# Cell Migration II:
# CNS Cell Migration

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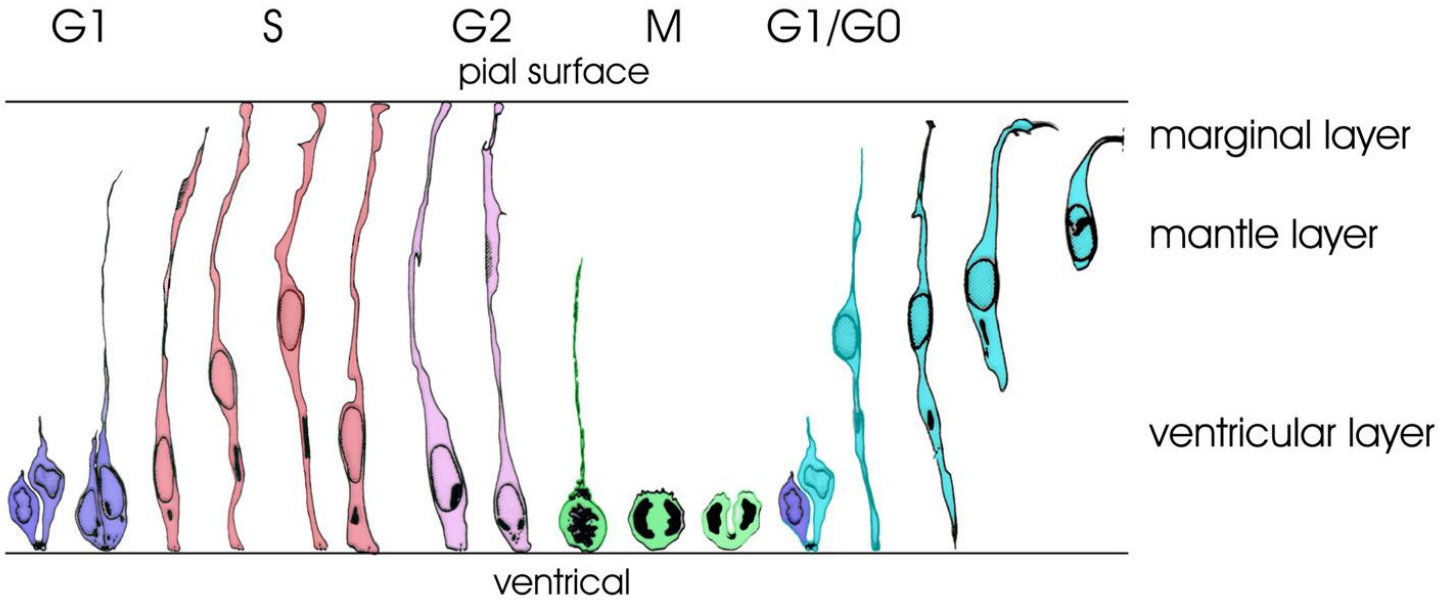
# Hey!

**The major concepts discussed relative to neural crest cell migration apply to cell migration in the developing CNS! … also to axon growth!**

# Modes of Cell Migration in the Developing CNS

Early postmitotic neurons migrate to the pial surface by mechanisms related to those used for cell division:

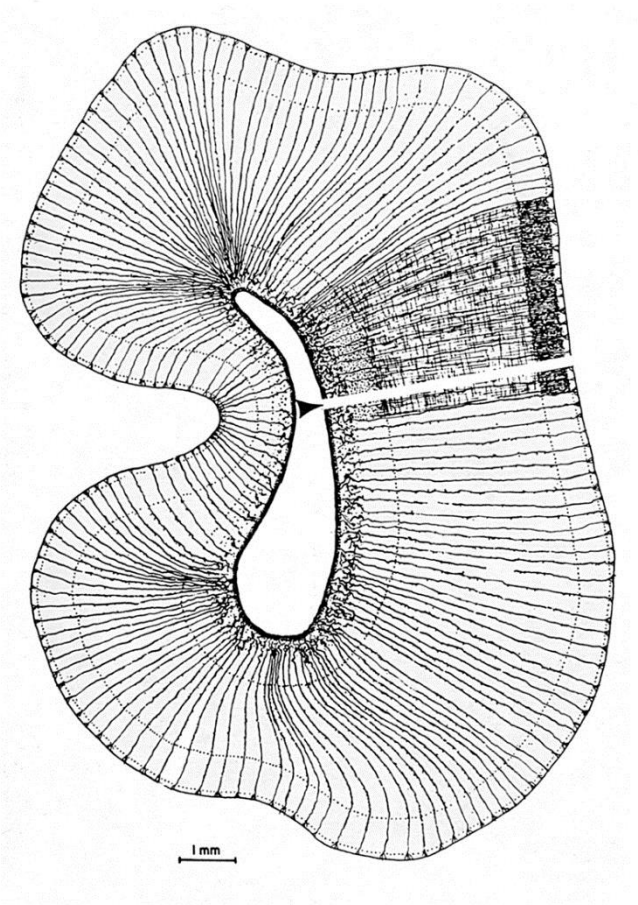
- cell extends a process by adhesion to adjacent progenitor cells
- nucleus translocates within the process towards the pial surface
- cell retracts trailing process



# Modes of Cell Migration in the Developing CNS

Later, as structures become thicker, progenitor cells express some characteristics of astrocytes, and are described as radial glia.

Radial glia span the entire thickness of the tissue.

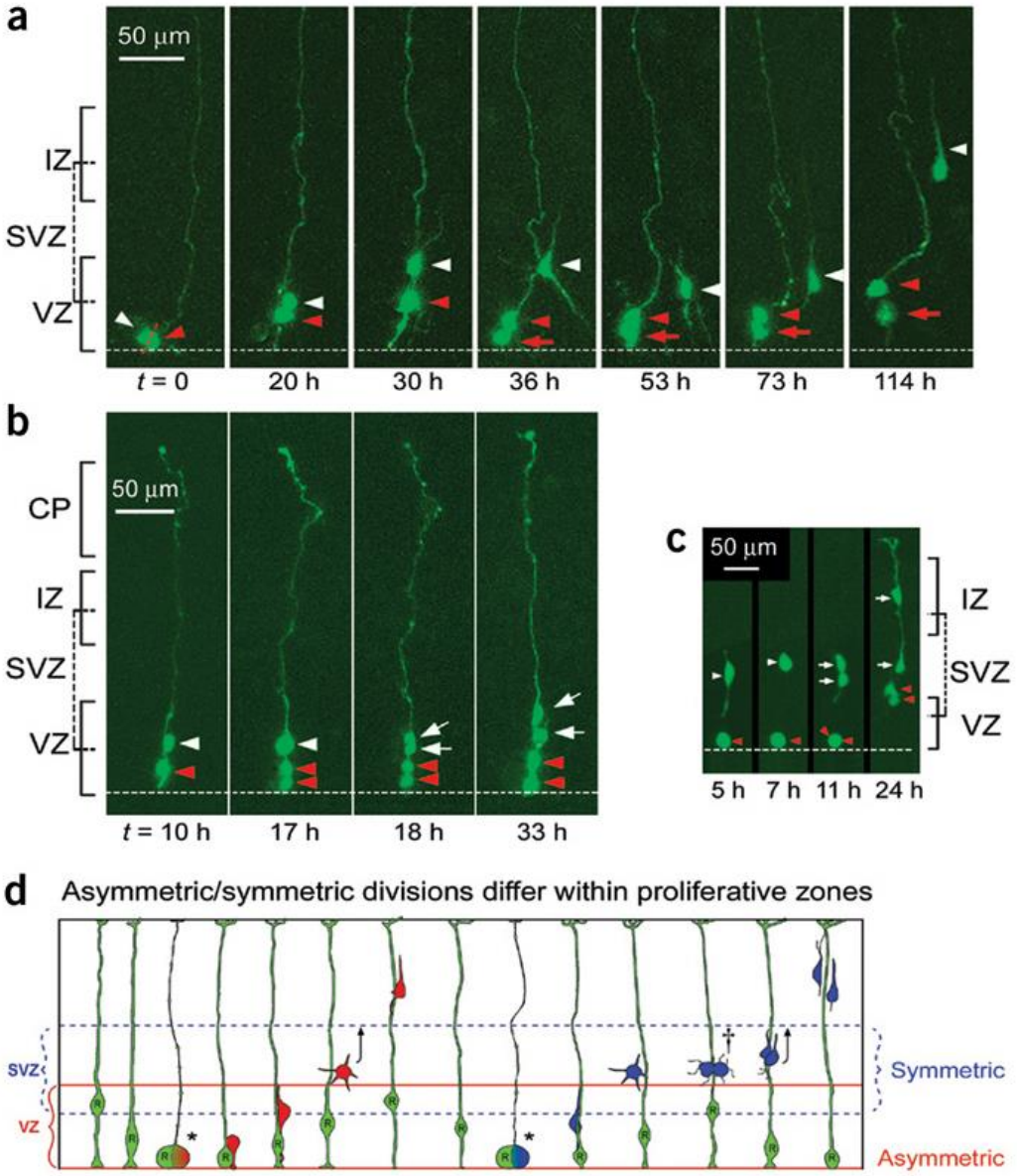


## Patterns of Cell Division and Radial Migration in Cortex

A small number of ventricular layer cells in developing cortex were transfected with a GFP expression vector.

Cell division and migration of cells expressing GFP were followed by time lapse video recordings in living slices of cortex.

# Patterns of Cell Division and Radial Migration in Cortex



# Modes of Cell Migration in the Developing CNS

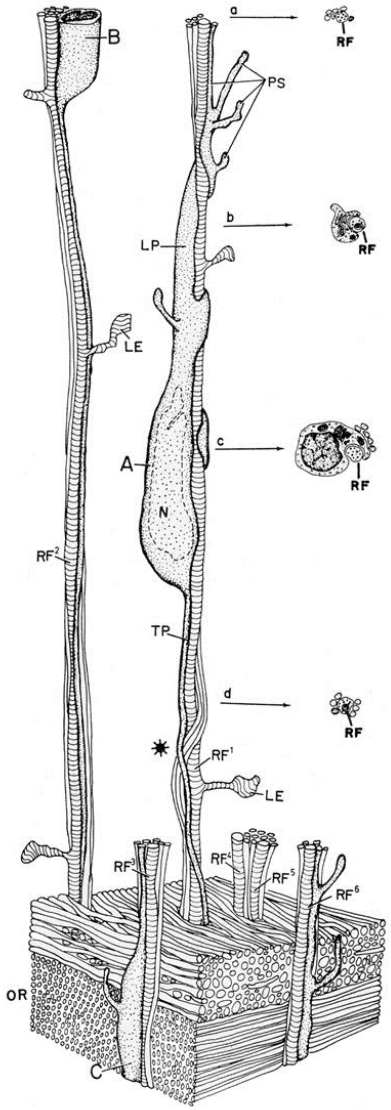
Radial glia divide with the nucleus at the ventricular surface.

Cells retain attachment to the pial surface through mitosis.

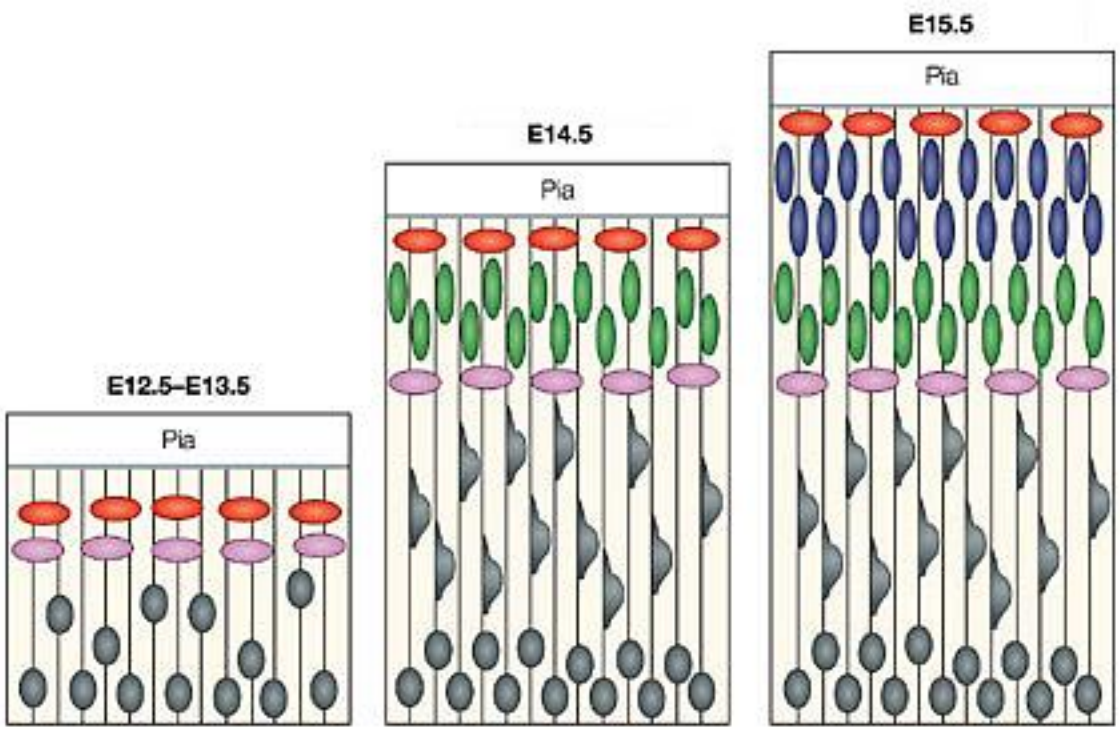
The daughter cell that inherits the basal process will usually divide again.

The cell that does not inherent the process can extend a process to the pial surface and become a radial glial cell or can migrate in association with radial glia processes towards the pial surface.

Neuron-radial glia association is mediated by CAMs, $\alpha_3\beta_1$ integrin & connexins.



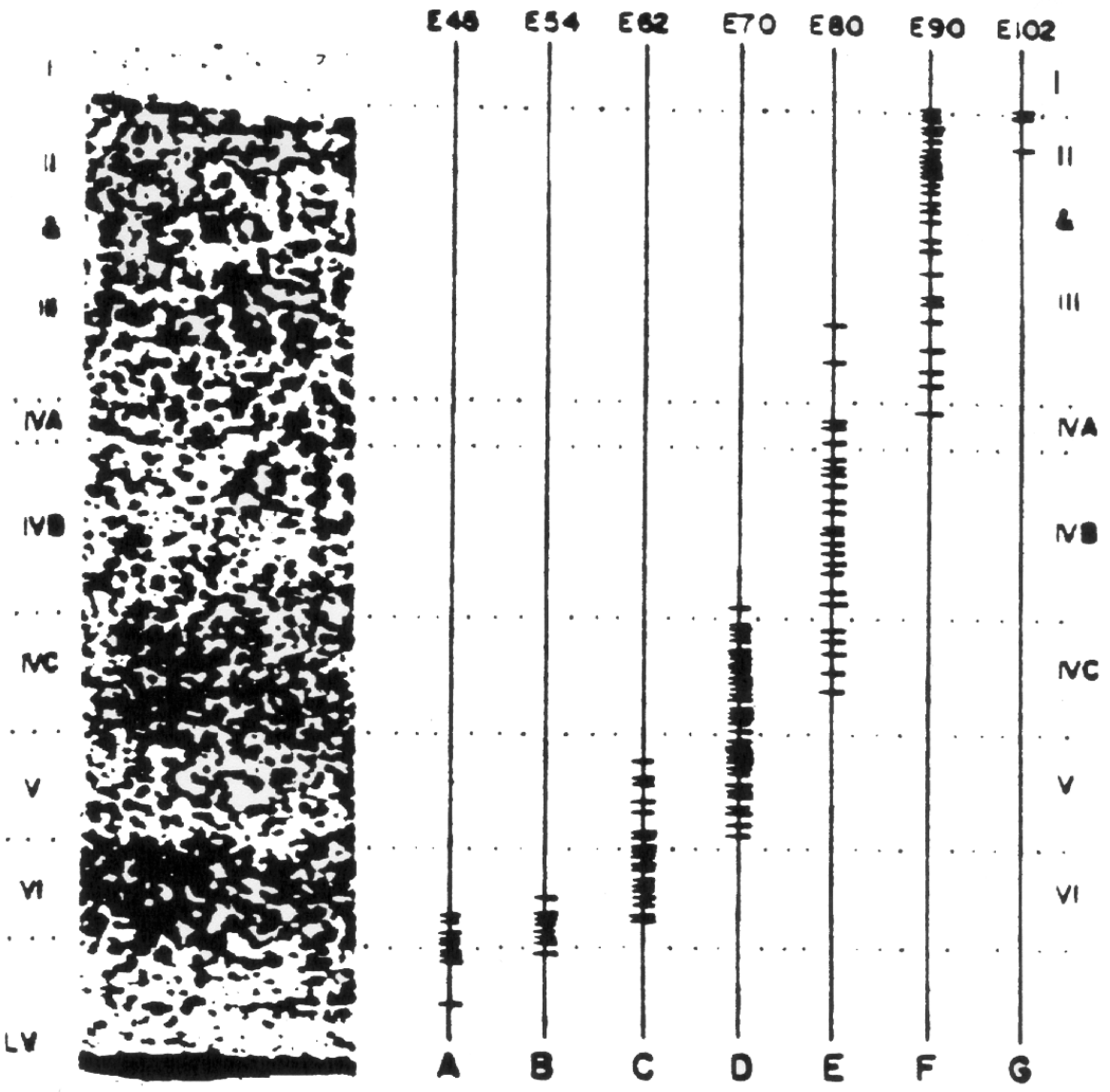
# Development of Cortex



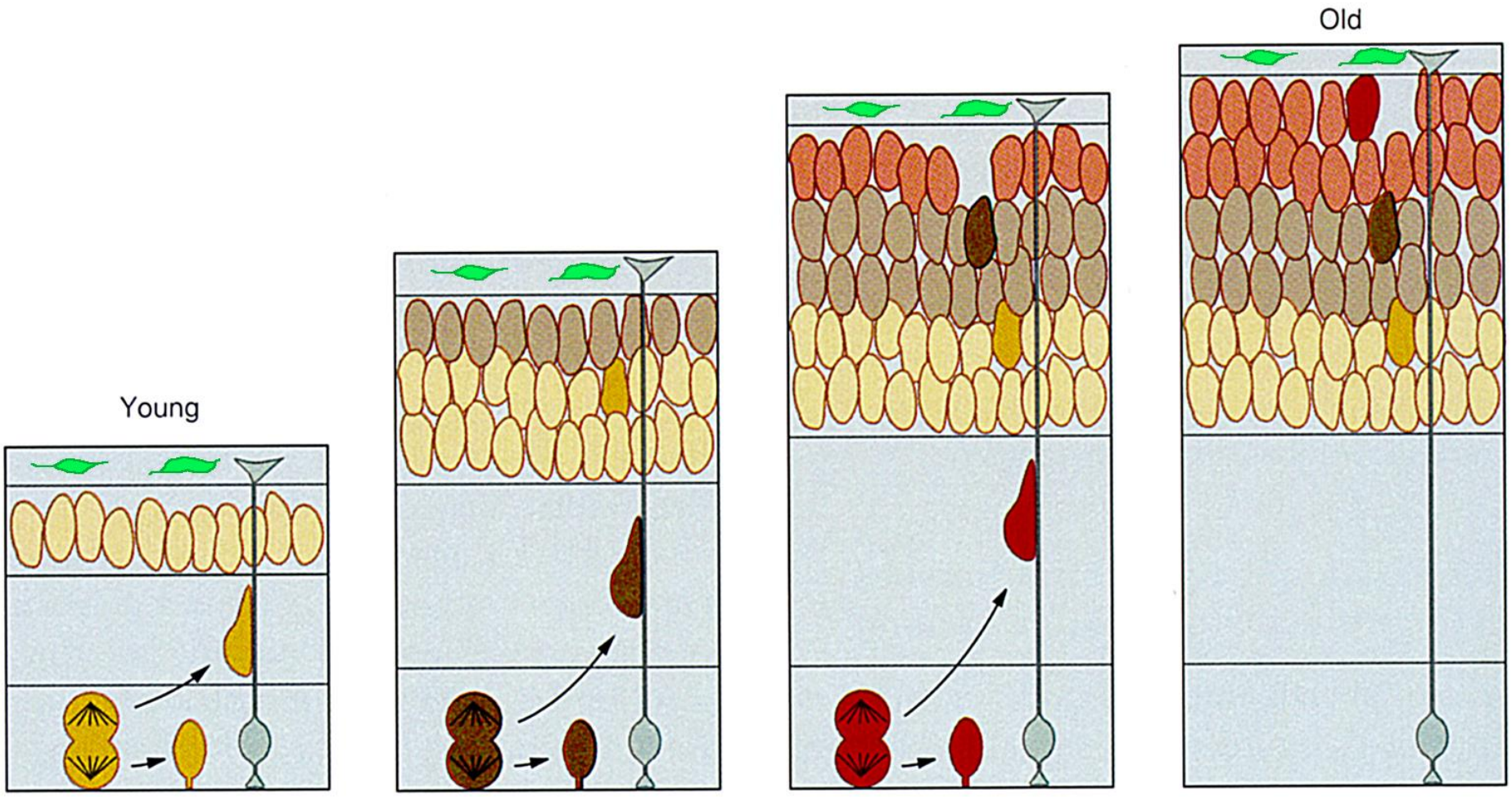
## Patterns of Cell Division and Radial Migration in Cortex

Projection neurons for the most part migrate in this radial pattern using radial glia as their adhesive substrate.

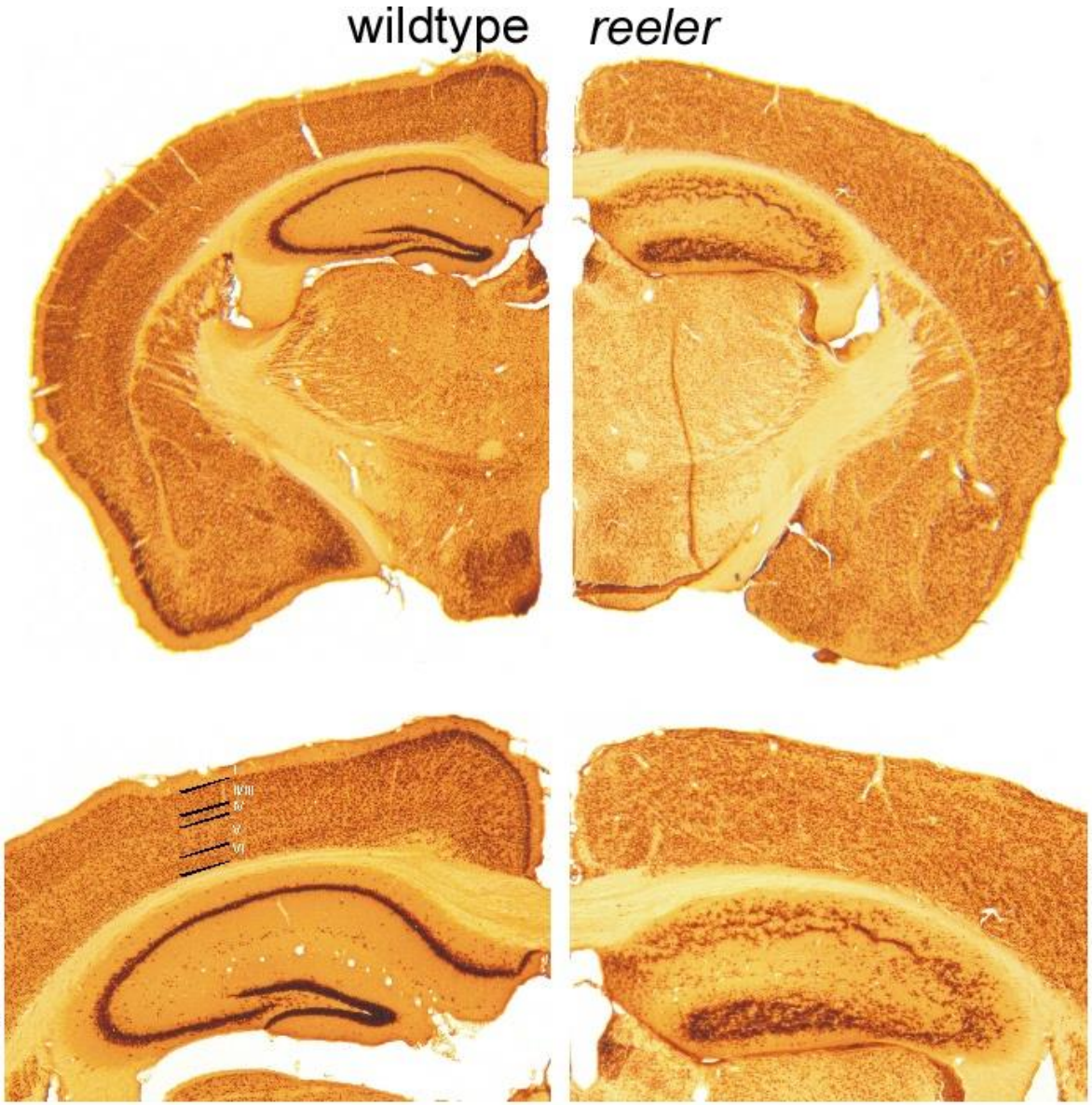
**The cortical plate is built (mostly) from the inside out.**



# The cortical plate is built (mostly) from the inside out.

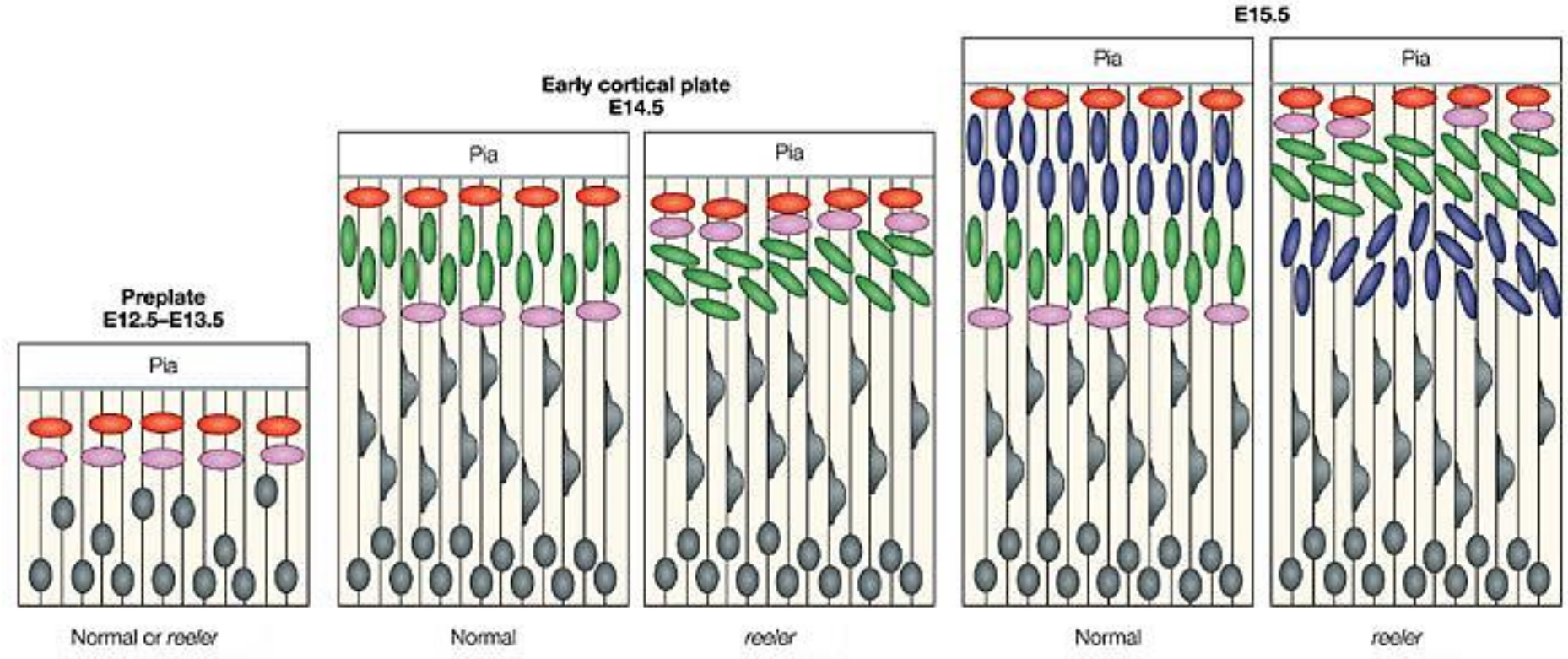


**Spontaneous mutations in mice that resulted in motor abnormalities revealed molecules involved in cell migration.**



# *reeler* Mouse

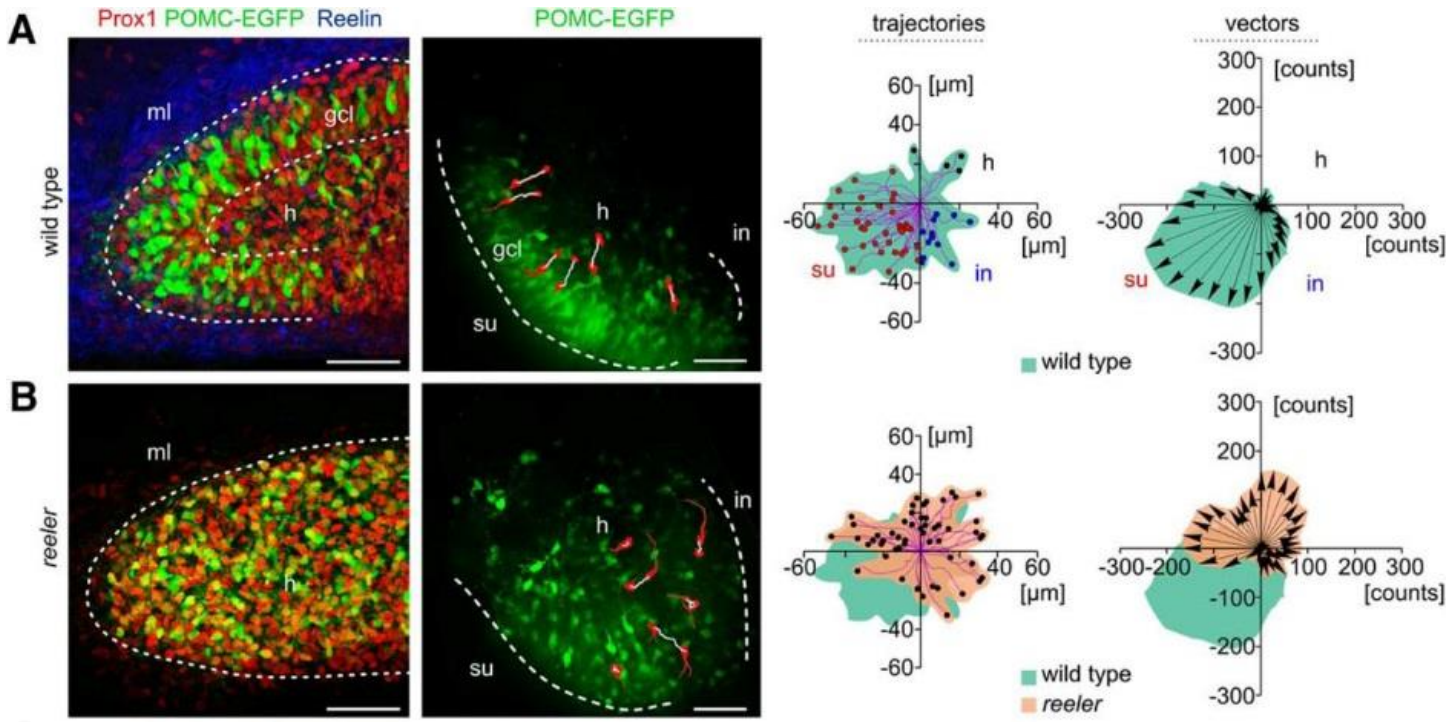
- Cortical layers are inverted.
- Cells are generated at the correct time, and migrate in correct sequence & rate.
- Radial glia look normal, and in culture cells migrate on radial glia.
- Most CNS cell groups are affected.



# *reeler* Mouse

- Cells starting to migrate are disorganized and misdirected.

- As cells reach the marginal zone, they fail to dissociate from radial glia.

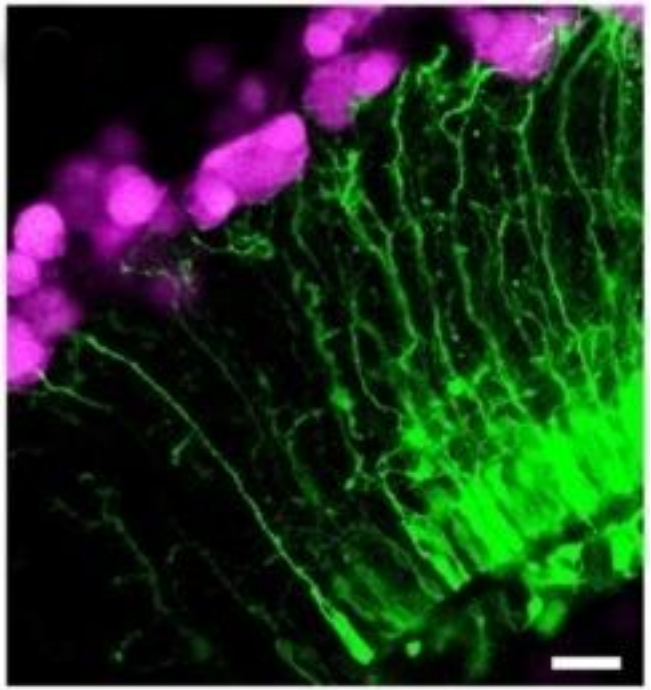



(Wang S et al., 2018)

# Reelin

- Mutation is in the reelin gene.

- Reelin is a glycoprotein of the ECM secreted by Cajal-Retzius cells in the marginal layer.

# Reelin

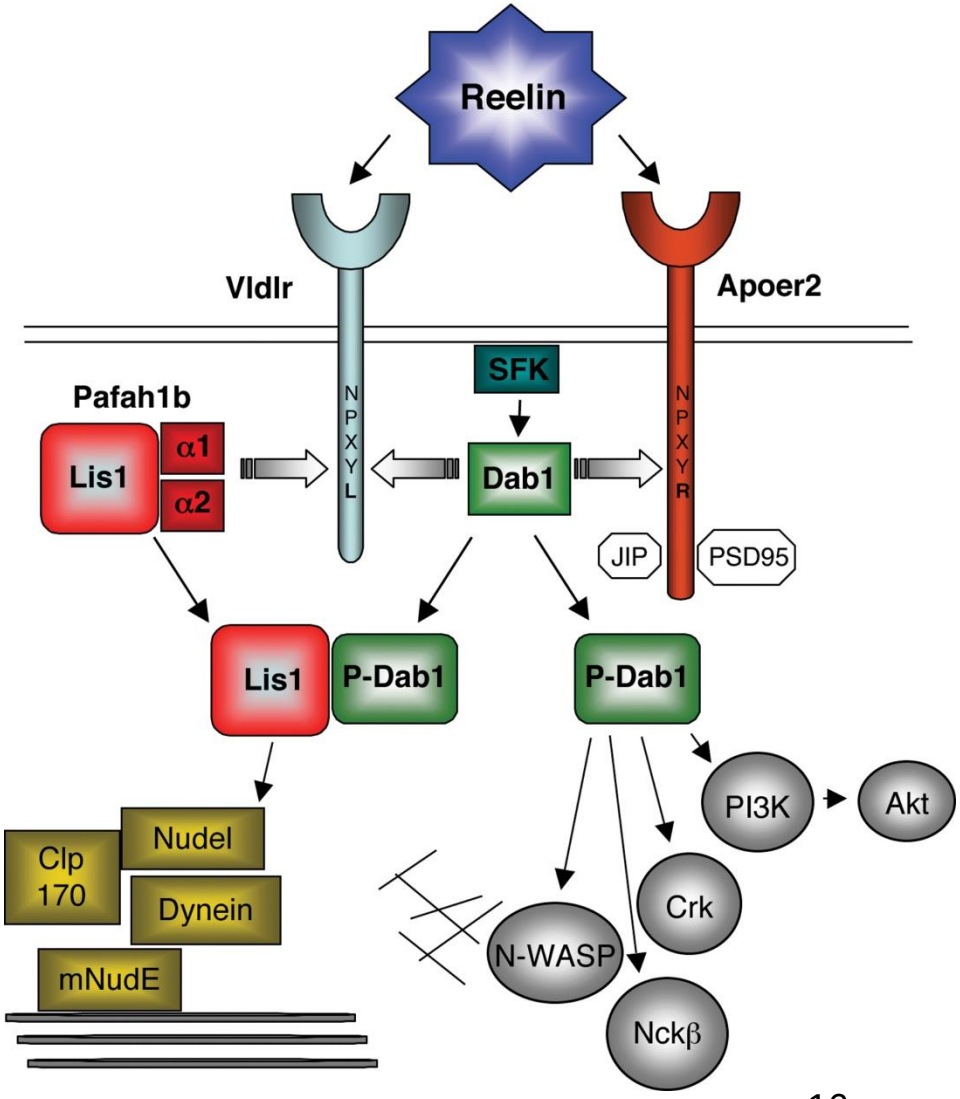
VLDLr & ApoEr2:

- Reelin activates the VLDL and ApoE receptors.
- Both are expressed by cells migrating in the CNS.
- Double kockout of these genes results in a ‘reeler’ phenotype.

Scrambler mutant mouse:

- Brain looks similar to reeler.
- Mutation is in *disabled (Dab1)* gene.
- Dab1 is a cytoplasmic adaptor protein, which is activated by reelin through its receptors.

-Dab1 has many targets including Lis1.



# Reelin

What happens after Dab1 is activated is unclear and probably multi-faceted.

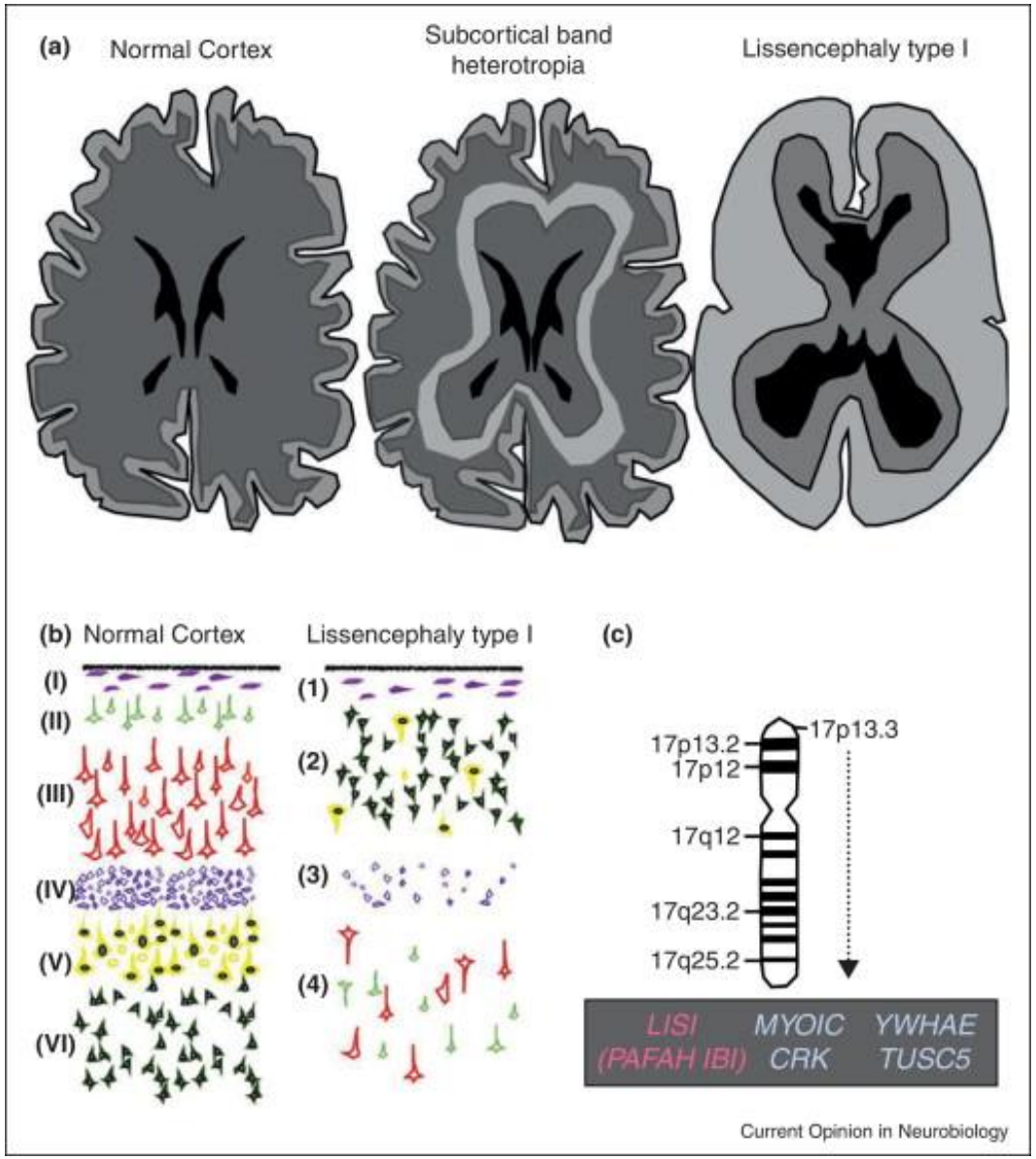
# Reelin

Lis1 is a target of Dab1.

Lis1 mutations also result in a phenotype similar to reelin mutations.

Lis1 interacts with multiple motor proteins and microtubule associated proteins.

Lis1 may have a role in promoting and directing cell movement.



# Reelin

The final steps of neuronal migration into the cortical plate are independent of radial glia.

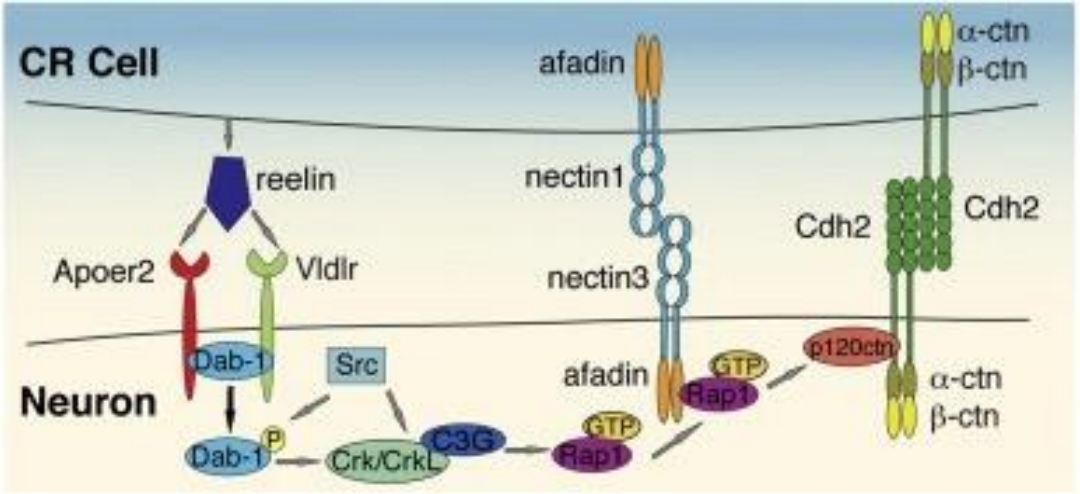
Migrating cells must lose attachment to radial glia, use a new substrate to migrate up to the marginal zone, and ultimately stop migrating and start differentiating.

Reelin has been implicated in these processes.

# Reelin

The reelin/Dab1 pathway promotes adhesion between migrating neurons and Cajal-Retzius (CR) cells, allowing the neurons to finish migration.

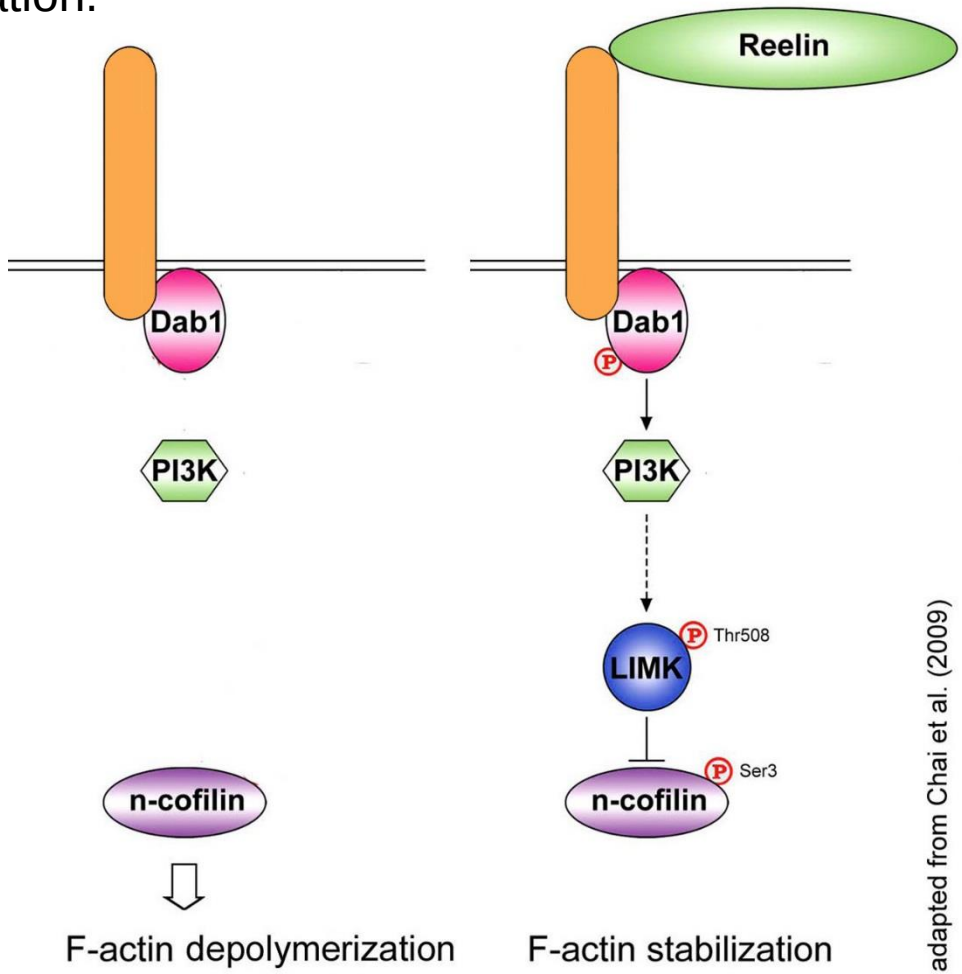
Reelin promotes heterphilic binding between the Ig-CAMS nectin 1 and nectin 3 and homophilic binding between N-cadherin (Cdh2).




(Gil-Sanz C, et al., 2013, Neuron 79:461)

# Reelin

It has been shown that the reelin/Dab1 signaling pathway activates LimK, which inactivates n-cofilin, resulting in actin stabilization.



# Reelin

Reelin appears to have two functions for migrating cortical neurons:

- As cells start migration, reelin via the Apoer2 receptor may give cells polarity and direction.
- As cells approach the marginal zone, reelin via the Vldlr receptor may terminate migration.
- Different domains of reelin activate the two receptors.

(based partly on Ha et al., 2017, *J Neurosci* 37:960)

# Hey!

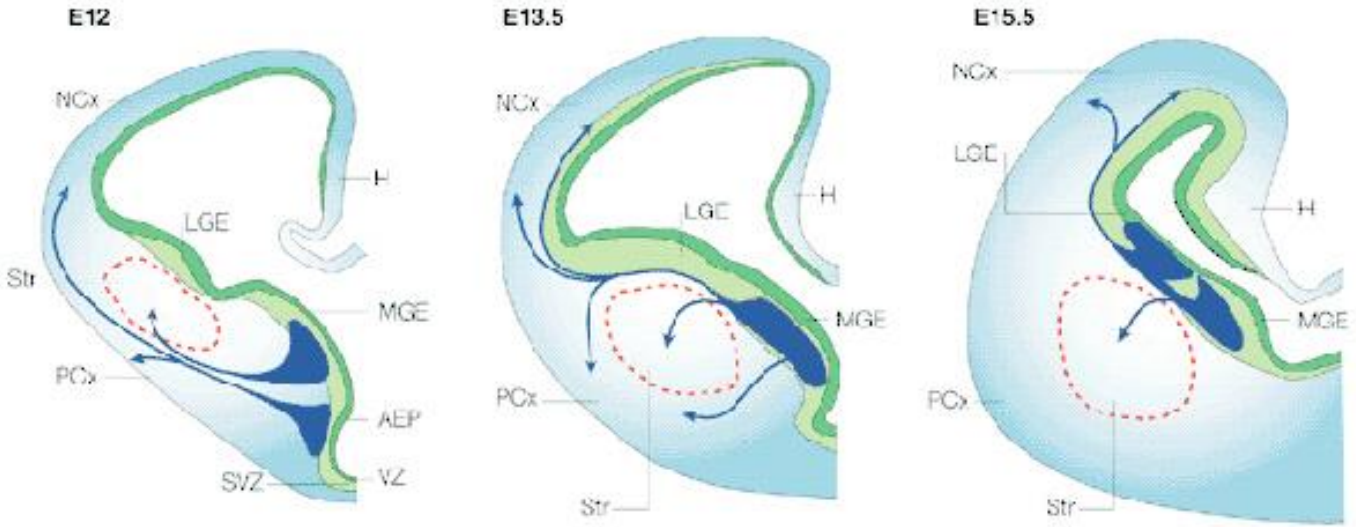
**The reelin story is complicated. It appears that reelin may be a tropic factor at the start of migration and have a guidepost function at the end of migration (in cortex).**

# Tangential Migration in Developing Forebrain

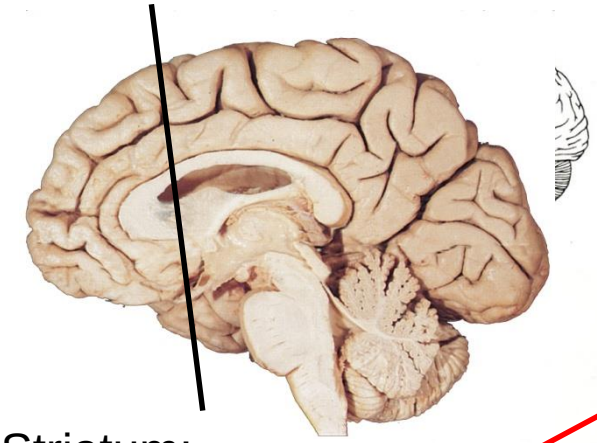
Lineage tracing studies showed that >30% of neurons in the cortex reached their final location by tangential migration mostly in the marginal and subventricular zones.

# Tangential Migration in Developing Forebrain

- Lateral and medial ganglionic eminences (LGE & MGE) of the ventral telencephalon (i.e. basal plate) give rise to the cells of the striatum and globus pallidus by radial migration.

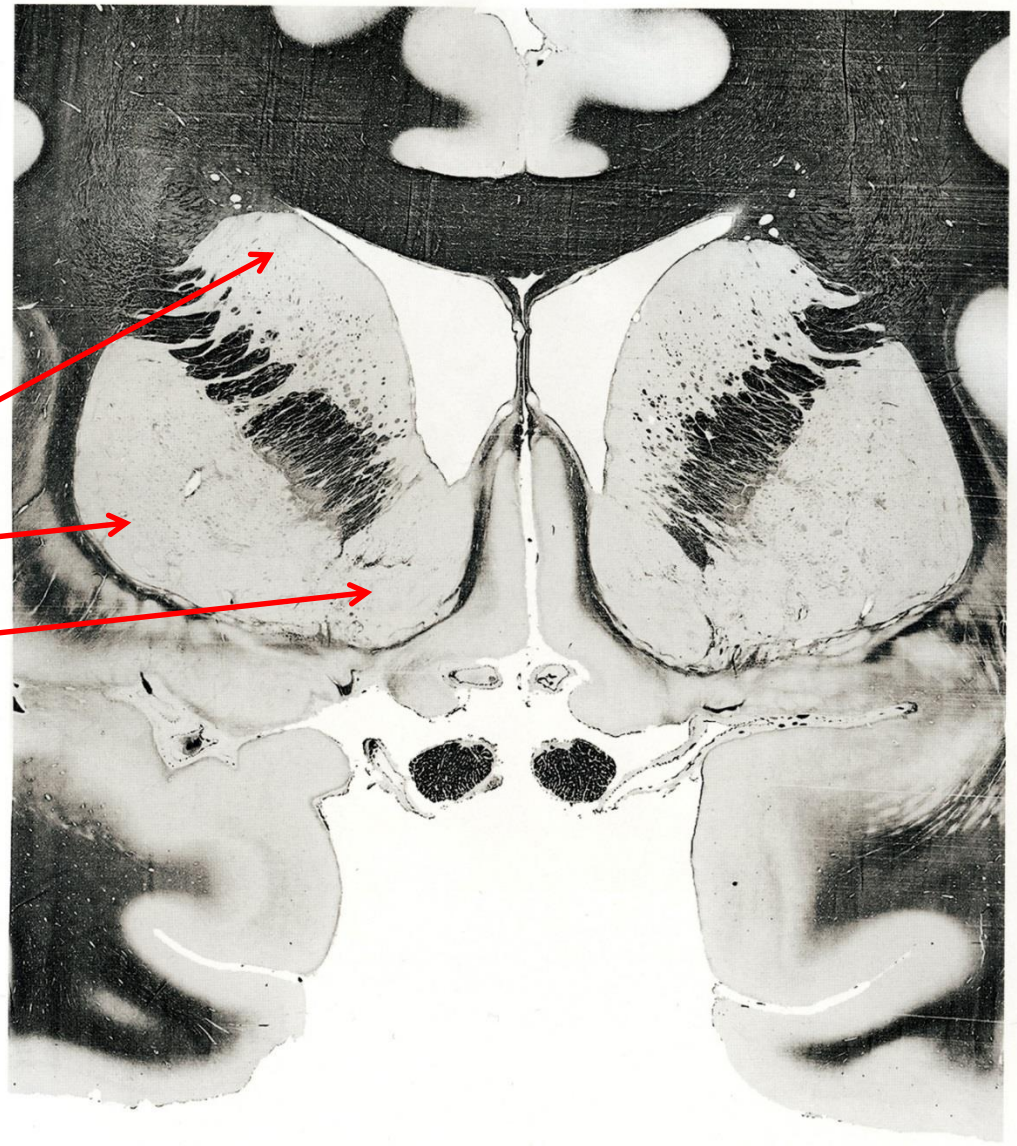


**The two forebrain components of the basal ganglia are the striatum and globus pallidus.**



Striatum:

- caudate nucleus
- putamen
- nucleus accumbens



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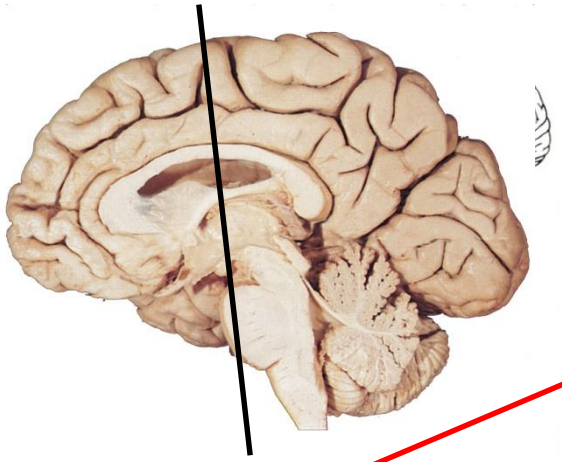
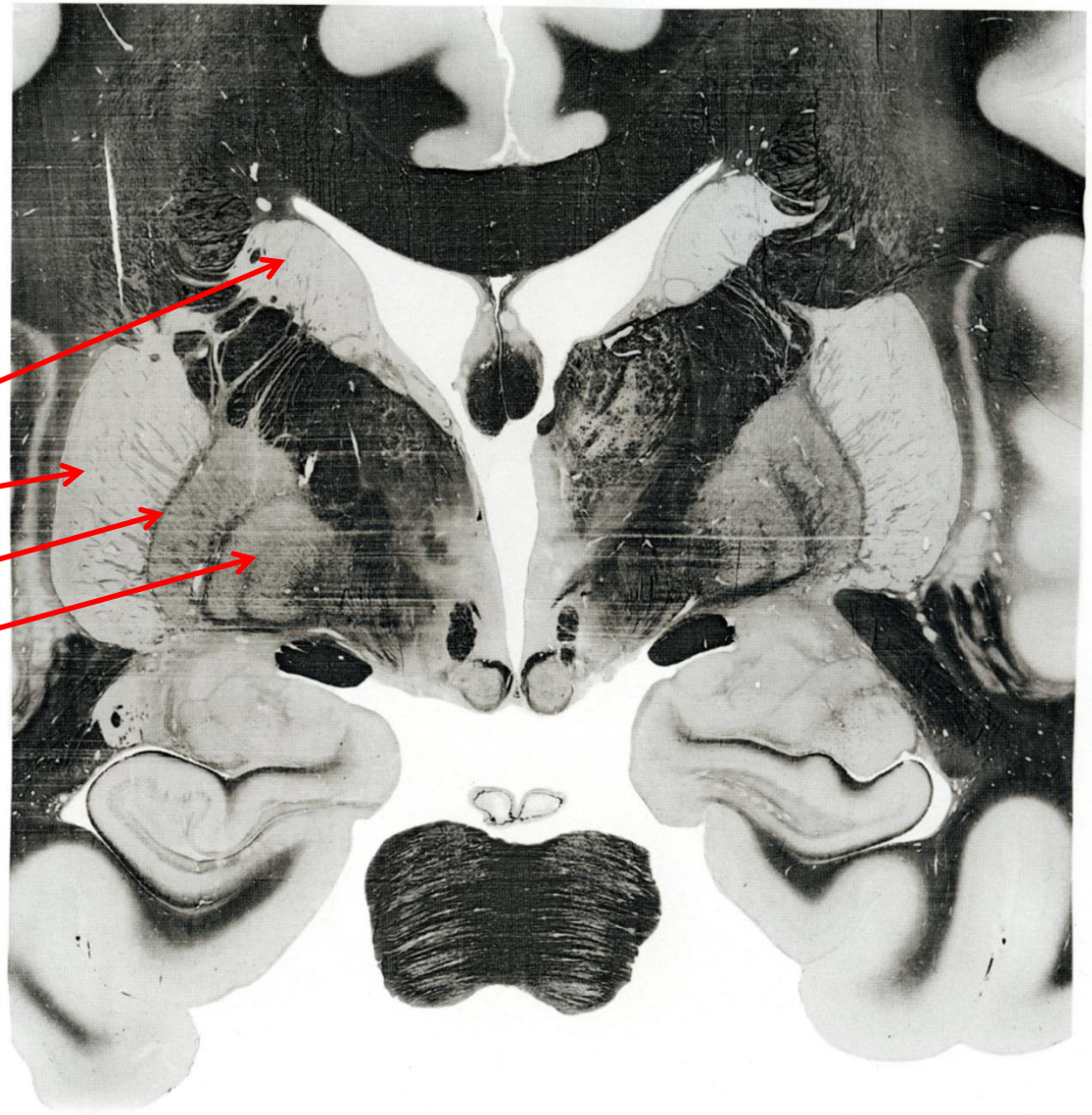
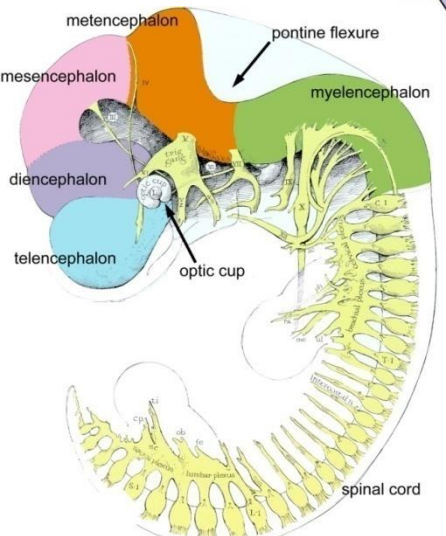




- caudate nucleus
- Putamen

- GPe
- GPi

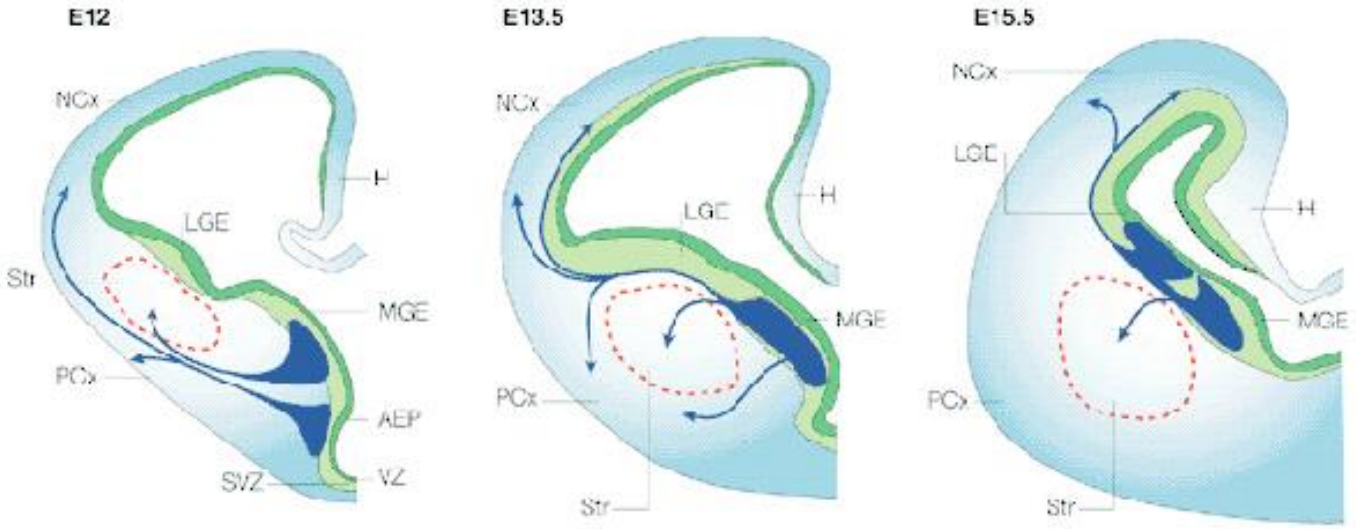
# Telencephalon




hippocampus
hem
medial pallium
neocortex
dorsal pallium
piriform cortex
lateral pallium
ventral pallium
amygdala & claustrum
LGE
caudate nucleus
putamen
MGE
subpallium
globus pallidus

## Tangential Migration in Developing Forebrain

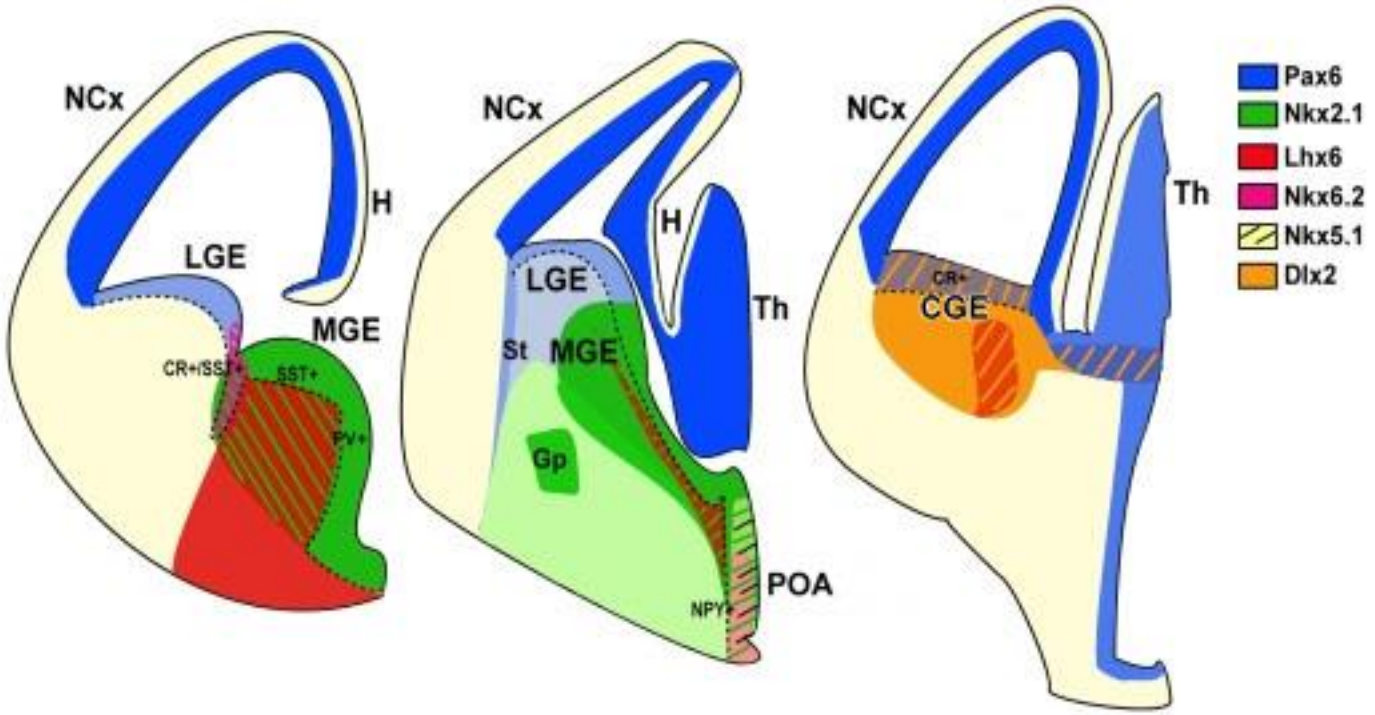
- MGE, caudal ganglionic eminence and preoptic area also gives rise to the GABAergic interneurons and many oligodendrocytes of cortex, which migrate tangentially.



# Tangential Migration in Developing Forebrain

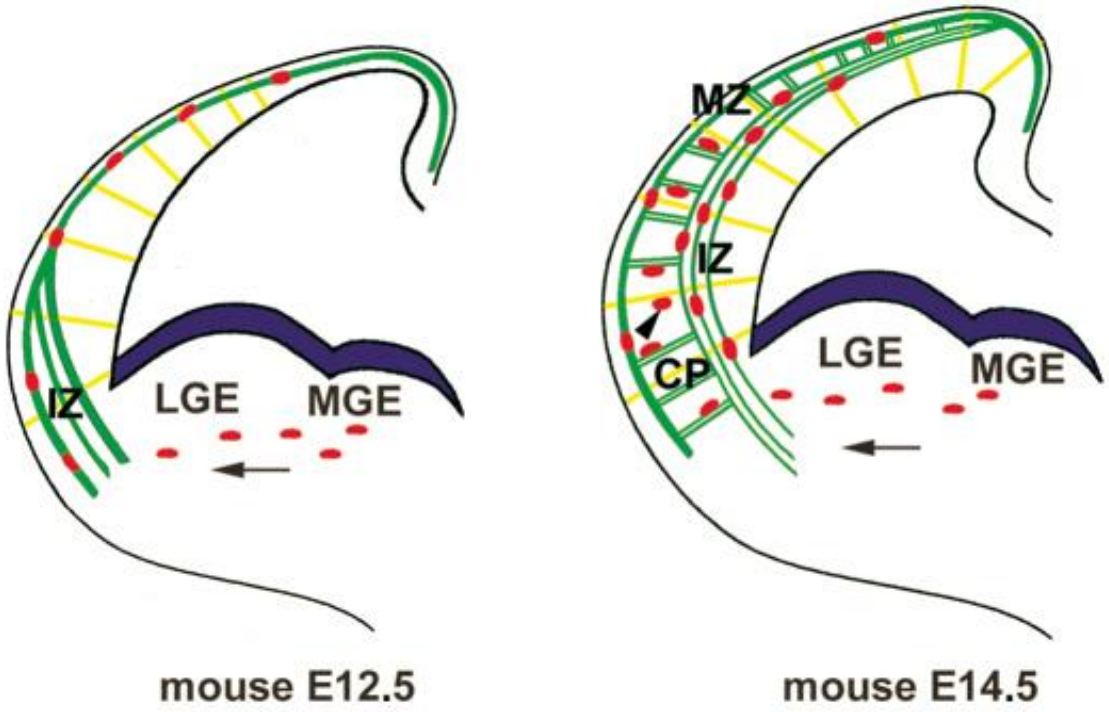
| *origin* | *radial destination* | *tangential destination (cortical interneurons)* | *pathway* |
|---|---|---|---|
| POA | amygdala | [undefined] interneurons (early) | superficial migratory stream |
| MGE | globus pallidus | parvalbumin & somatostatin interneurons (early) | deep migratory stream |
| LGE | caudate & putamen | none | |
| CGE | ? | calretinin interneurons (late) | ? |

Calbindin expression = immature (migrating) cortical interneuron



# Tangential Migration in Developing Forebrain

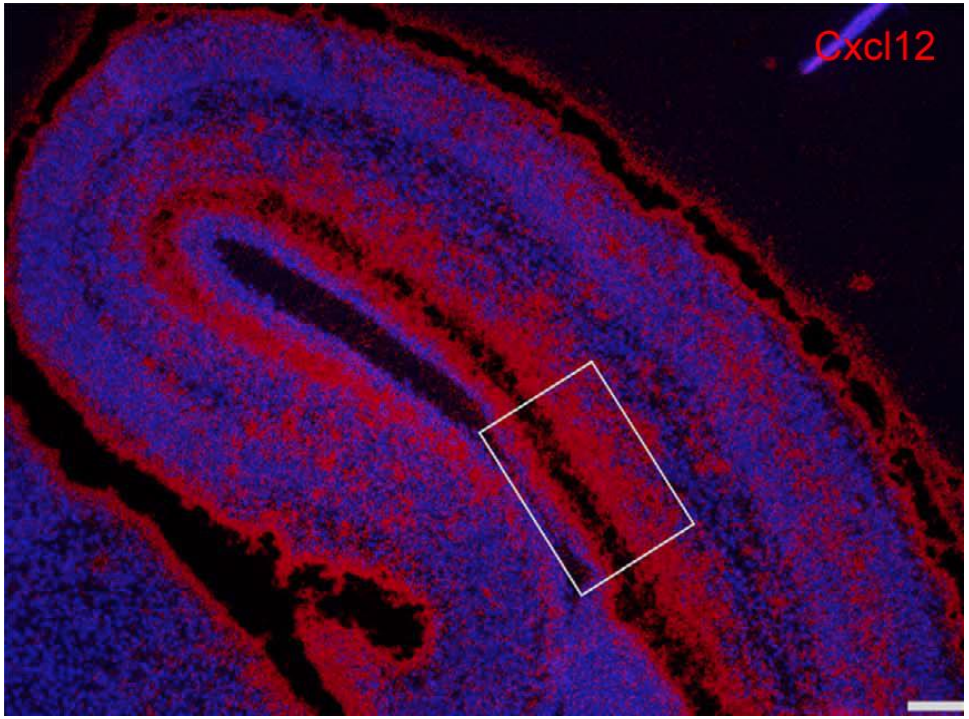
- Interneurons (red) migrate from the MGE into the cortical plate in association with cortical axons (green).
- Migrating cells adhere to the axons via TAG1, an Ig-like CAM.
- Migrating cells are repelled [possibly] by Slit1 (blue) from the ventricular layer.



# Tangential Migration in Developing Forebrain

- The chemokine, SDF1 (Cxcl12) is expressed and secreted by the meninges and subventricular zone cells in the developing cortex.

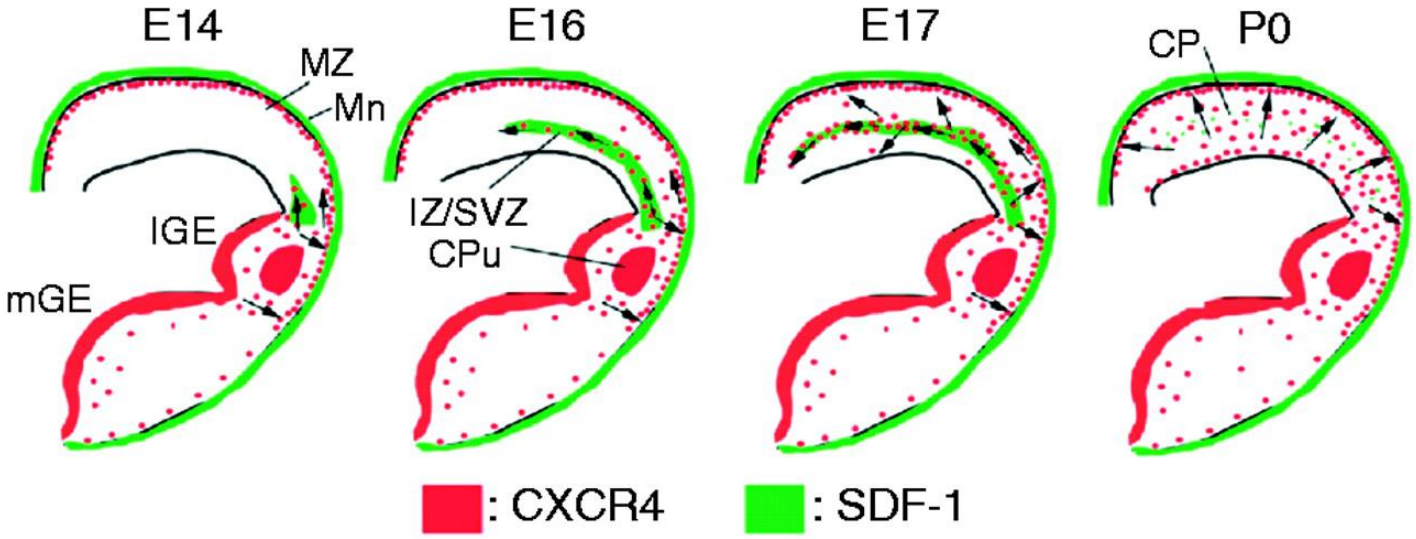
SDF1 = stromal cell-derived factor 1
Cxcl12 = C-X-C motif chemokine 12




Arno et al., 2014

## Tangential Migration in Developing Forebrain

- Cells migrating from the ganglionic eminence express the chemokine receptor, CXCR4.
- In culture, CXCR4+ forebrain neurons migrate towards SDF1.
- These cells fail to migrate with a knockout of the SDF1 or CXCR4 genes.



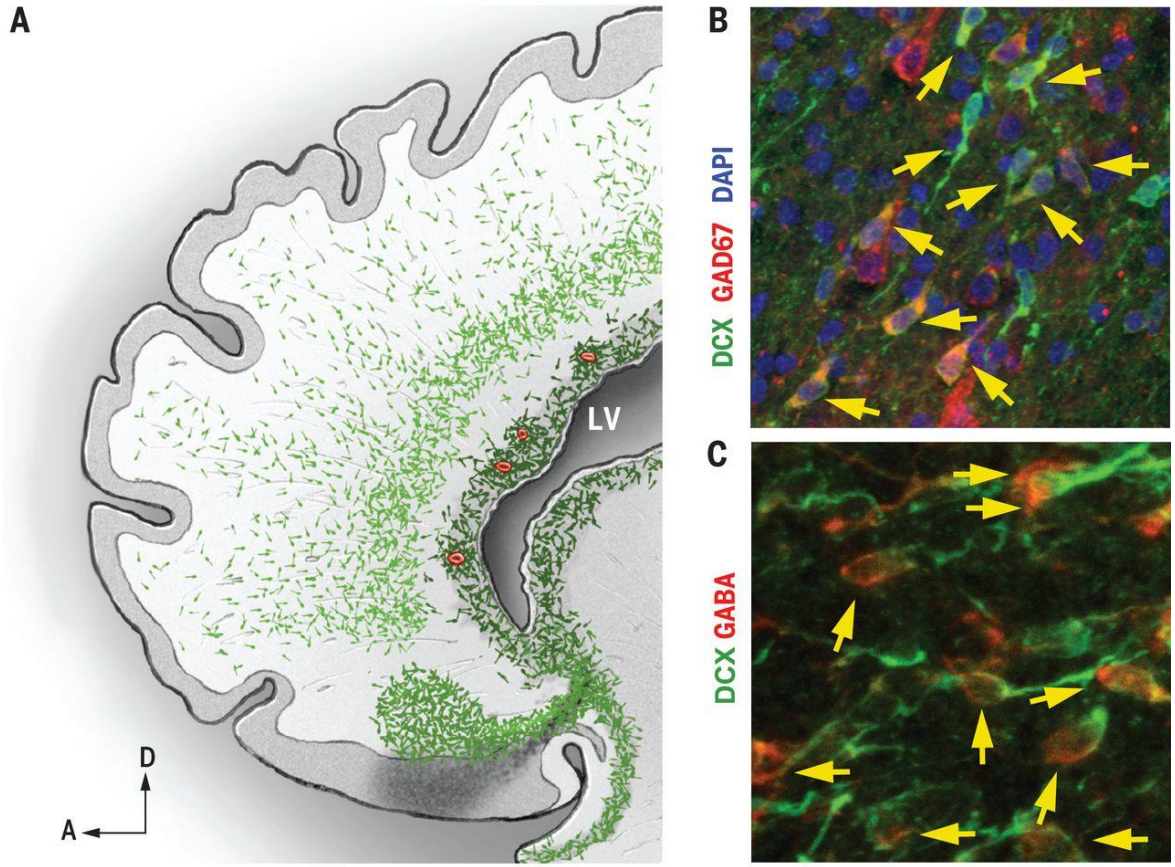
## Tangential Migration in Developing Forebrain

Thus, for inhibitory neurons migrating from basal forebrain into cortex:

- TAG-1 appears to be a substrate for adhesion between these cells and the axons.
- Slit1 maybe a repulsive guidance cue.
- SDF1 appears to be an attractive guidance cue (i.e. tropic factor).

# Interneuron Migration into Cortex in Humans

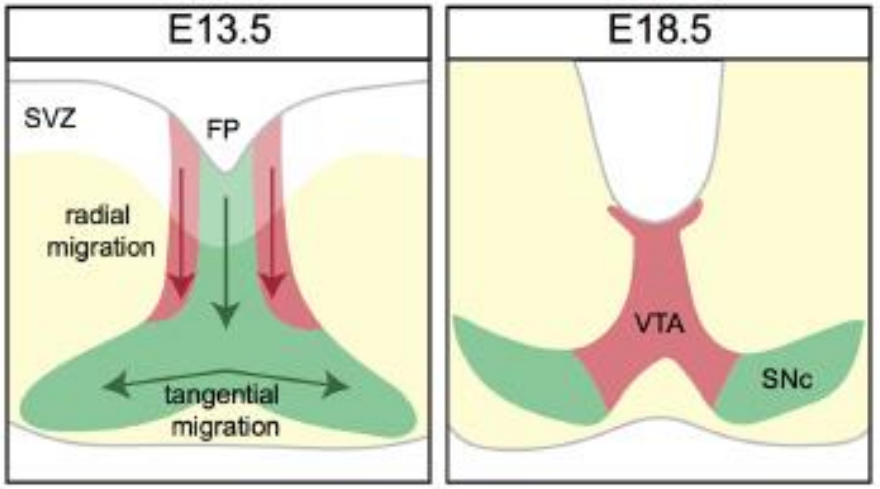
- Interneurons continue to migrate into medial prefrontal cortex and cingulate gyrus in humans through at least 5 months of age.




Paredes MF et al. (2016) Science 354:81

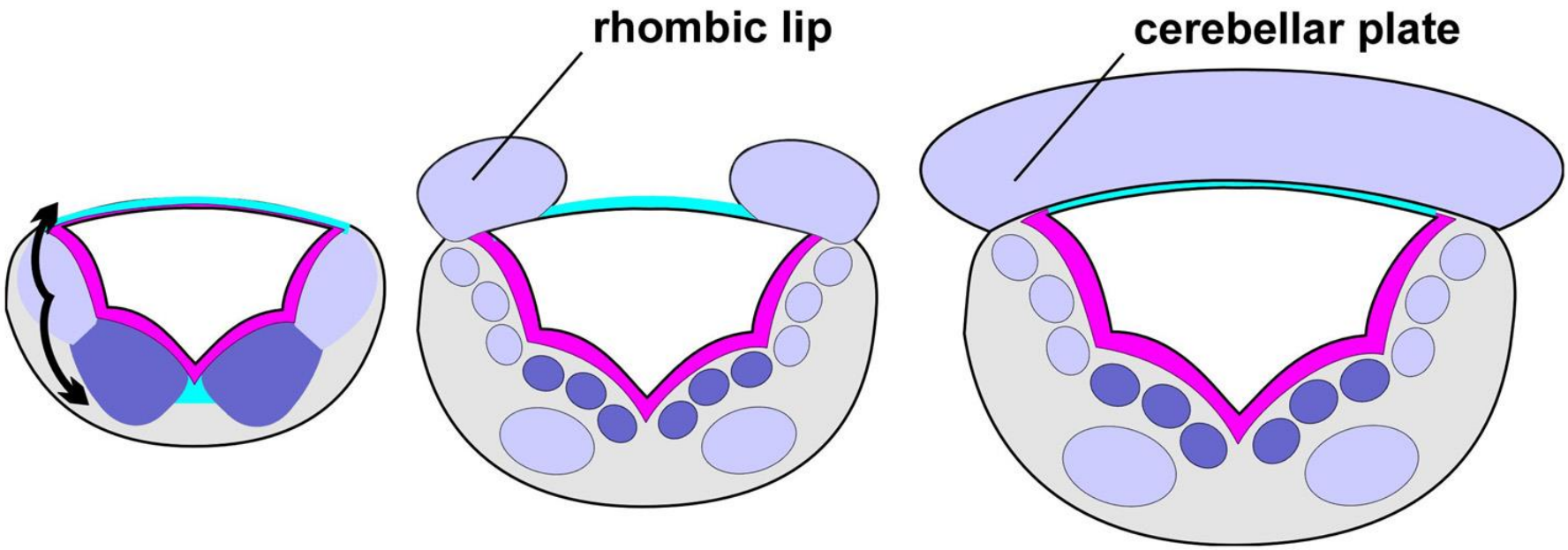
## Radial & Tangential Migration in the Midbrain

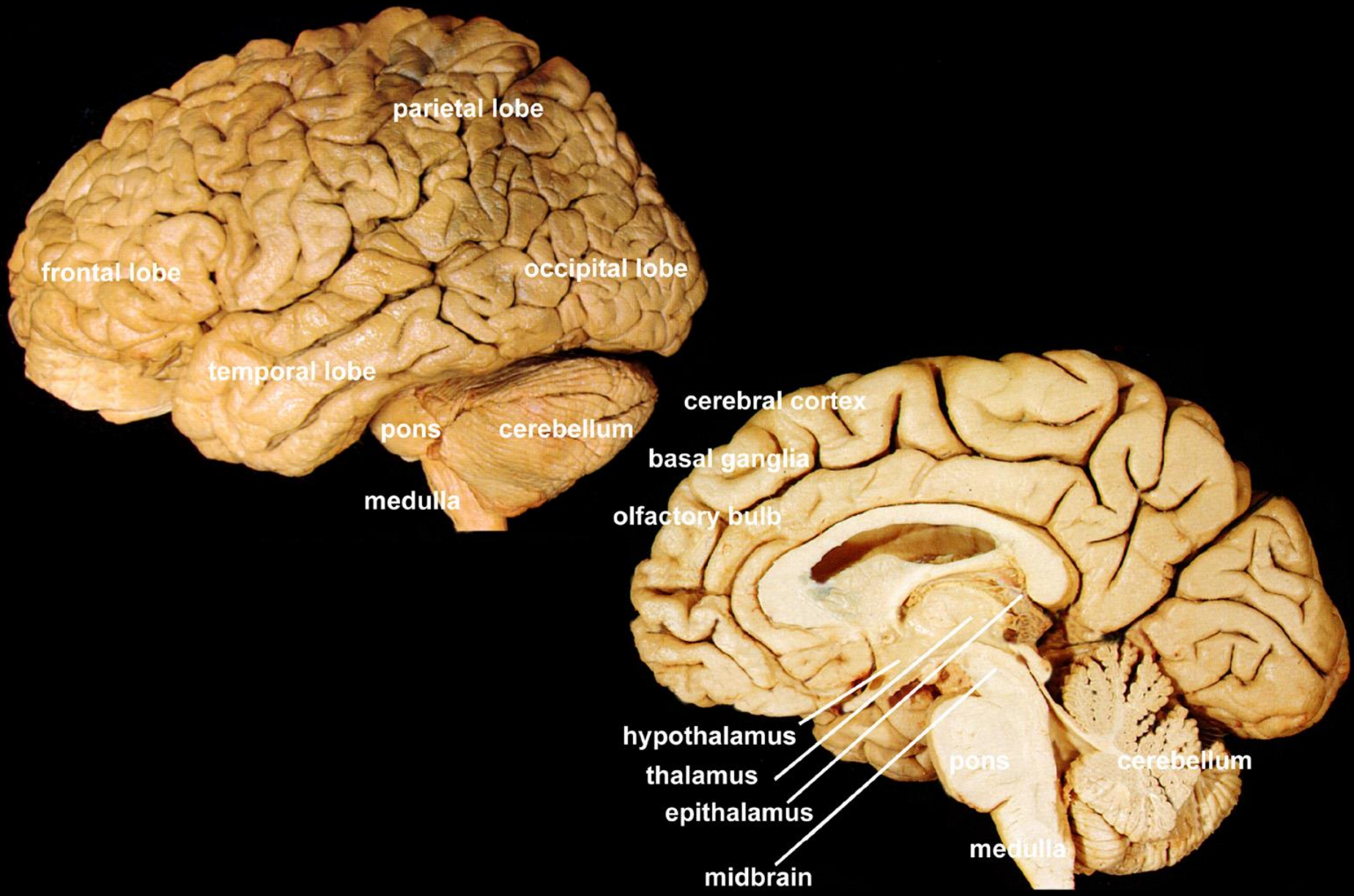
- Dopaminergic  neurons in the substantia nigra are born in the ventricular zone of the midbrain floor plate.
- The cells first migrate radially in association with radial glia.
- They express the chemokine receptor CxcR4, and are attracted to Cxcl12 (SDF1) released by the meninges.
- Then they migrate tangentially. Reelin is required for this migration. Reelin is expressed by the red nucleus.



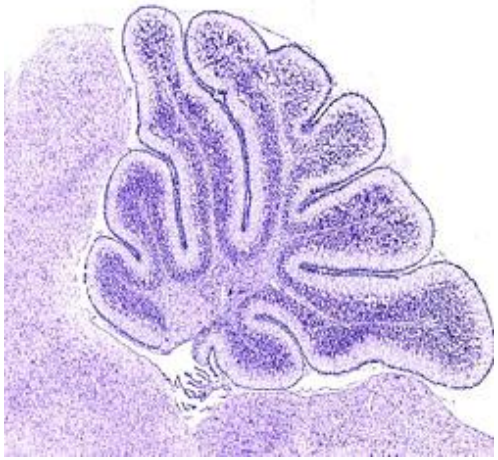

Brignani and Pasterkamp, 2017

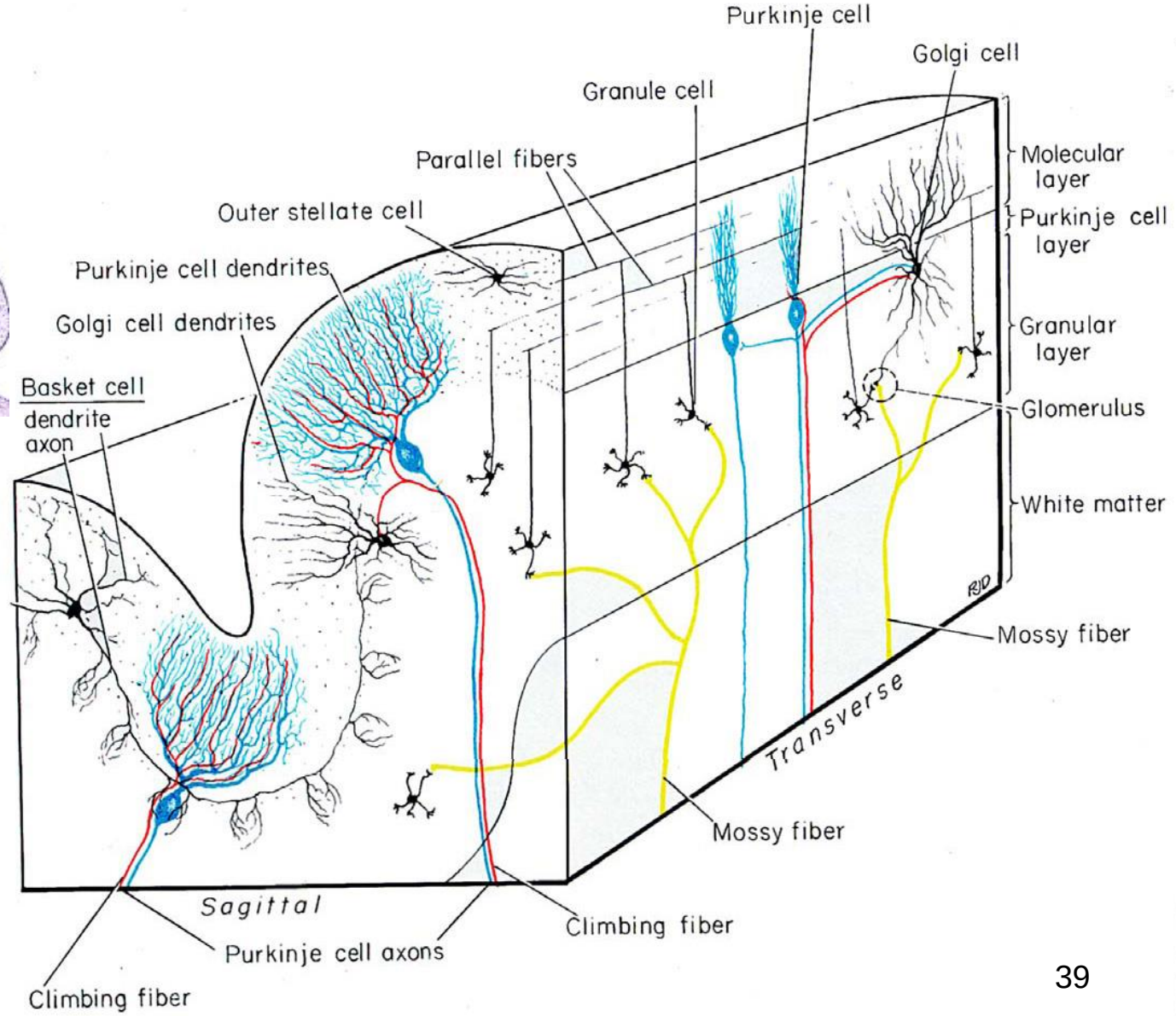
# Migration in the Cerebellum



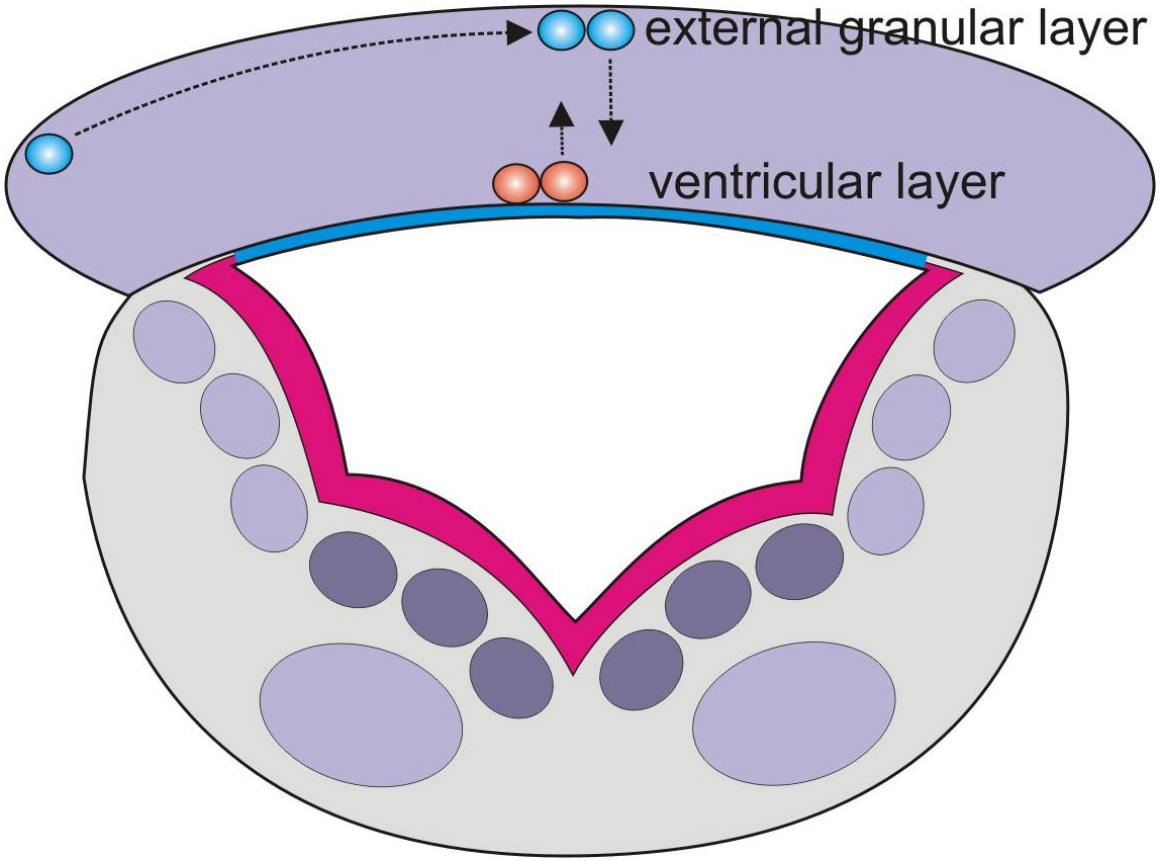

parietal lobe
frontal lobe
occipital lobe
temporal lobe
pons
cerebellum
medulla
cerebral cortex
basal ganglia
olfactory bulb
hypothalamus
thalamus
epithalamus
midbrain
pons
cerebellum
medulla

# Migration in the Cerebellum

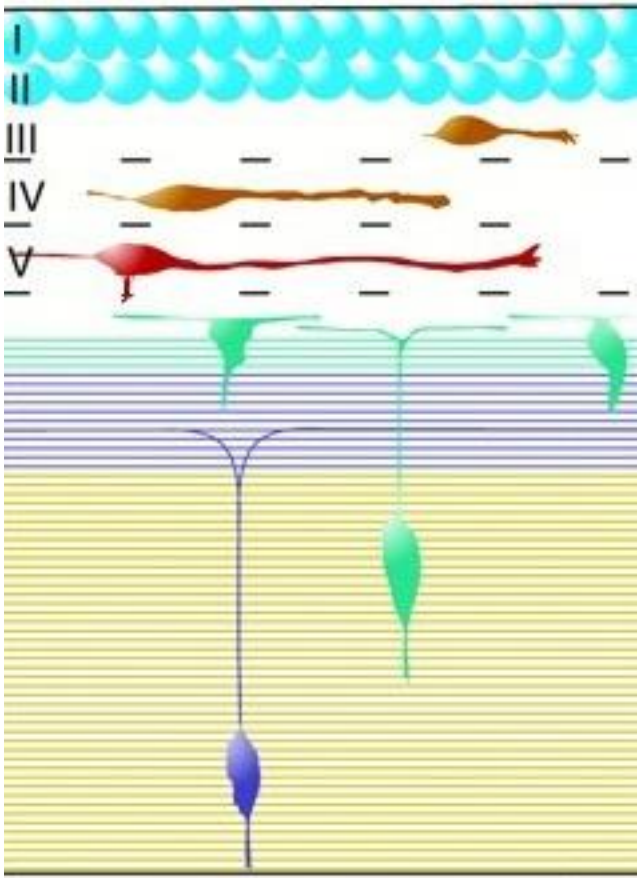




# Migration in the Cerebellum



# Migration in the Cerebellum



**Mutations affecting proteins involved in cell migration result in abnormal cell distribution in the human brain.**