

NS201B

November, 2016

Neural Circuit
Development

Part 1

Michael P. Stryker

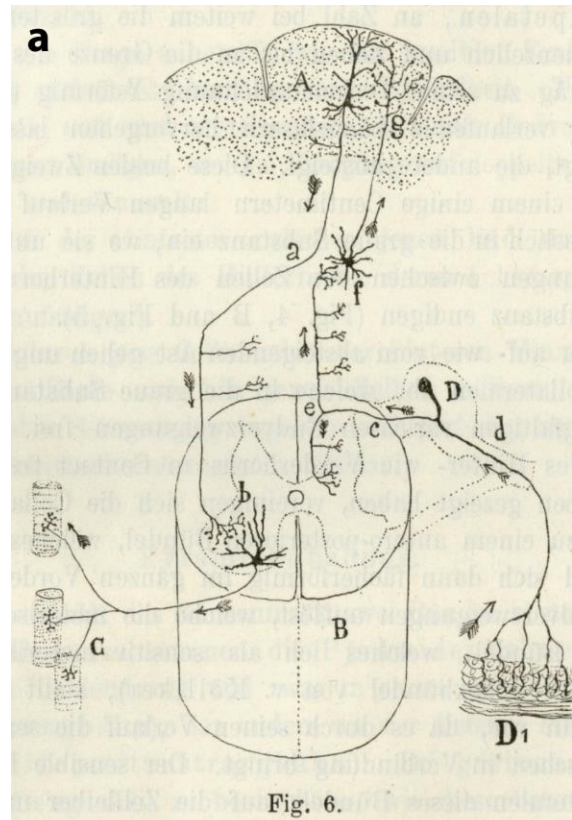


Fig. 6.

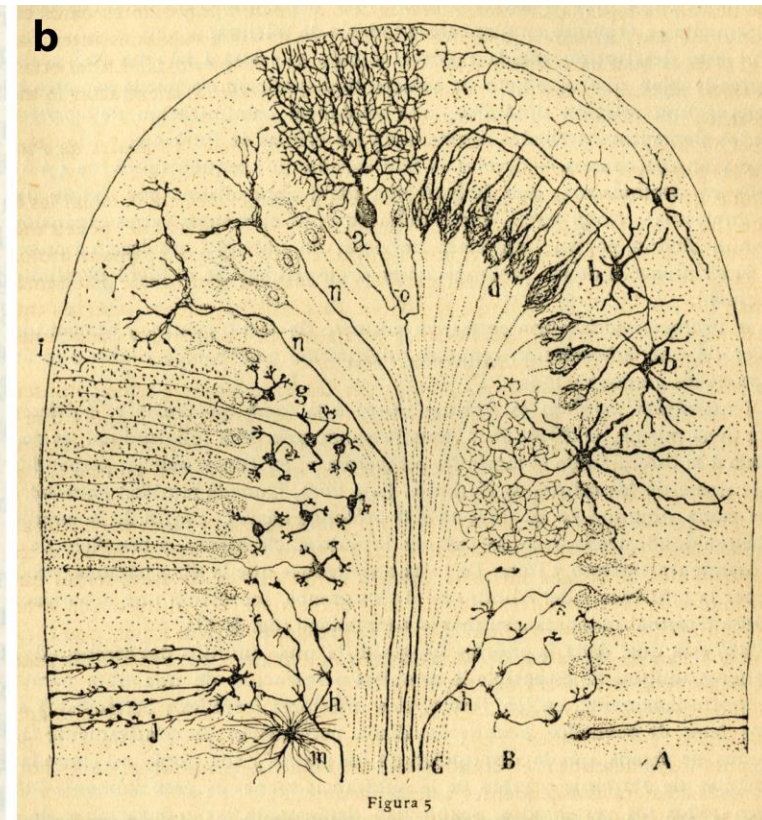
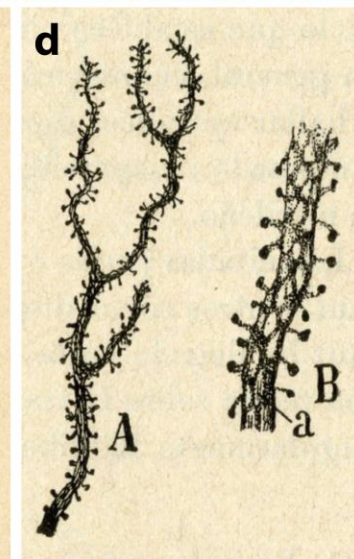
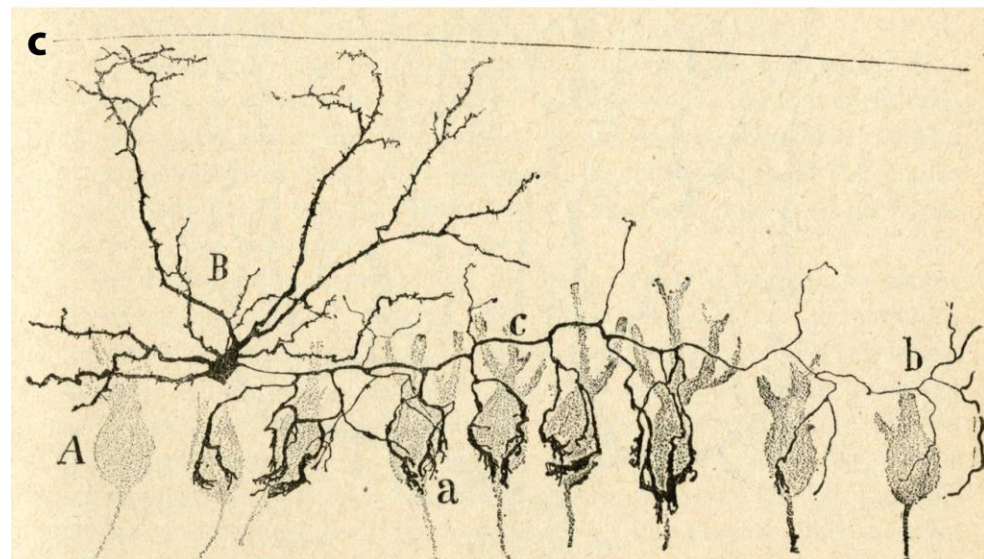


Figura 5



What does it take to build a brain?

- Neurons of the appropriate types must be generated in appropriate places in appropriate numbers.
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Acquisition of neuronal identity takes place by different means in different neurons:

Response to widespread signals

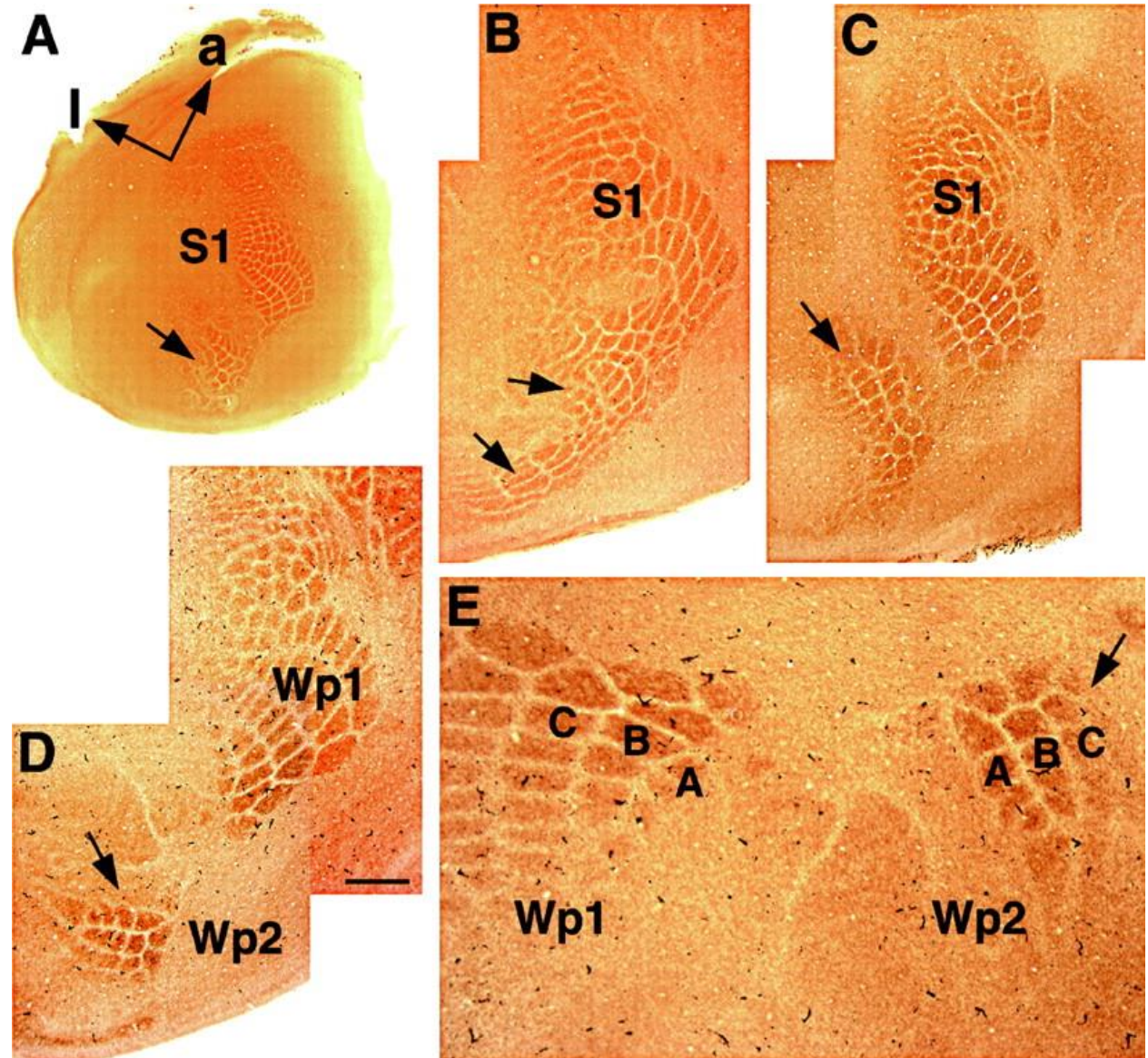
Localized signals

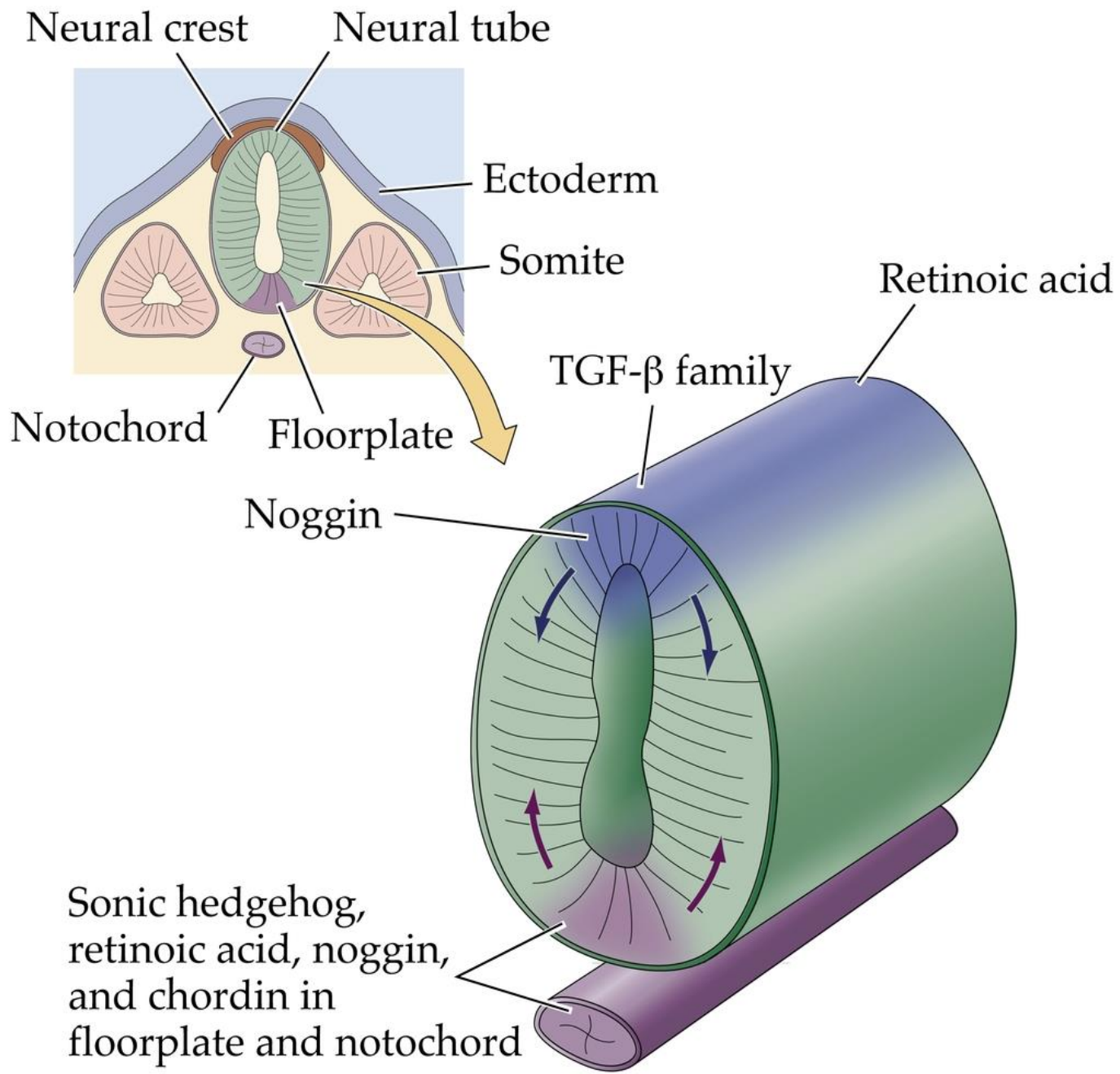
Intrinsic programs

Upstream signals (CoupTF1, Emx1/2, Pax6, Fgf8) in fetal life confer identity on cortical cells and determine maps.

Proof:
Ectopic
expression of
Fgf8 causes
duplication of
whisker
barrel fields.

Tomomi Fukuchi-
Shimogori and
Elizabeth A. Grove
(2001) Neocortex
Patterning by the
Secreted Signaling
Molecule FGF8
Science 294: 1071 -
1074





The Neural Crest Derivatives: 1 sensory, 2 autonomic, 3 adrenal neurosecretory, 4 non-neural (eg, melanocytes)

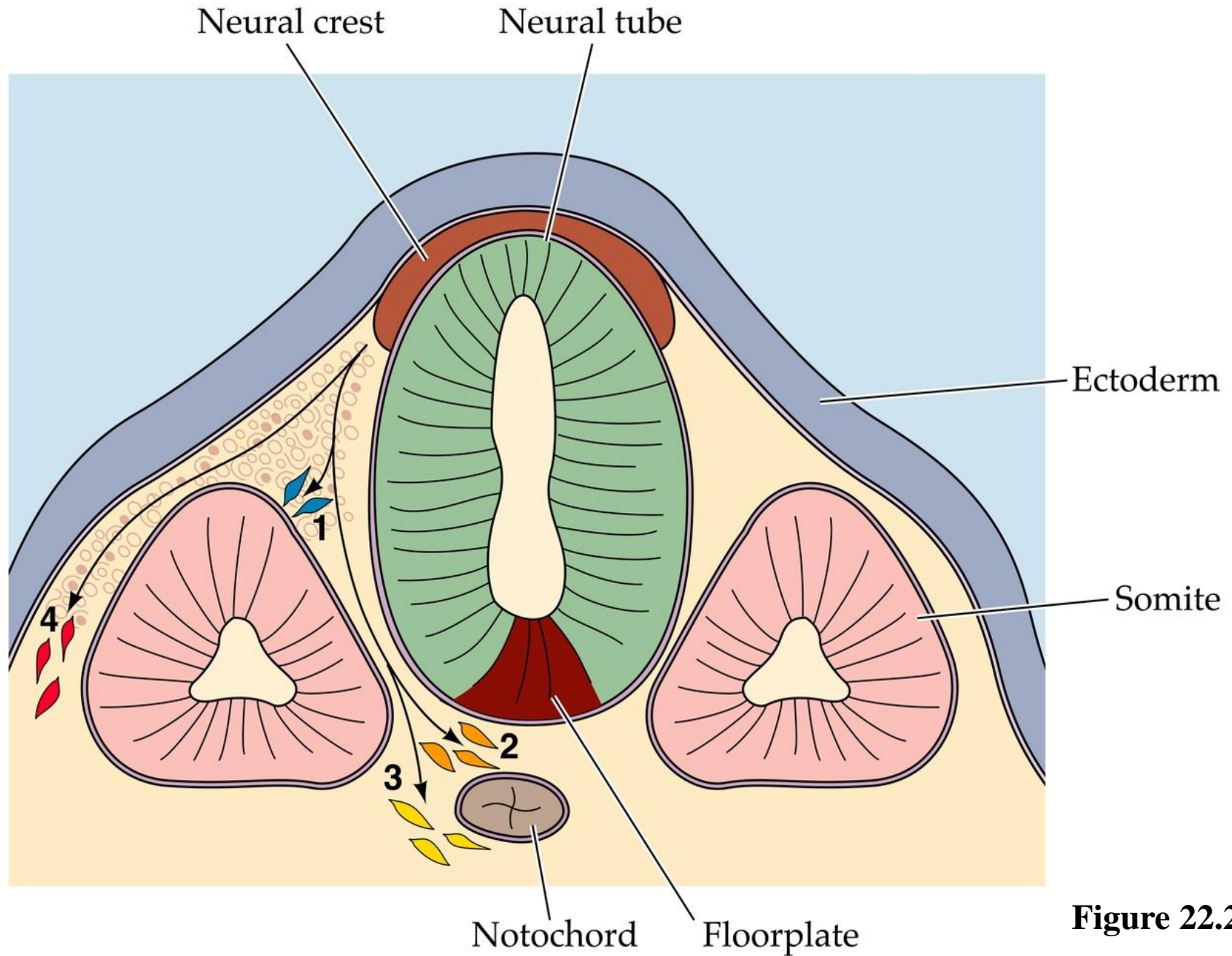


Figure 22.2 B

Cell Signaling During the Migration of Neural Crest Cells

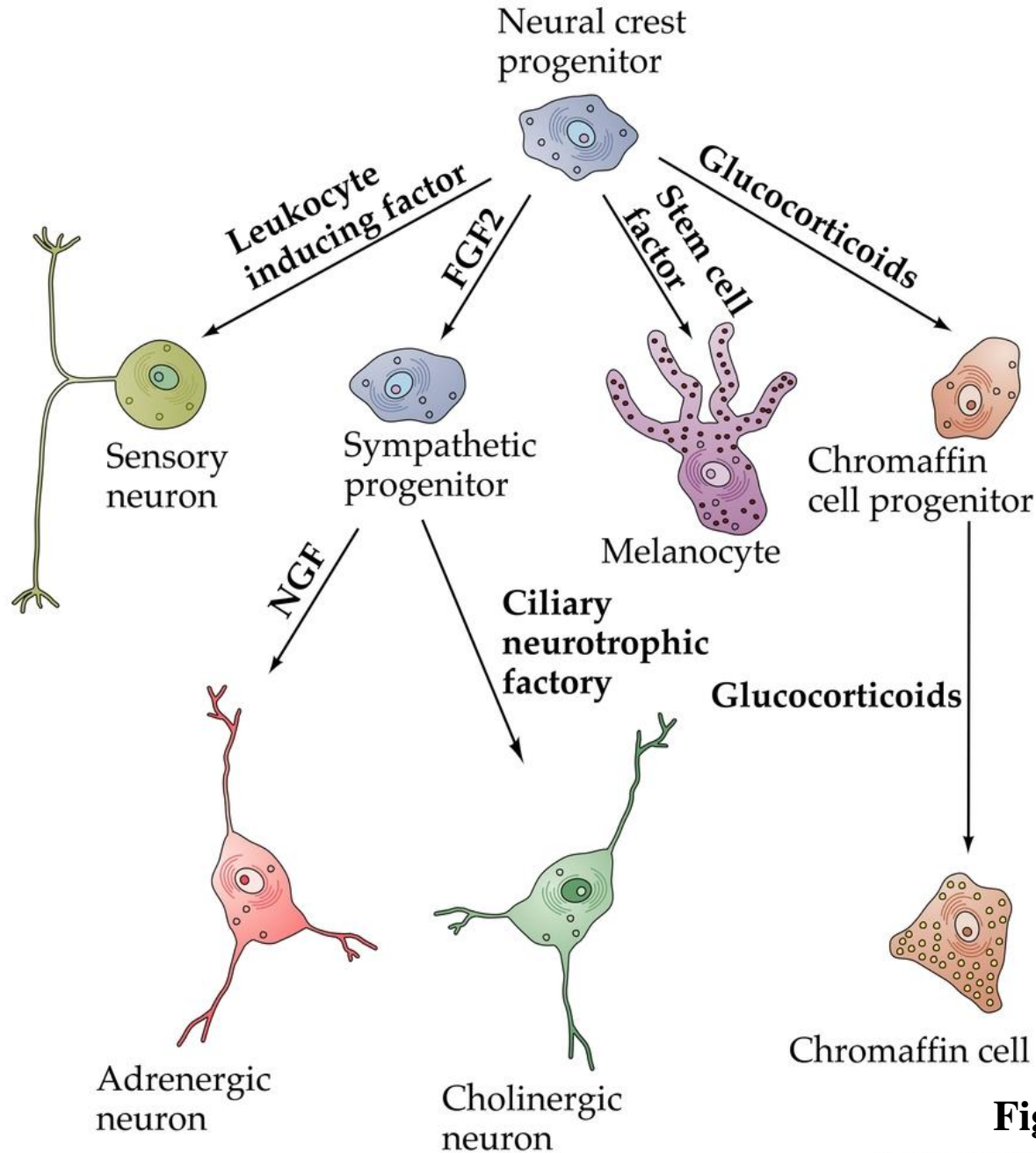
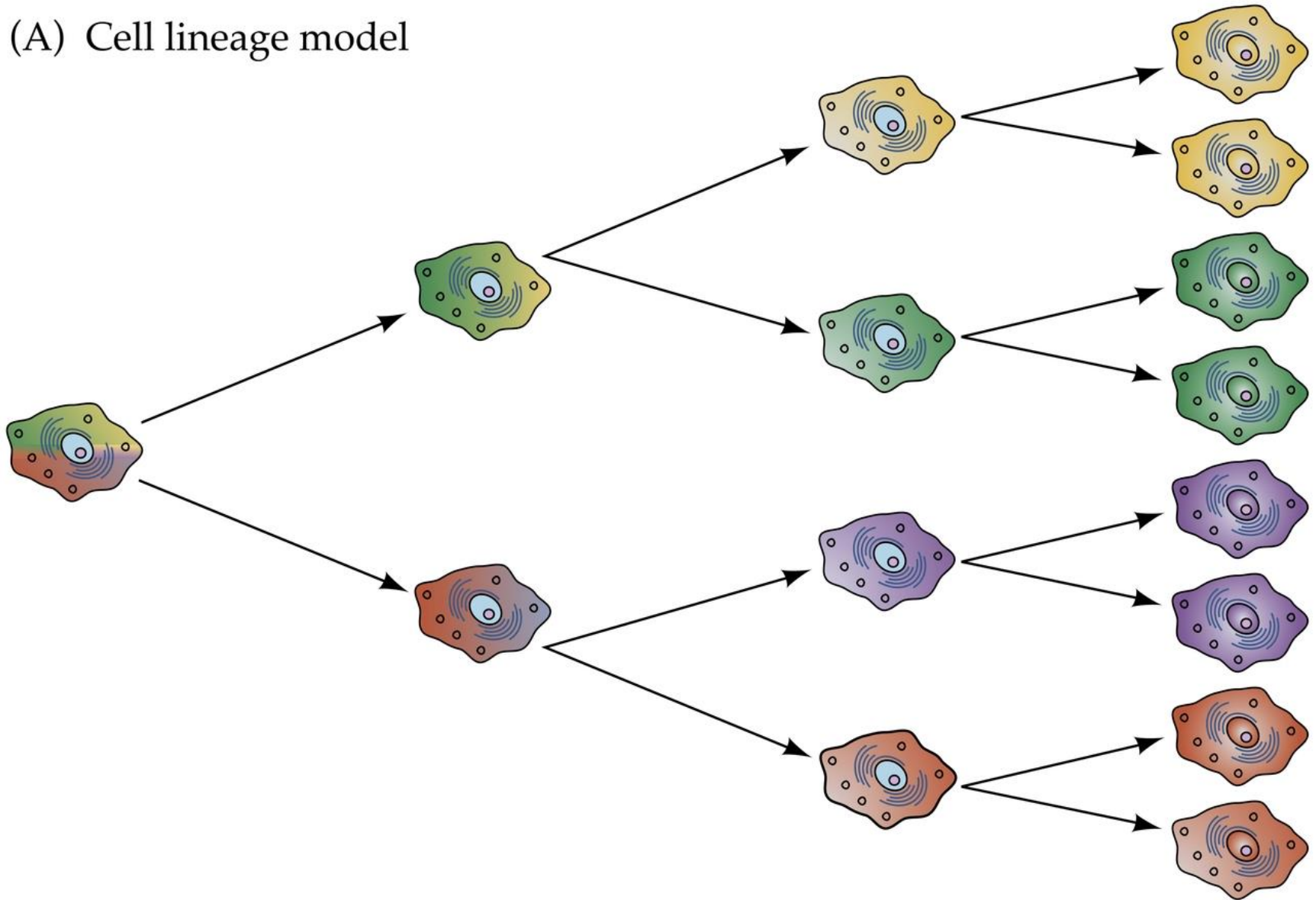


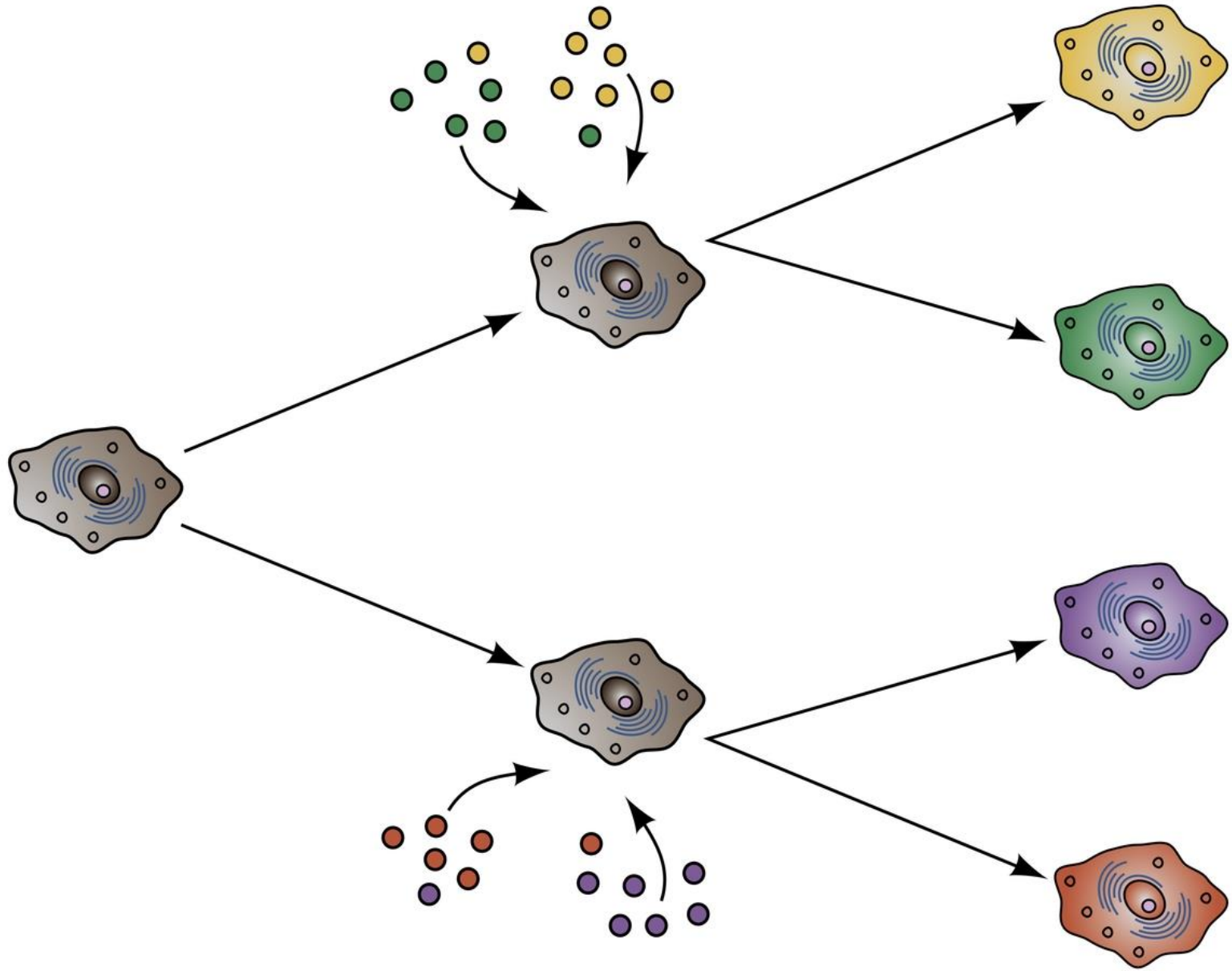
Figure 22.11 C

How do cells acquire their identities?

(A) Cell lineage model



(B) Cellular interactions model



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Regulation of cell number is poorly understood

Current hypotheses include the number of cycles of proliferative lineages (where each parent gives rise to two similar daughters producing an exponential increase in cell number) as opposed to stem cell lineages (where each parent gives rise to one differentiating daughter).

In many situations, excess cells are generated, of which only some survive after competition for neurotrophic survival factors.

Nerve Growth Factor (NGF) was the first neurotrophin

Fig 23-12

(A)



(B)

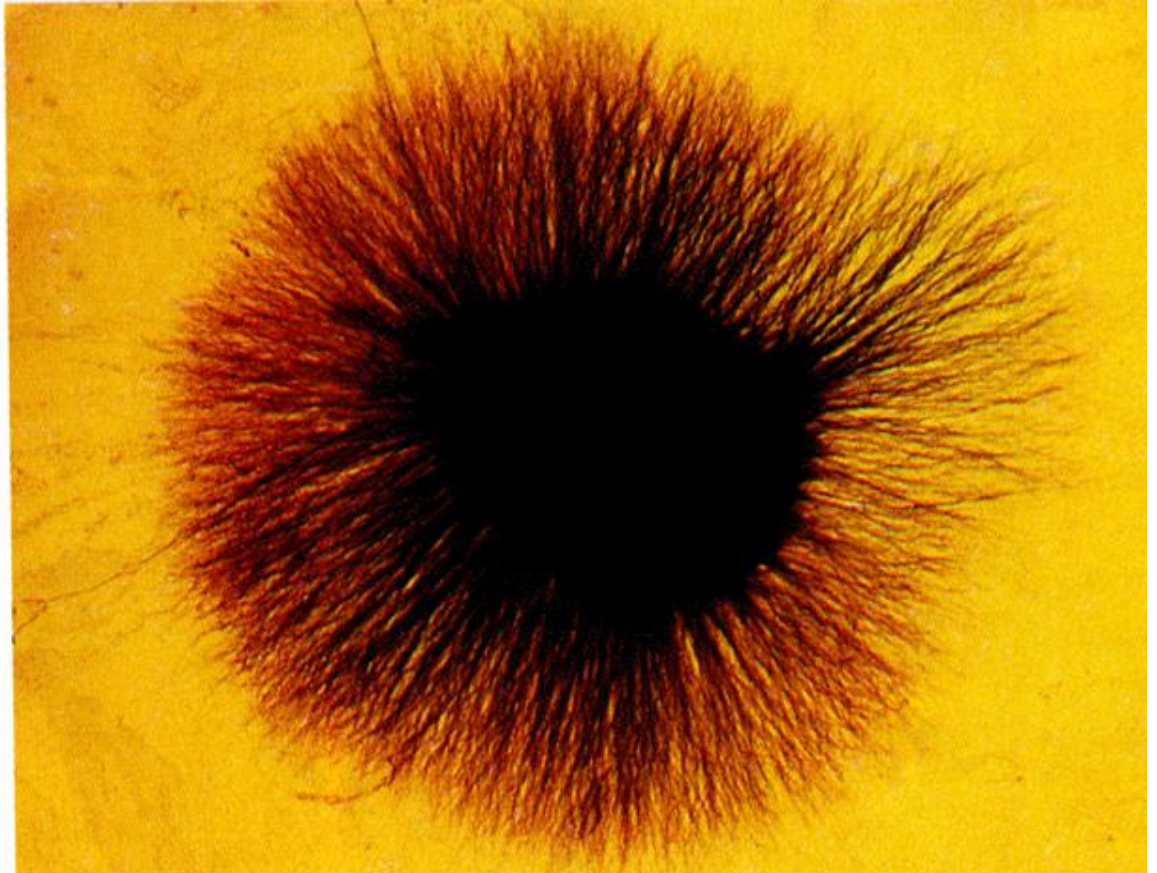


Figure 23.12 A B

Now we know
of 3 major
families of
neurotrophins:
NGF, Brain
derived
neurotrophic
factor and NT-
4/5, and NT-3

Fig 23-15

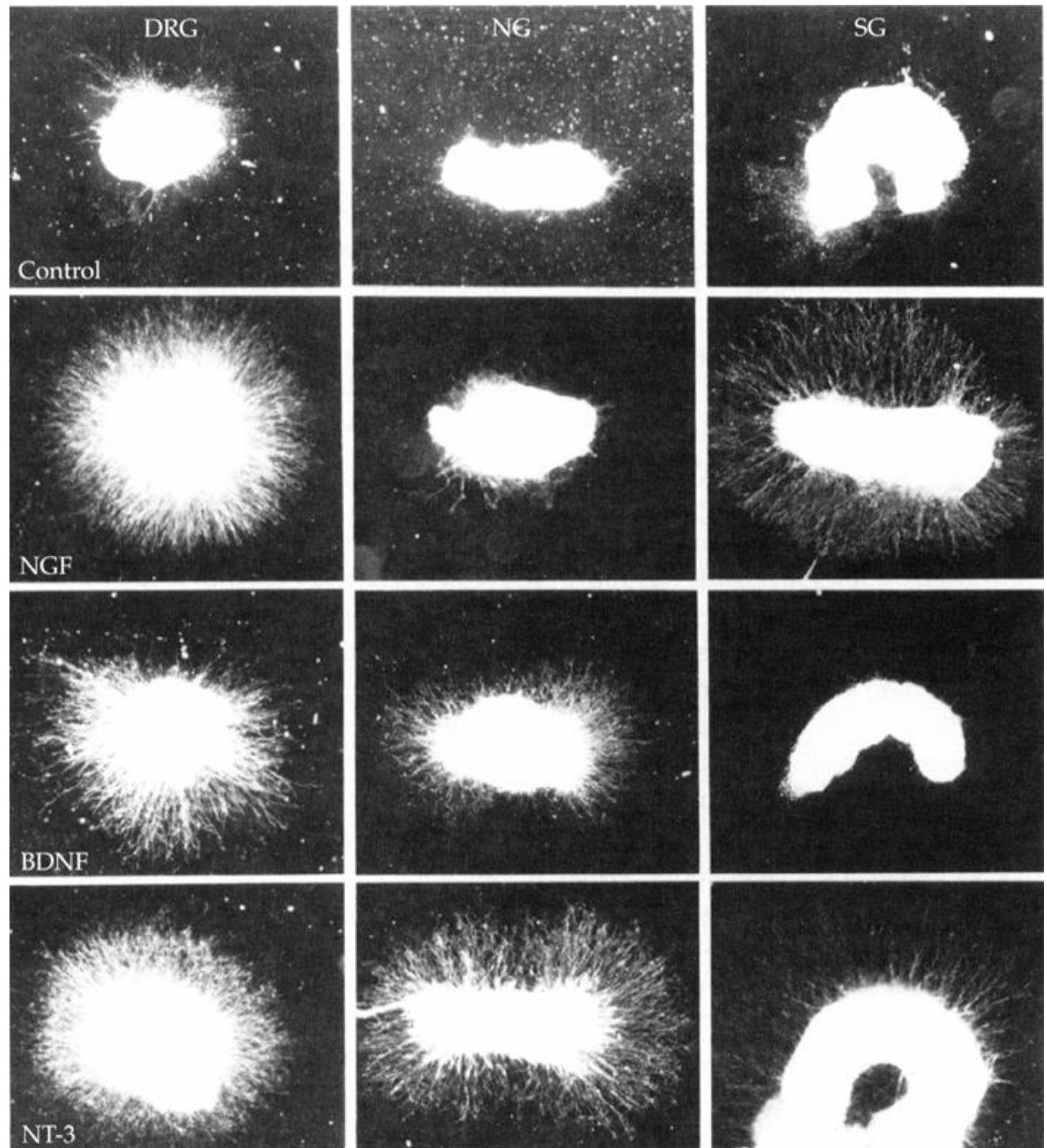


Figure 23.13 A

The Trk Family of Receptor Tyrosine Kinases for the Neurotrophins

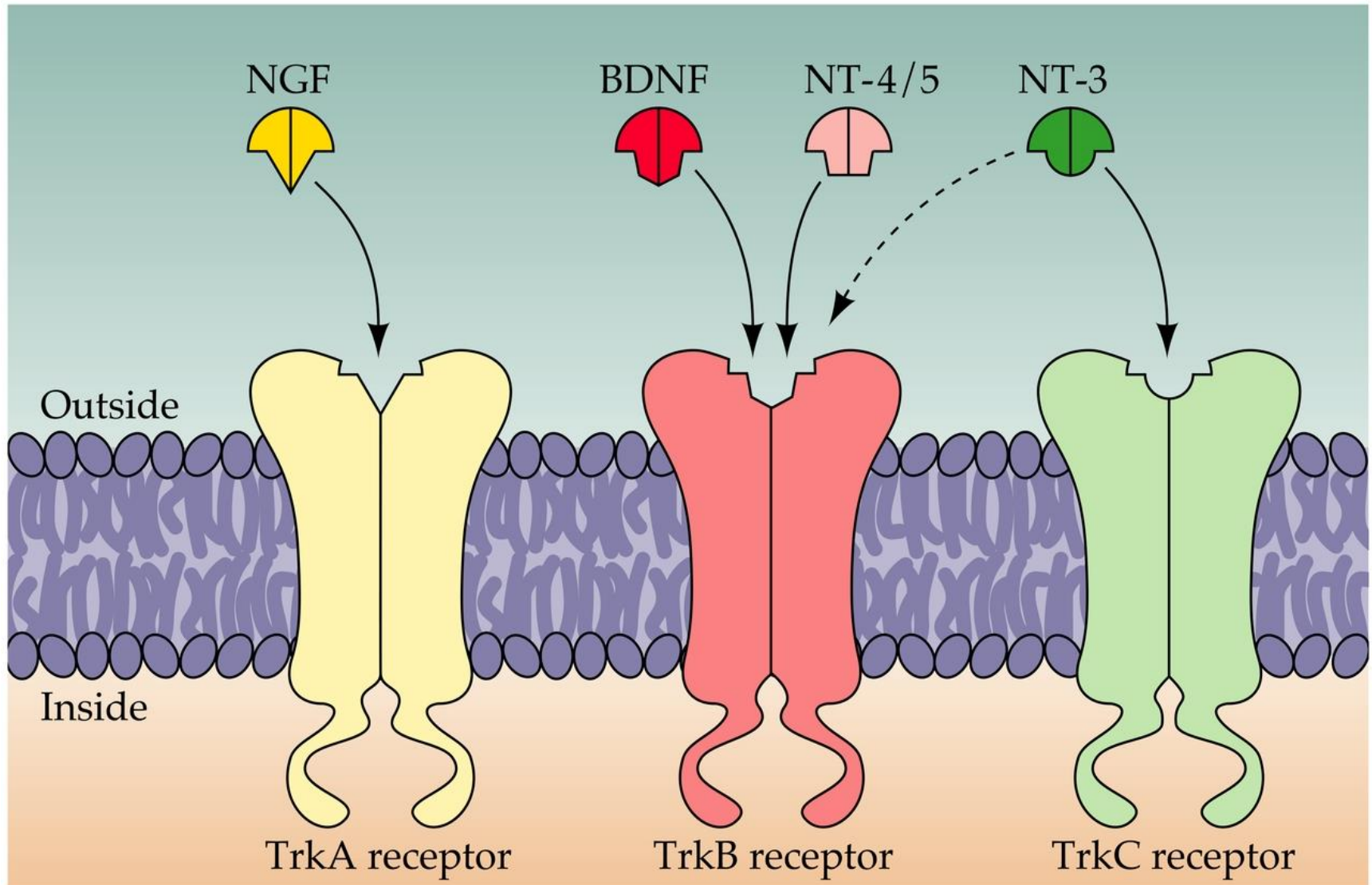


Figure 23.15 A

Neurotrophins and other molecules promote survival of particular classes of neurons.

Neurotrophins secreted by the target can regulate cell number during development, matching input numbers to target.

Programmed cell death (apoptosis) is a prominent feature of the normal development of the central nervous system.

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Early neural tube cells stretch from the ventricle to the pia. Neurons are born in the ventricular zone, and migrate radially to form the cortex.

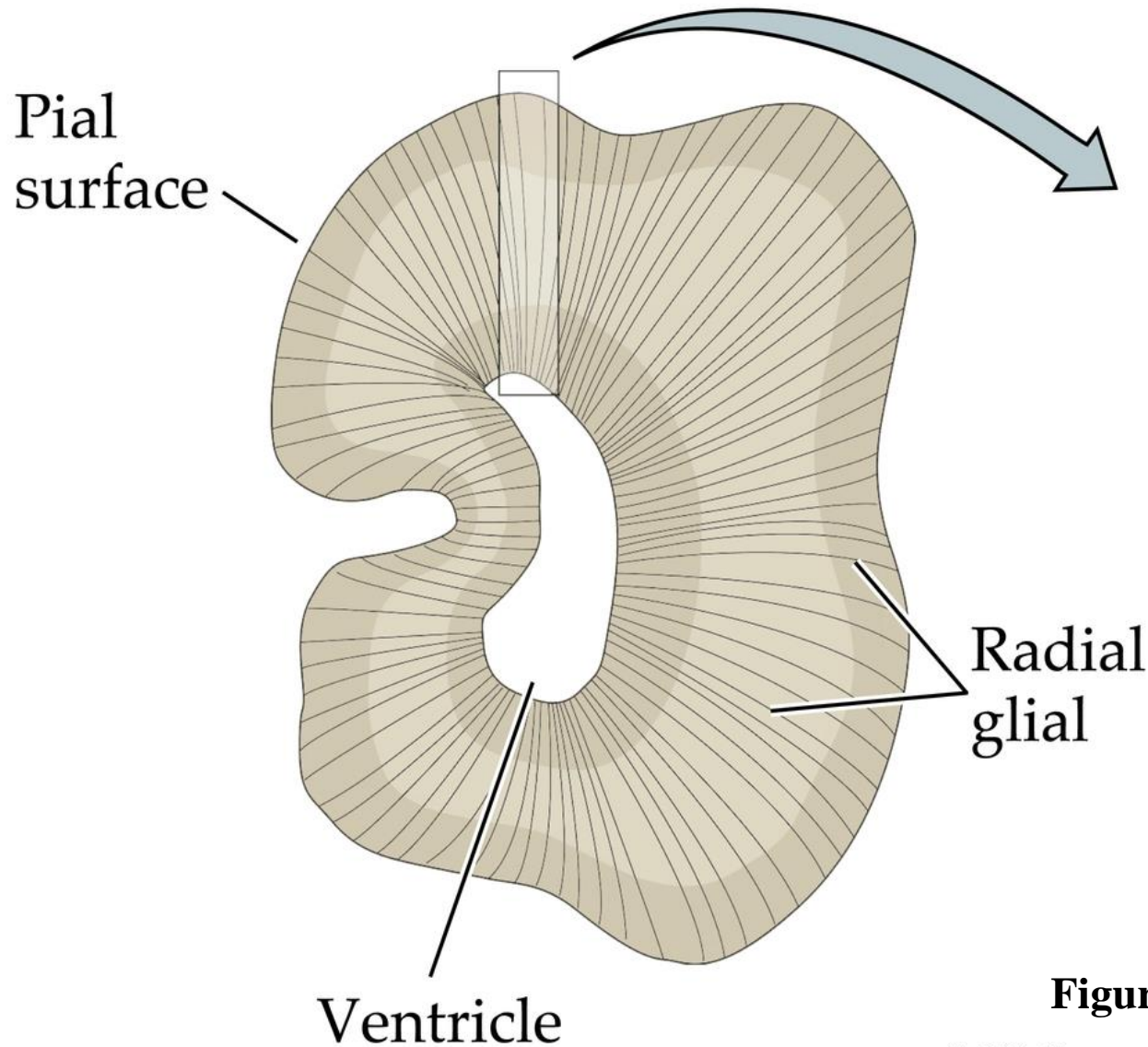


Figure 22.12 A

Stereotyped pattern of Cell Movements of Dividing Precursor Cells as they Progress Through the Mitotic Cycle

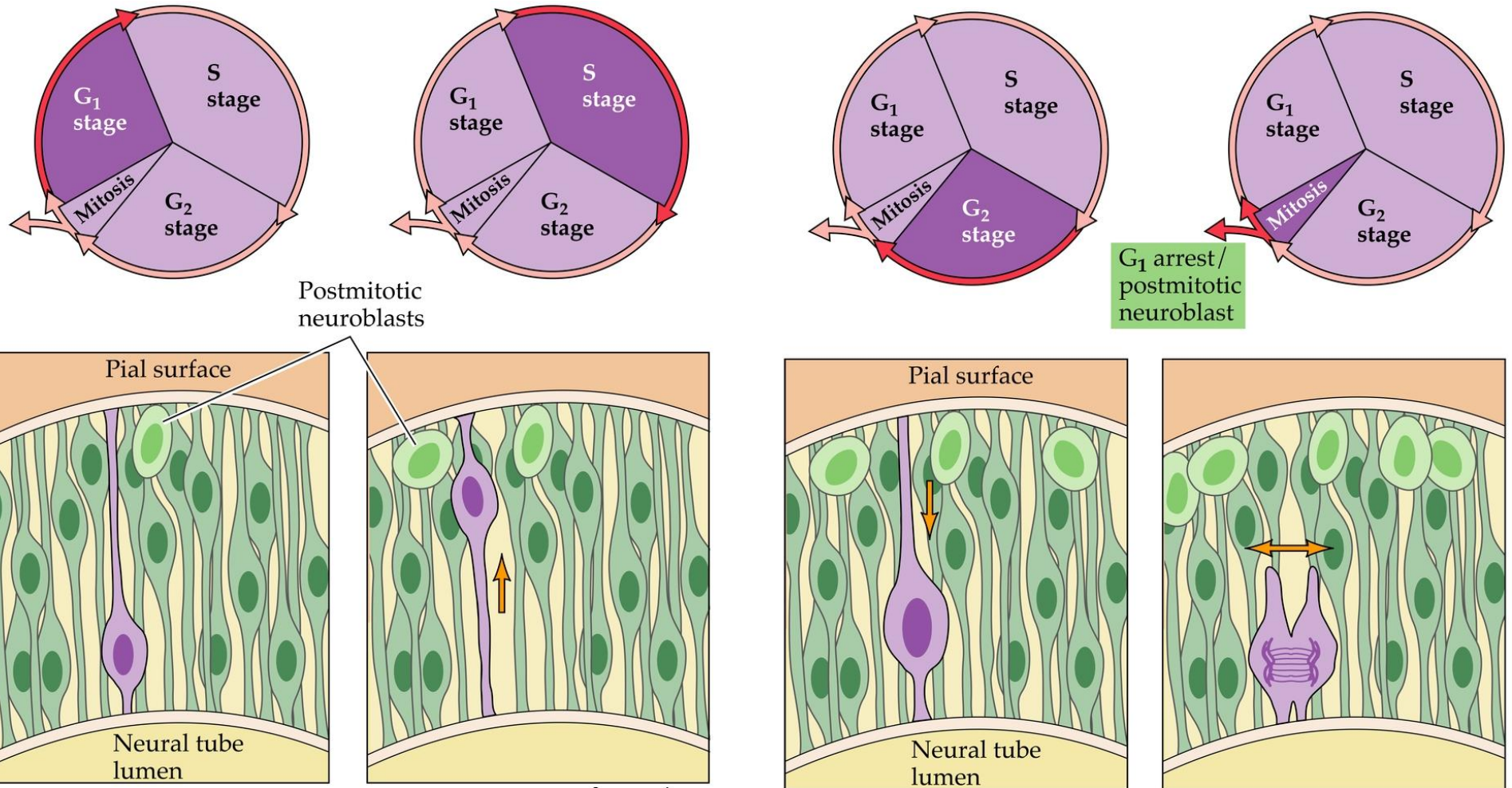


Figure 22.7

Radial Migration in the Developing Cortex

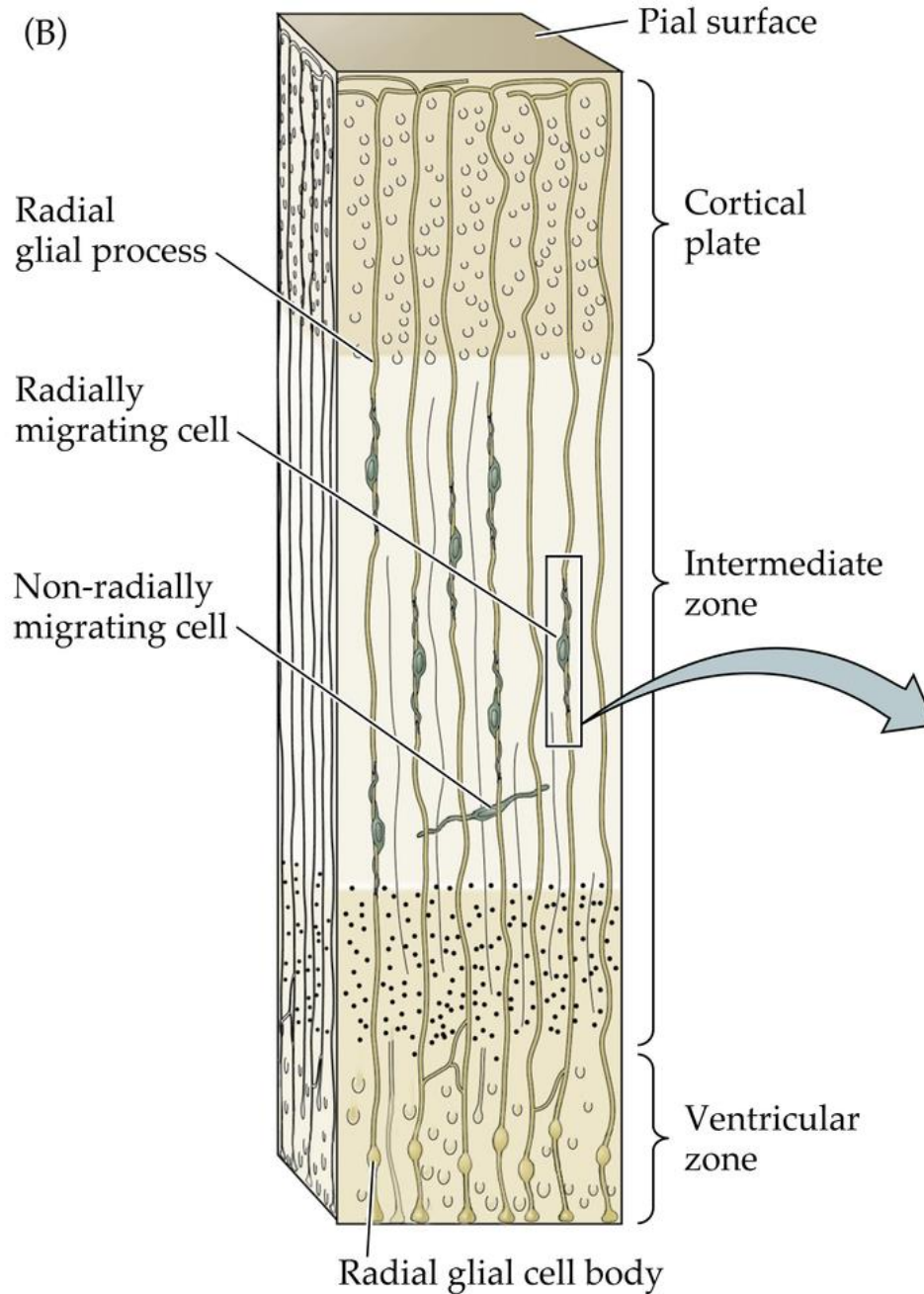


Figure 22.12 B

Radial Migration in the Developing Cortex

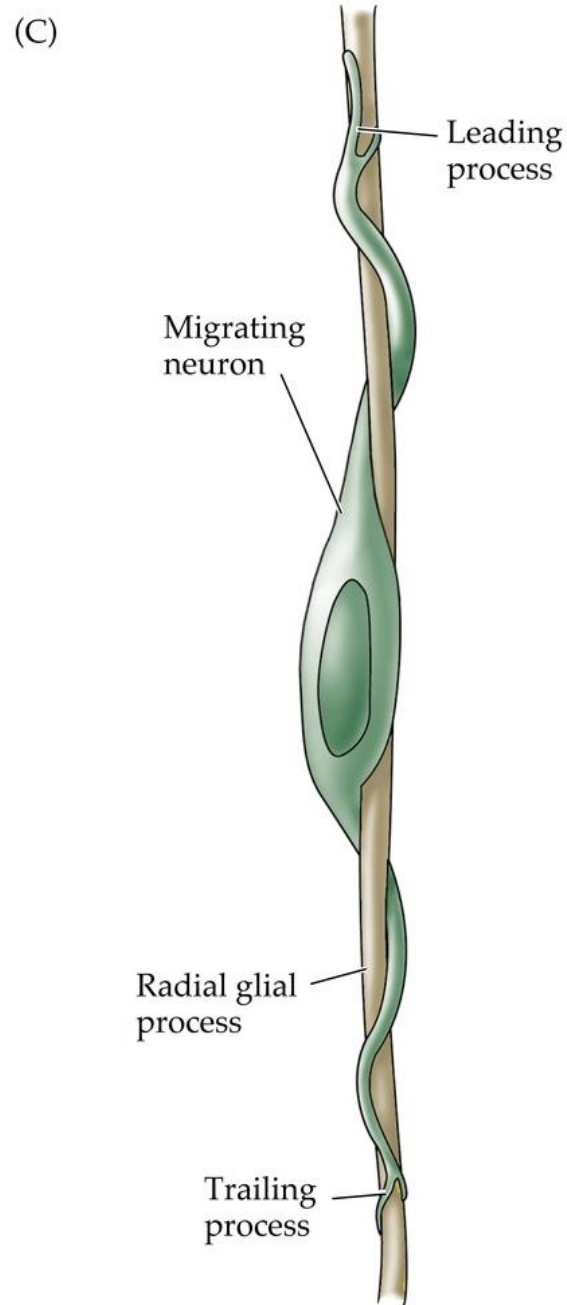


Figure 22.12 C

Generation of Cortical Neurons During the Gestation of a Rhesus Monkey

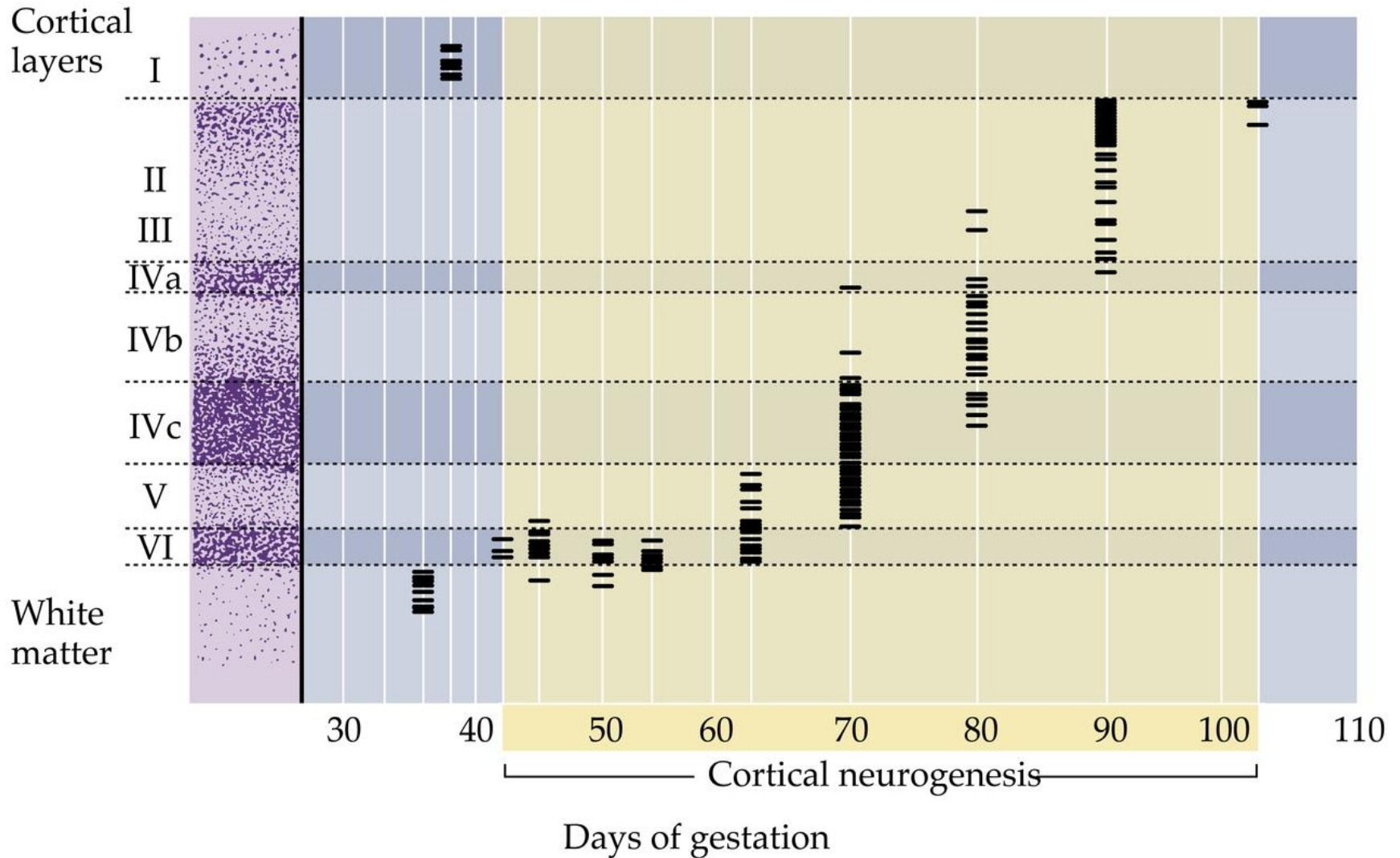
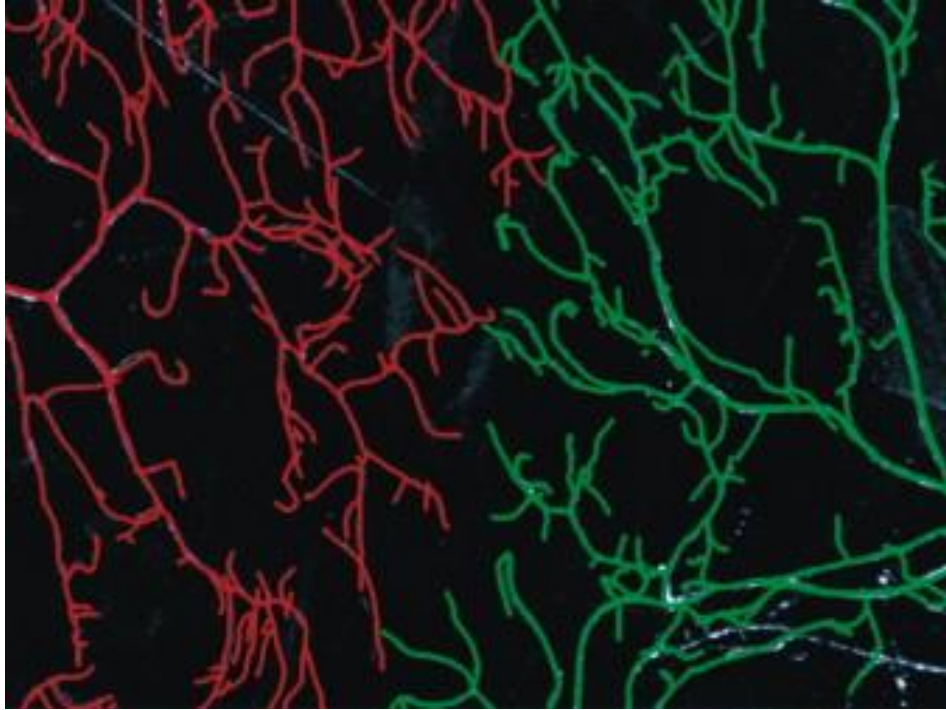


Figure 22.8

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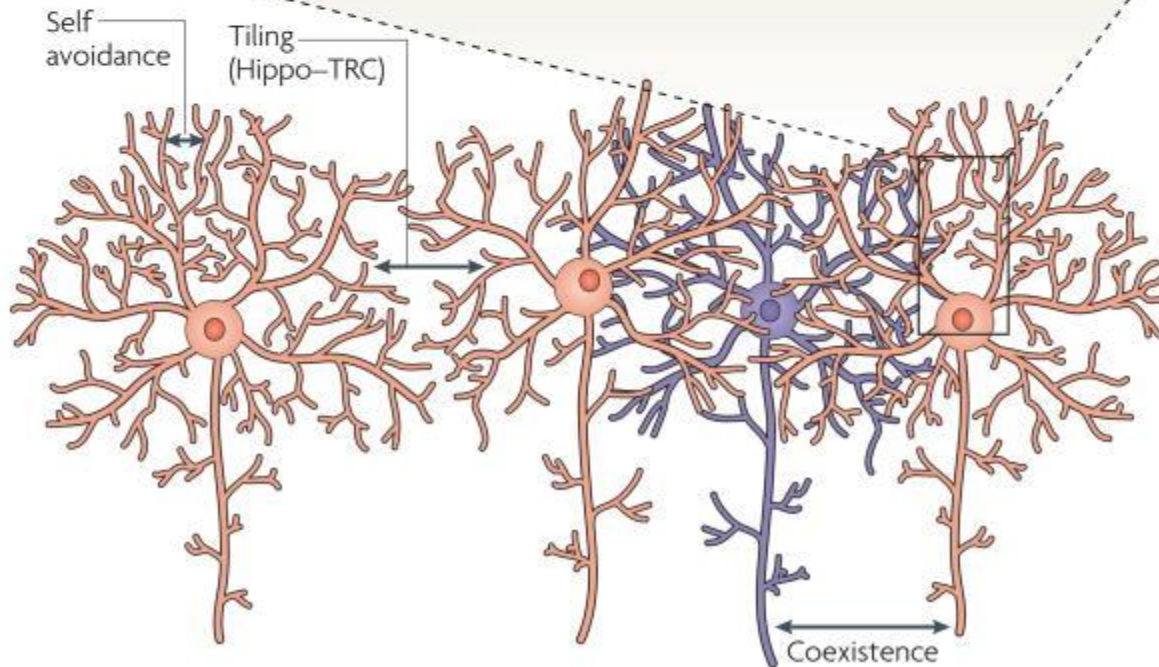
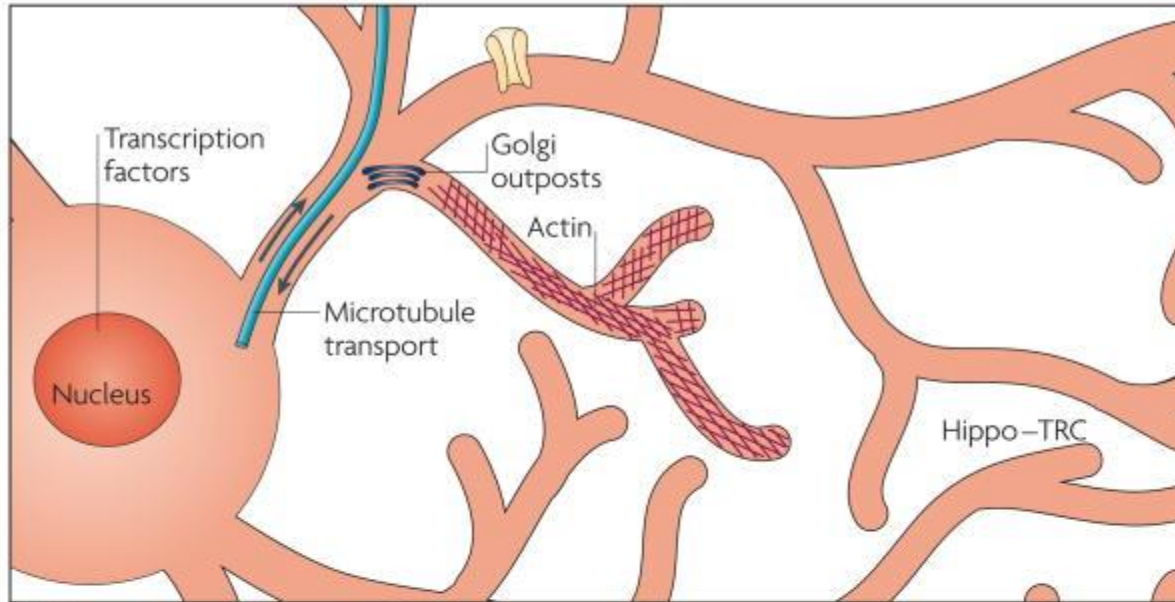
Multiple molecular mechanisms regulate dendritic arborization



Tiling

Figure 1 Tiling The dendrites of two dendritic arborization (da) neurons of the same class (class IV) do not overlap. The dendrites of those two neurons were colored red and green, respectively, to illustrate tiling. (Courtesy of Dr. Wes Grueber, UCSF.)

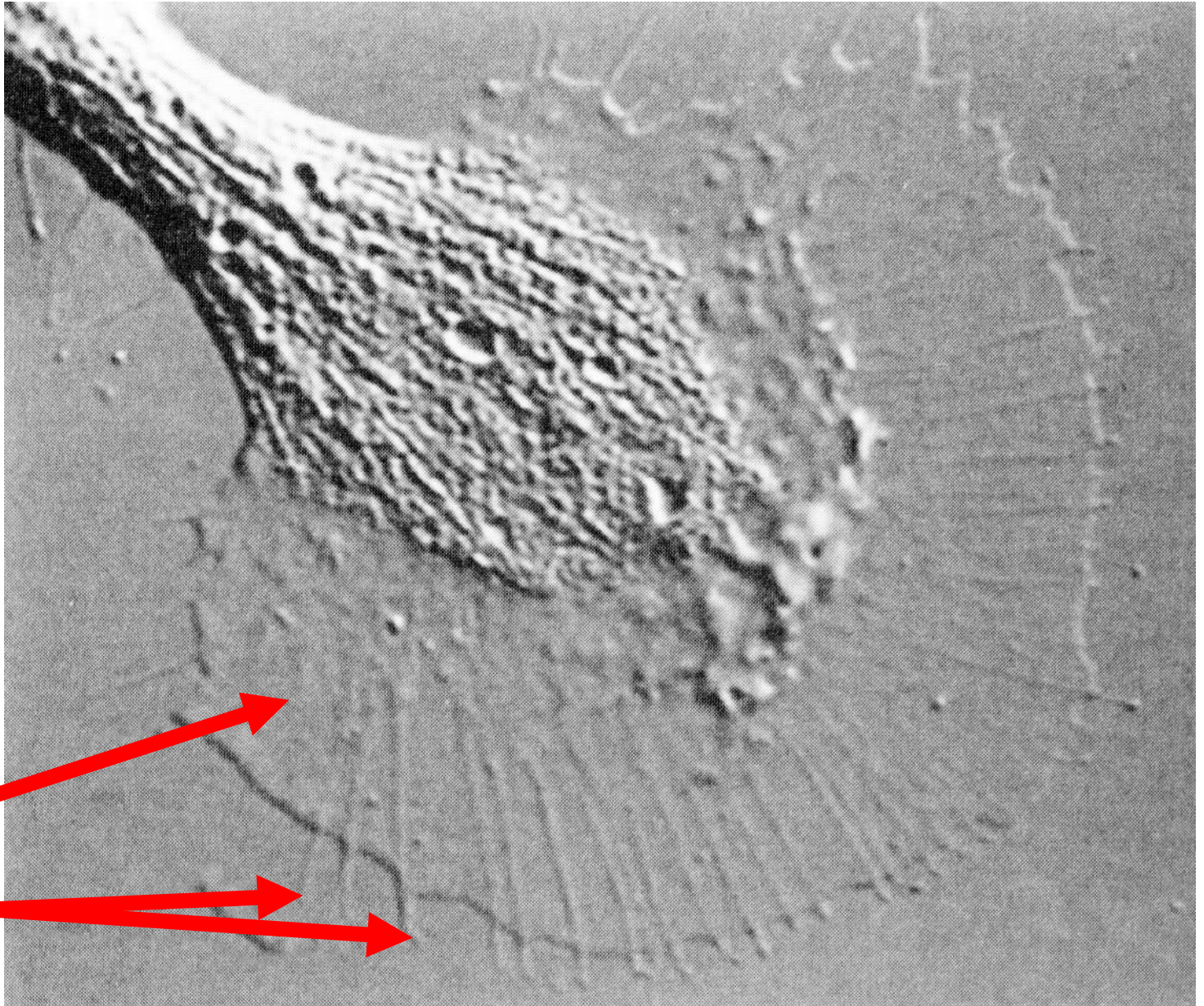
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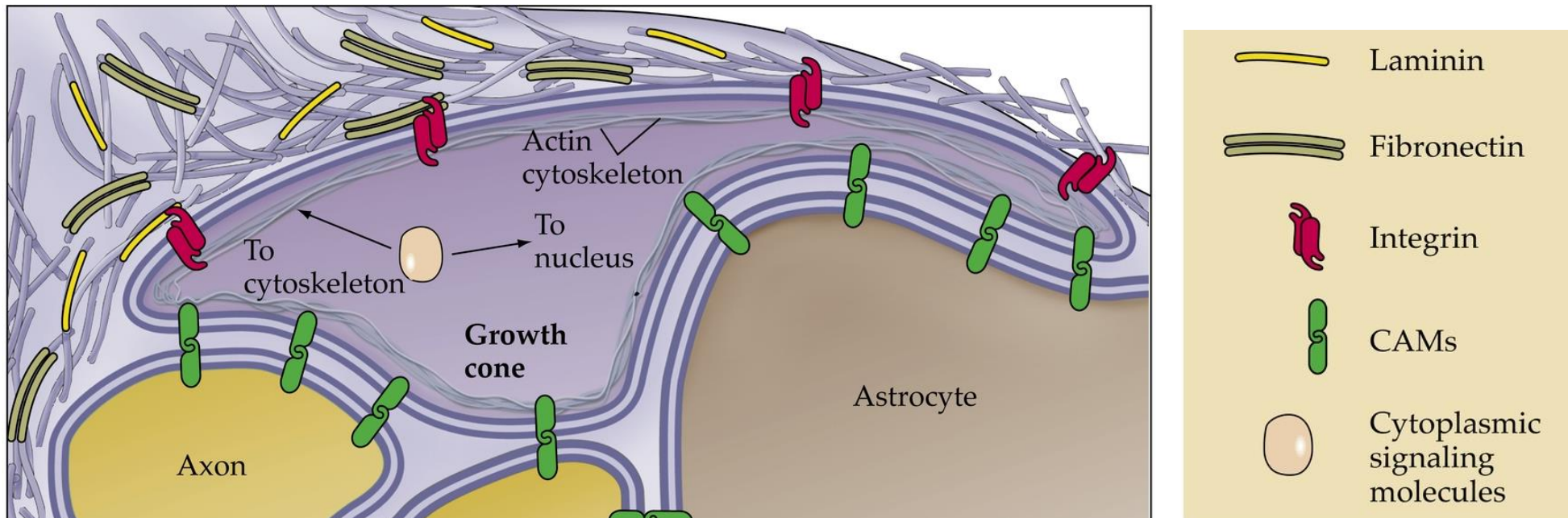
Neuronal Growth Cone



Lamellapodium

Filopodia

Molecular Interactions in Growth Cone Navigation



- Laminin and Fibronectin are major components of the extracellular matrix (ECM).
- Integrins mediate attachment between the cell surface and the ECM or other cells. Integrins are very diverse, consisting of heterodimers of 18 alpha and 8 beta subunits. They may signal as well as attach.
- Cell Adhesion Molecules (CAMs) mediate specific forms of attachment and signaling between specific types of cells.

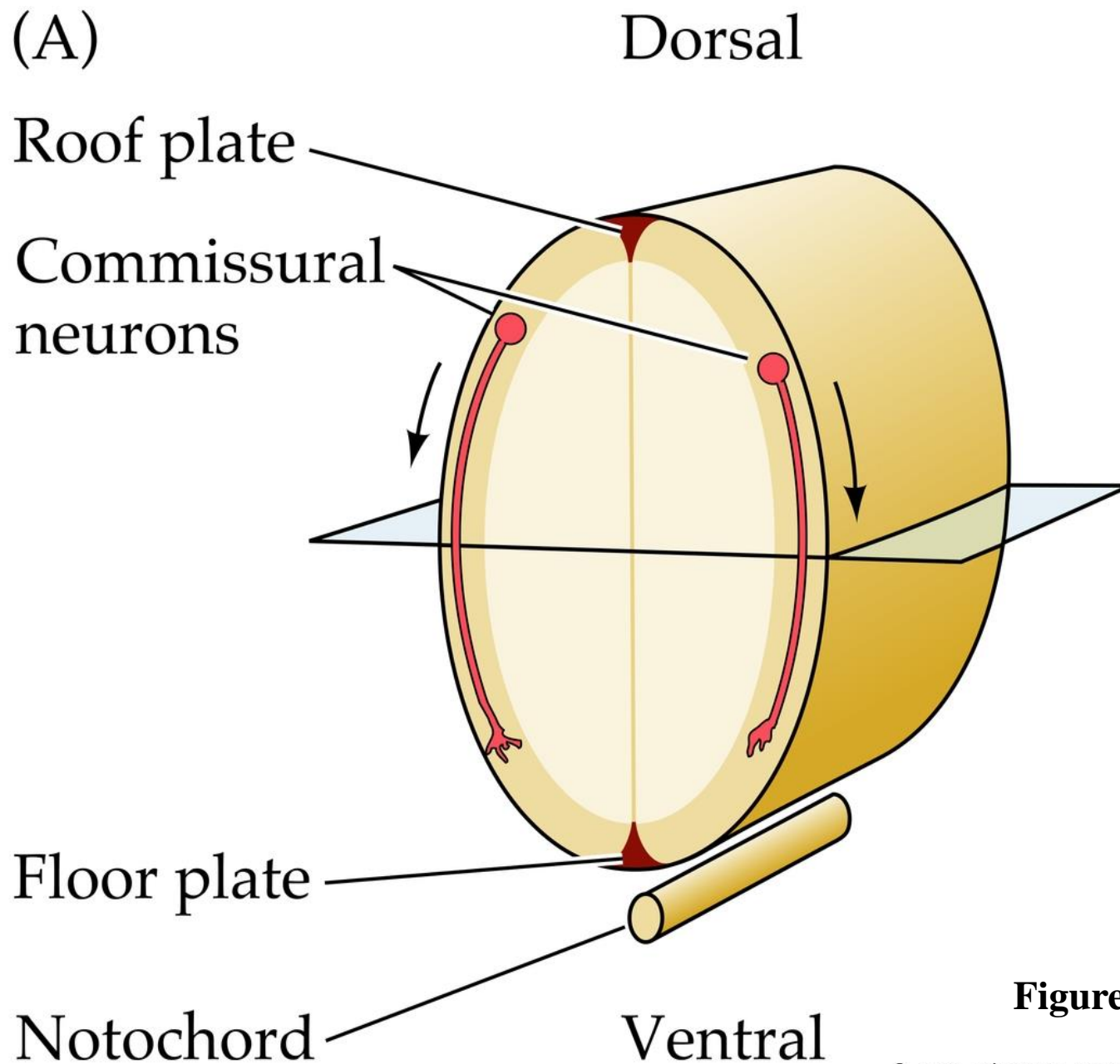


Figure 23.5 A

© 2001 Sinauer Associates, Inc.

Floor plate cells secrete the diffusible chemoattractant **netrin**, which attracts commissural axons to grow ventrally.

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Genetic and co-culture experiments show that many neurons recognize the types of cell with which they should make connections cell-autonomously and independent of neural activity.

Cells in bits of thalamus grown over, under, or to one side of bits of cortex in the same dish, even in TTX, have specific connections to layer 4 cells.

The reeler mouse has a disorganized but inside out cortex because of a failure in migration. Nevertheless its thalamocortical and corticosubcortical and many intracortical connections are correct, despite the fact that the cells are in the wrong place. The neural circuit that is assembled in primary visual cortex gives responses with near-normal specificity.

Mutant mice without synaptic release seem to have normal anatomy.

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Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

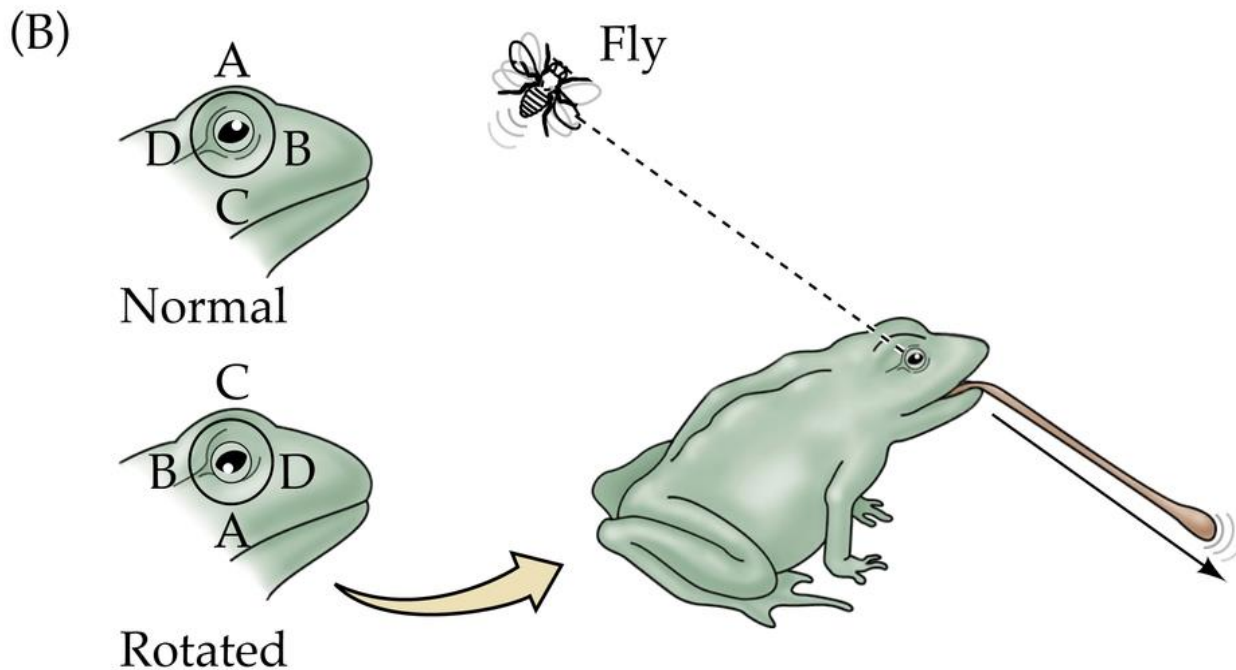
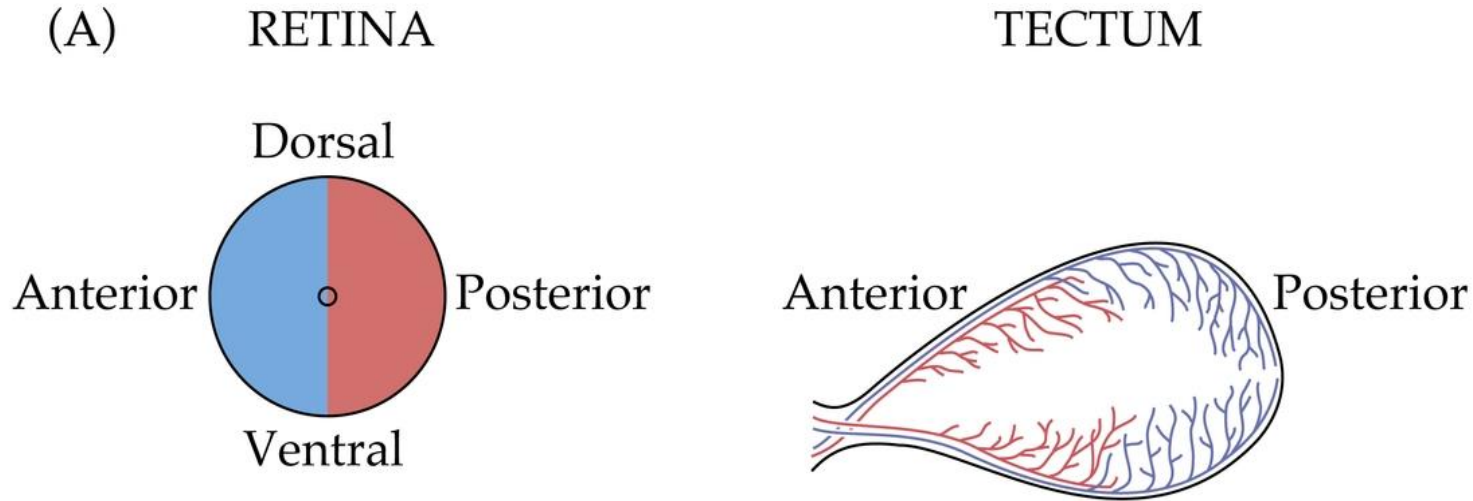


Figure 23.6 A B

Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

Temporal axons are repelled by posterior tectum

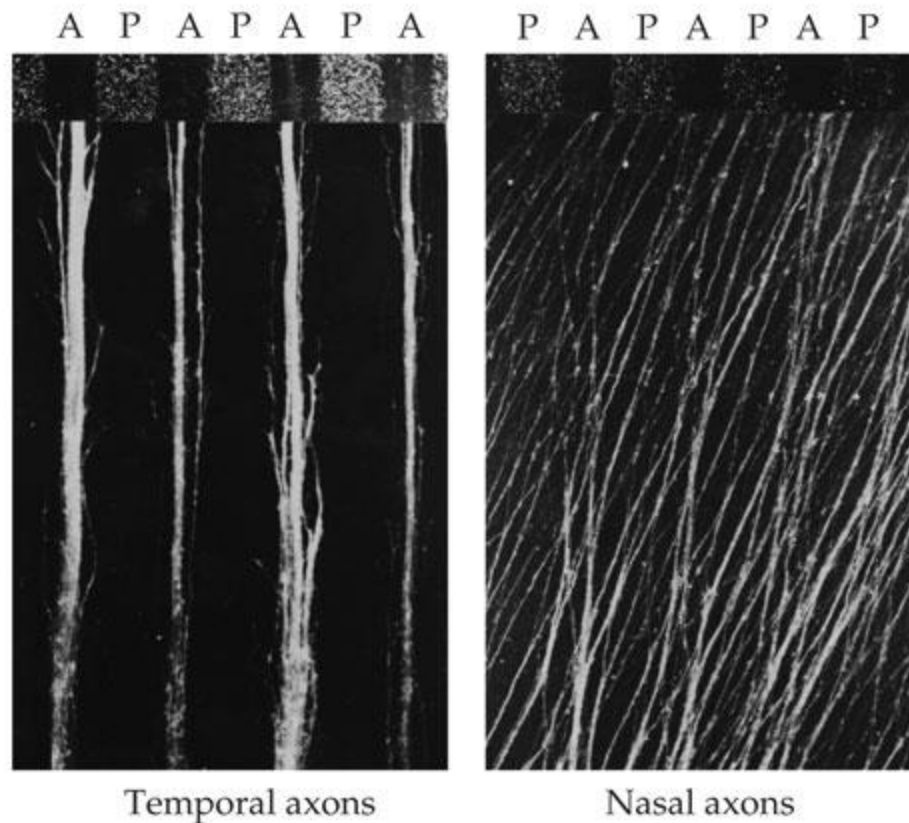
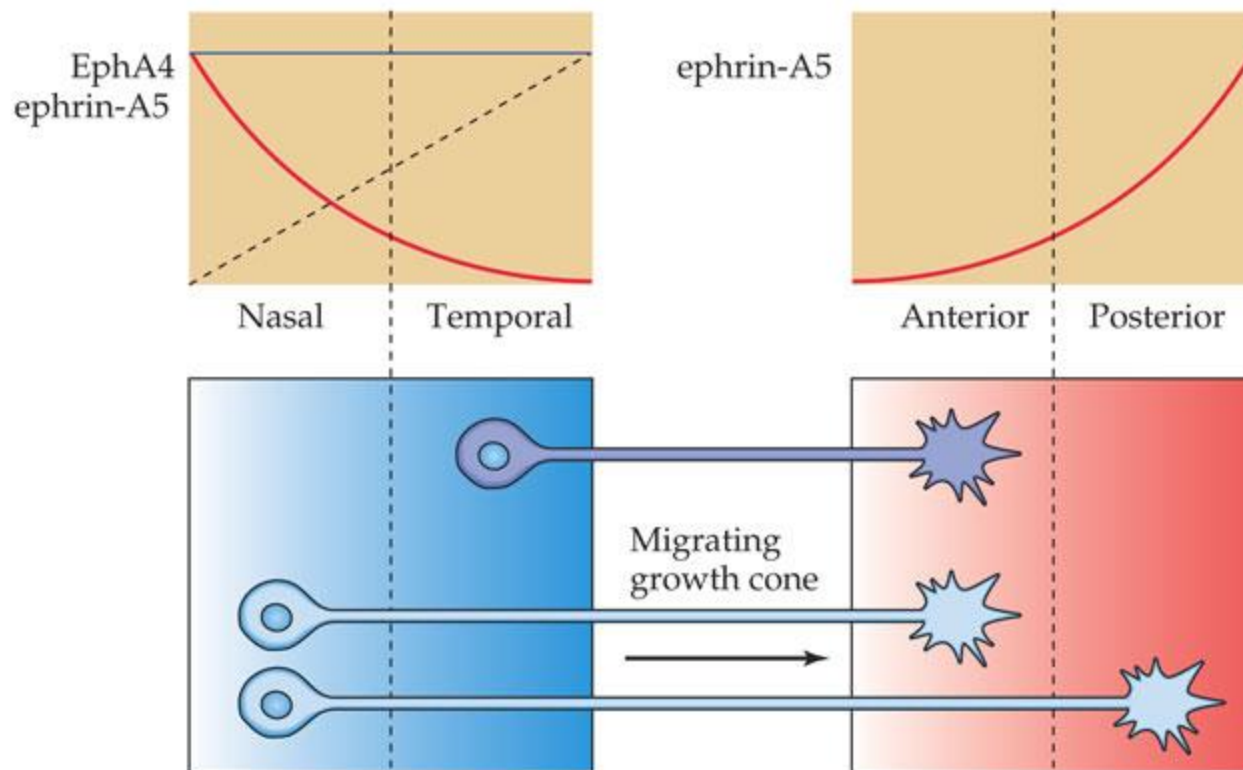


Figure 23.6 C

Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

The repulsion of temporal axons by posterior tectum is caused by opposite gradients of Eph-A and ephrin-A. This ensures orderly maps.



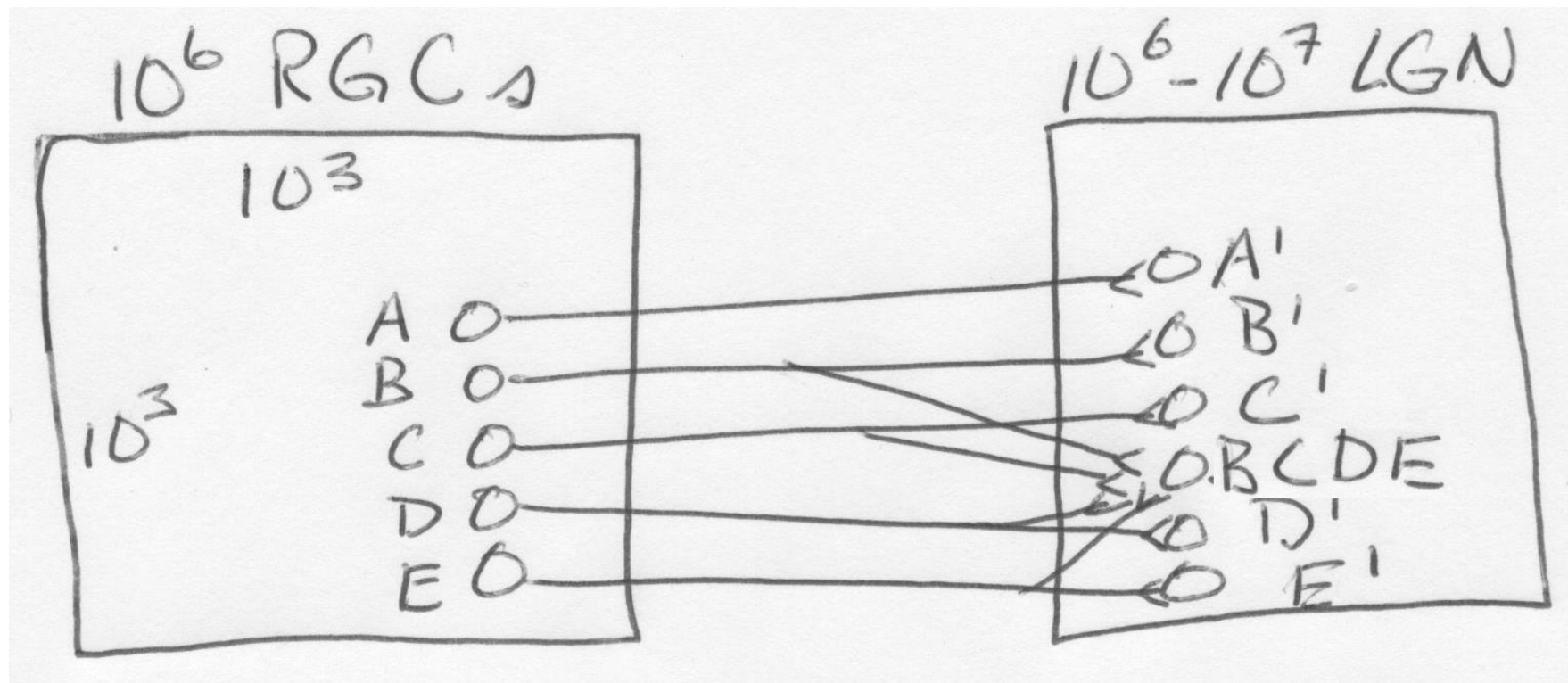
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At least some maps are essentially perfect.

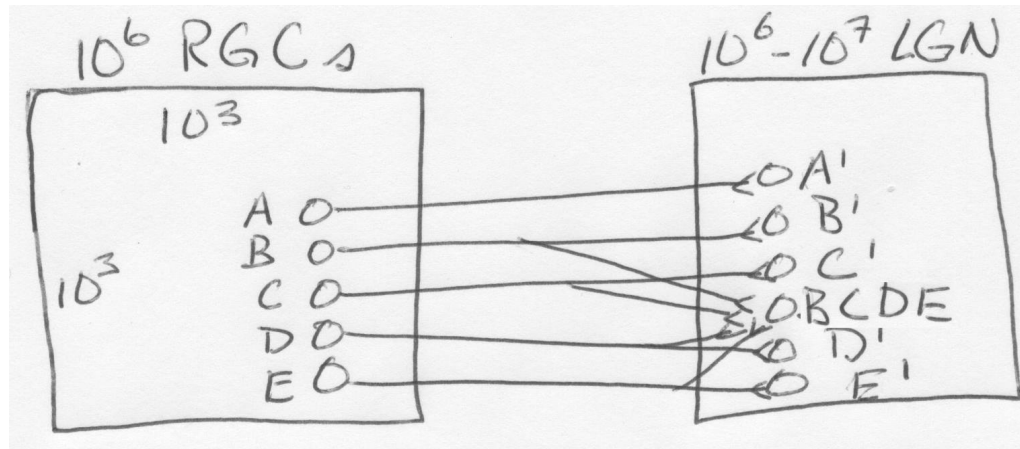
In the fly, the visual system maps are formed by a process resembling the growth of crystals.

Not so in the mammalian visual system, where in between the eye and the LGN, neighbor relations between axons do not persist, yet physiology shows that adult retinogeniculate connections are essentially perfect: about half are single-input RFs, and multi-input RFs are perfectly compact.

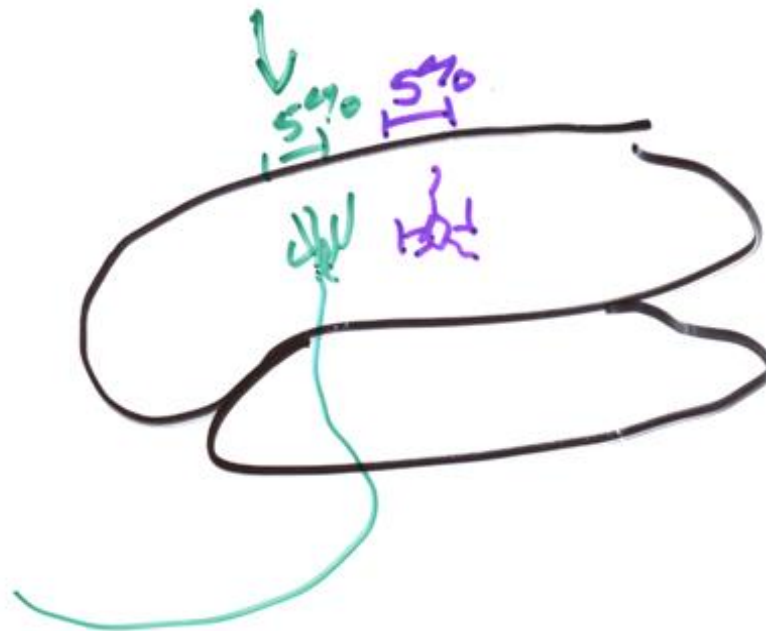


How can we reconcile this precision seen in physiology with the shaggy axonal and dendritic arbors seen by anatomy?

The apparent precision in connectivity is much better than the size of the axonal or dendritic arbors.

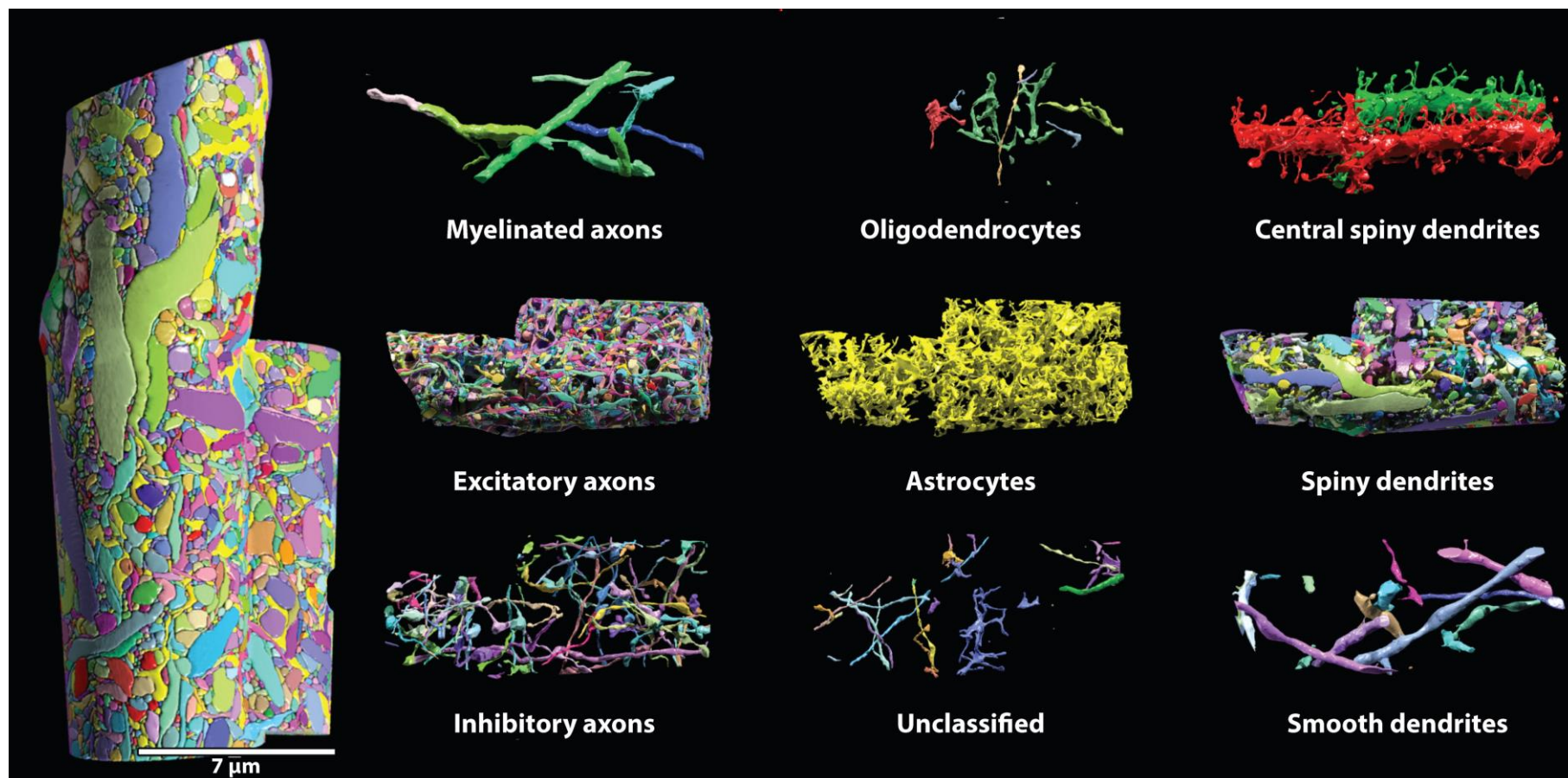



Precision ~
0.1%



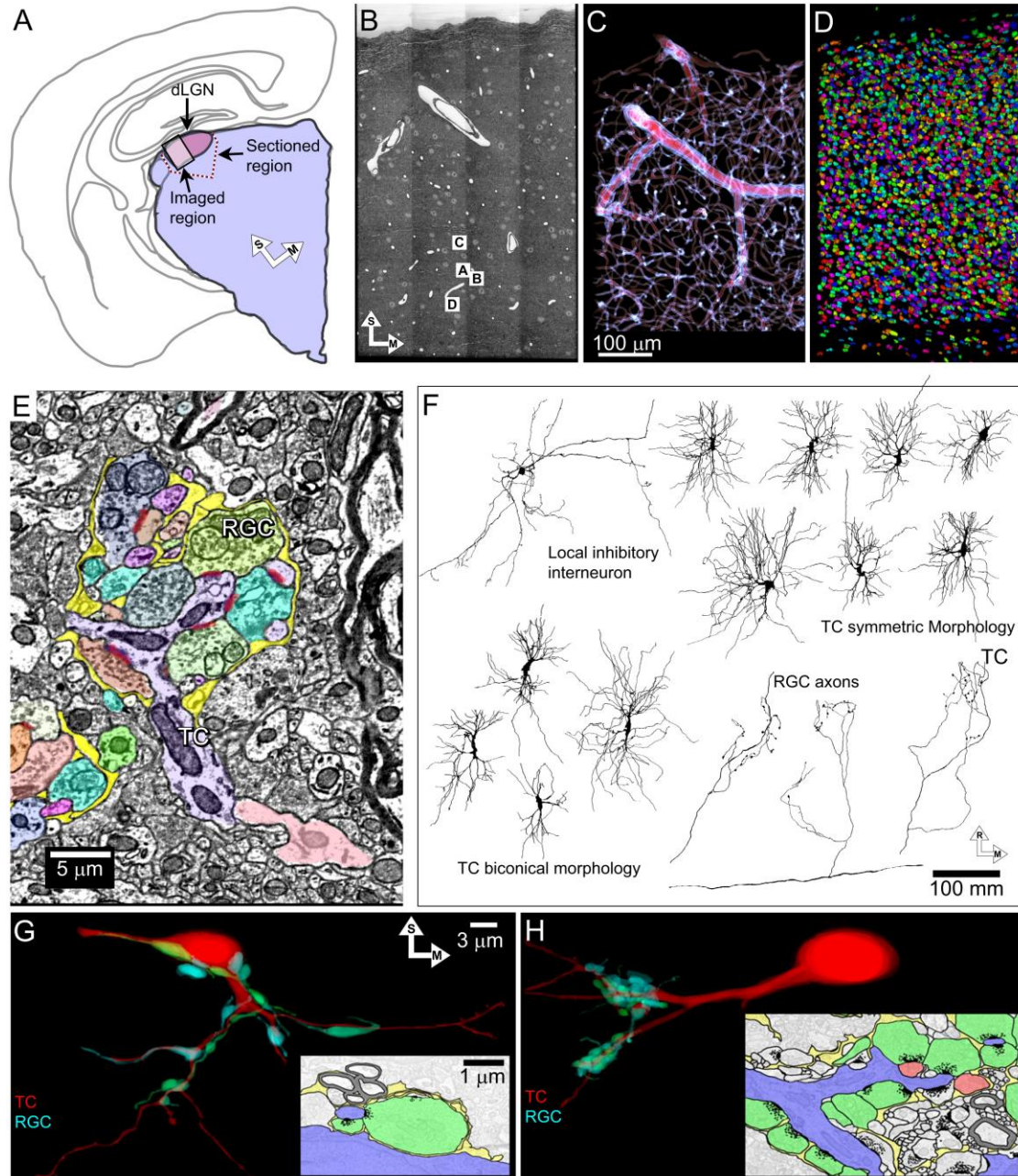
Precision ~ 5%,
apparently

The reality is more complicated, as we are just beginning to learn from EM reconstructions, some dense as below:

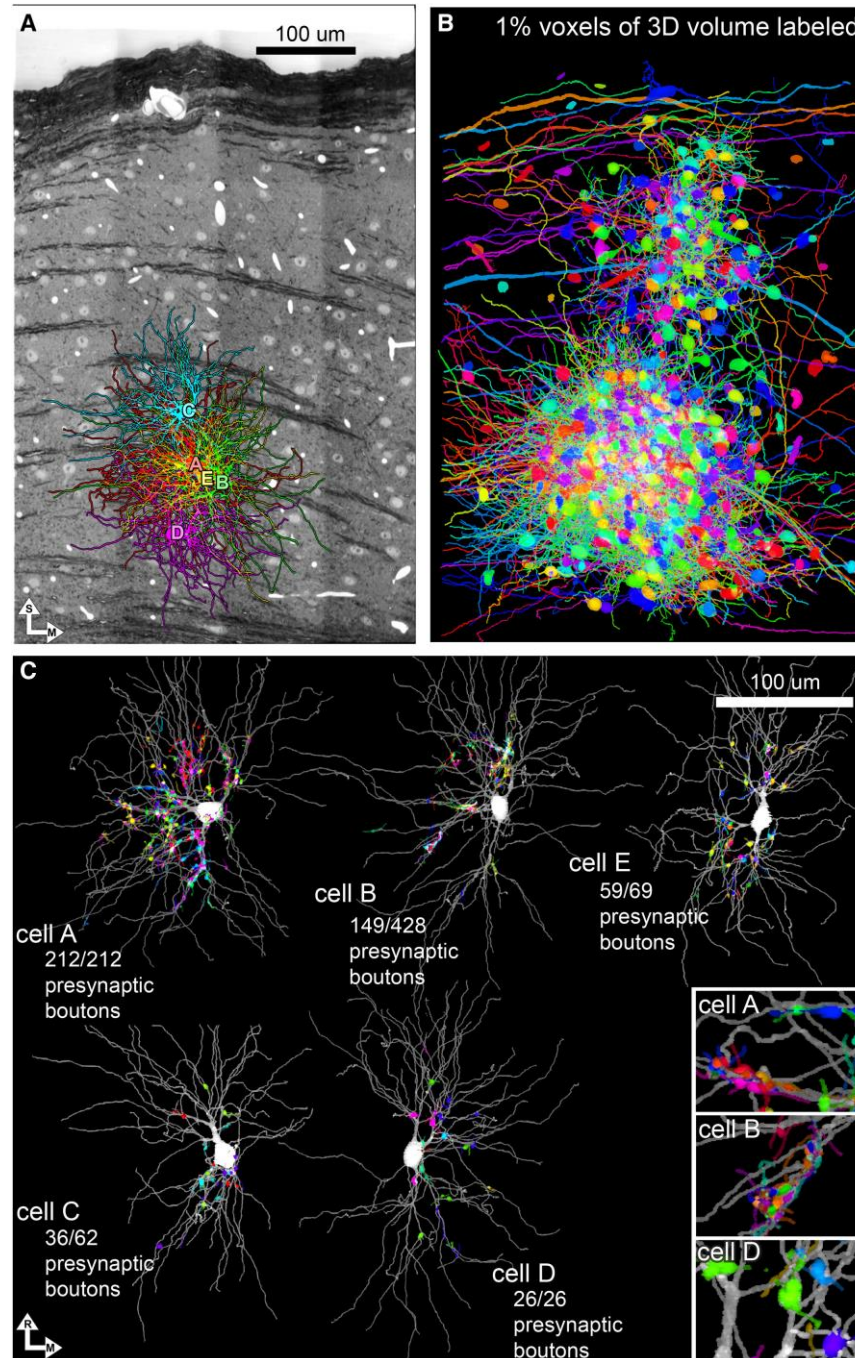


 Swanson LW, Lichtman JW. 2016.
Annu. Rev. Neurosci. 39:197–216

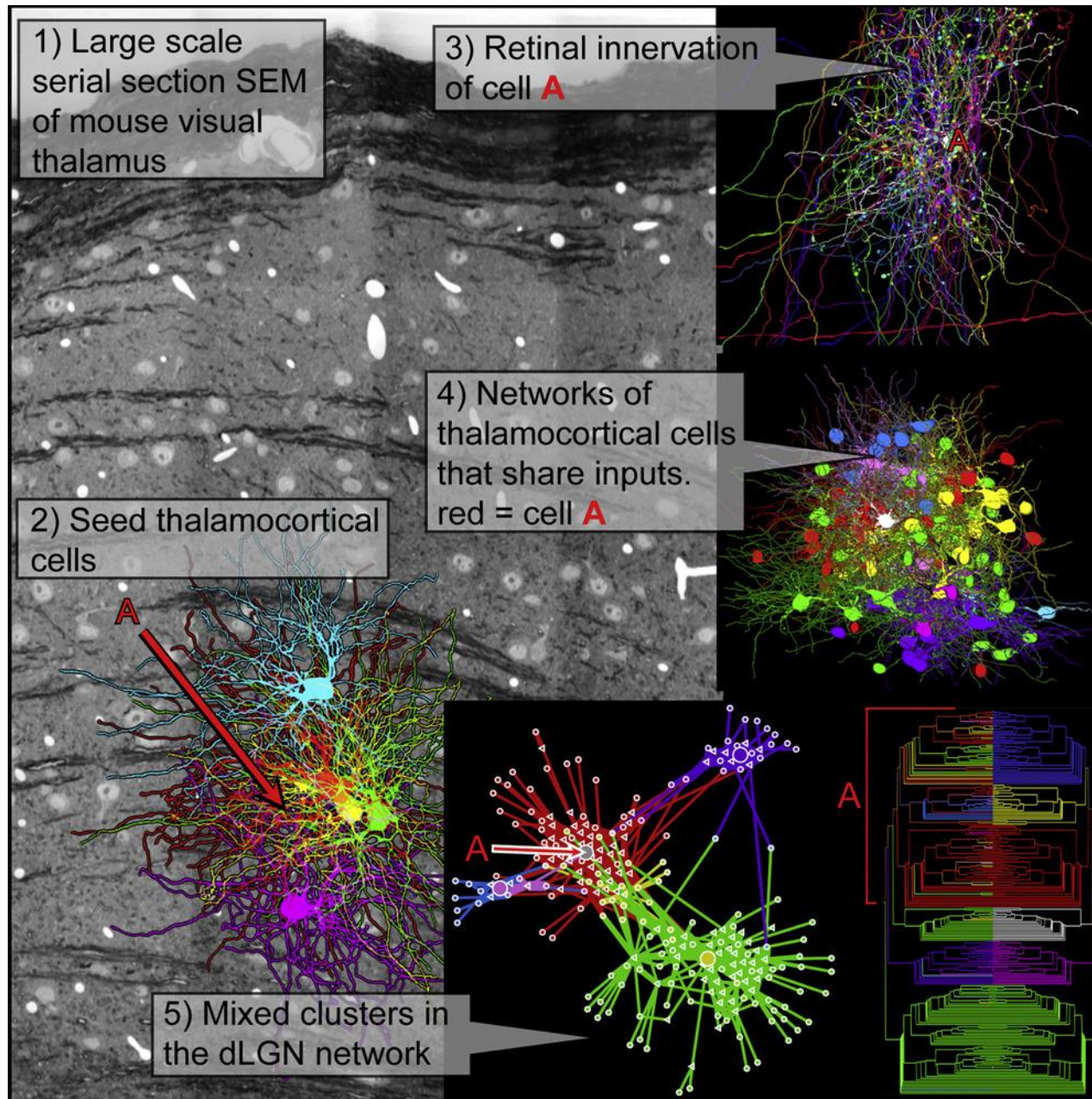
And some sparse, with interesting analyses



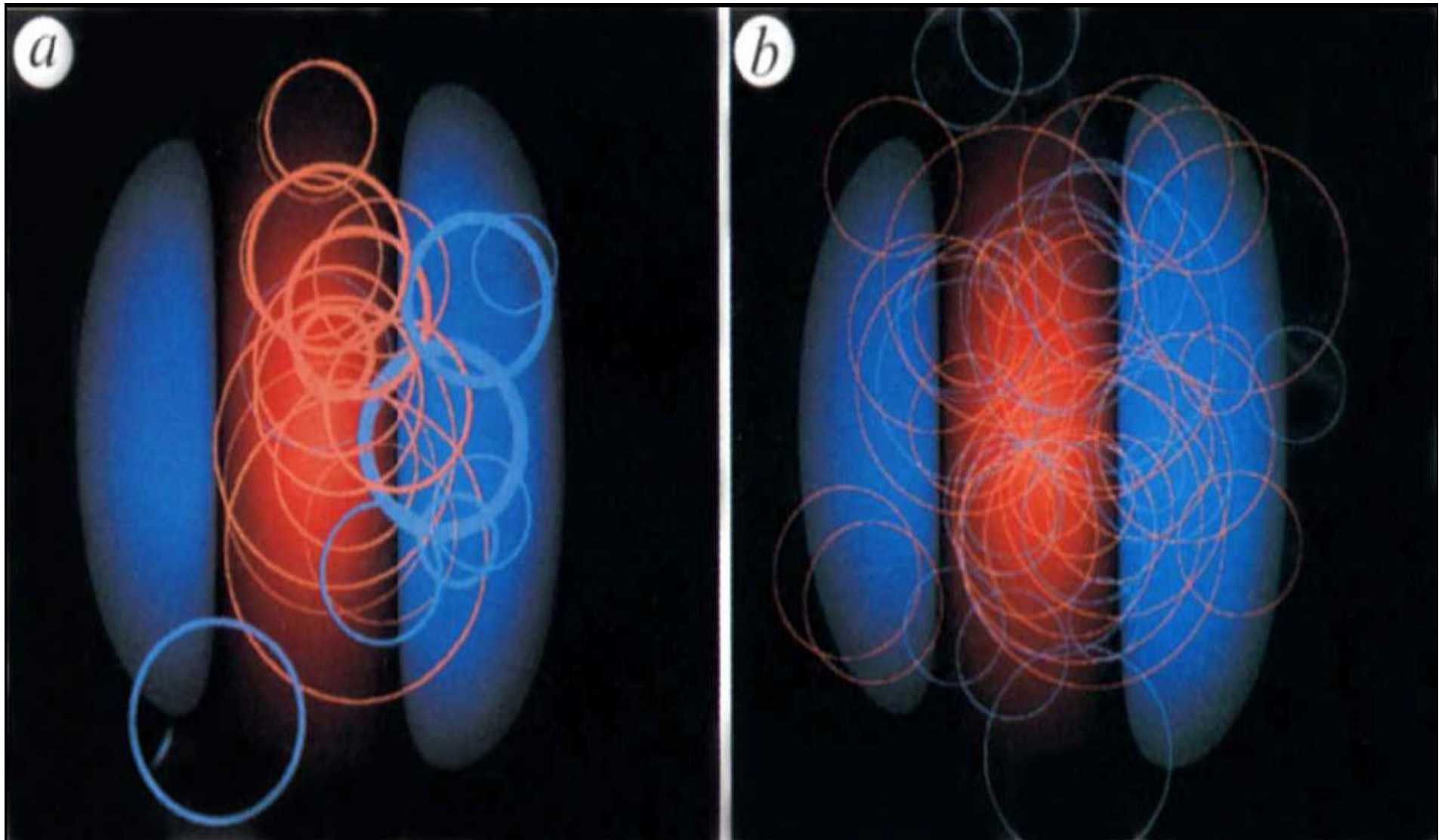
Connectomics has now arrived at the EM scale



Some steps in a connectomic analysis



Monosynaptic Geniculate Inputs to Simple Cells in Cat V1 from Cross Correlation
Connected Pairs Unconnected pairs



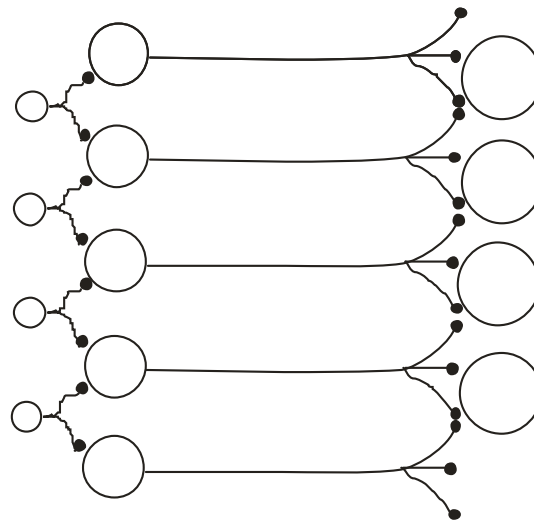
What signal is present at the cells of origin that could be used to attain such precision of connections in the target structure?

Neural activity is such a signal.

Willshaw, D. J & von der Malsburg, C. (1976) How Patterned Neural Connections Can Be Set Up by Self-Organization. PRSB 194: 431-445 showed that maps can be set up by either chemical labels that are shared among neighbors or by neural activity.

Correlated activity of neighbors in the input array plus a reinforcement of the connections that are effective in driving the target cells can produce map refinement. Hebb's rule.

Input -----far away-----Output



A big controversy in systems neuroscience in the early 1970s was the initial specification and the plasticity of maps, particularly that of the eye onto the optic tectum (superior colliculus) of fish and frogs (*Xenopus laevis*).

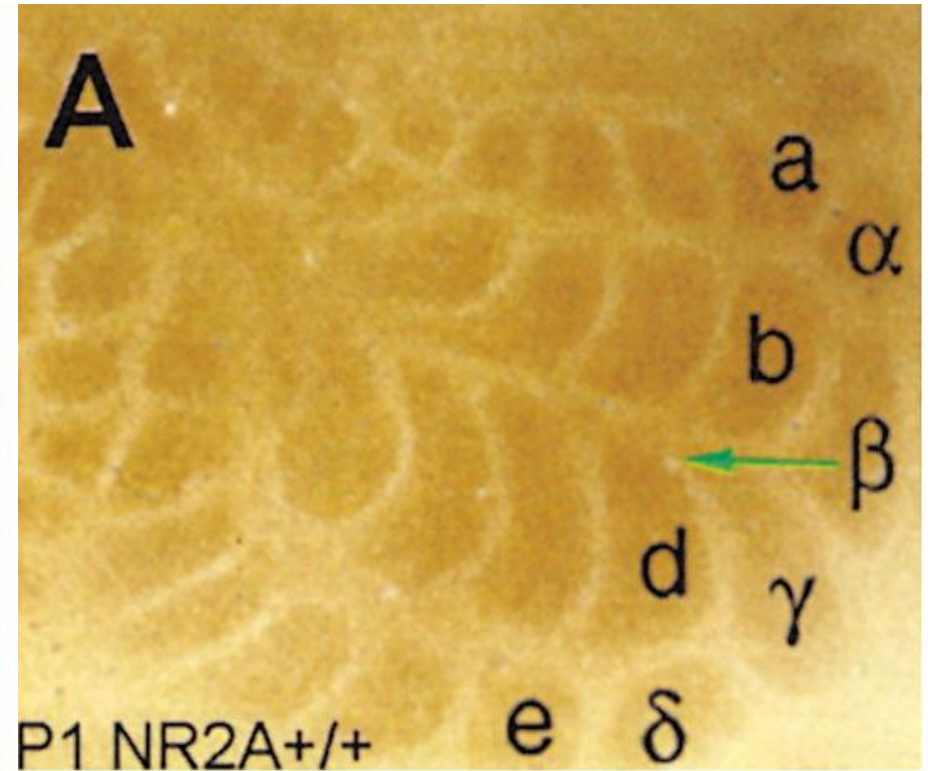
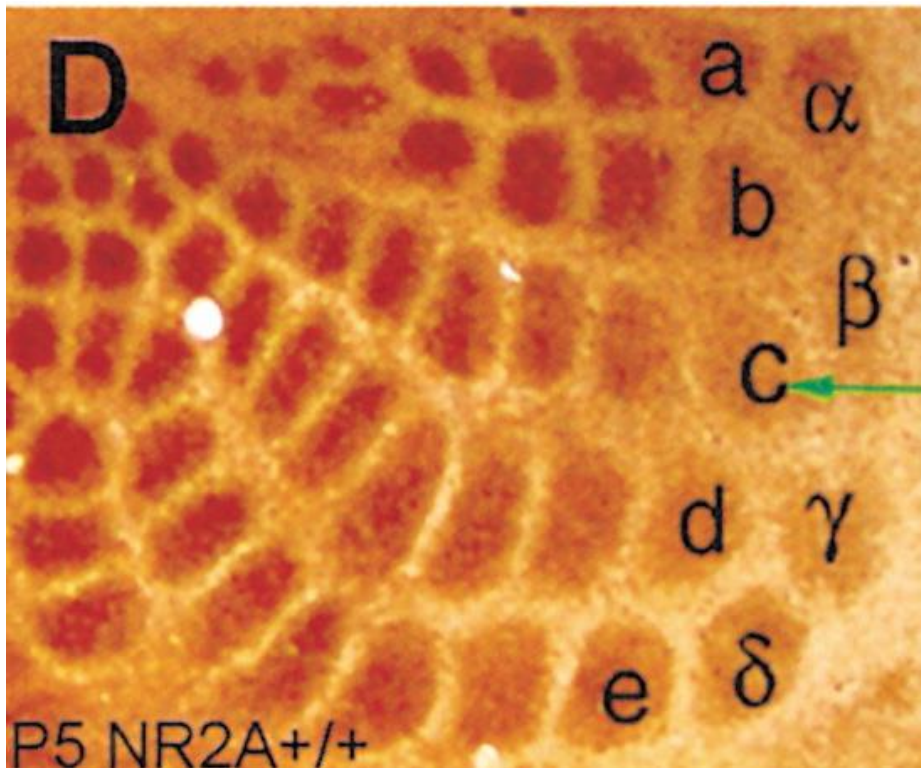
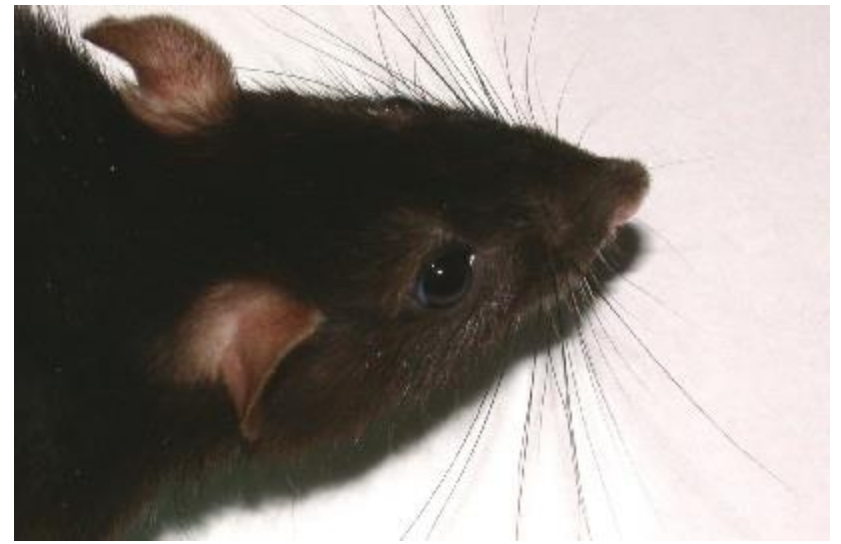
One side claimed that it was possible to re-specify the axes of the maps by transplantation of the eye rudiment onto the flank during a critical period in early life.

Everyone agreed that the initial map in these species could be compressed or expanded after partial lesions of eye or tectum.

What does it take to build a brain?

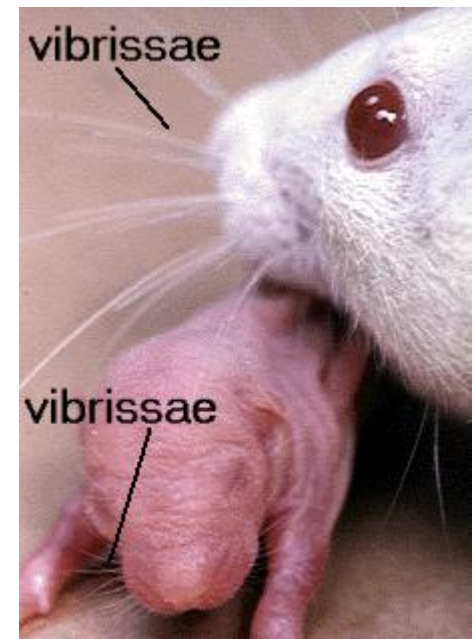
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Plasticity of “whisker barrels”
in primary somatosensory
cortex of mouse during the
first few days after birth



Lu et al (2001) Neuron

Critical period for “whisker barrel” plasticity in primary somatosensory cortex



Lesion of row C whisker follicles performed at postnatal ages below, serotonin transporter antibody shows thalamocortical afferents at P7-P9

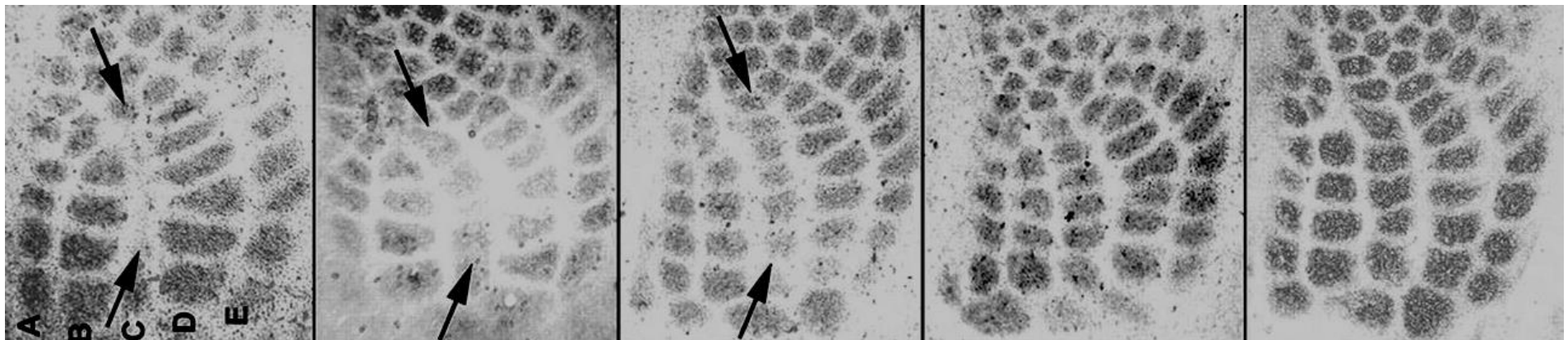
P0

P2

P3

P4

P5



There is a Critical Period for Learning Language

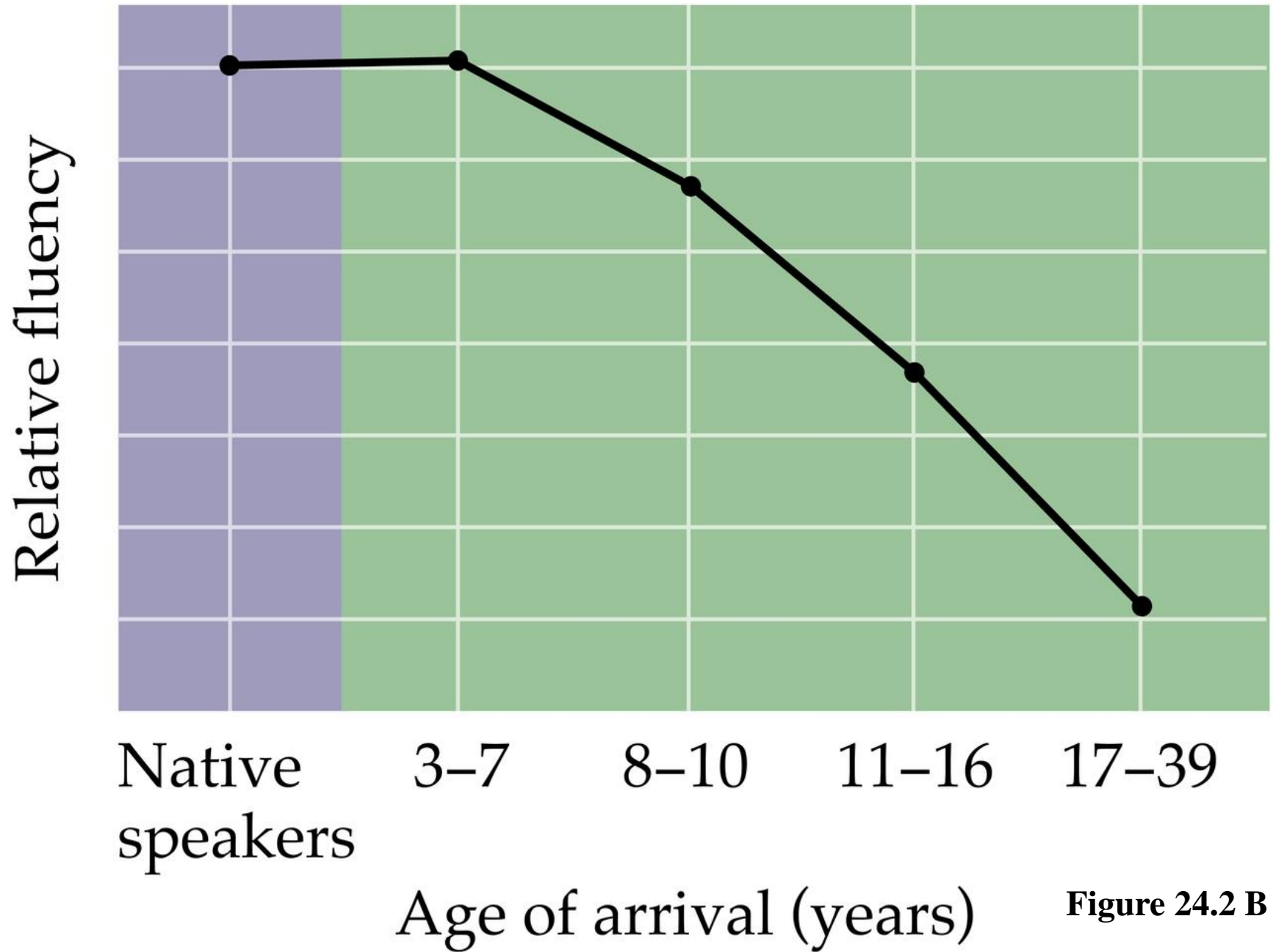
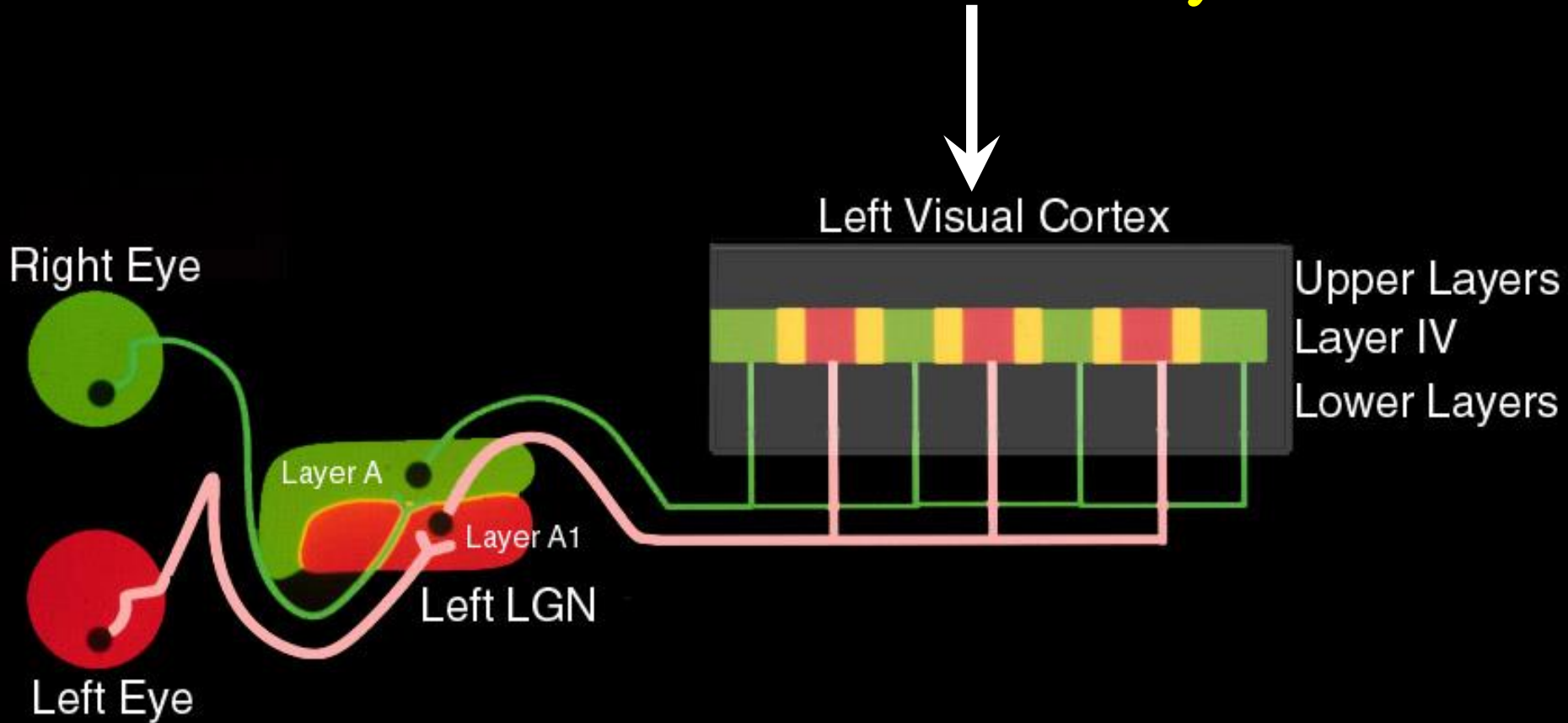
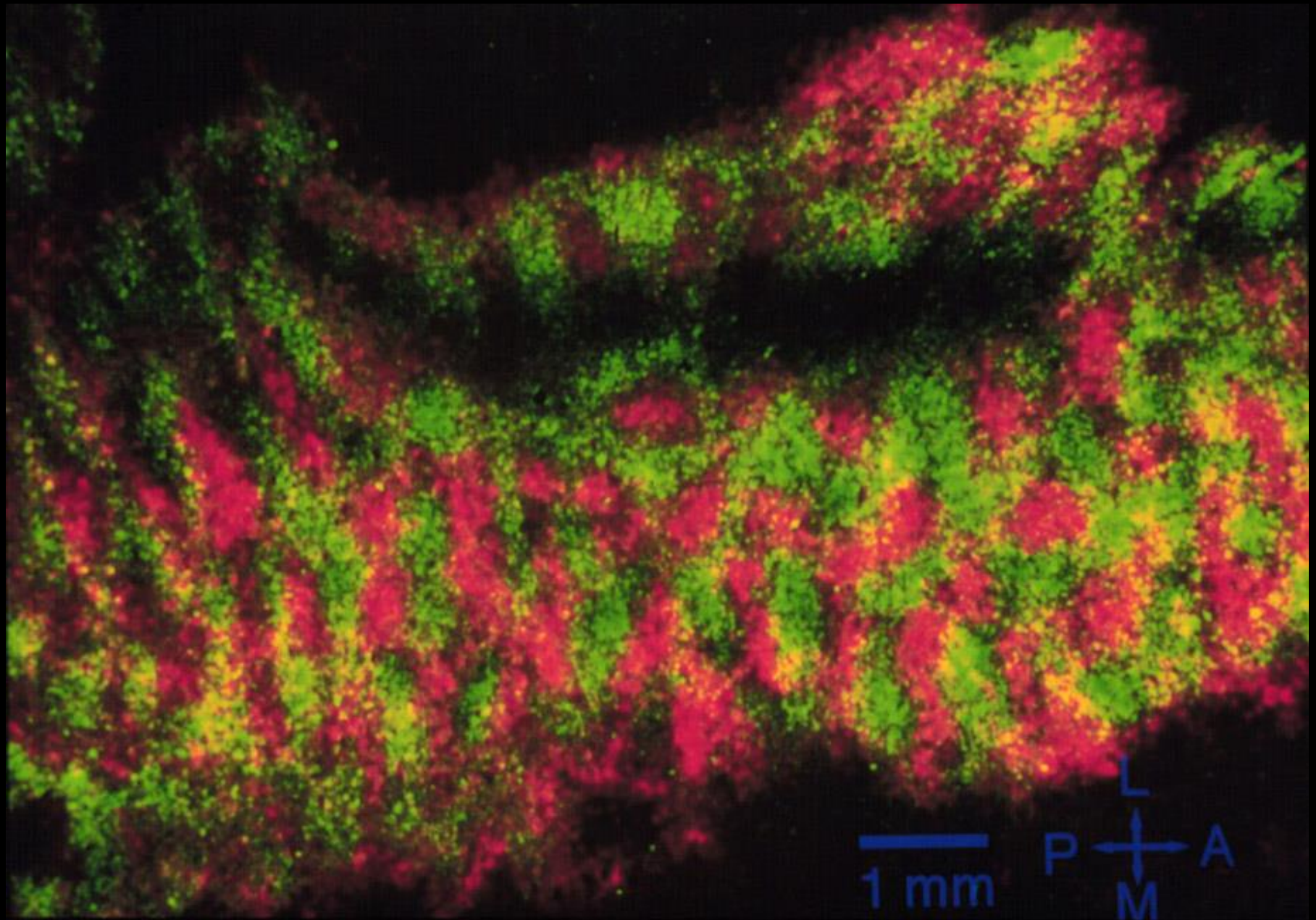


Figure 24.2 B

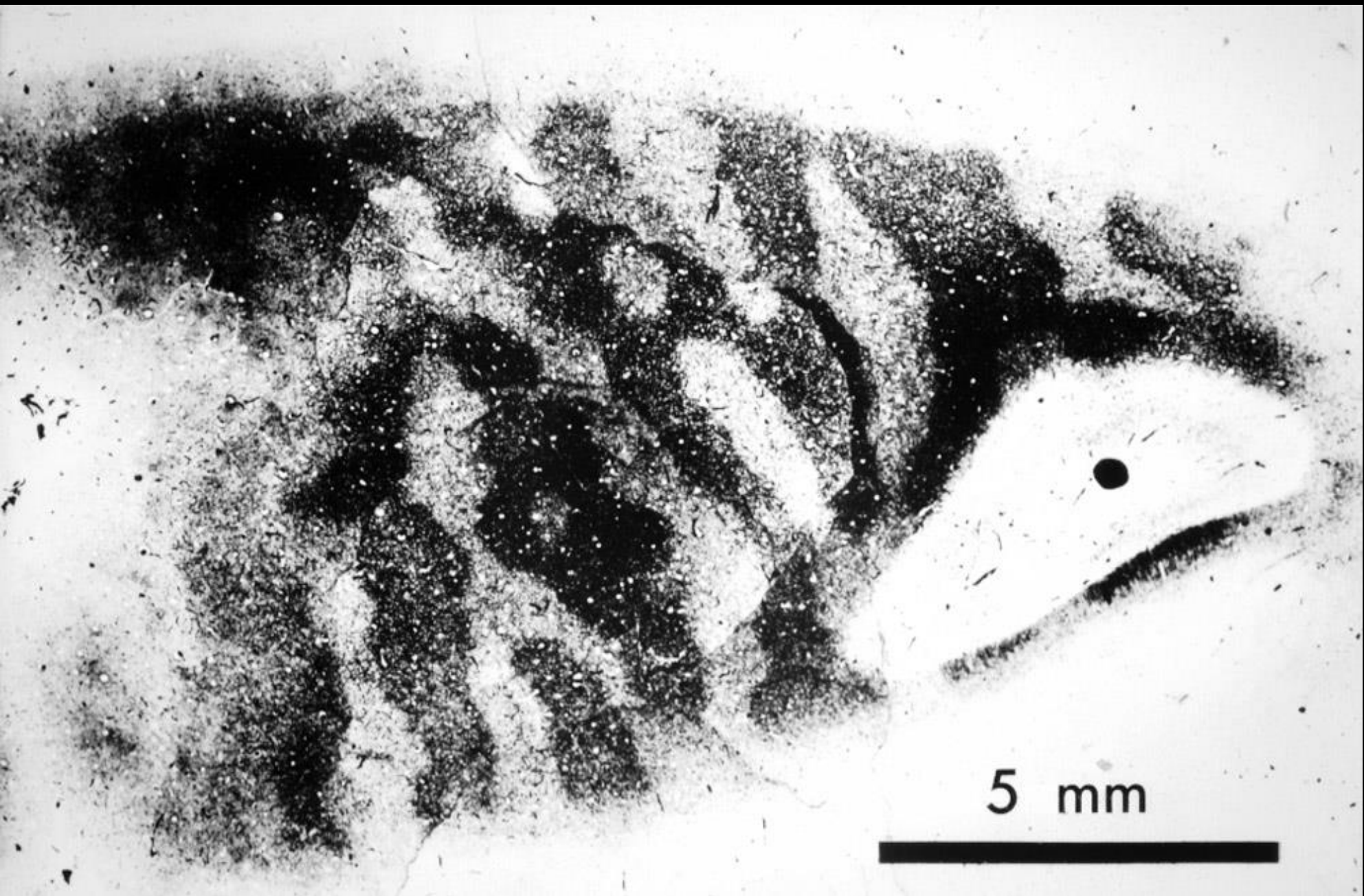
Outline of Geniculocortical Visual System



Normal Cat Ocular Dominance Columns

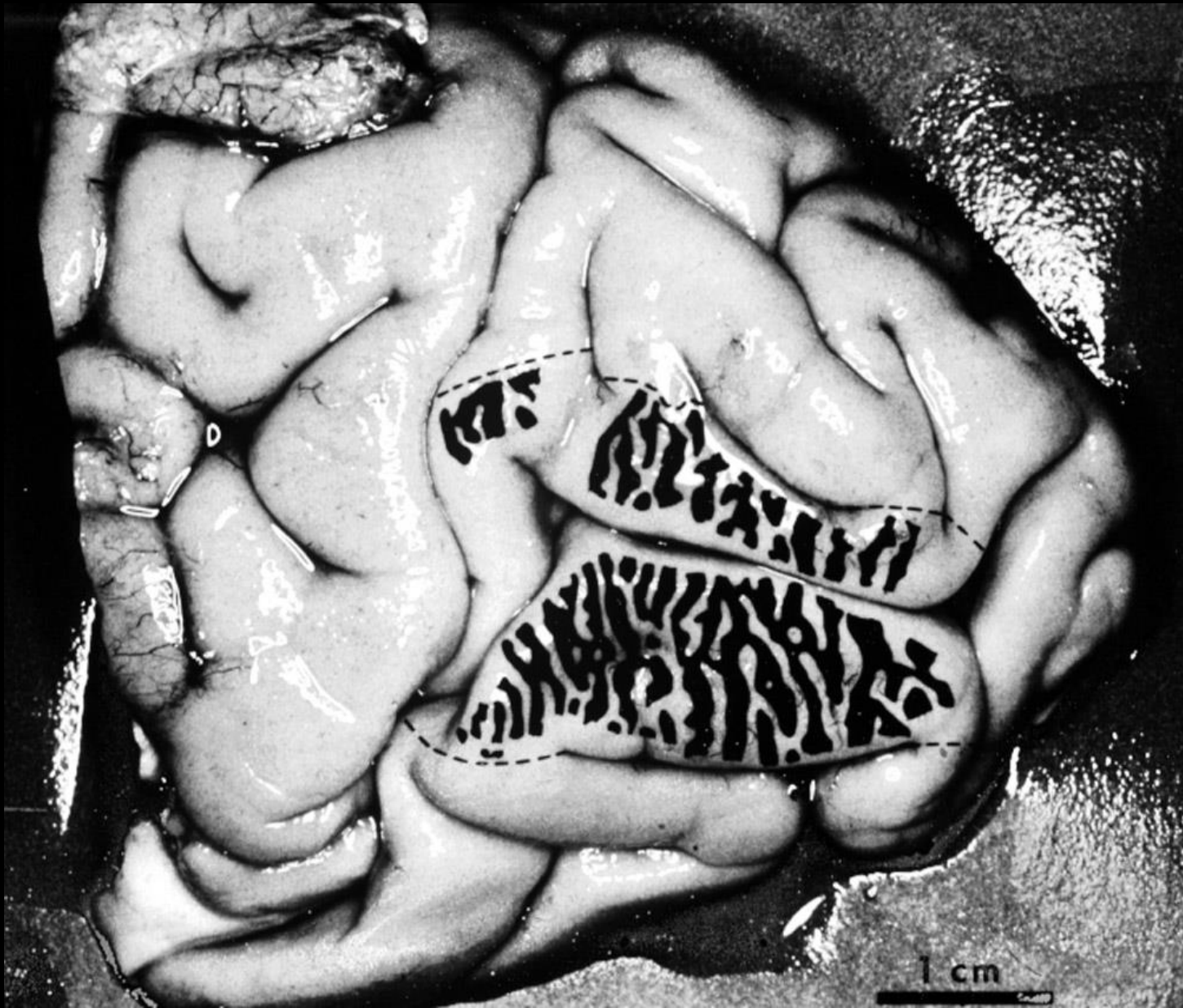


Human Ocular Dominance Columns



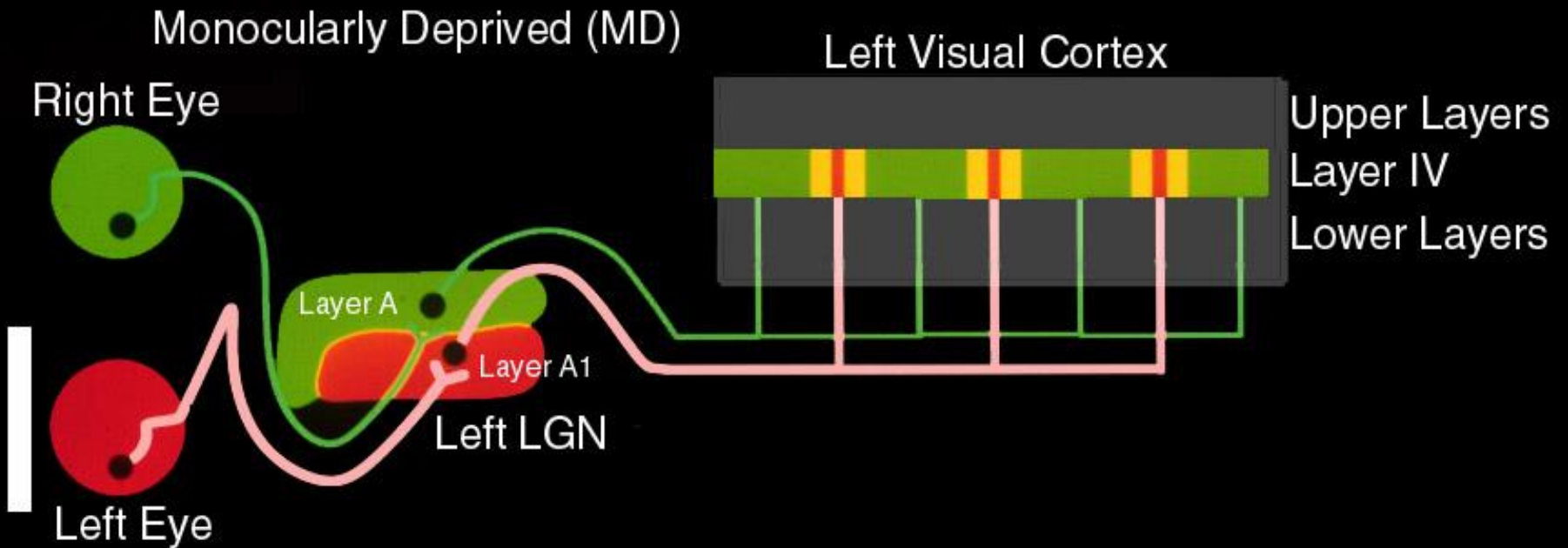
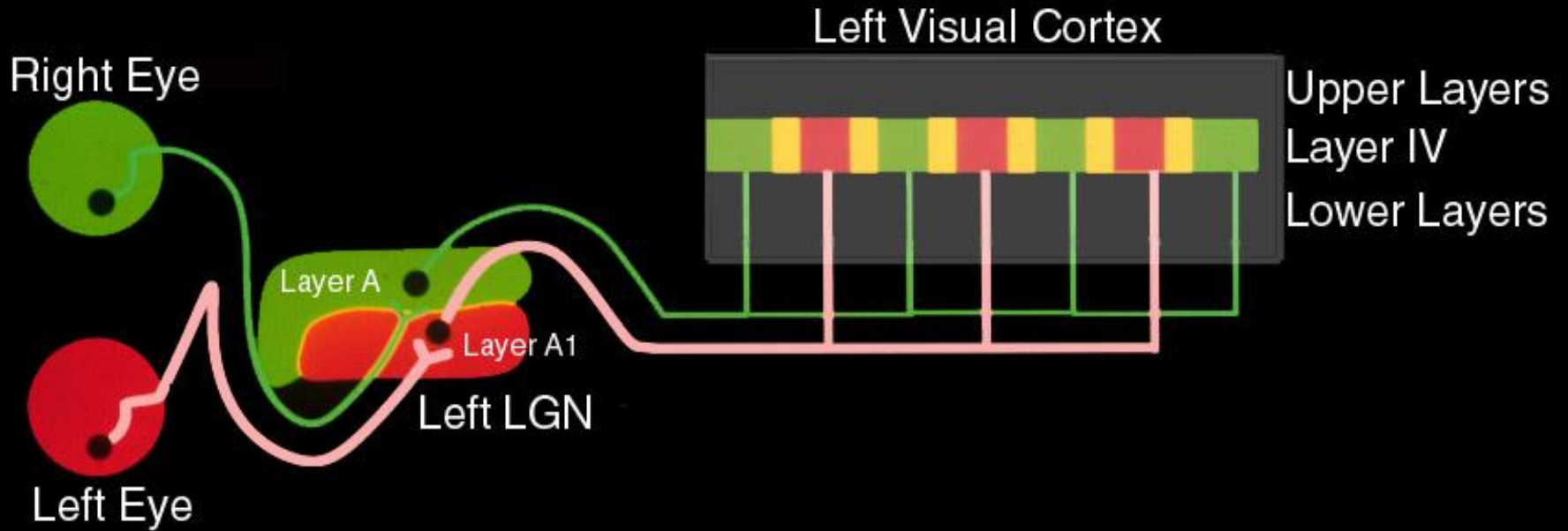
Courtesy of Dr. Jonathan Horton, UCSF

Human Ocular Dominance Columns Drawn Onto Photograph of Brain



Courtesy
of Dr.
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Ocular Dominance Plasticity in the Cat



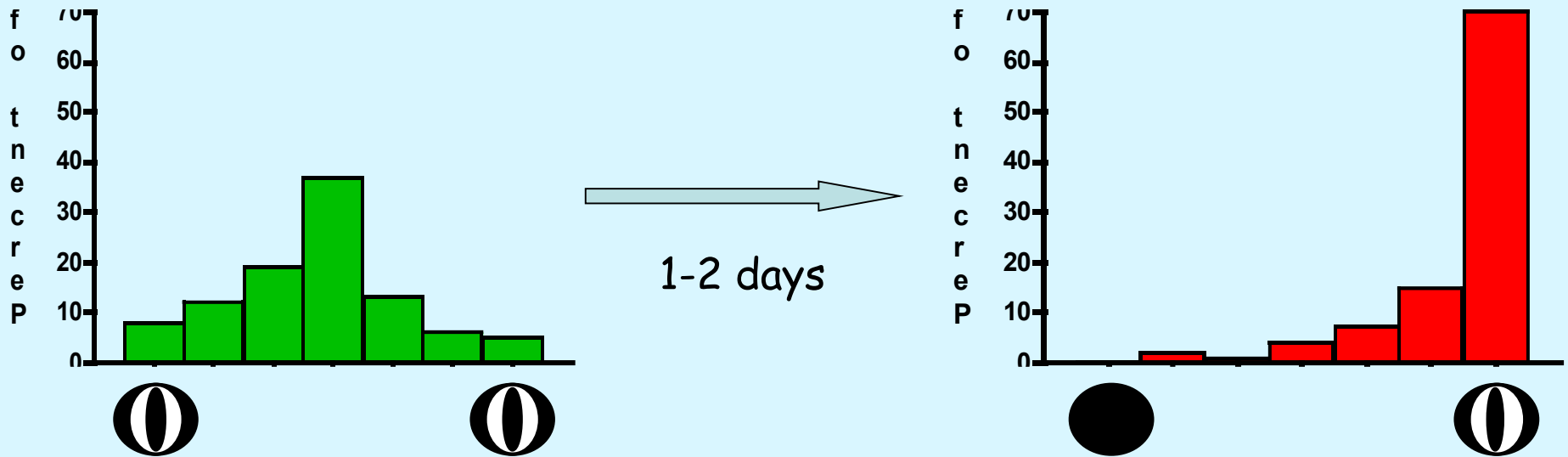
Monocular visual deprivation shrinks the thalamic input to the cortex from the deprived eye. This process takes only one week, and results in the loss of at least half the input.



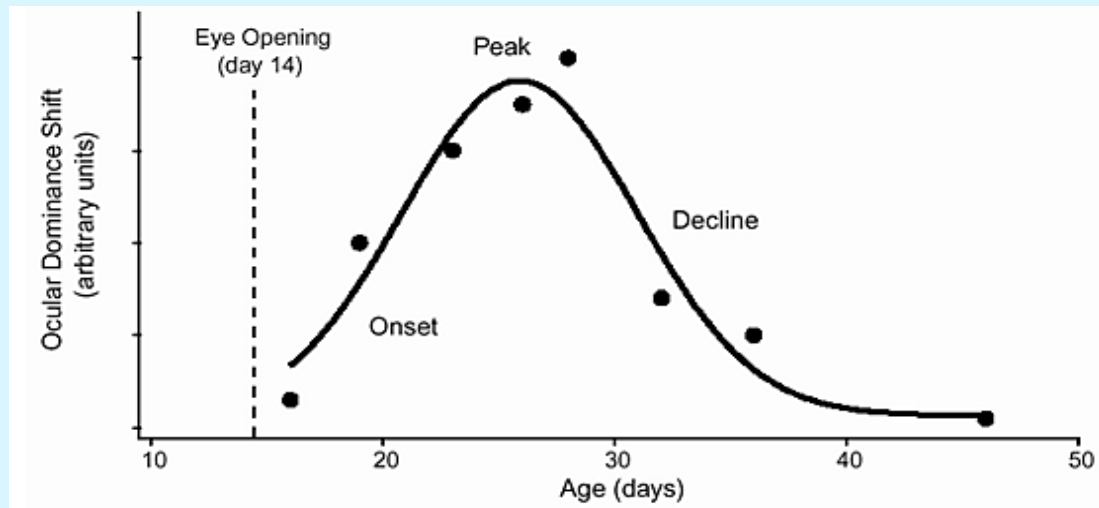
Changes in the visual responses of input-layer (layer 4) neurons matched these anatomical changes.

The process is competitive: closing both eyes does not cause such shrinkage.

Beyond the input layer of the cortex, physiological changes in responses to the two eyes were much faster, taking only 1-2 days.



These changes have a well-defined critical period. Deprivation outside the critical period has much less effect.



Correlated activity in the two eyes is necessary to maintain binocular connections.

Ocular Dominance Histograms From Normal and Strabismic Cats

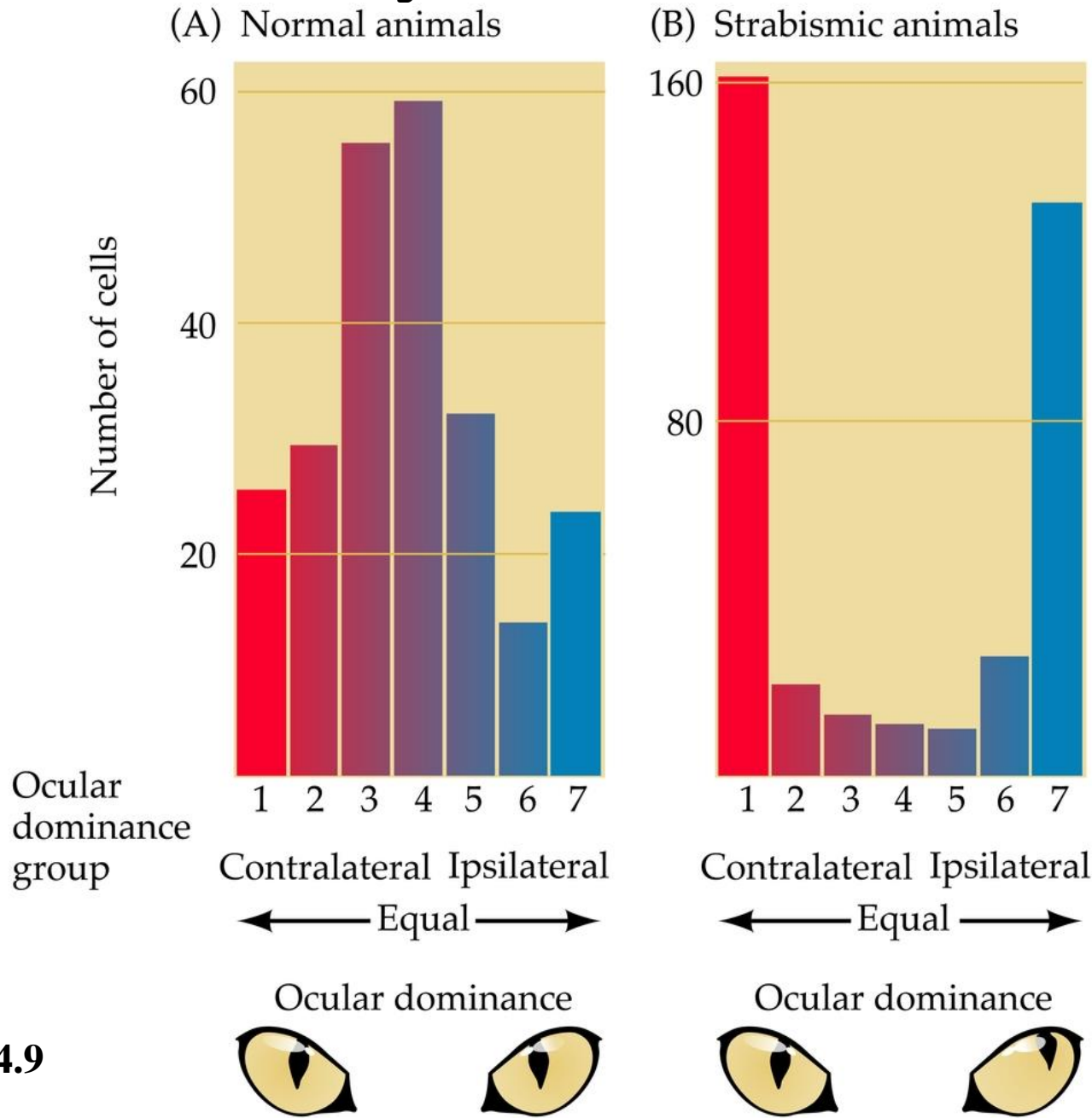
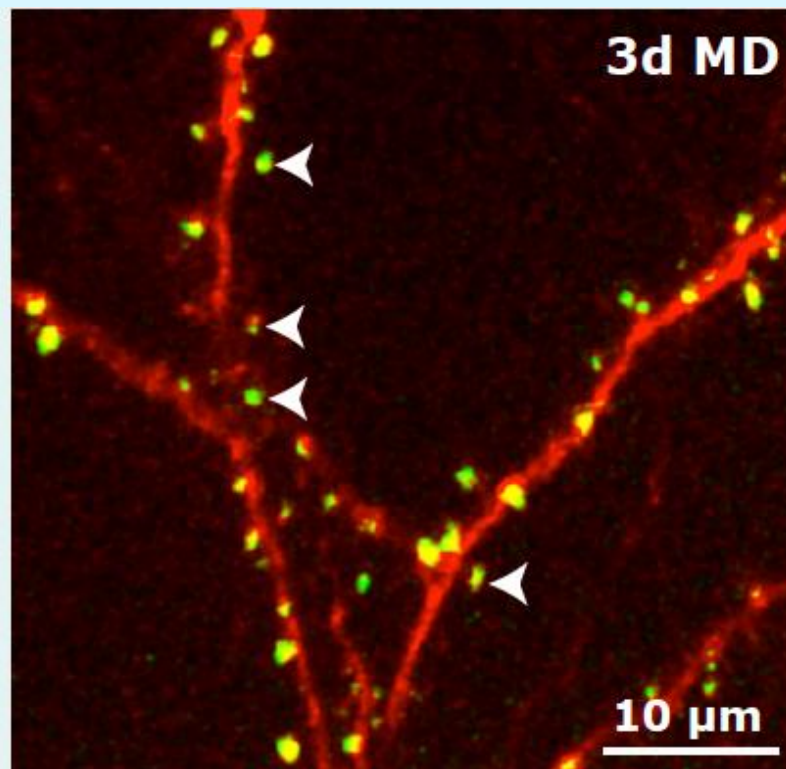
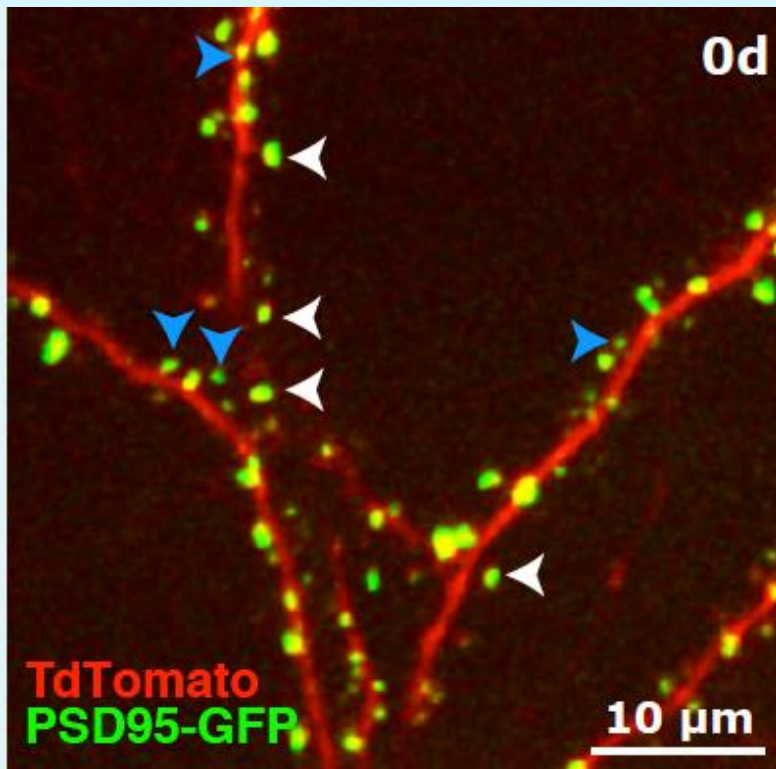
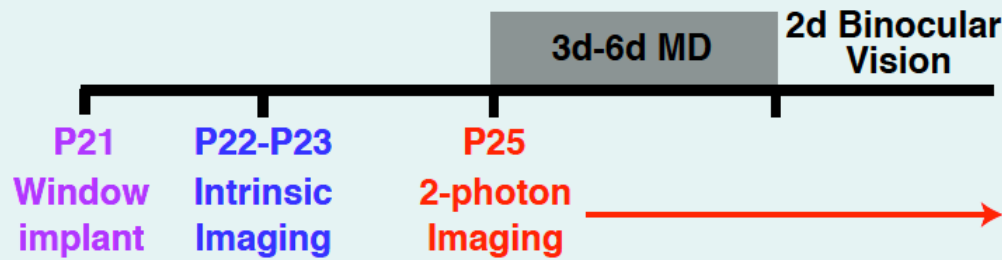


Figure 24.9

2-photon microscopy in vivo of plasticity



Correlated Activity in the developing visual system can produce changes in gene expression through calcium signaling as well as through other pathways.

Correlated activity can be detected by the flux of calcium through NMDA receptors. Remember that NMDA receptors are blocked by magnesium ions at normal resting potential. When the postsynaptic cell is depolarized, the magnesium block is relieved, and calcium then flows through the NMDA receptors when glutamate binds to them. The calcium influx then occurs only when the presynaptic cell is active at the same time as the postsynaptic cell. This calcium flux is at the head of a train of signals that lead to changes in synaptic strength and connectivity, and help to guide development.

(end of Part 1)