Late Embryonic and Fetal Development of the Nervous System

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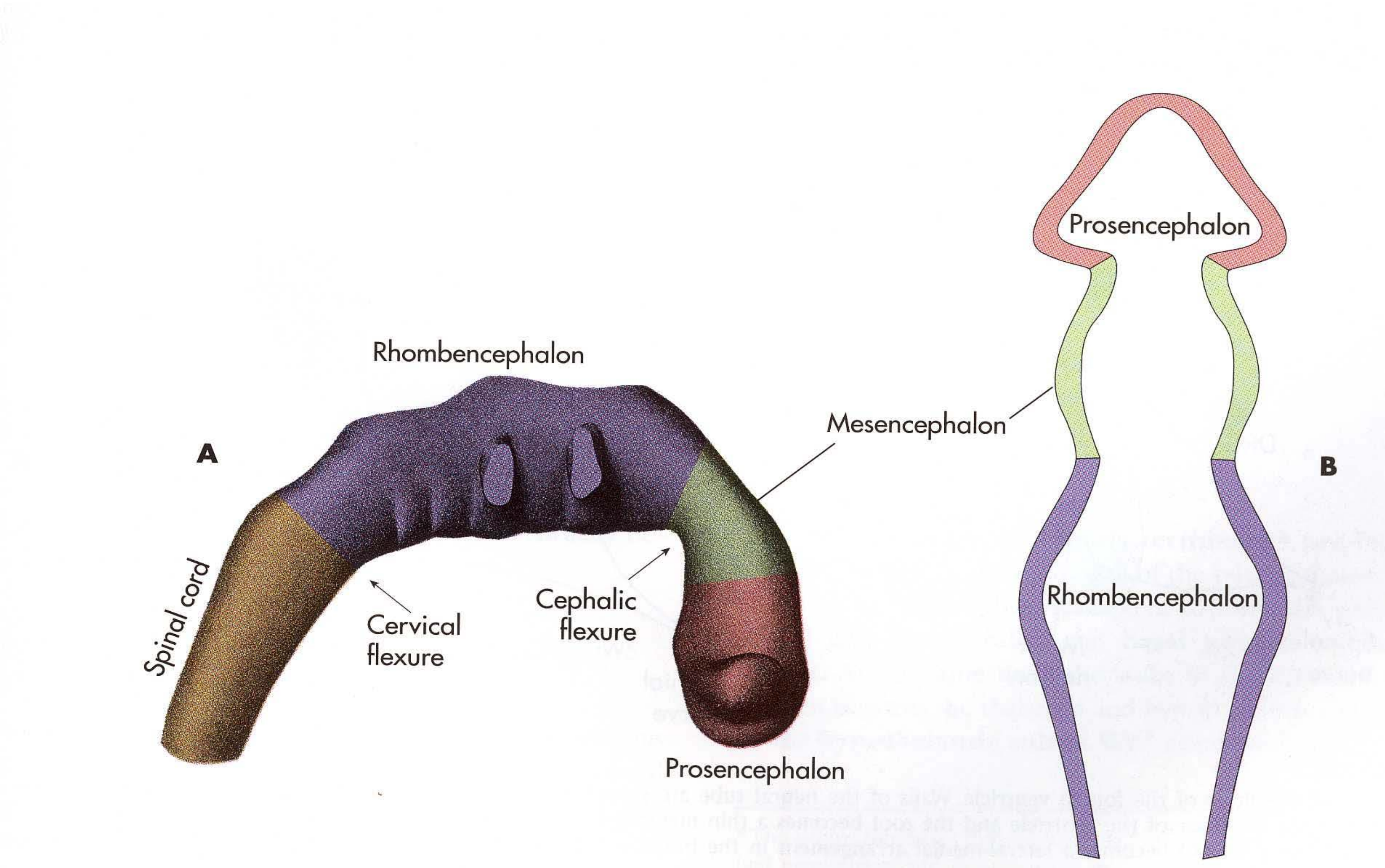
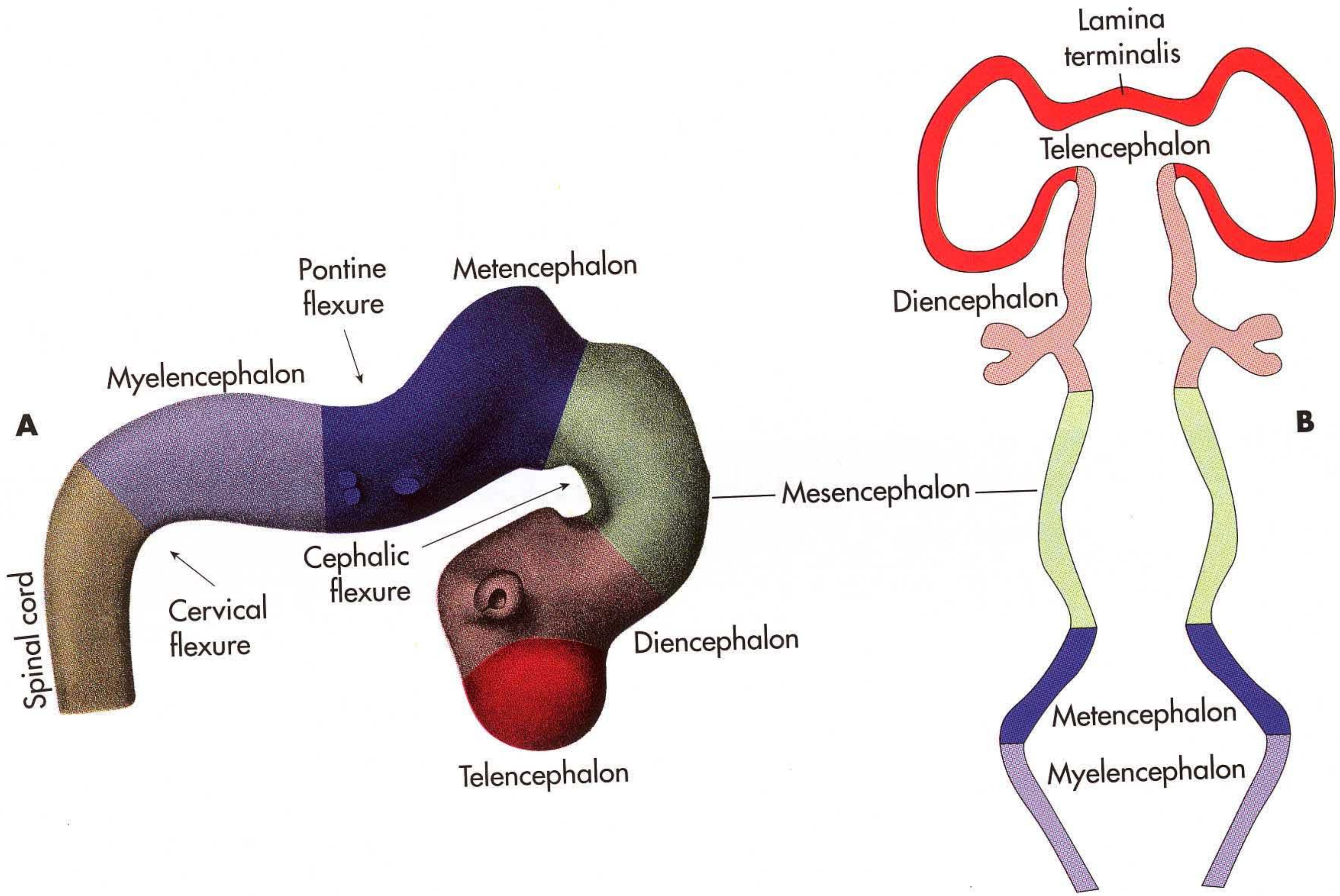
The Developing Brain Vesicles 1

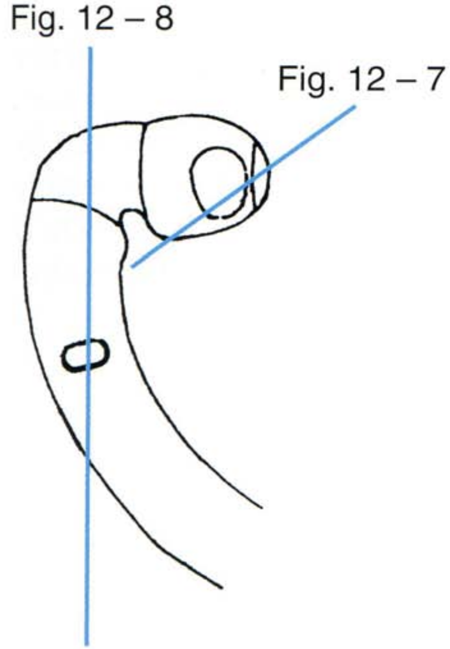
(The Traditional View)

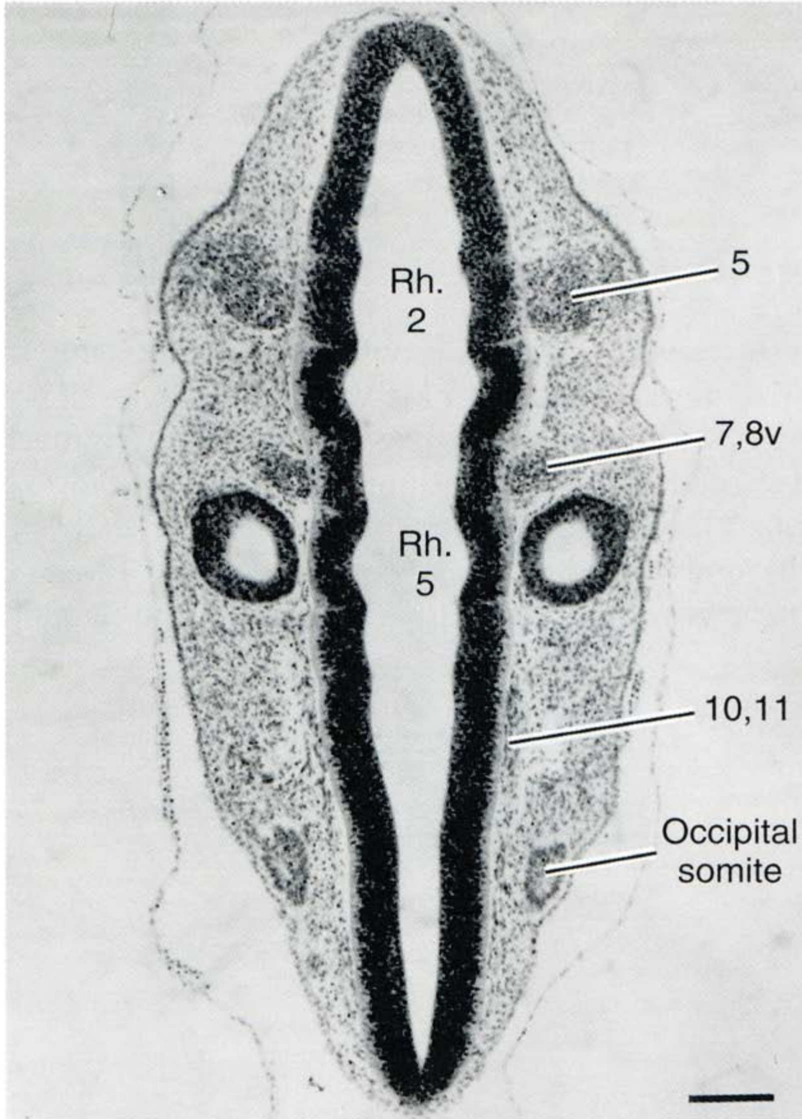


The Developing Brain Vesicles 2
(The Traditional View)



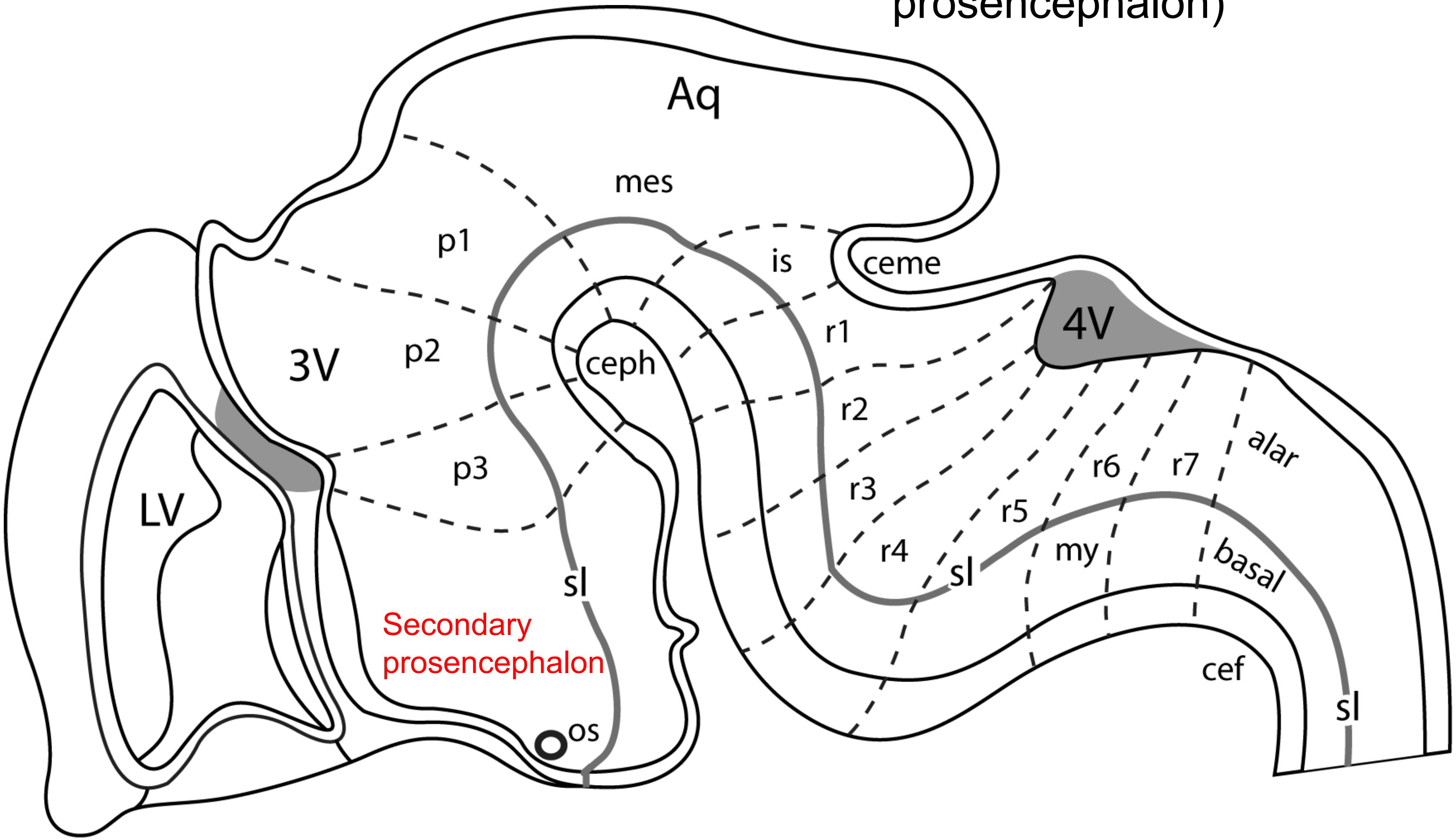
Neuromeric Organization



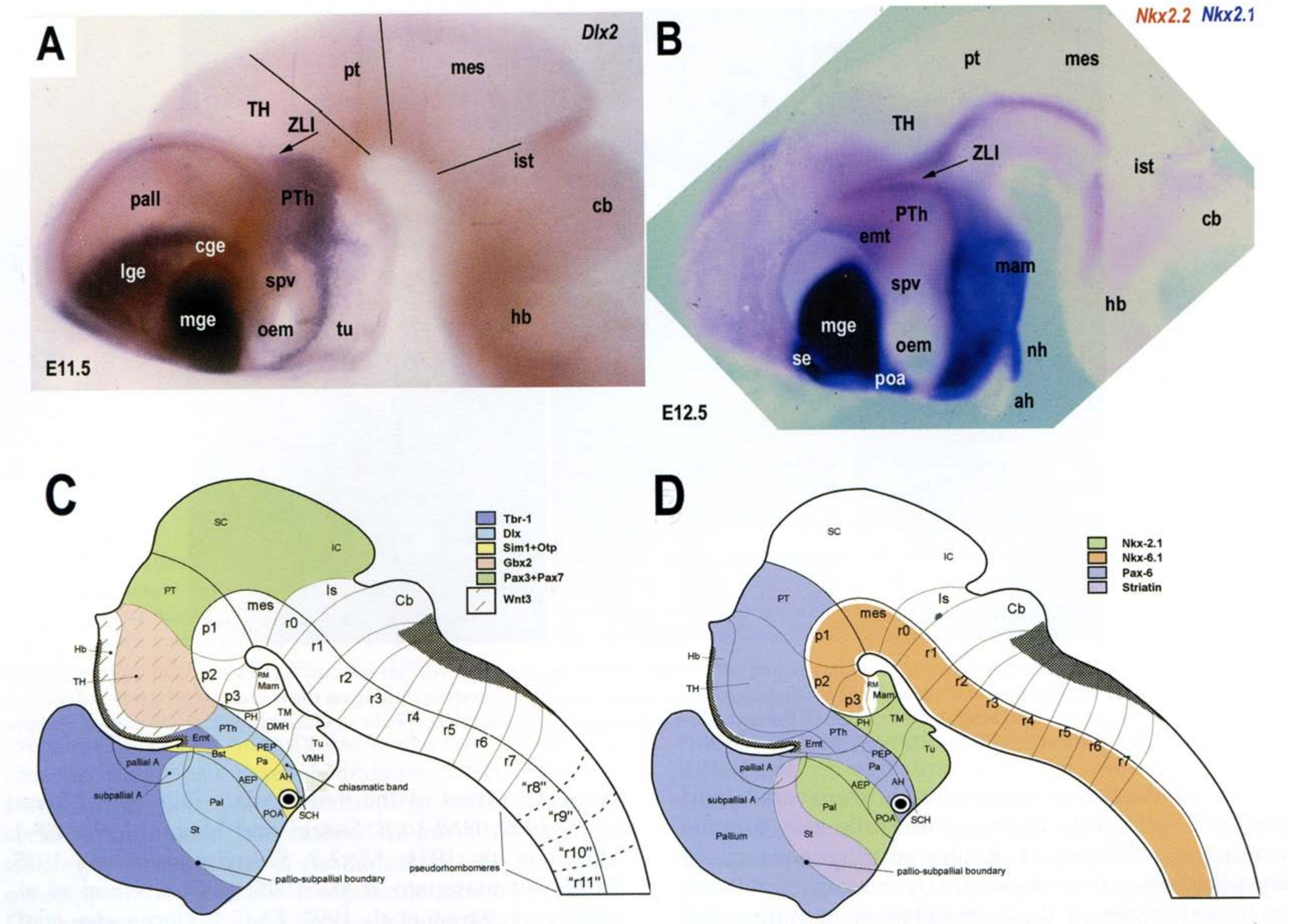


Neuromeres

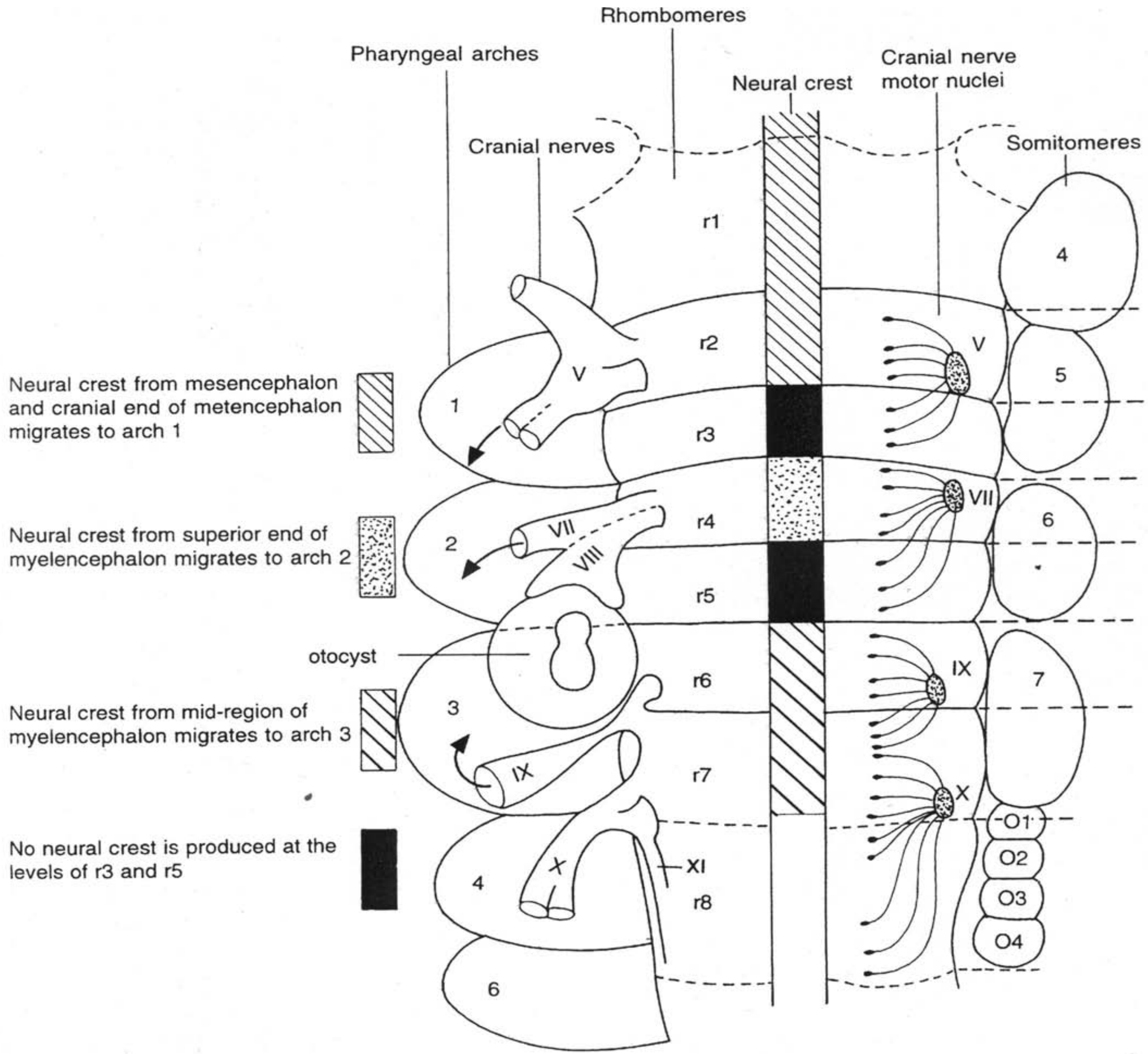
- Rhombomeres: r1 to r7 (8)
- Isthmic neuromere: is
- Mesencephalic neuromere: mes
- Prosomeres: p1 to p3
- Proneuromere zone (secondary prosencephalon)



Gene Expression and Neuromeric Organization of the Brain



Derivatives of the Rhombomeres



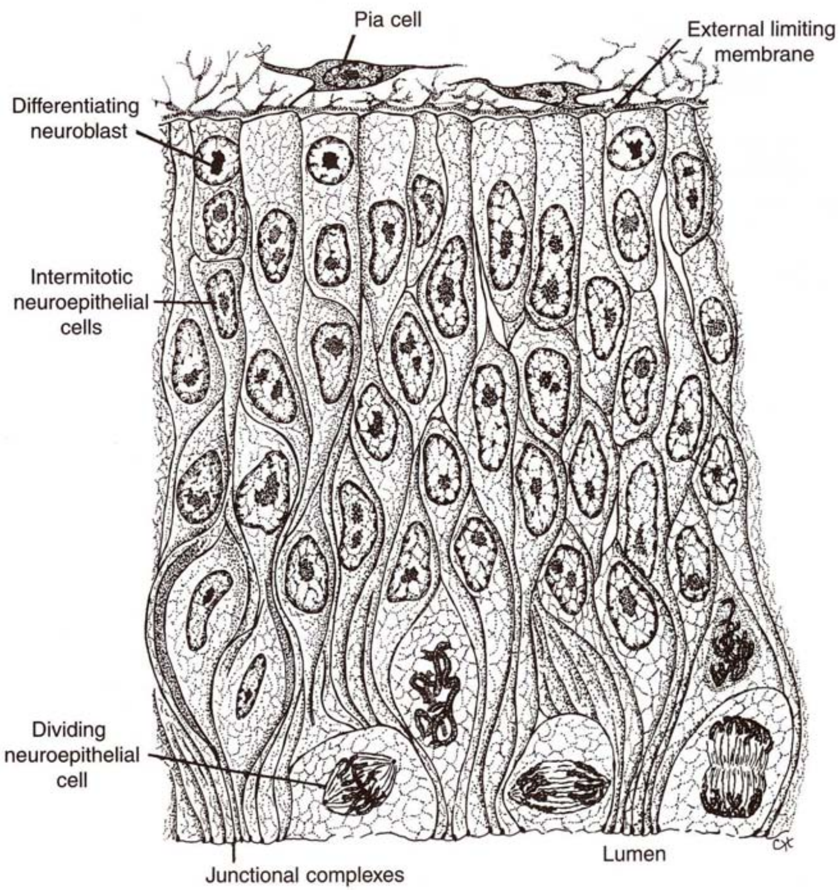
Derivatives of the Prosomeres

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

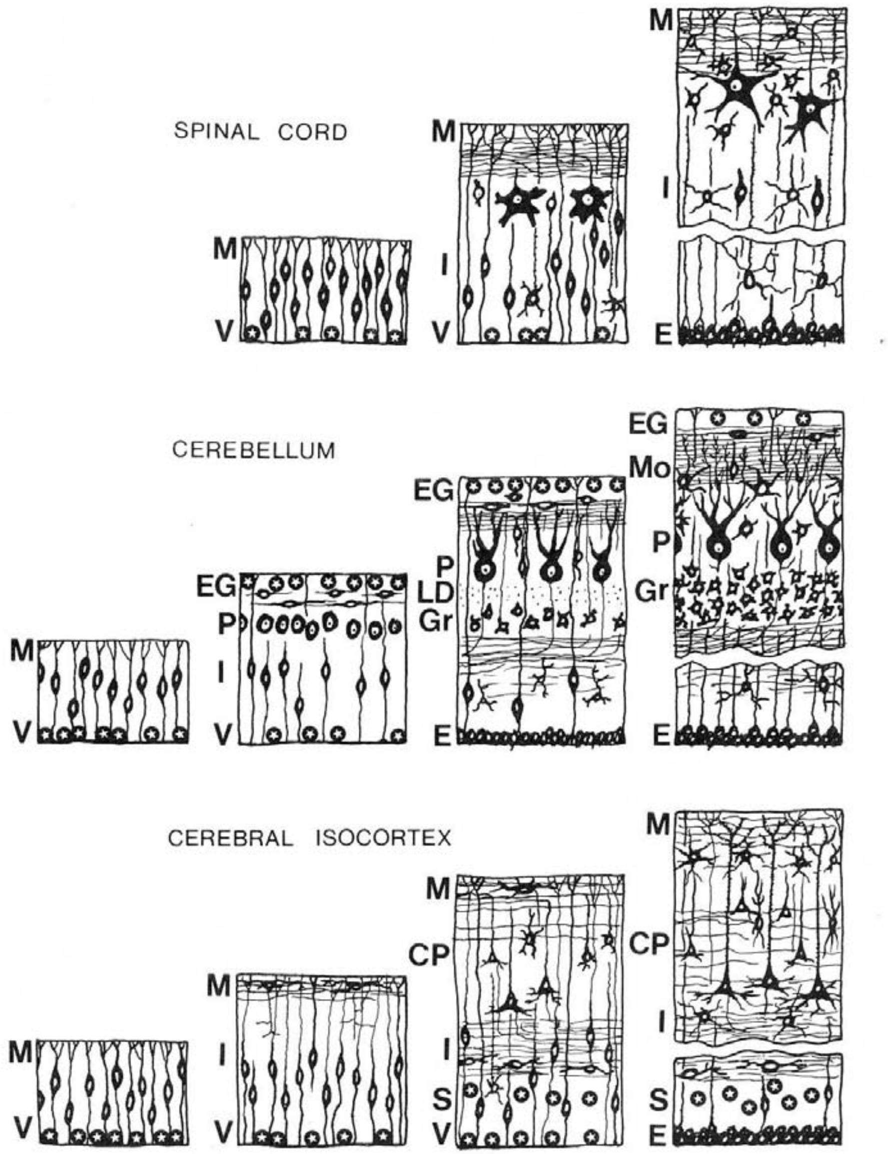
Derivatives of the Proneuromere Zone

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

Primary and Secondary Proliferative Zones



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

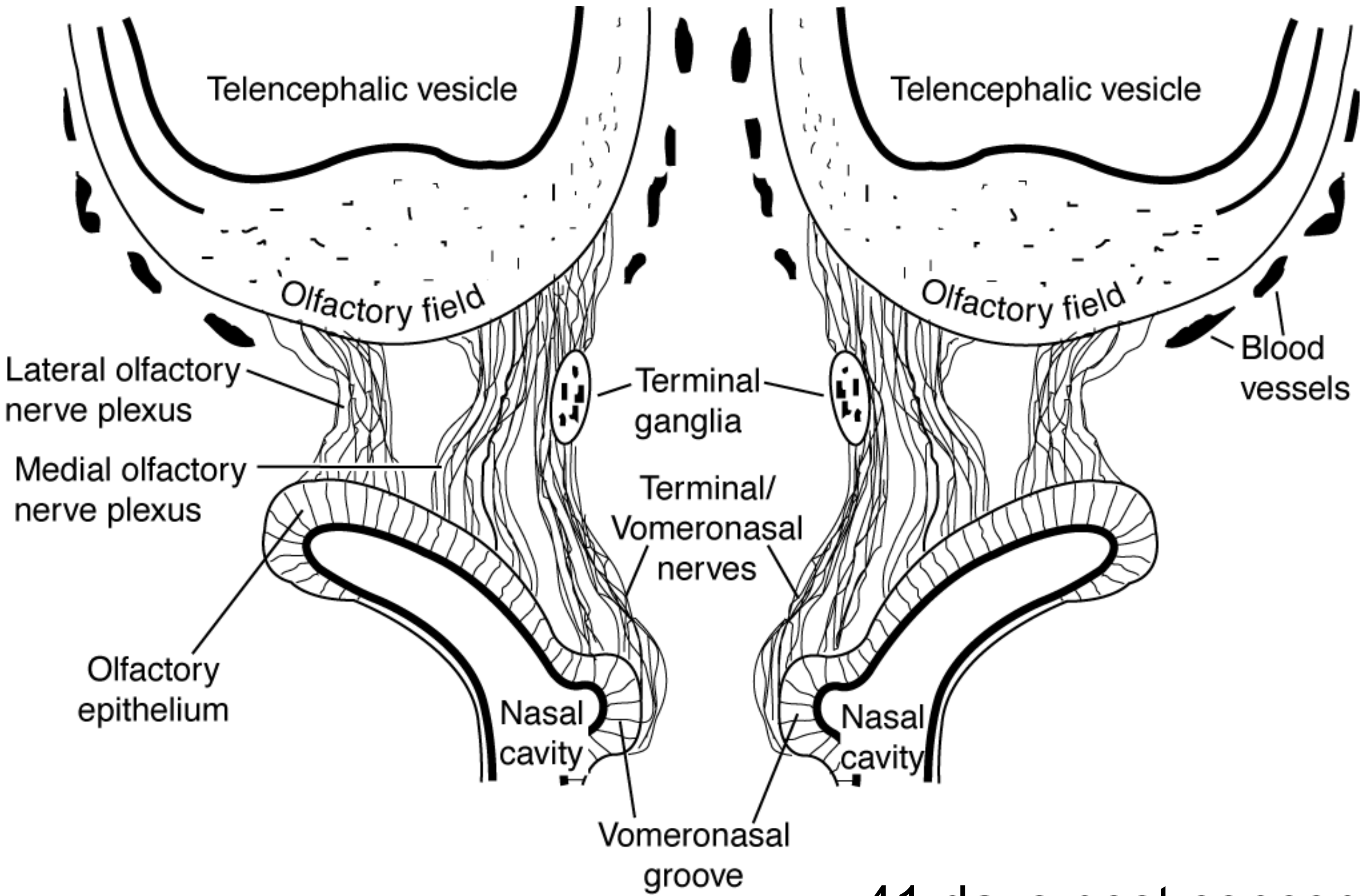
The SVZ is found beneath developing cortex and in developing basal ganglia (ganglionic eminences).

Layers of Developing Human Cortex

20 wg

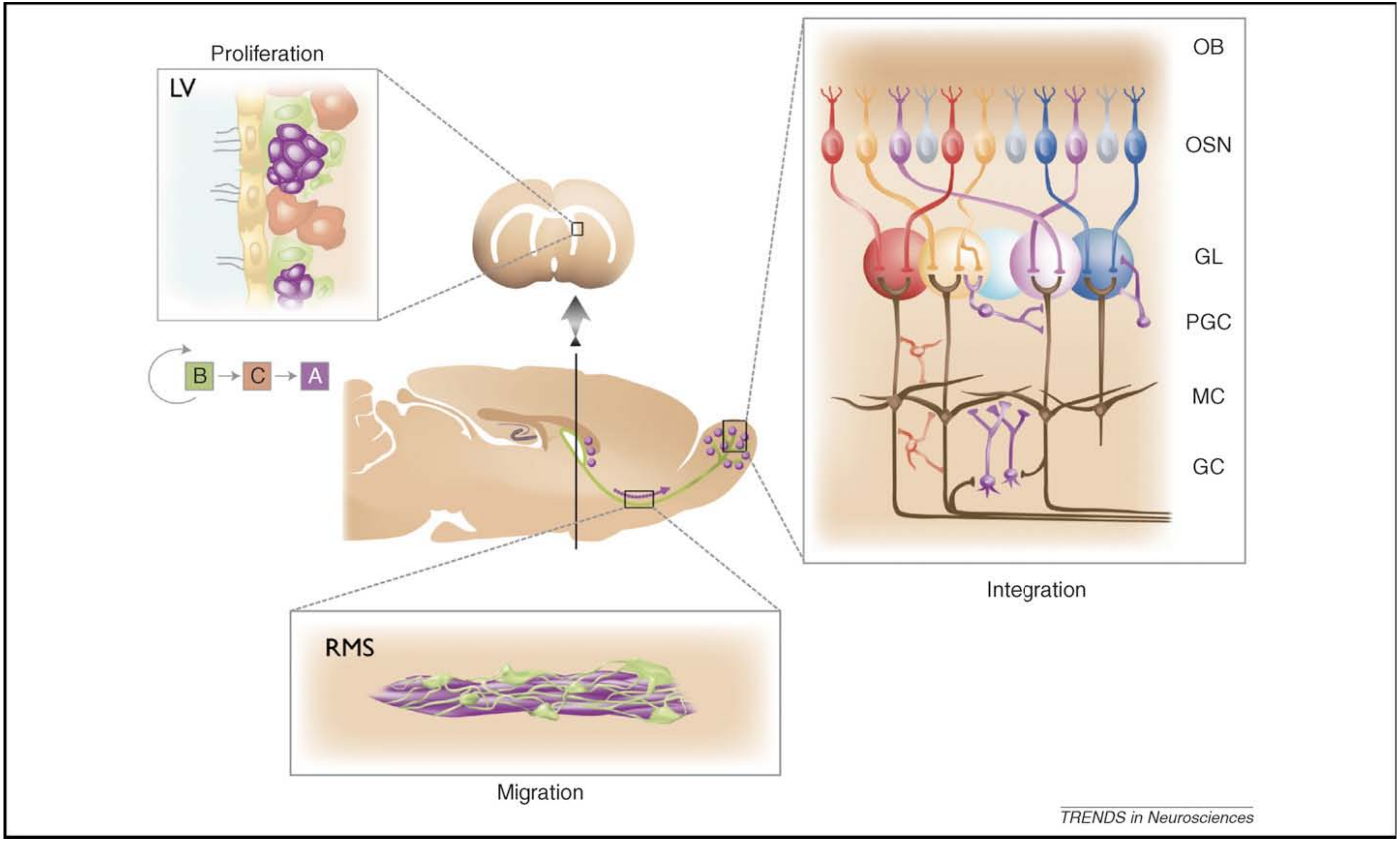
24 wg

Olfactory Development



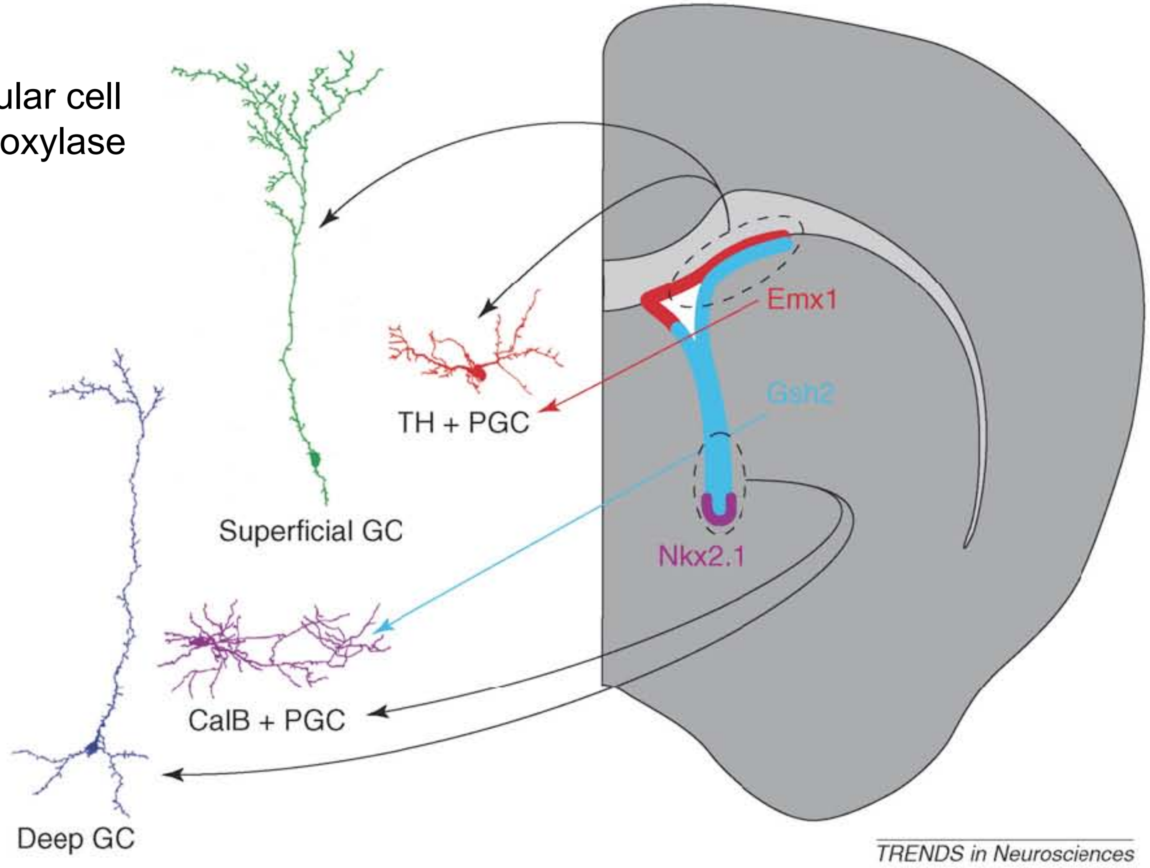
41 days post conception (pc)

Many Small Olfactory Neurons are Derived from SVZ of Forebrain



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

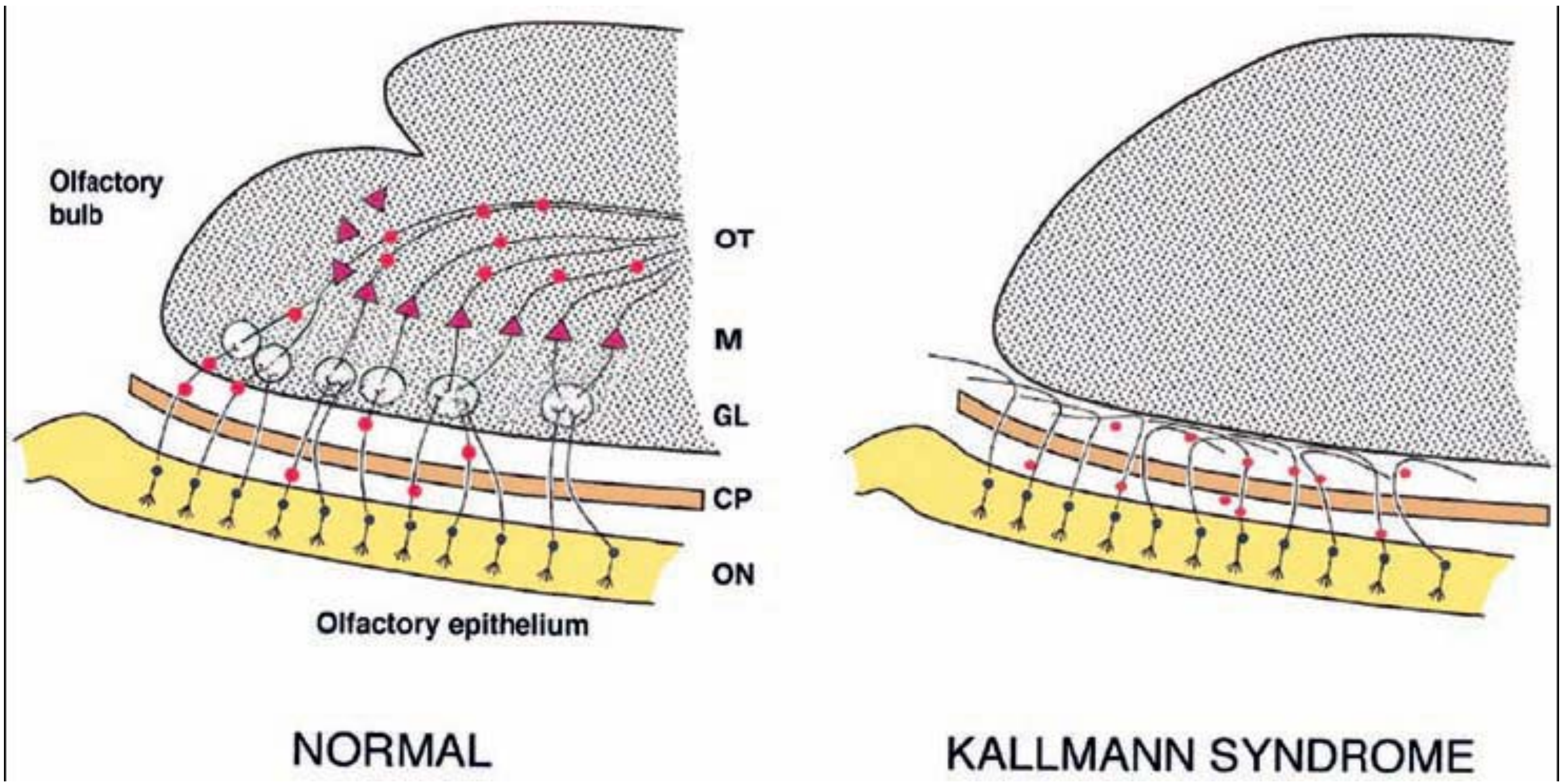
GC - granule cell
PGC – periglomerular cell
TH – tyrosine hydroxylase
CalB - calbindin



The Link Between Olfaction and Neuroendocrine Development

- Vomeronasal organ and terminal nerve are major source of gonadotrophin releasing hormone (GnRH) producing cells for hypothalamus.
- GnRH can be detected in human olfactory epithelium as early as 5.5 weeks pc.
- Migration of GnRH cells along the developing vomeronasal/terminal nerve complex occurs during weeks 6 to 8 pc.

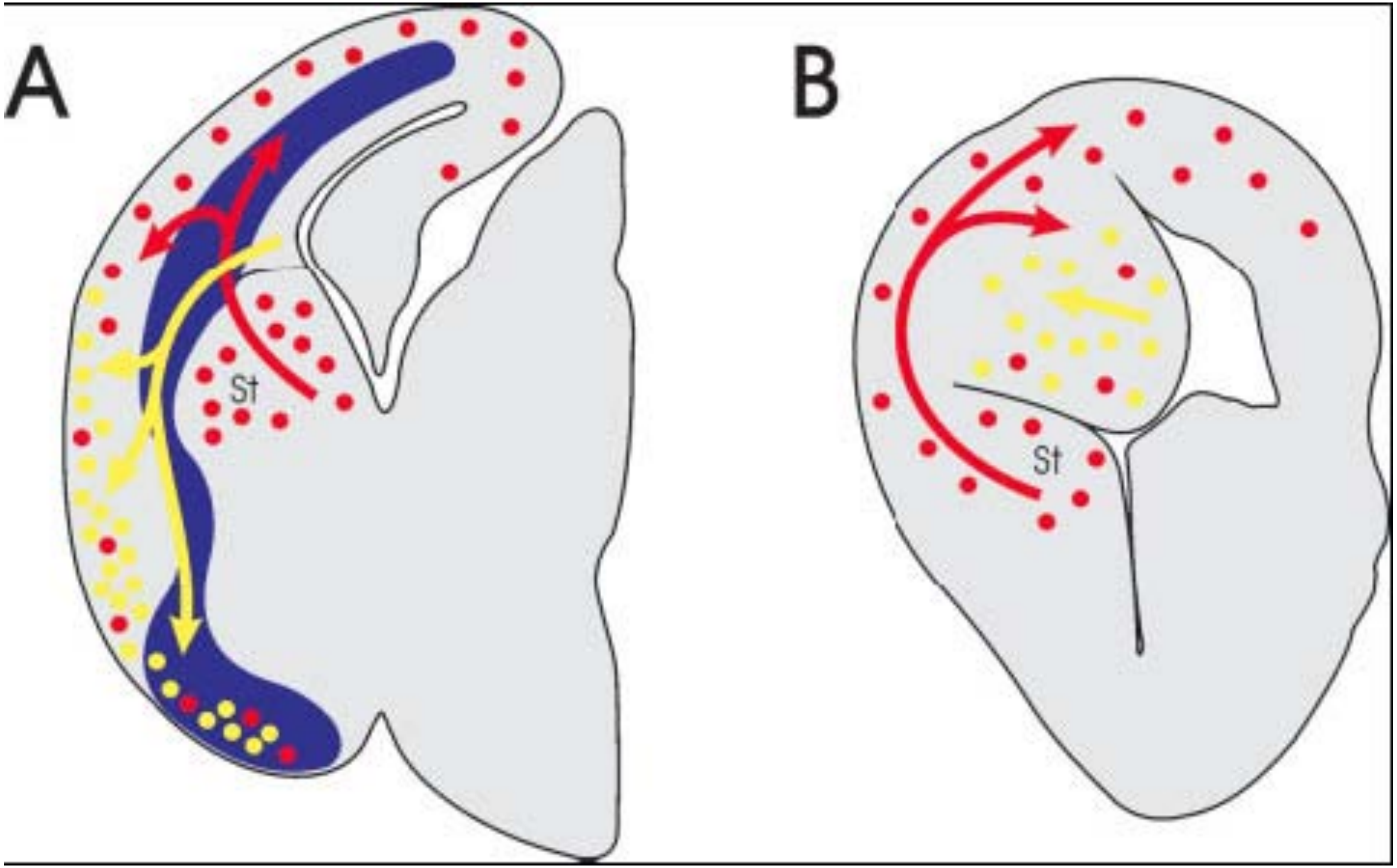
Kallmann Syndrome



Kallman's Syndrome

- Hypogonadotrophic hypogonadism associated with reproductive dysfunction and (often) anosmia.
- In human fetuses with Kallmann's syndrome, the olfactory, vomeronasal and terminal nerves terminate in the meninges (i.e. do not enter brain).
- Two different genes responsible for the disease.
  - KAL1 encodes anosmin 1, present along the migration path of GnRH neurons and the central roots of the terminal nerve.
  - KAL2 encodes fibroblast growth factor receptor 1 (FGFR1).

Origins of Cortical Neurons



Mammal

Bird

Cortical neurons come from several distinct sources

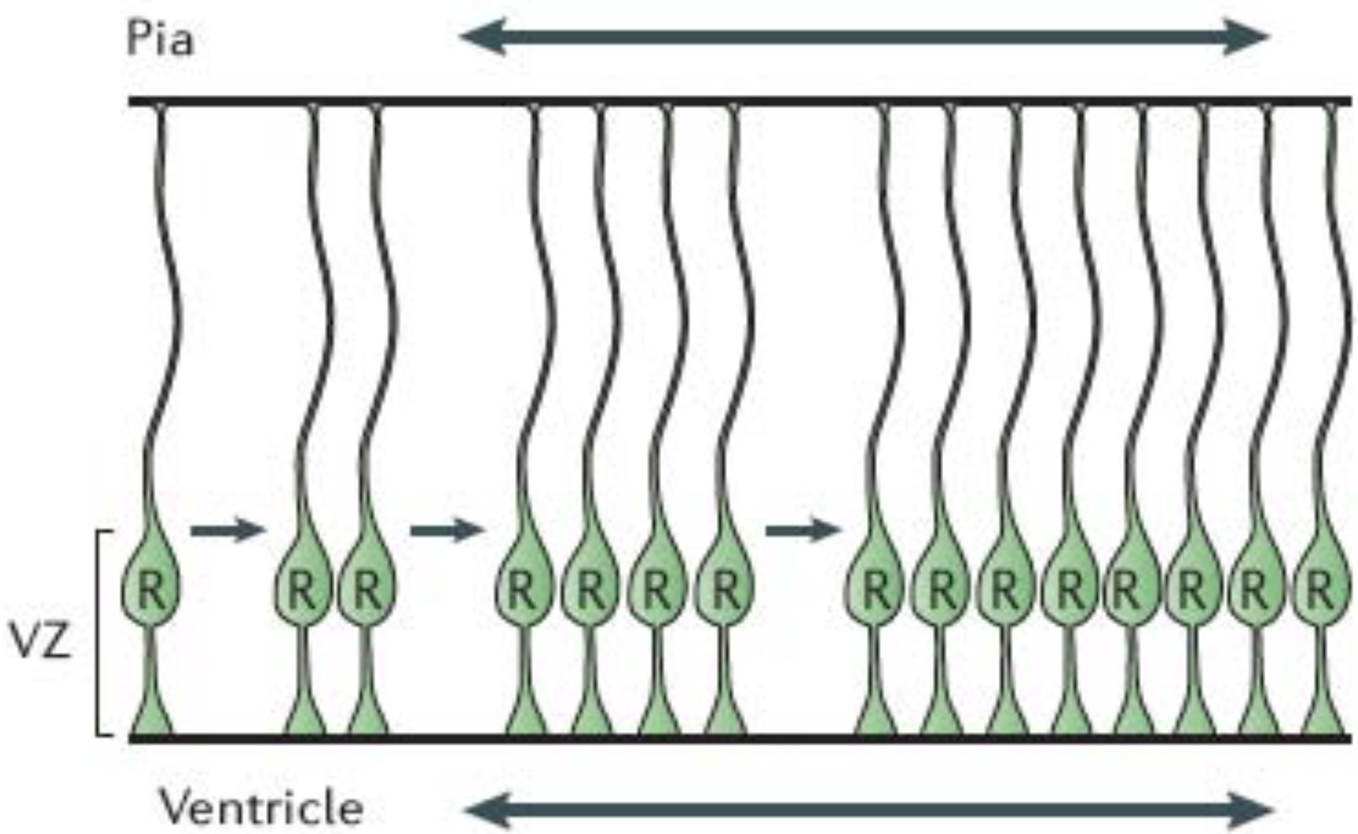
1 Local (pallial) ventricular zone ⟹ early generated glutamatergic neurons.

2 Local (pallial) subventricular zone, which may itself be derived from precursor cells migrating out of the nearby ventricular zone ⟹ late generated glutamatergic neurons.

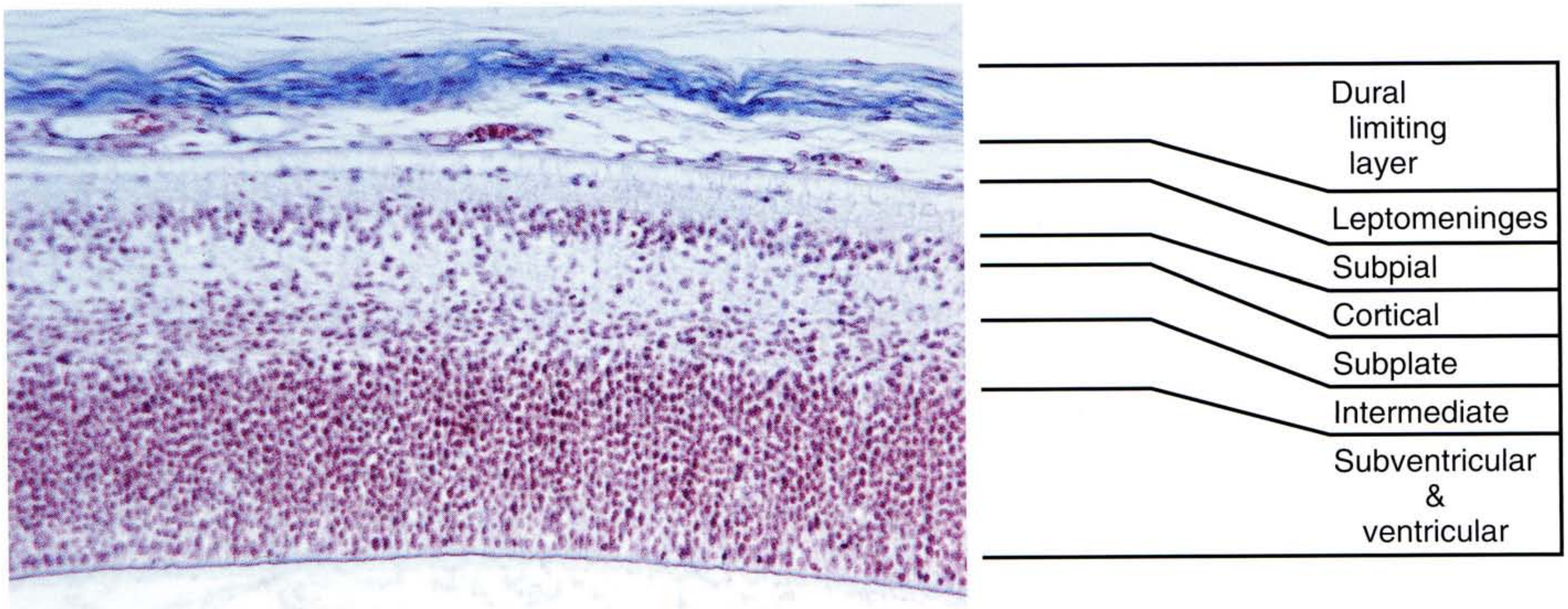
3 Subventricular zone of the lateral and medial ganglionic eminences of the ventral telencephalon ⟹ GABAergic neurons.

Expansion of the Cortical Surface

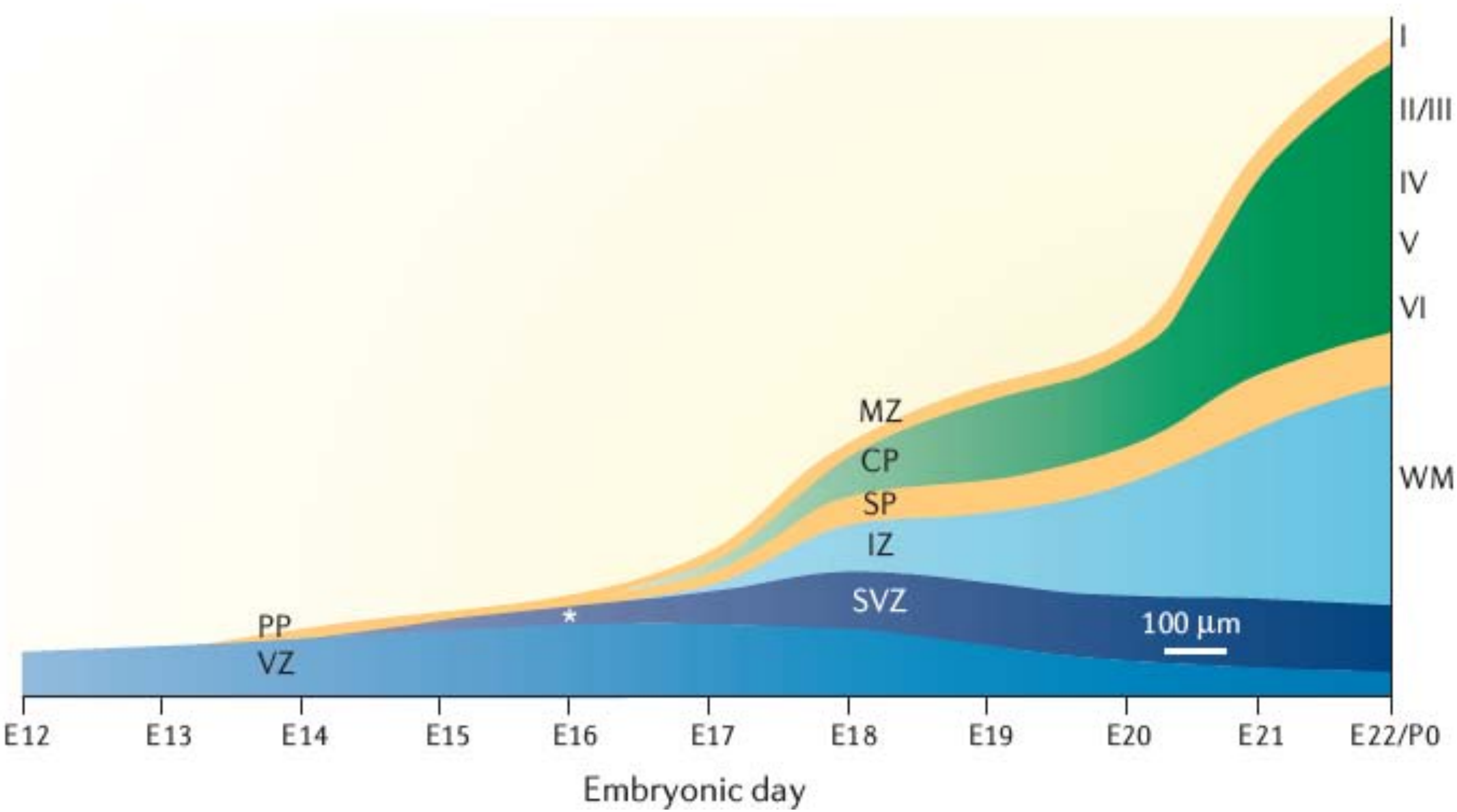
a **Symmetric progenitor divisions**

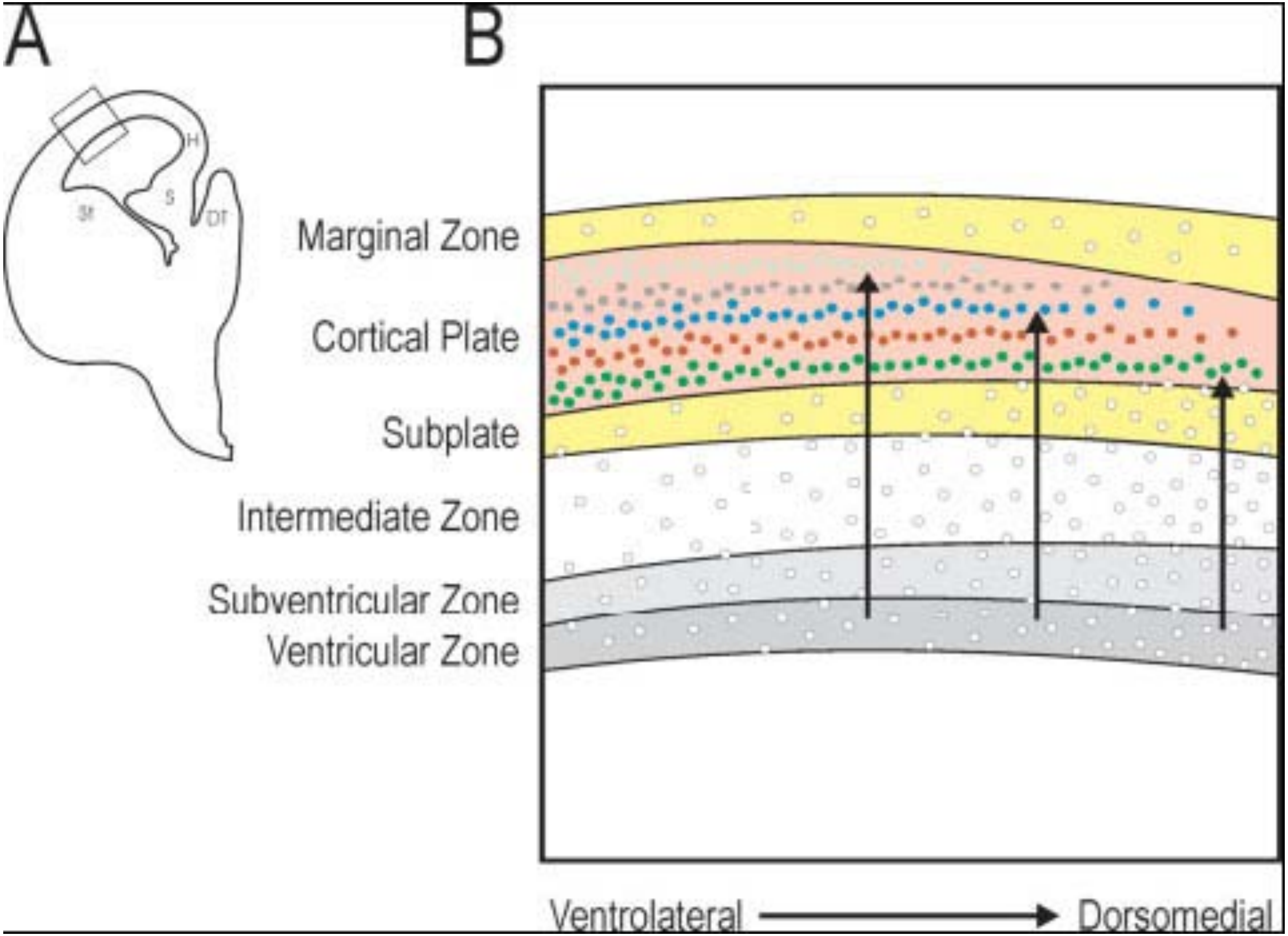


Layers of Developing Cortex

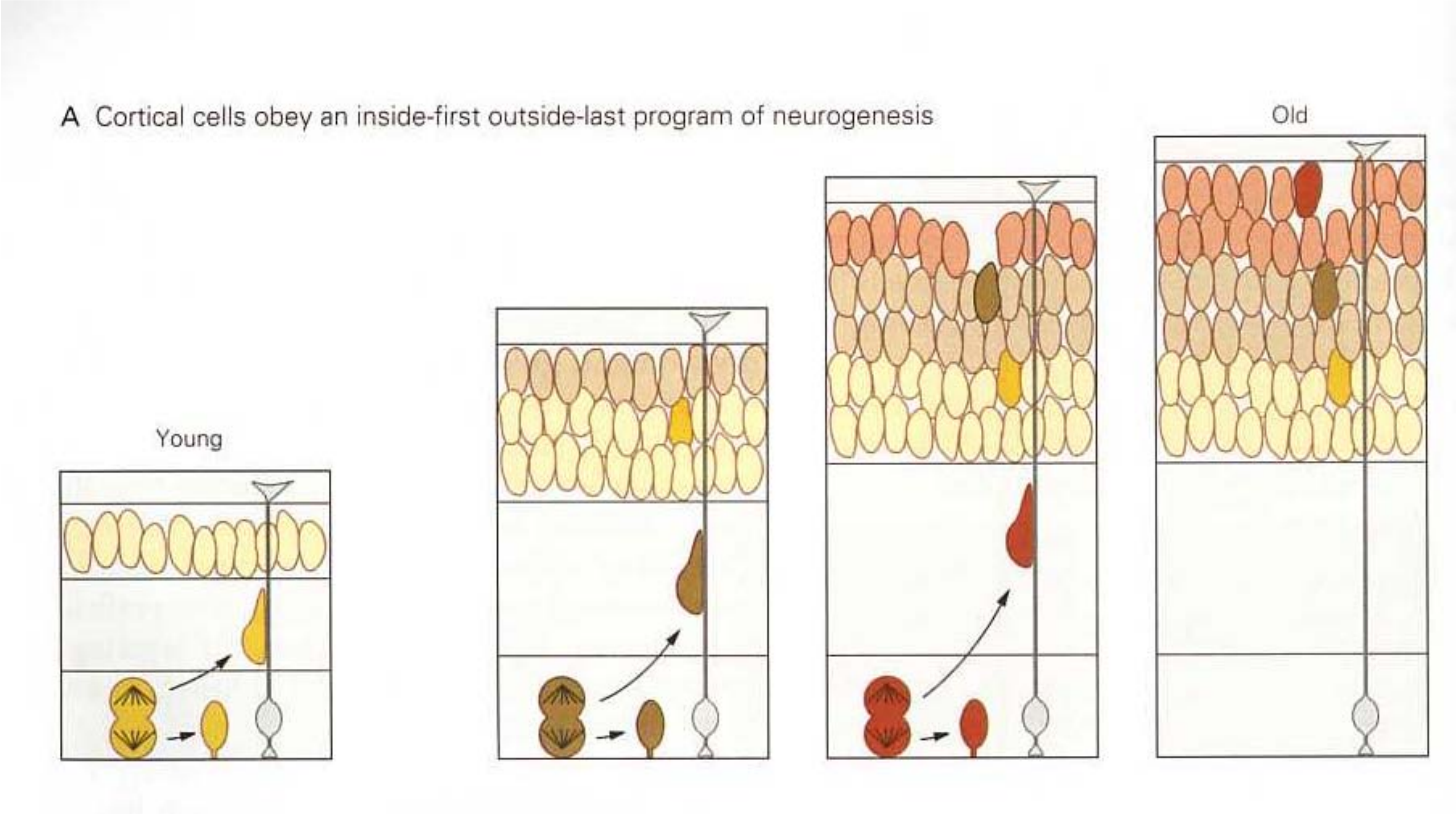


Development of Cortex

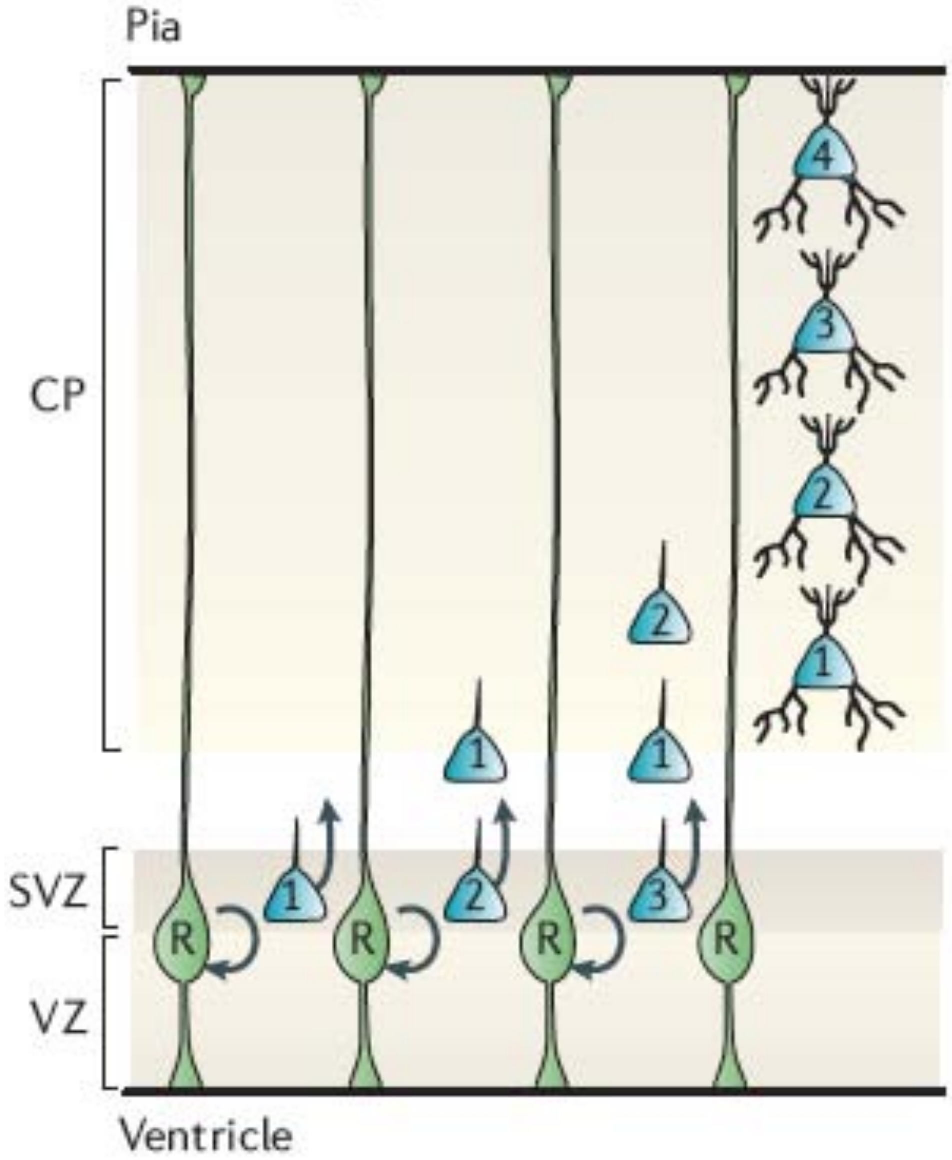



A
B
H
S
St
DT
Marginal Zone
Cortical Plate
Subplate
Intermediate Zone
Subventricular Zone
Ventricular Zone
Ventrolateral
Dorsomedial

The Developing Cerebral Cortex

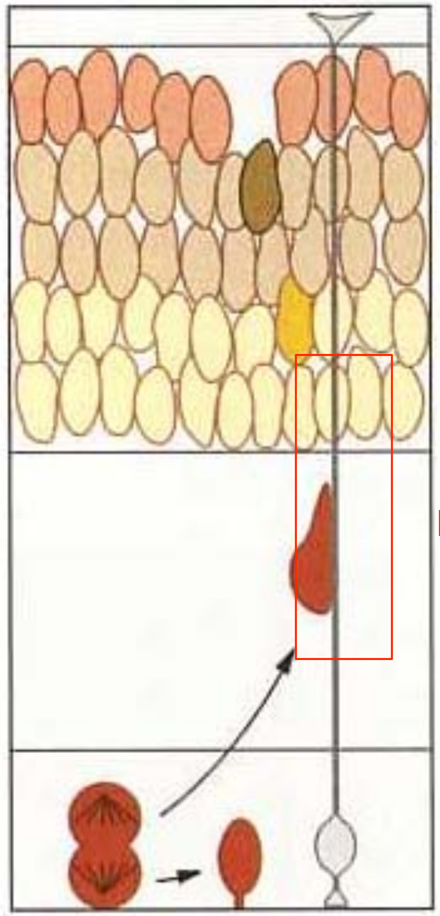


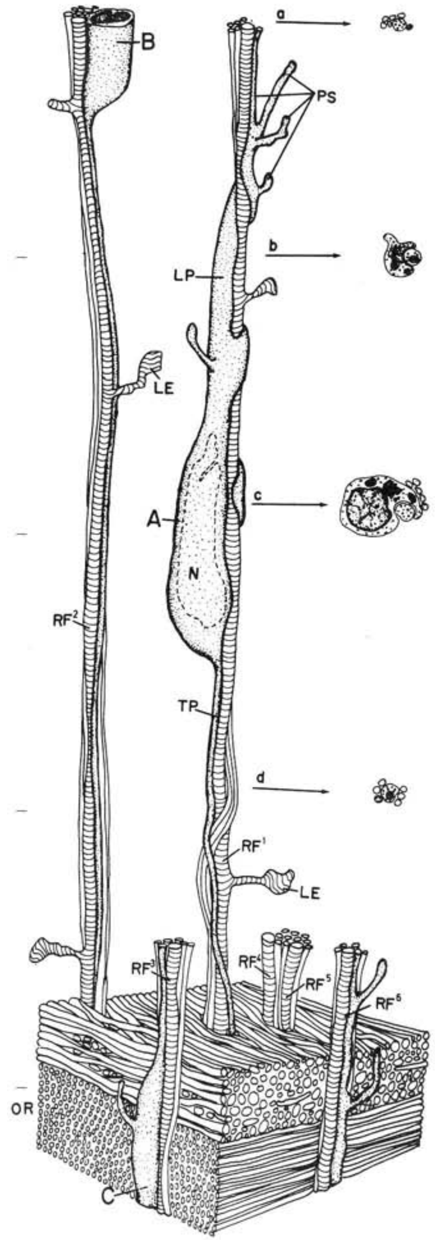
b **Asymmetric neurogenesis (radial unit hypothesis)**



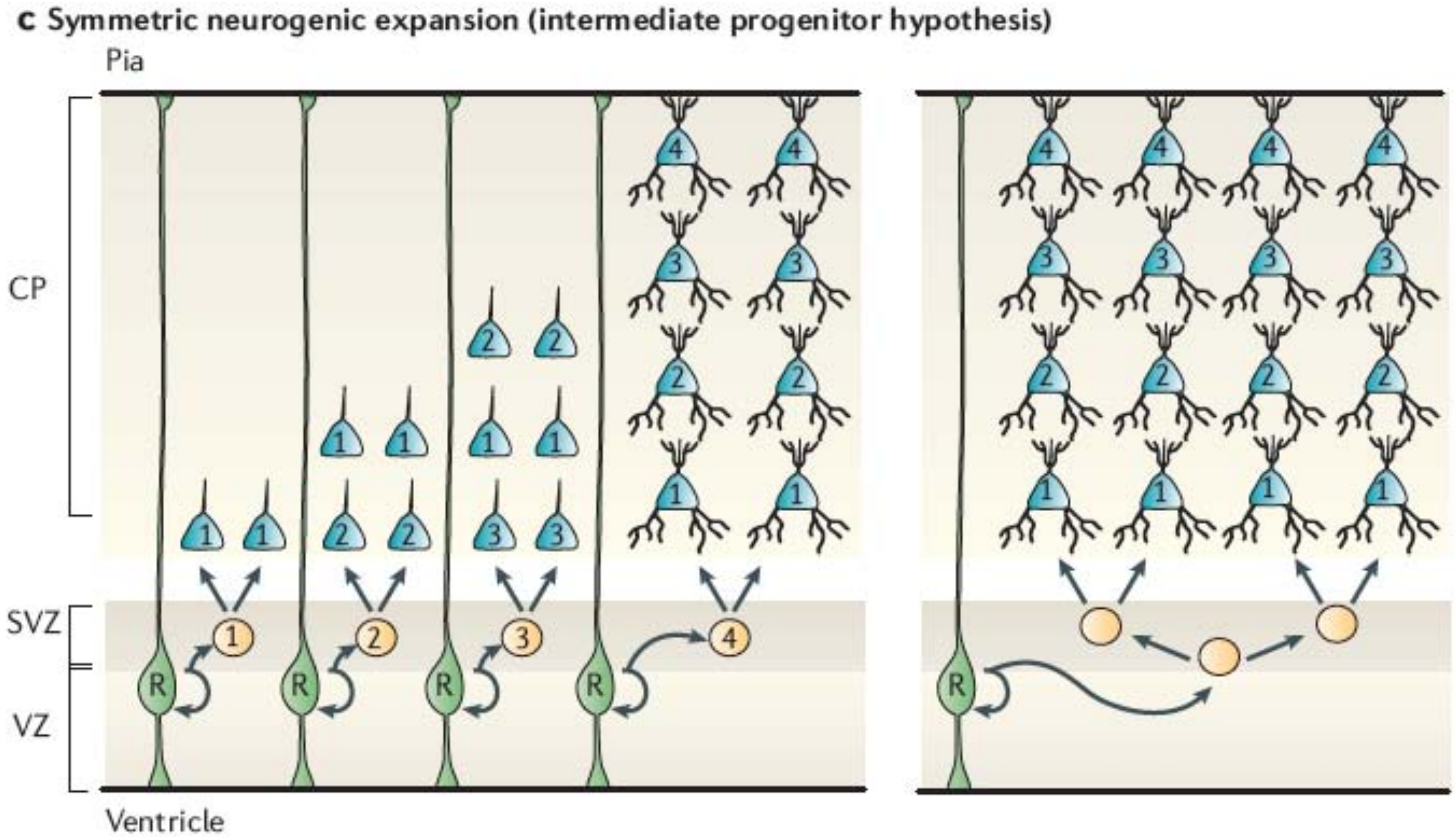
How Do Neurons Migrate?

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

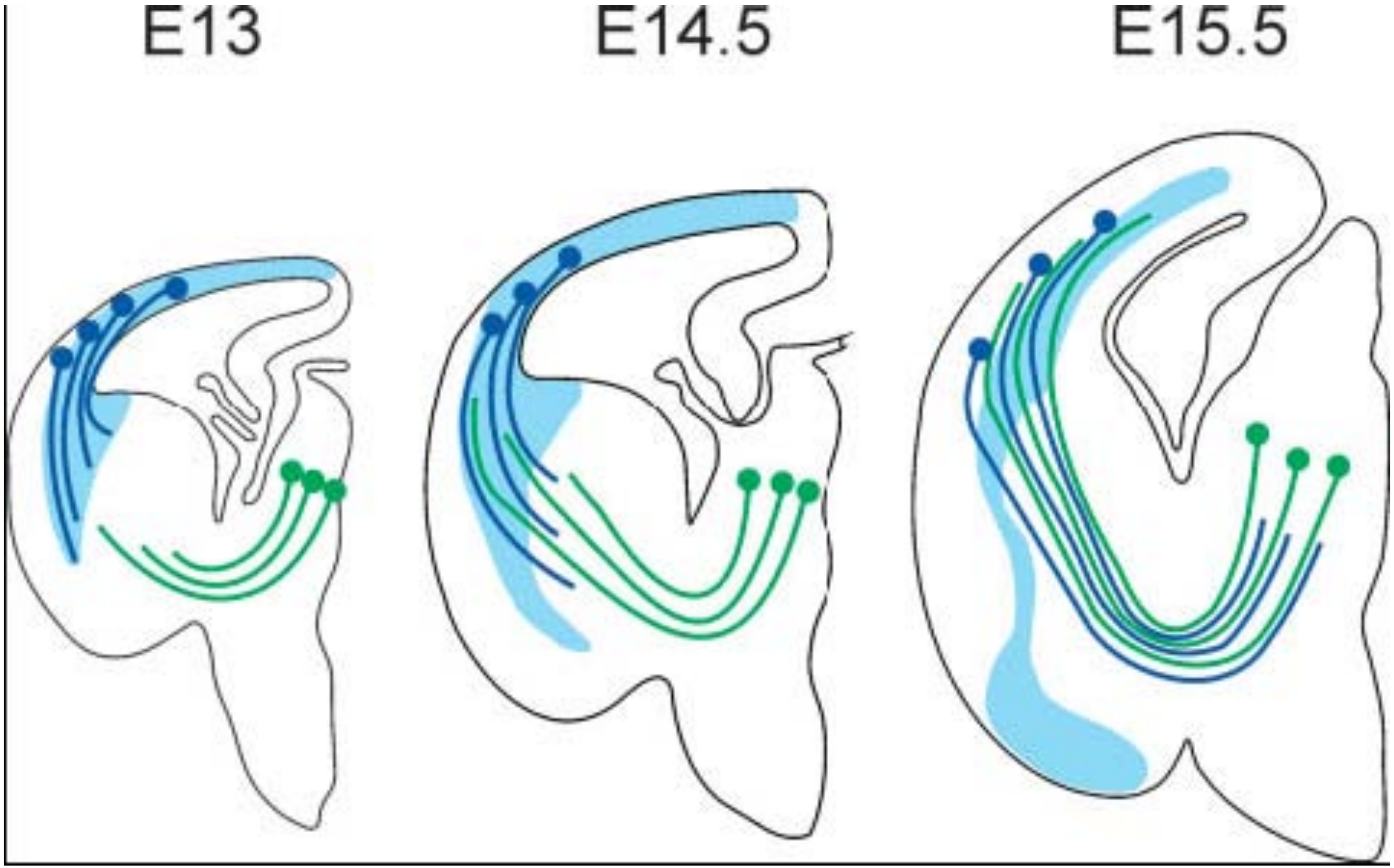




Intermediate Progenitors in SVZ



Formation of Cortical Connections (Rat)



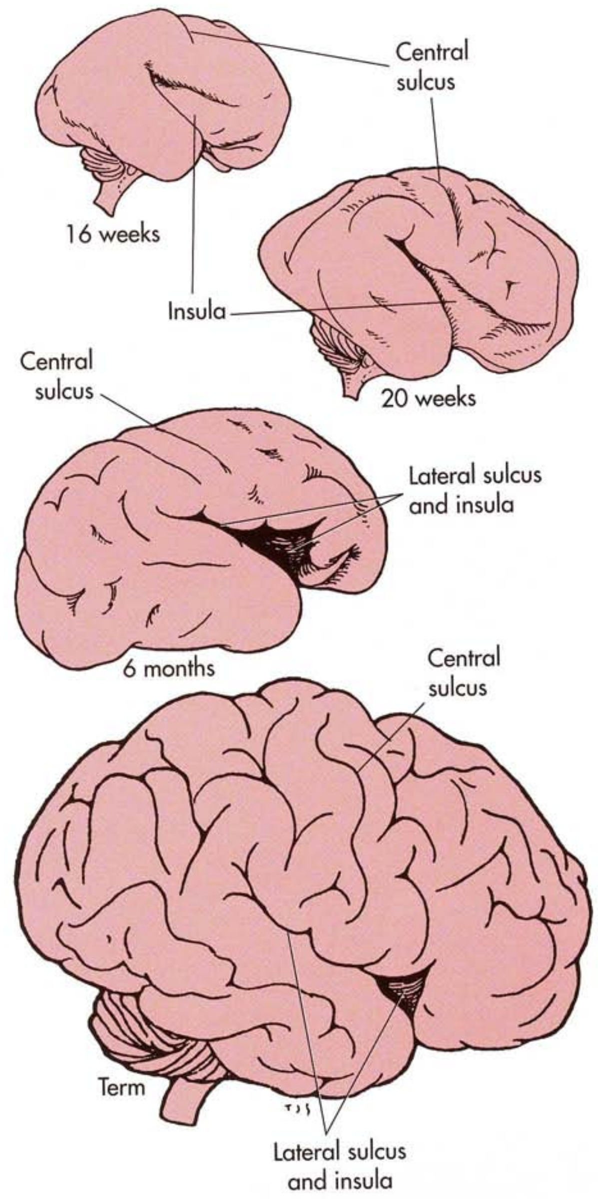
The Role of the Cortical Subplate

- 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

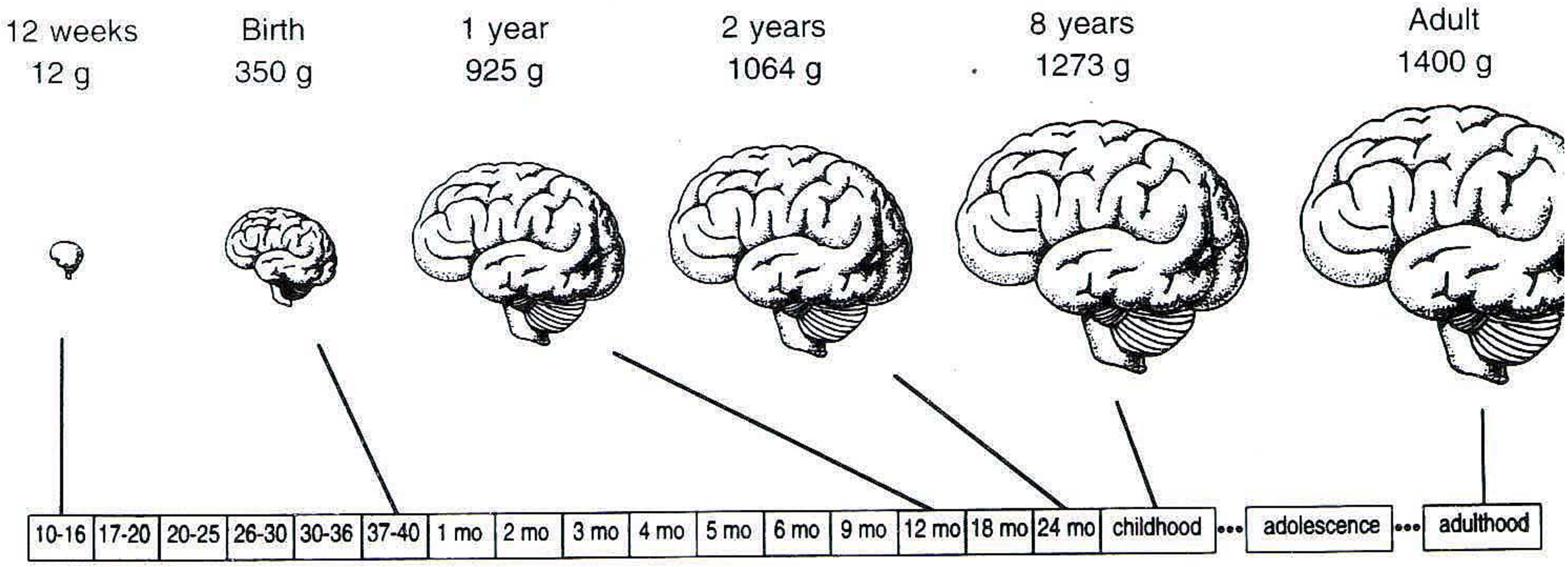


Most of the brain growth after birth is in the cerebral cortex.

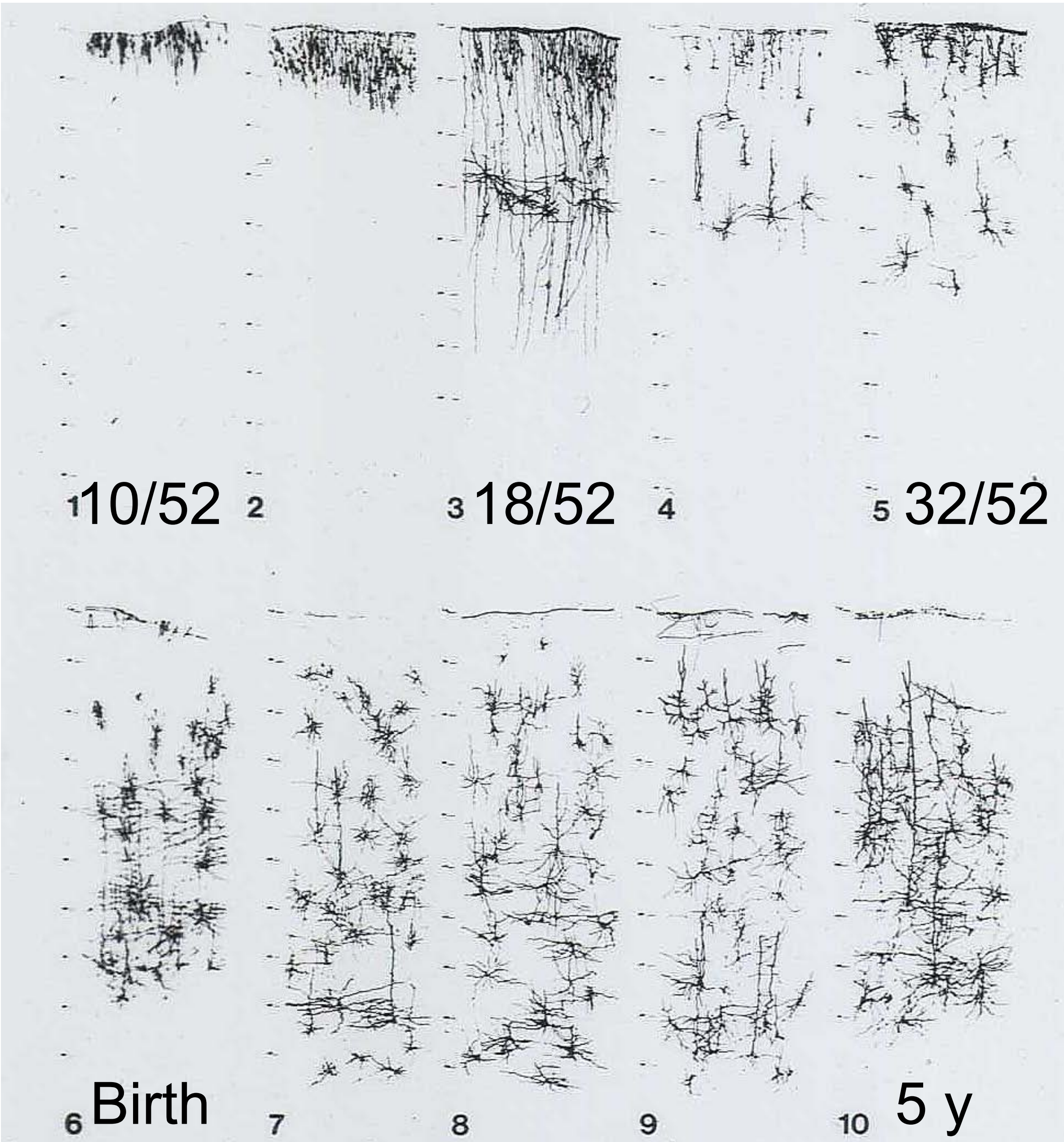
Brain growth continues until 5 to 7 years of age.

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

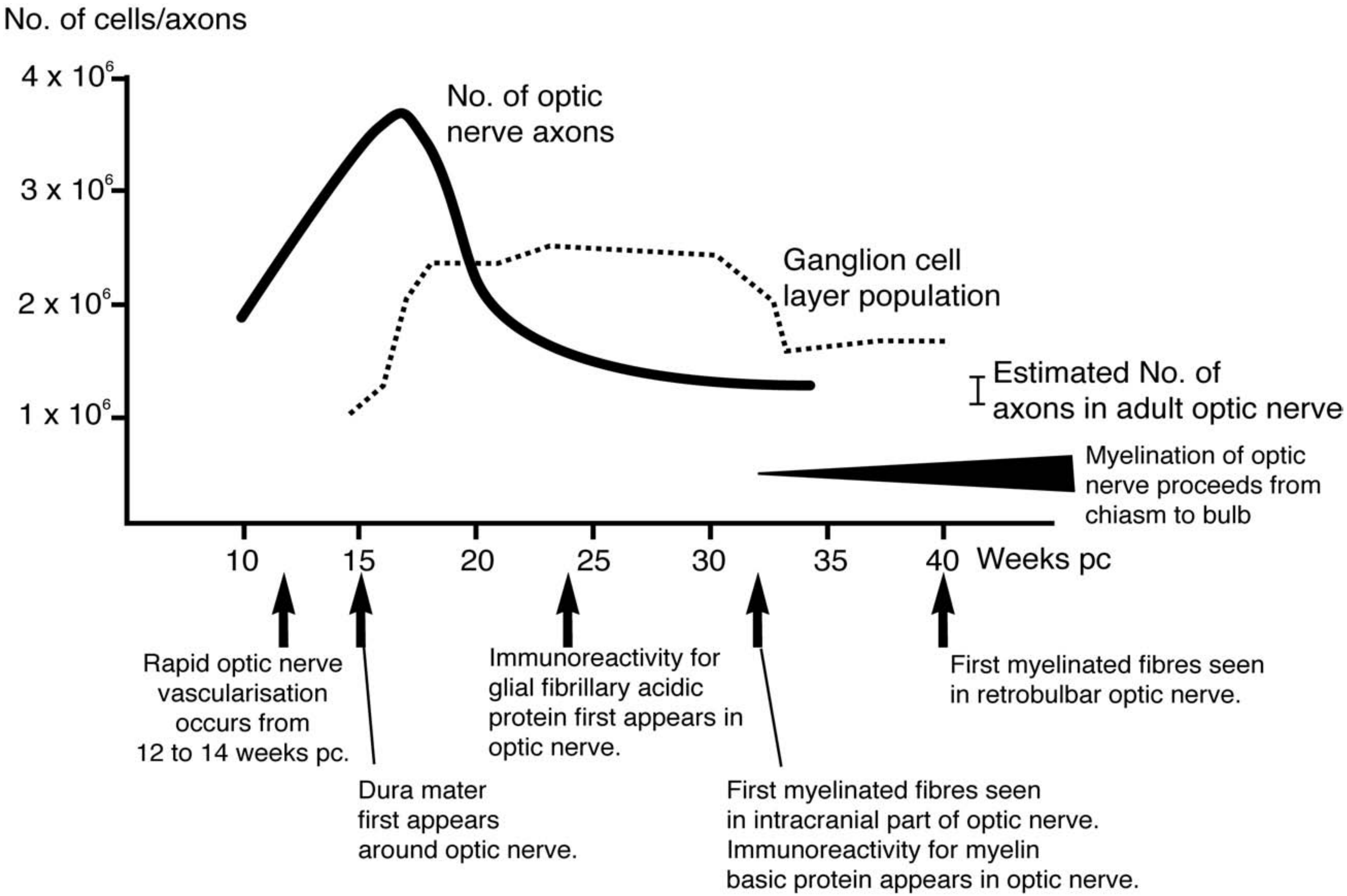
Brain Growth



Growth of Nerve Cell Processes



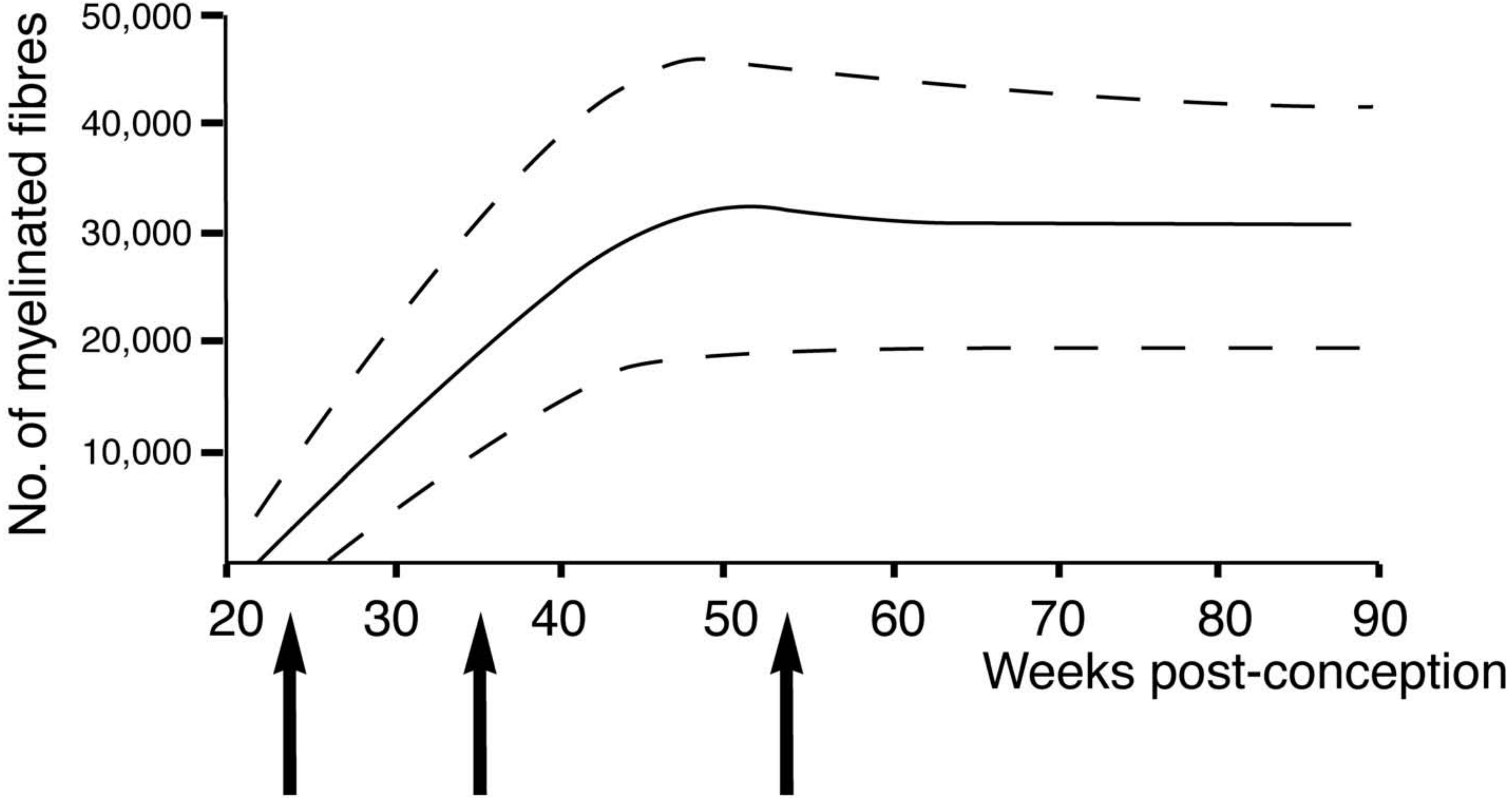
Developmental Neuronal Death



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



Inferior vagal ganglion cells resemble adult neurons ultrastructurally

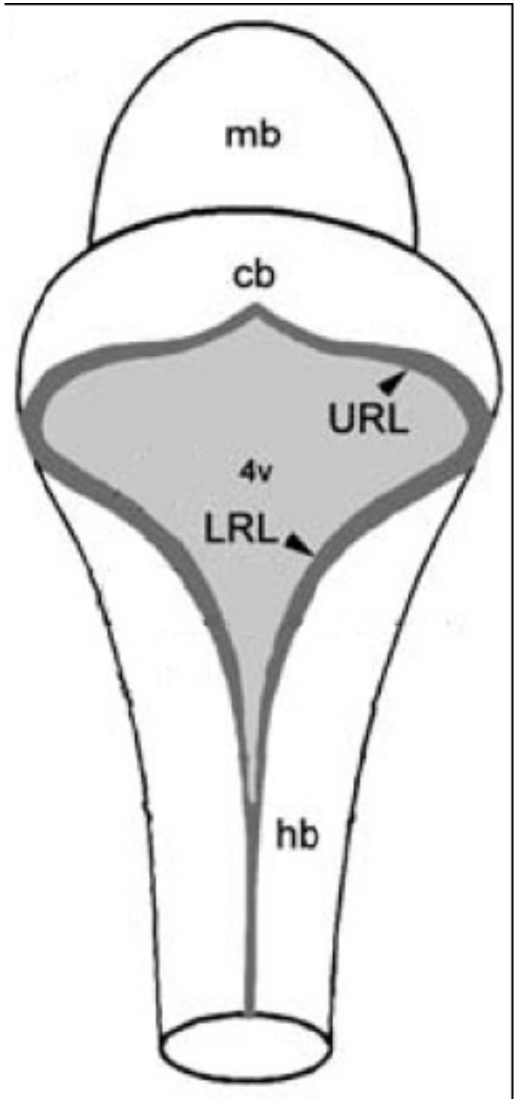
Hering Breuer reflex begins to appear

Multimodal fibre calibre distribution begins to appear

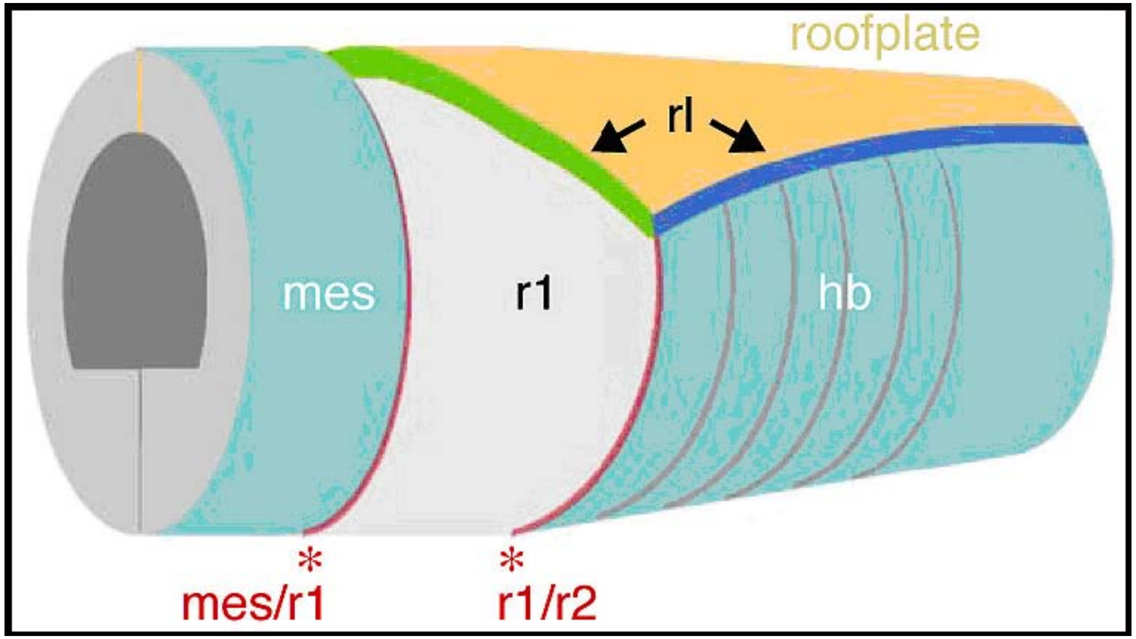
Development of the Cerebellum

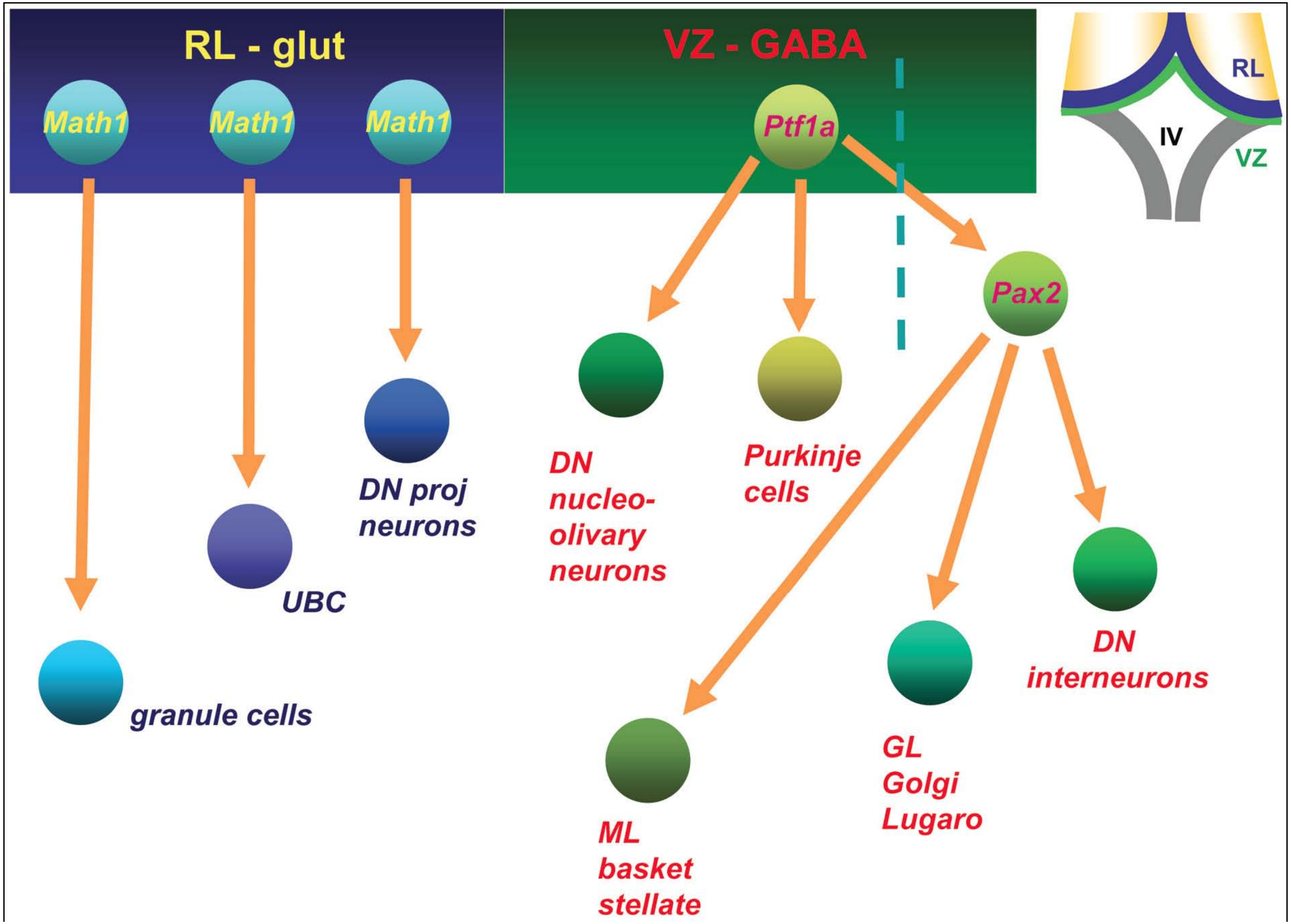
- Two distinct progenitor zones:
  - **Cerebellar ventricular zone** (*Ptf1a*+) gives rise to **GABAergic** (inhibitory) deep cerebellar projection neurons (i.e. nucleo-olivary neurons), basket, stellate, Golgi and Lugaro cerebellar interneurons, and Purkinje cells.
  - **Rhombic lip** (*Wnt1, Math1*+) 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).

The Rhombic Lip

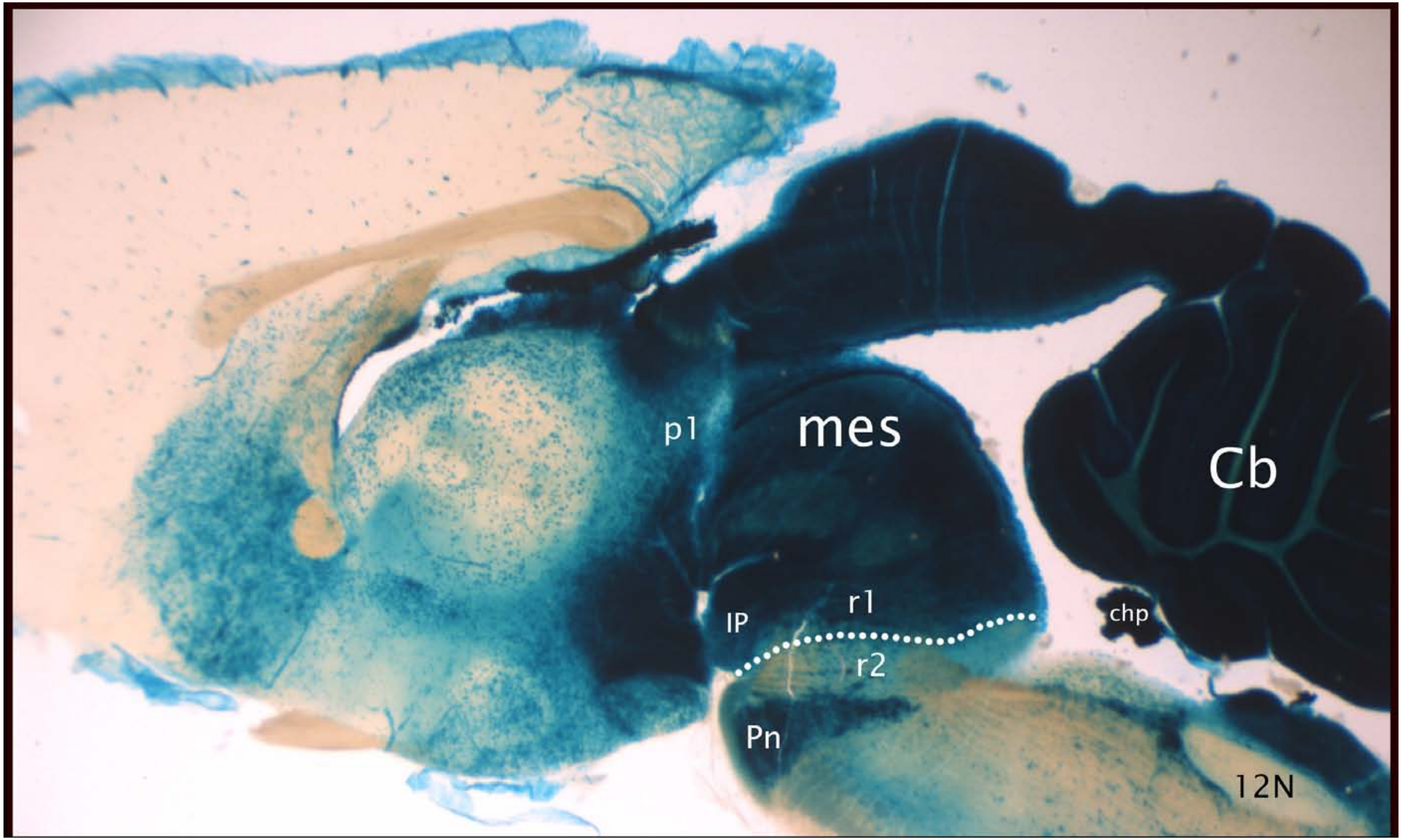


A dorsal view of the neural tube illustrating the rhombic lip (in dark grey). Abbreviations: mb, midbrain; cb, cerebellum; 4v, fourth ventricle; hb, hindbrain; URL, upper rhombic lip; LRL, lower rhombic lip. Adapted from Landsberg et al., 2005.



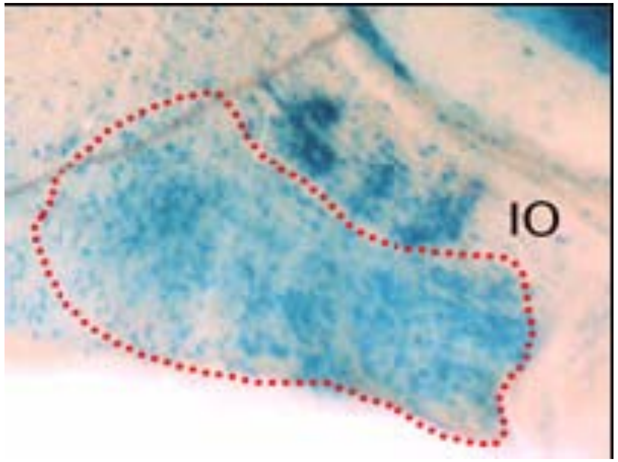

RL - glut
Math1
Math1
Math1
VZ - GABA
Ptf1a
Pax2
RL
IV
VZ
granule cells
UBC
DN proj neurons
DN nucleo-olivary neurons
Purkinje cells
ML basket stellate
GL Golgi Lugaro
DN interneurons

Derivatives of the Rhombic Lip

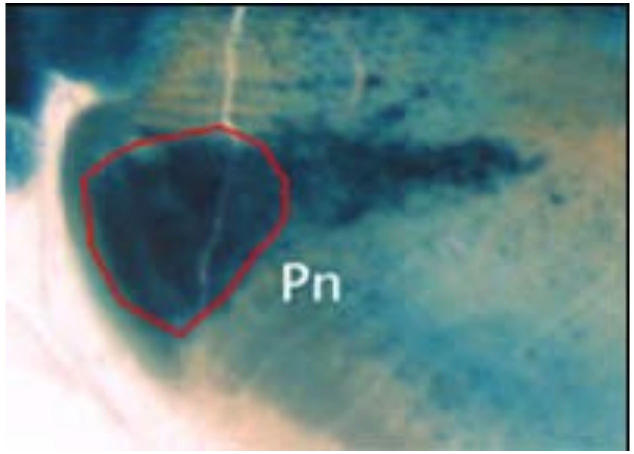


Wnt1 expression reveals rhombic lip derivatives

Precerebellar Nuclei are Rhombic Lip Derivatives



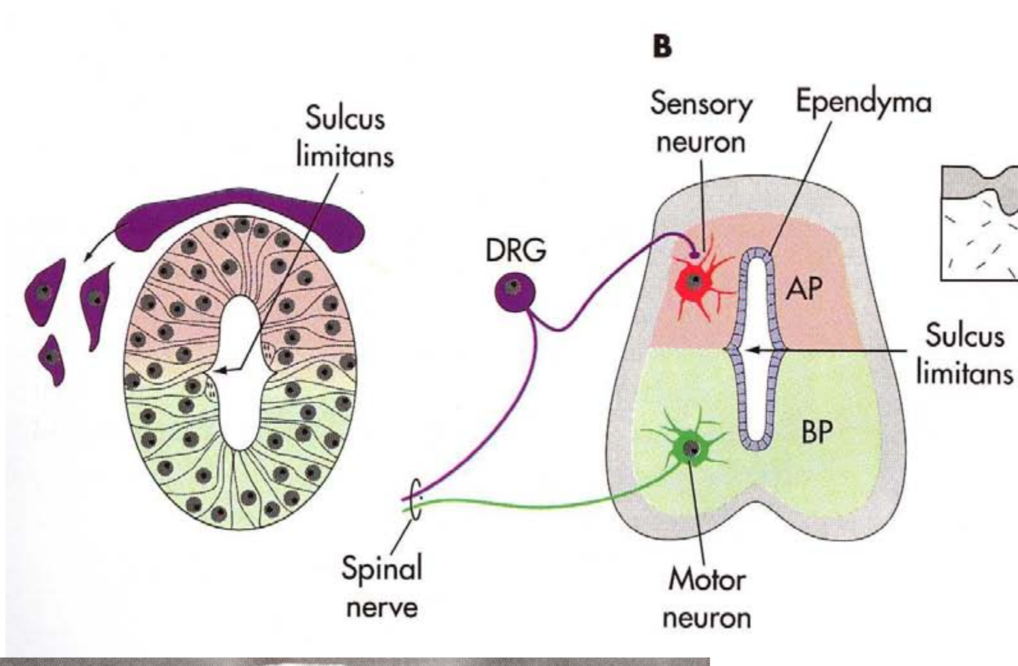
Inferior olive (climbing fibre projection)

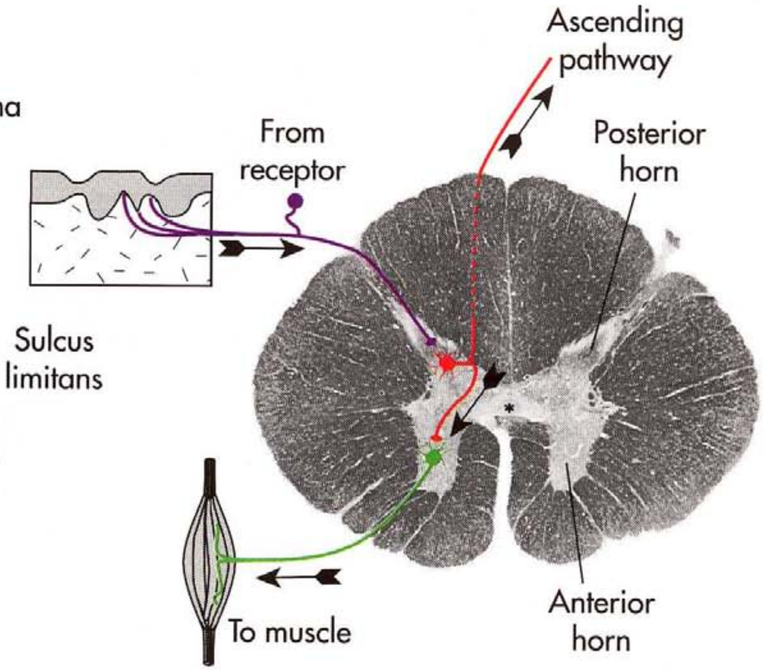


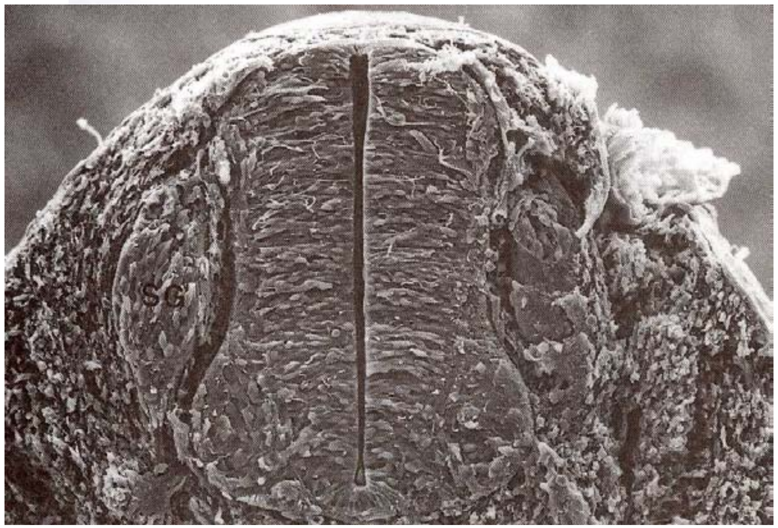
Pontine nuclei (mossy fibre projection)

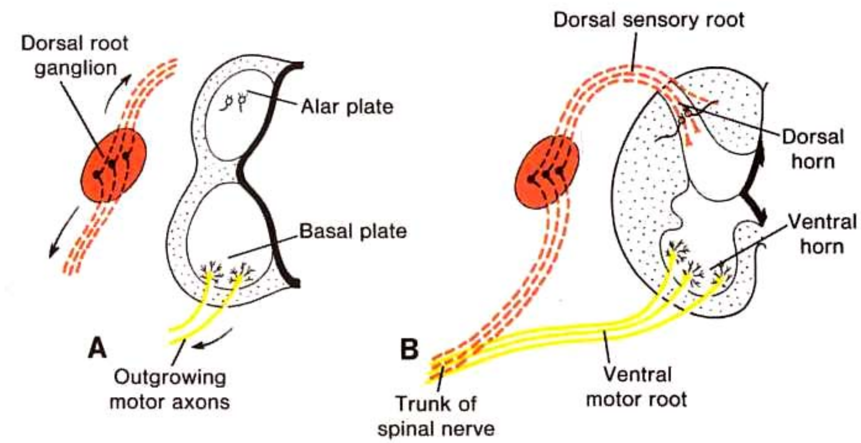
Other examples: reticulotegmental nucleus, external cuneate nucleus, lateral reticular nucleus

The Developing Spinal Cord

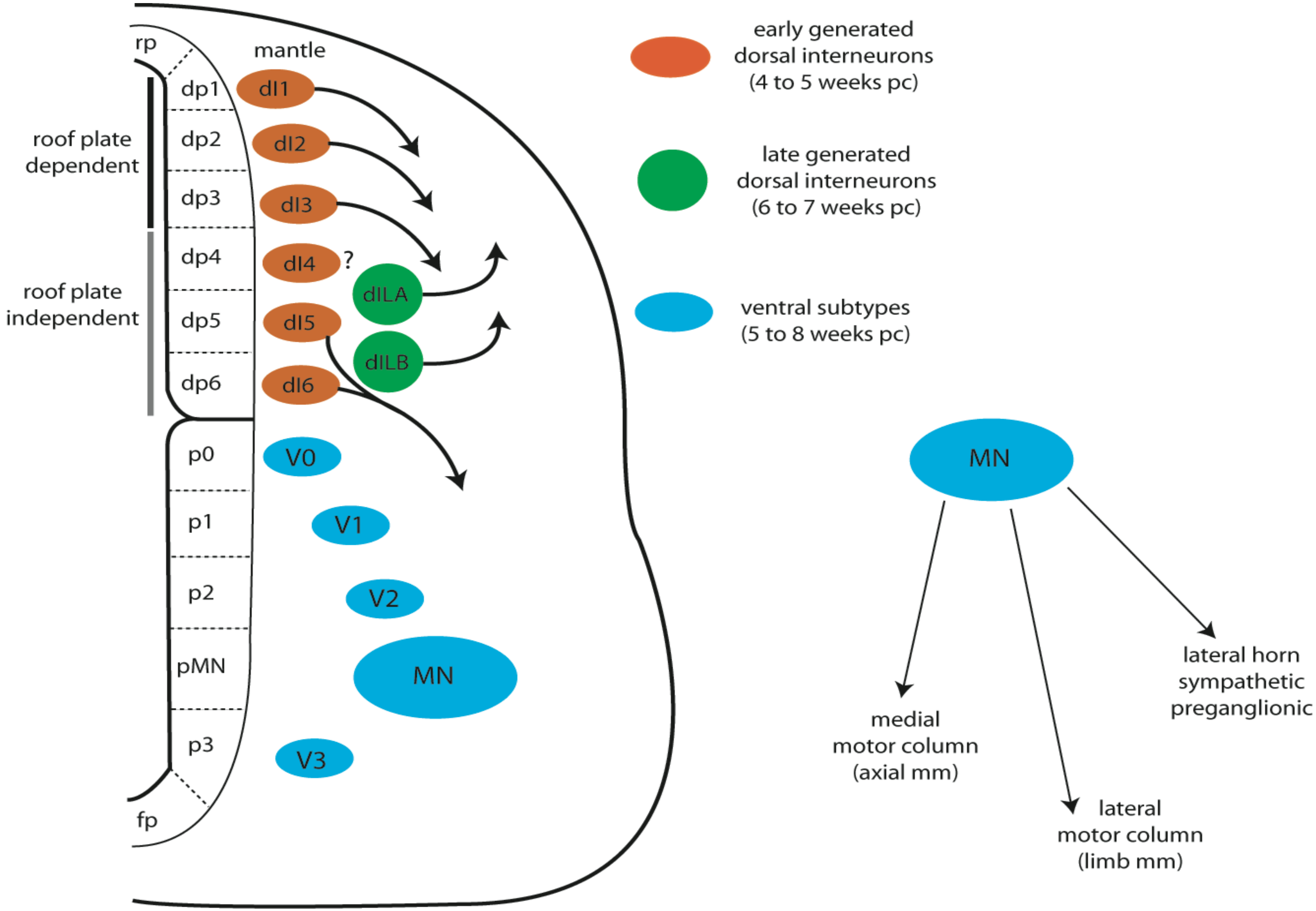




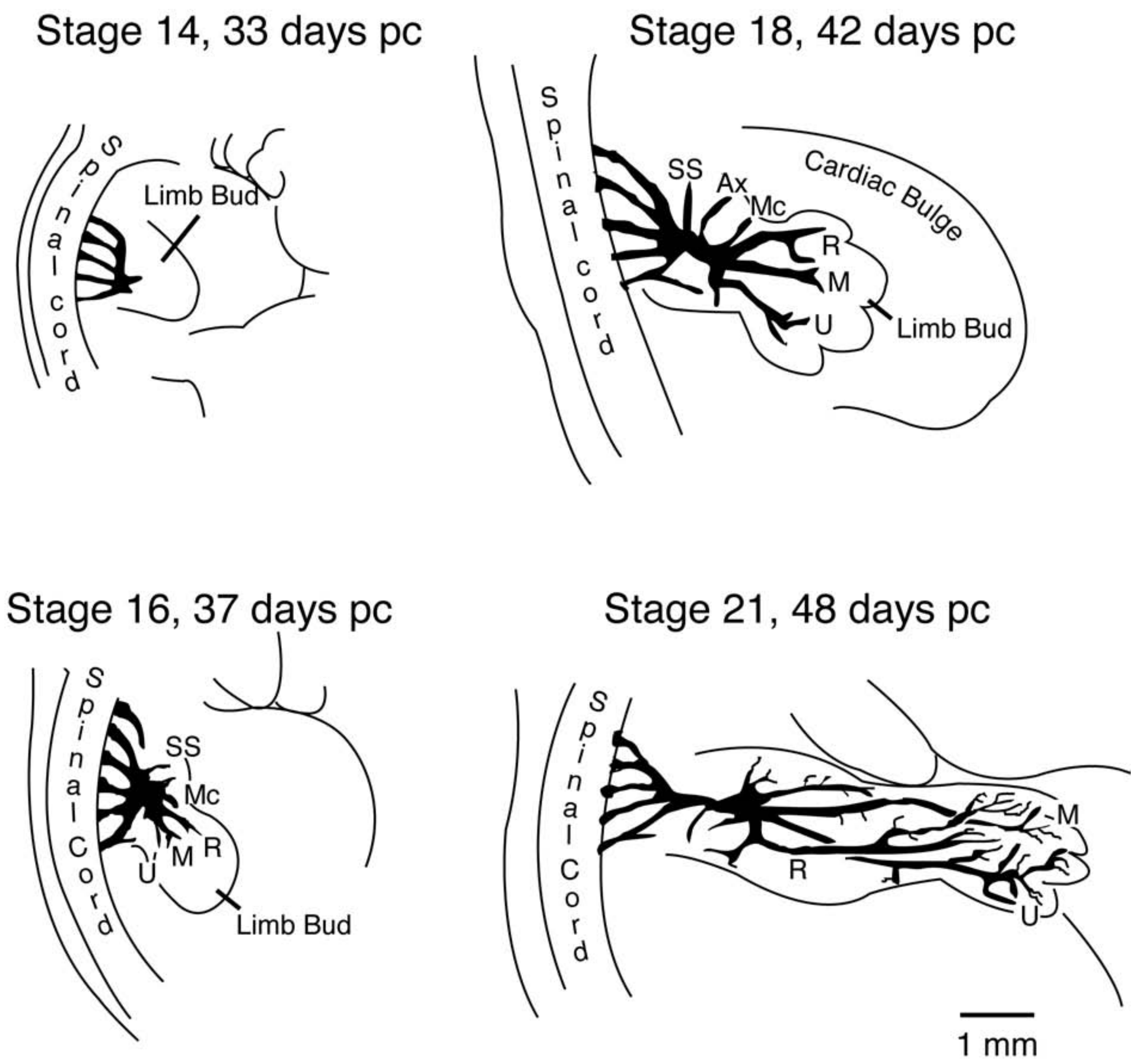




Origins of Spinal Cord Neurons



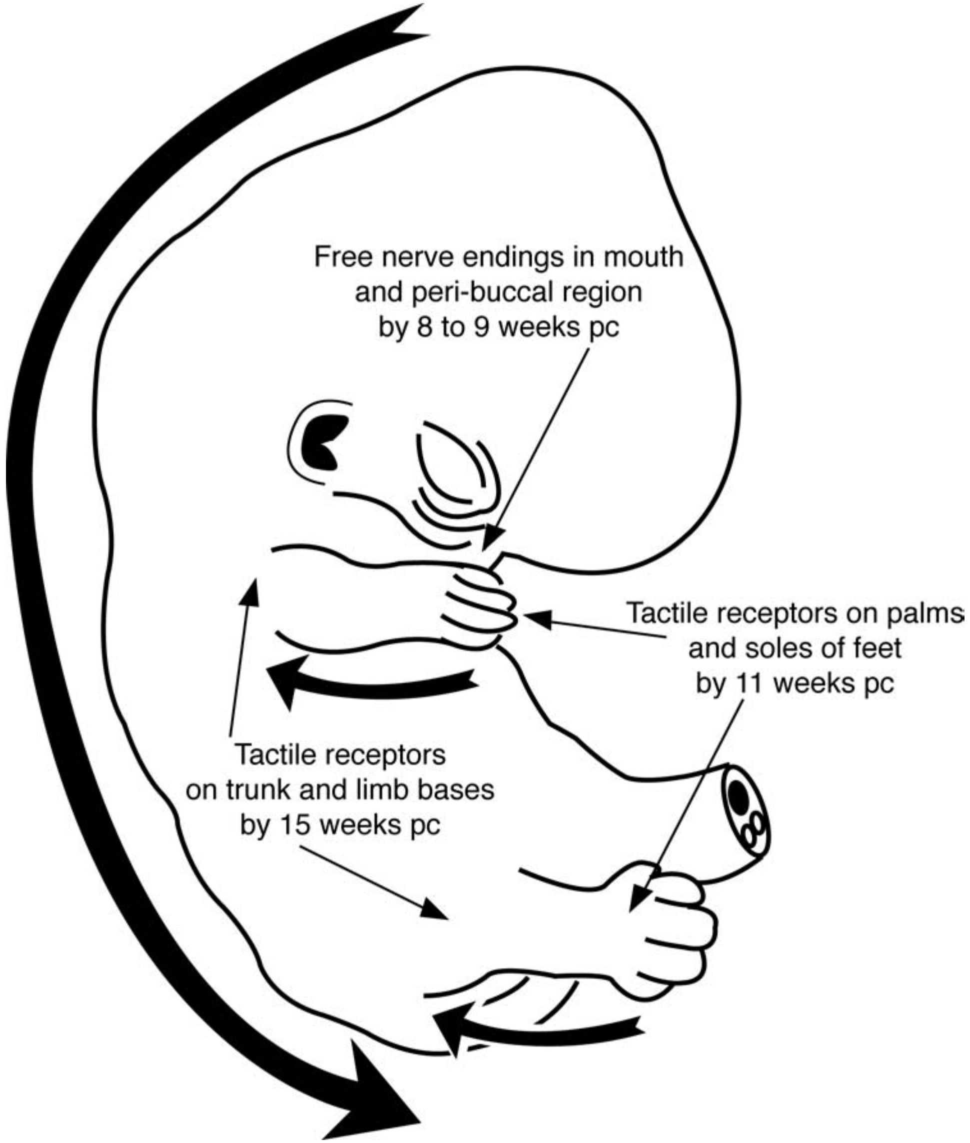
Development of Peripheral Nerves



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

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

Development of Sensory Receptors

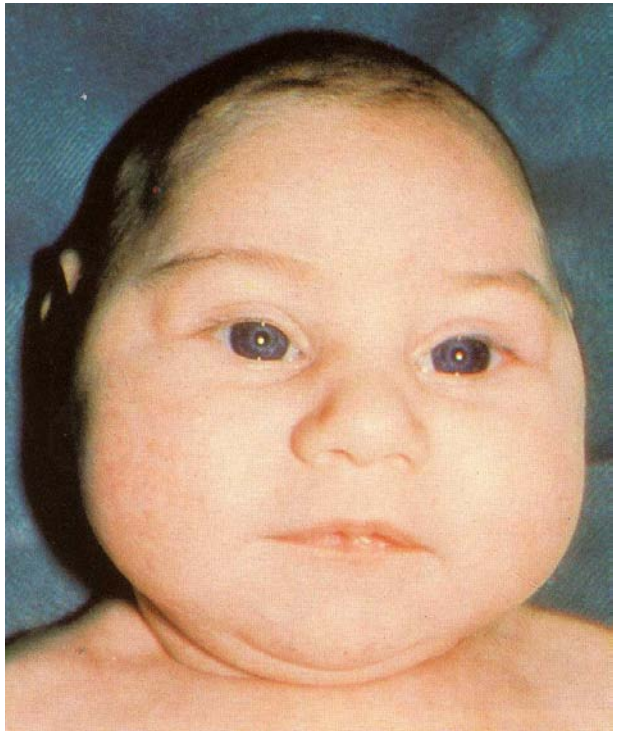


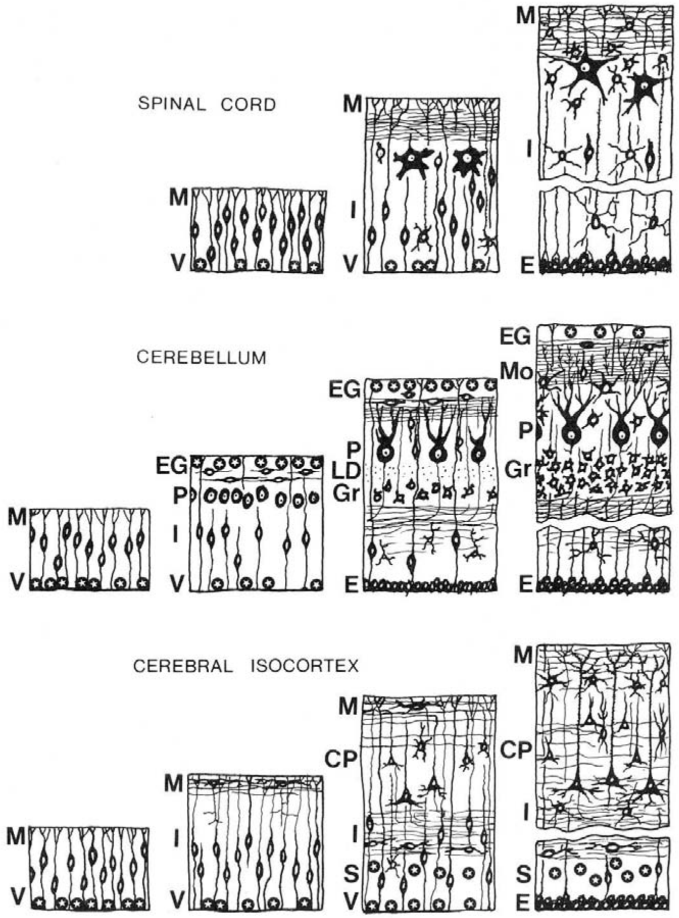
Development of receptors for the somatosensory system follows a rough rostrocaudal/distal-to-proximal pattern.

Free nerve endings develop before Meissner and Pacinian corpuscles.

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

Microcephaly

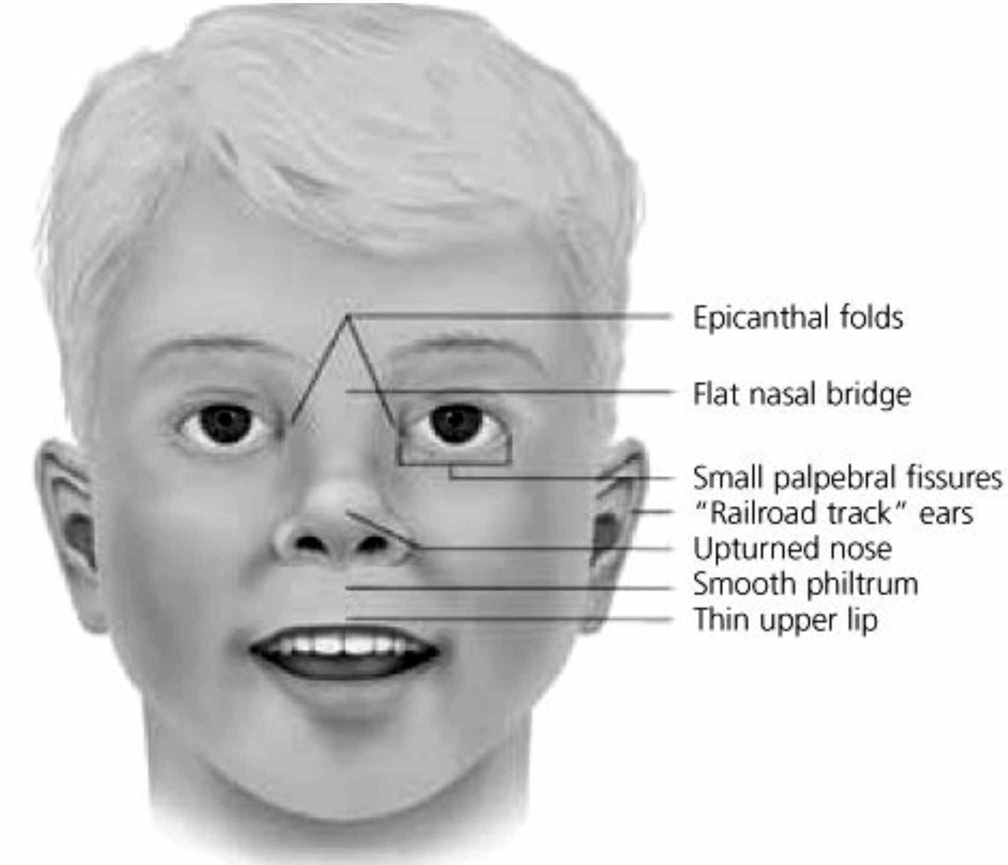




• Neurons and most glia of the brain are produced by proliferation of cells in the ventricular germinal zone

• Some physical (ionizing radiation, elevated maternal temperature), chemical (anticancer drugs) and biological (rubella, cytomegalovirus, herpes simplex virus) 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