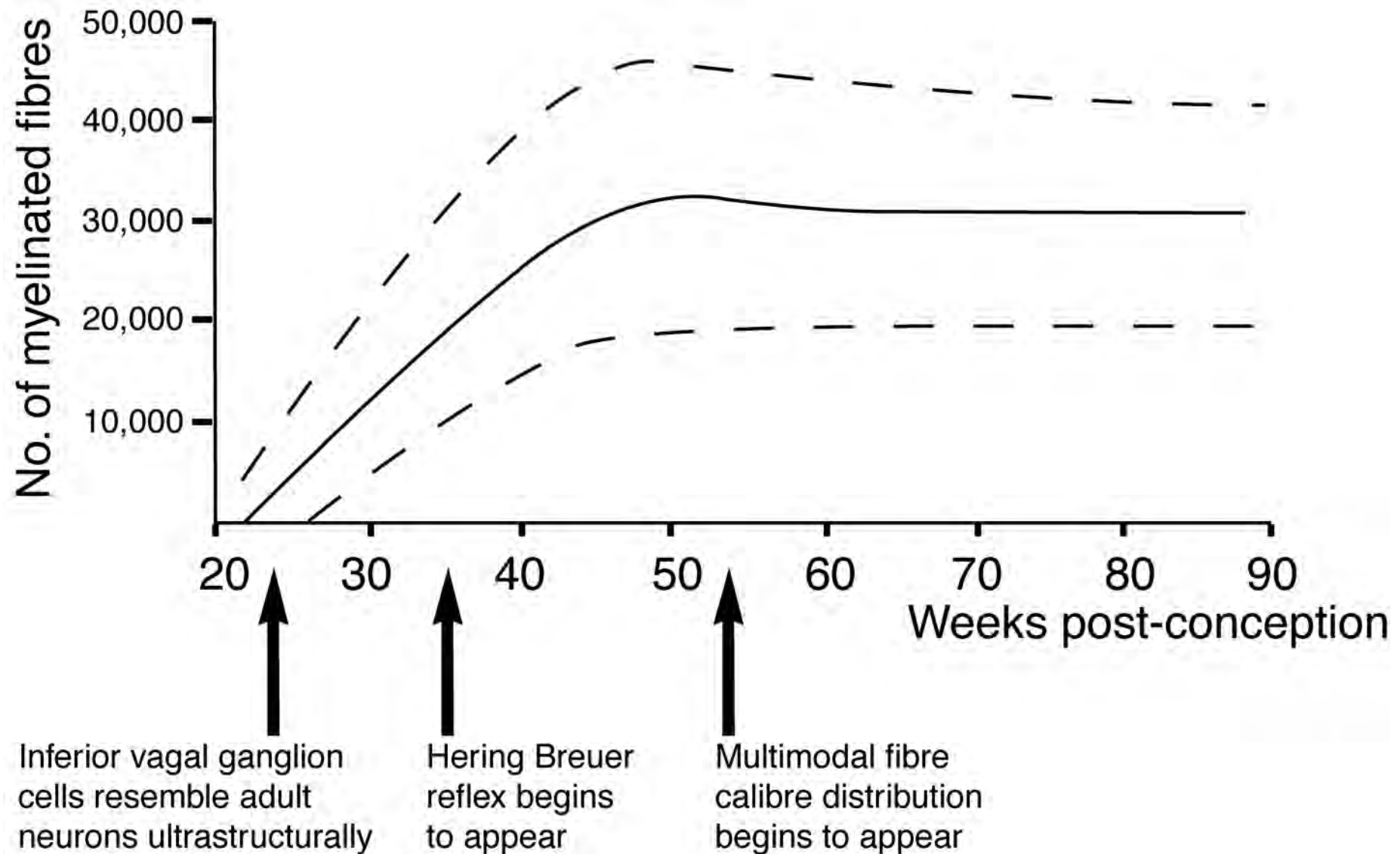
Other examples: reticulotegmental nucleus, external cuneate nucleus, lateral reticular nucleus

Development of Autonomic and Respiratory Centres

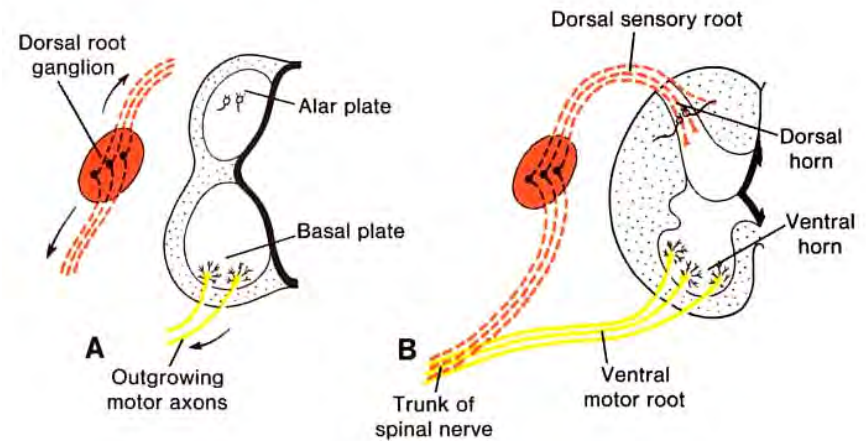
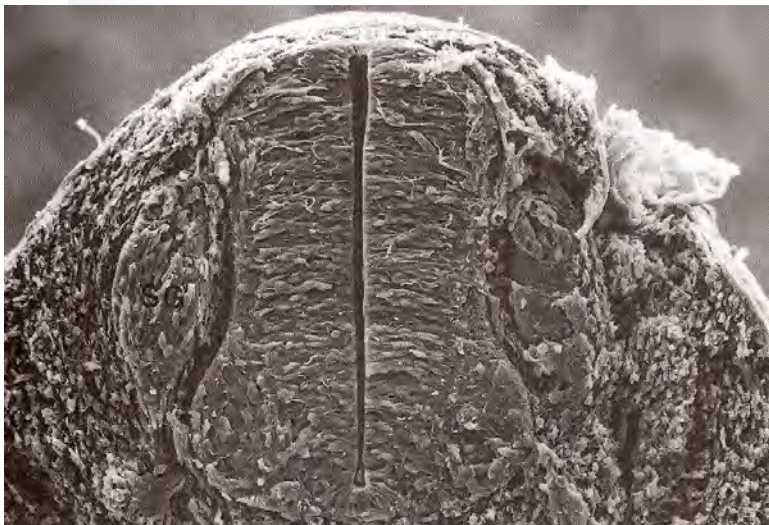
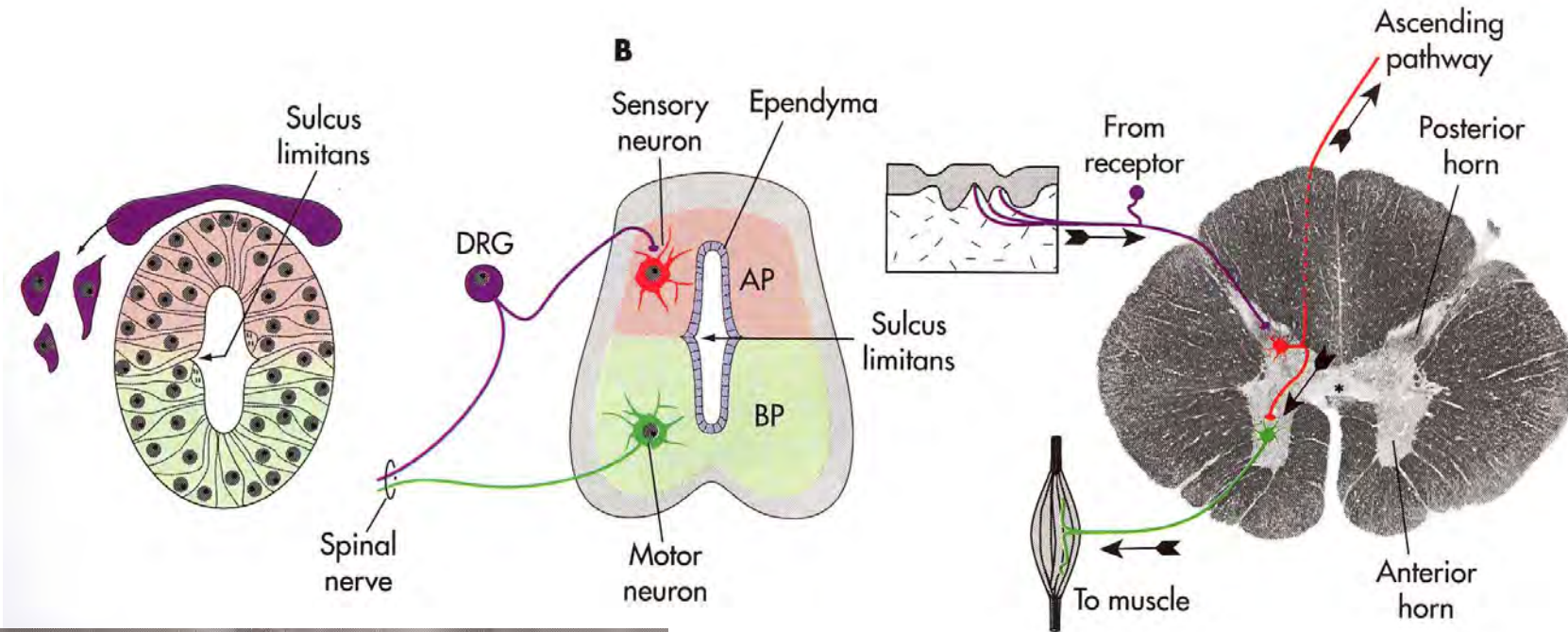
- Respiratory and cardiovascular centres are in the intermediate reticular zone of the medulla.
- Respiratory and cardiovascular centre maturation occurs in the third trimester.
- Premature infants are especially vulnerable to deficiencies in cardiorespiratory control.



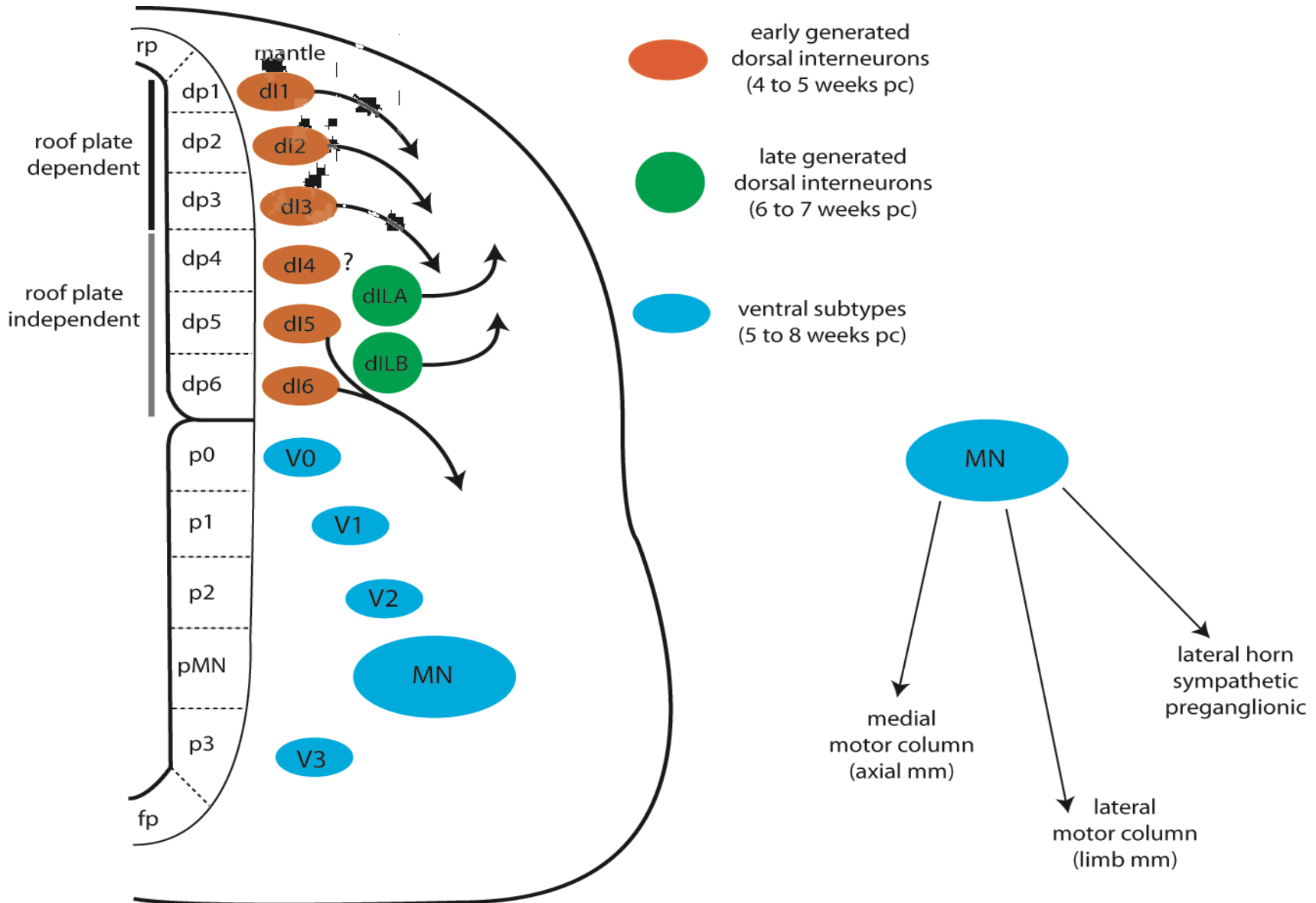
Development of Vagus Nerve



The Developing Spinal Cord

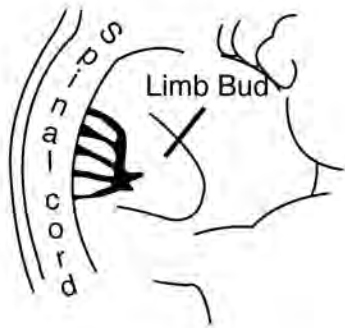


Origins of Spinal Cord Neurons

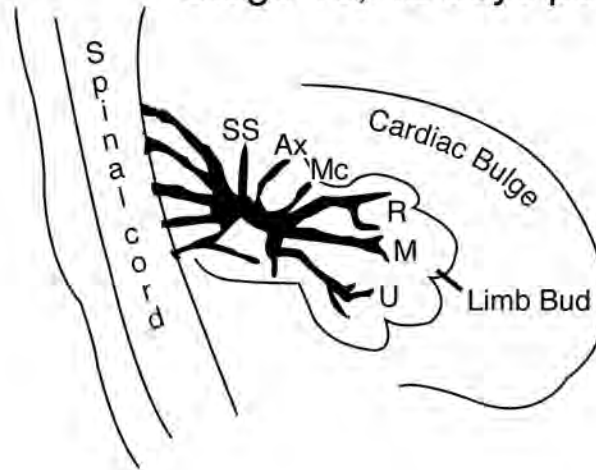


Development of Peripheral Nerves

Stage 14, 33 days pc

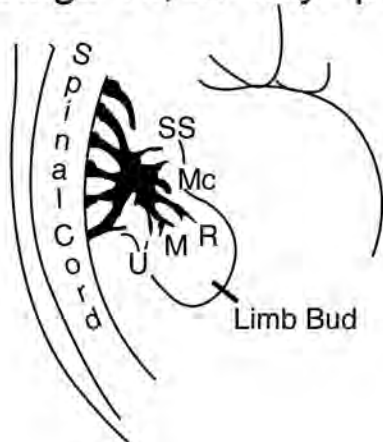


Stage 18, 42 days pc

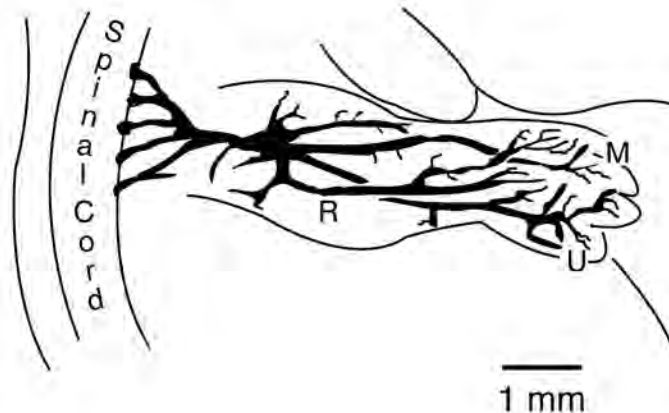


Invasion of limb buds by nerves is almost contemporaneous with limb muscle differentiation.

Stage 16, 37 days pc

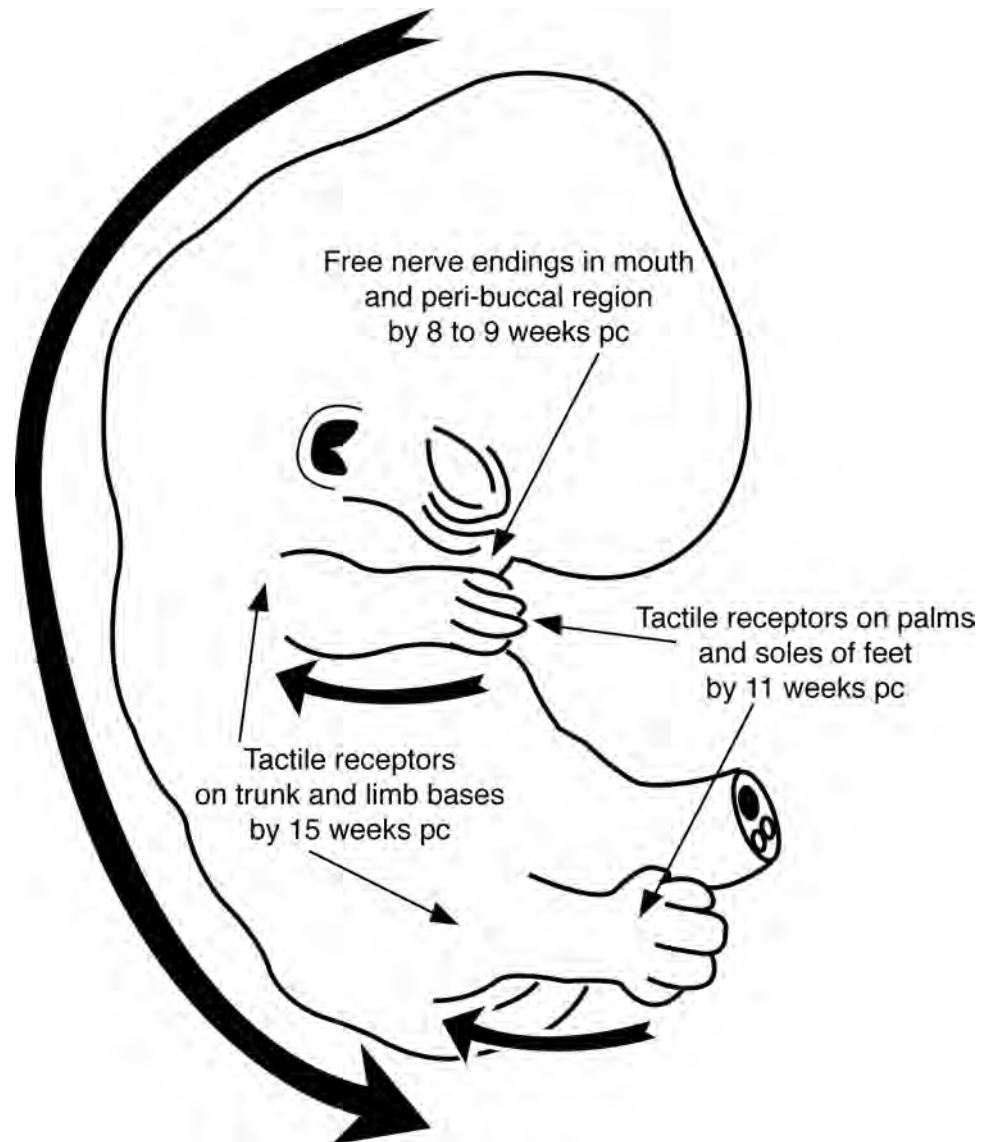


Stage 21, 48 days pc



Ax – axillary nerve
 M – median
 Mc – musculocutaneous
 R – radial
 SS – suprascapular
 U - ulnar

Development of Sensory Receptors



Development of receptors for the somatosensory system follows a rough rostral-caudal/distal-to-proximal pattern.

Free nerve endings develop before Meissner and Pacinian corpuscles.

Free nerve ending density is greater than in adult, suggesting early exuberance with later pruning.