

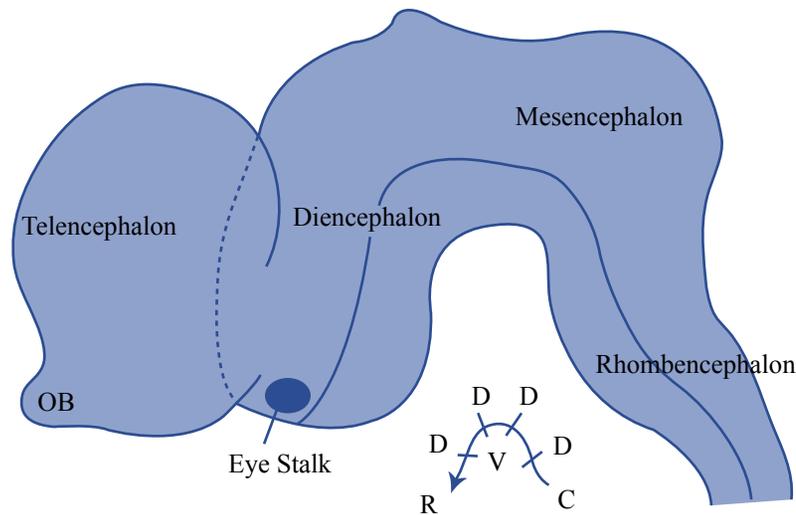
Questions, chapter 12

- 6) What are neuromeres? What are prosomeres?
CNS segments Segments of the forebrain
- 7) Describe the neuromeres of the diencephalon.
From caudal to rostral:
 - P1 = pretectal area;
 - P2 = dorsal thalamus & epithalamus;
 - P3 = ventral thalamus (subthalamus);
 - P4, 5, 6 = hypothalamus.

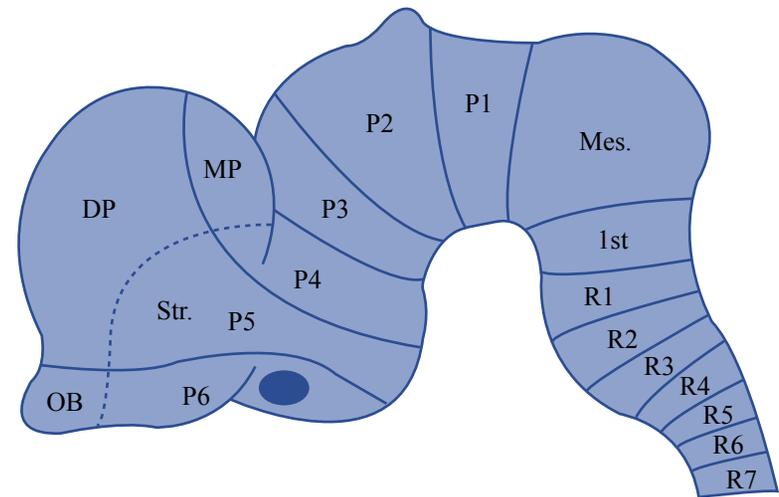
Notes on Evolution of Forebrain

Briefly: 3 topics

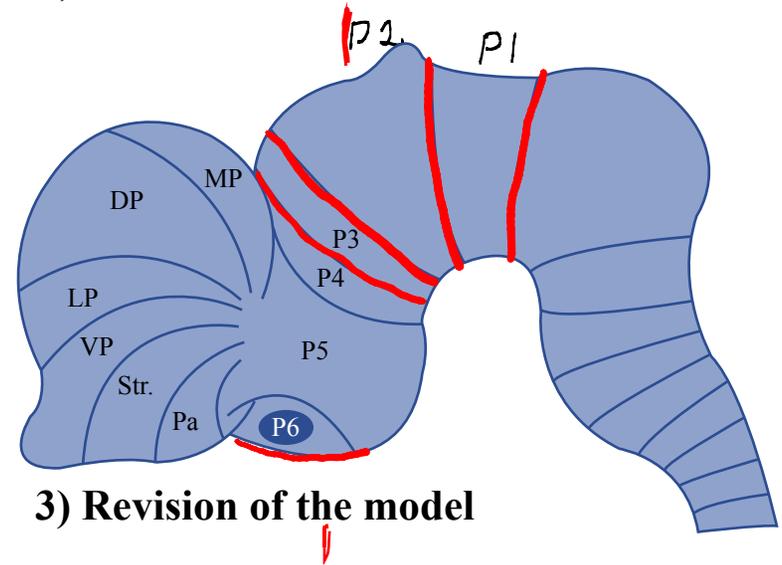
- **Neuromeres** of the forebrain
 - Segmentation rostral to rhombomeres and mesomere (initially seen in structural studies of developing diencephalon)
- Origins of neocortex
 - Structural studies give evidence that non-cortical structures in amphibians, reptiles and birds are related to neocortex of mammals
 - Gene expression studies have clarified the phylogenetic relationships



1) Embryonic brain with curved longitudinal axis



2) Puelles & Rubenstein, '93



3) Revision of the model

Images by MIT OpenCourseWare.

Neuromeric models of embryonic mammalian brain

Note that Frontal section cuts thru P2 → P6

Abbreviations for endbrain segments: see figure caption in the textbook

Gene expression data indicate existence of neuromeres also in the non-amniotes lamprey and zebrafish.

Lampreys appear to have fewer endbrain subdivisions according to gene-expression data.

Questions, chapter 12

- 8) What subpallial structure in sauropsids (reptiles and birds) has connections that are like the connections of the neocortex of mammals? What connections?

Structural studies give evidence that non-cortical structures in amphibians, reptiles and birds are related to neocortex of mammals

- Each sensory system connects to thalamic cell groups that are primarily unimodal, and these cell groups project mainly to the neocortex of mammals
- In birds, also in reptiles and amphibians, thalamus contains unimodal cell groups that project to structures that appear to be striatum (studies by Karten and others using, originally, Nauta methods for silver-staining of degenerating axons).
- A novel proposal was put forth by Harvey Karten when he was with Nauta at MIT: He proposed that embryonic cells migrate from a striatal location to neocortex. Thus, many neocortical cells in mammals are directly homologous to striatal cells in birds (more specifically, cells of ~~what was called the neostriatum, now called the nidopallium~~).
 - This has recently been tested, with surprising results.

Figure removed due to copyright restrictions. Please see course textbook or:
Reiner, Anton, Kei Yamamoto, et al. "Organization and Evolution of the Avian Forebrain." *The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology* 287, no. 1 (2005): 1080-102.

Illustrations of H. Karten's proposal that the DVR of Sauropsids and the lateral portions of the neocortex of mammals originated from the same region of proliferating embryonic cells that migrated differently as the two groups separated in evolution..

How has Karten's hypothesis been tested?

- Gene expression studies
- Studies of embryonic cell migration
 - Migration from the lateral ventricular angle region in mammals to lateral regions of neocortex
 - Migrations from medial and lateral ganglionic eminence (striatal locations): cells that become inhibitory interneurons

Questions, chapter 12

9) The neocortex has layers that are not present in the dorsal cortex of reptiles and amphibians. The layers are the more superficial layers 2-4. Those layers contain many inhibitory interneurons that do not arise from the ventricular layer of the developing cortex. Where do they come from? *See previous slide and the following slides*

10) The lateral ventricular angle region of the mammalian embryonic brain is at least partly homologous to the dorsal ventricular ridge of sauropsids. There is some evidence from Golgi studies that some neuroblasts from this region migrate into neocortex, but such studies, and also gene expression studies, indicate that they migrate into non-neocortical structures as well. Which structures?

Amygdala and claustrum

*↑
a major limbic forebrain structure derived from both striatum and pallidum of embryo*

Homeobox gene expression:

Emx-1

Dlx-1

Archetypal embryonic stage

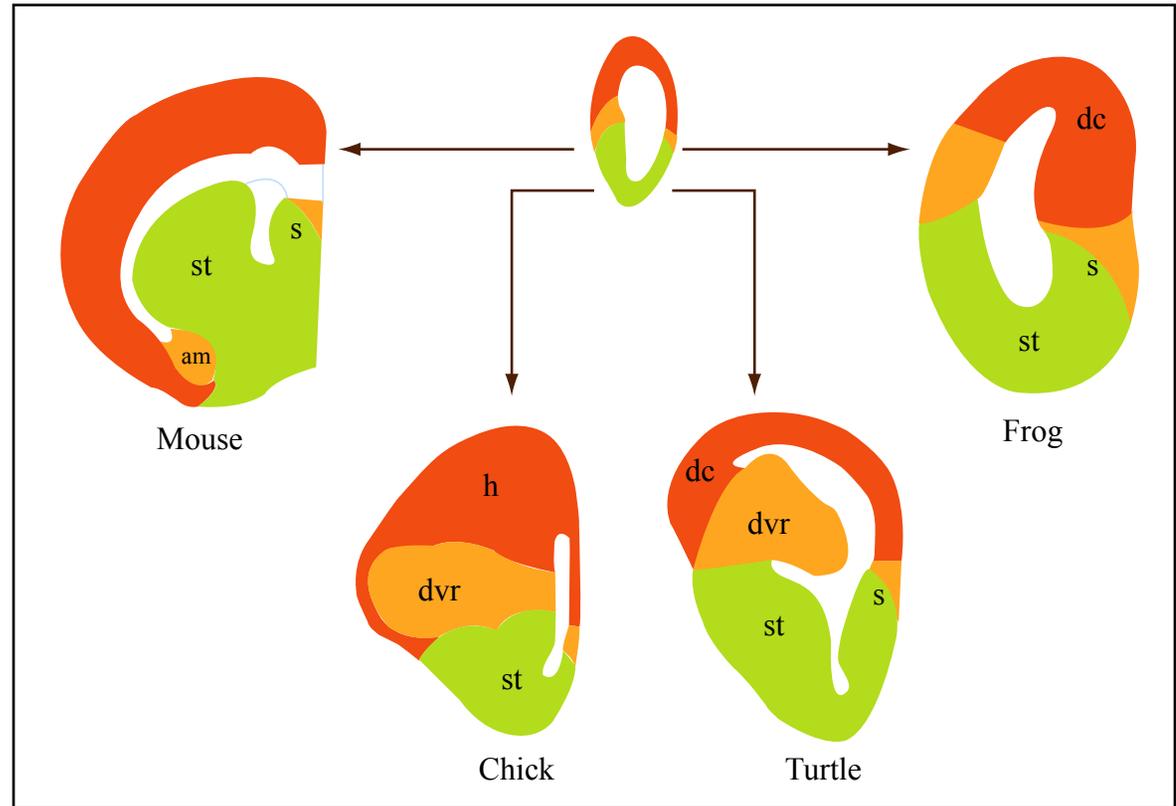


Image by MIT OpenCourseWare.

am = amygdala & claustrum

Cx = neocortex

dc = dorsal cortex

dvr = dorsal ventricular ridge

h = hyperpallium

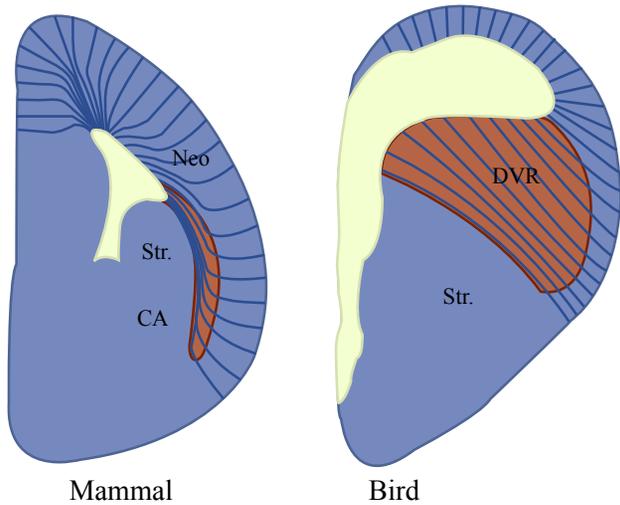
lp = lateral pallium

s = septum

st = striatum

Evolution of telencephalon based on expression patterns of regulatory genes during development

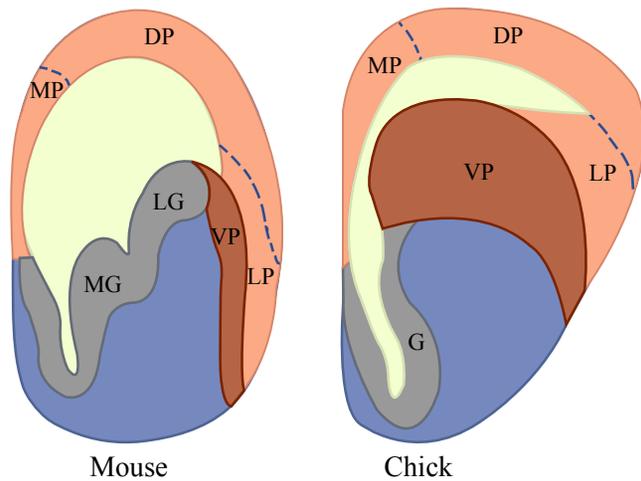
Radial Glia in Embryonic Mice and Chicks



A) Radial glia cells (black lines) in embryonic mammals and birds

Embryology and the Claustroamygdalar DVR Hypothesis

Regulatory Gene Expression in Mice and Chicks



B) Transcription factor expression:

Tbr-1

Tbr-1 and Emx-1

Dlx-2

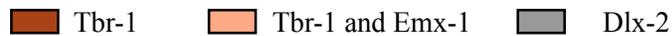
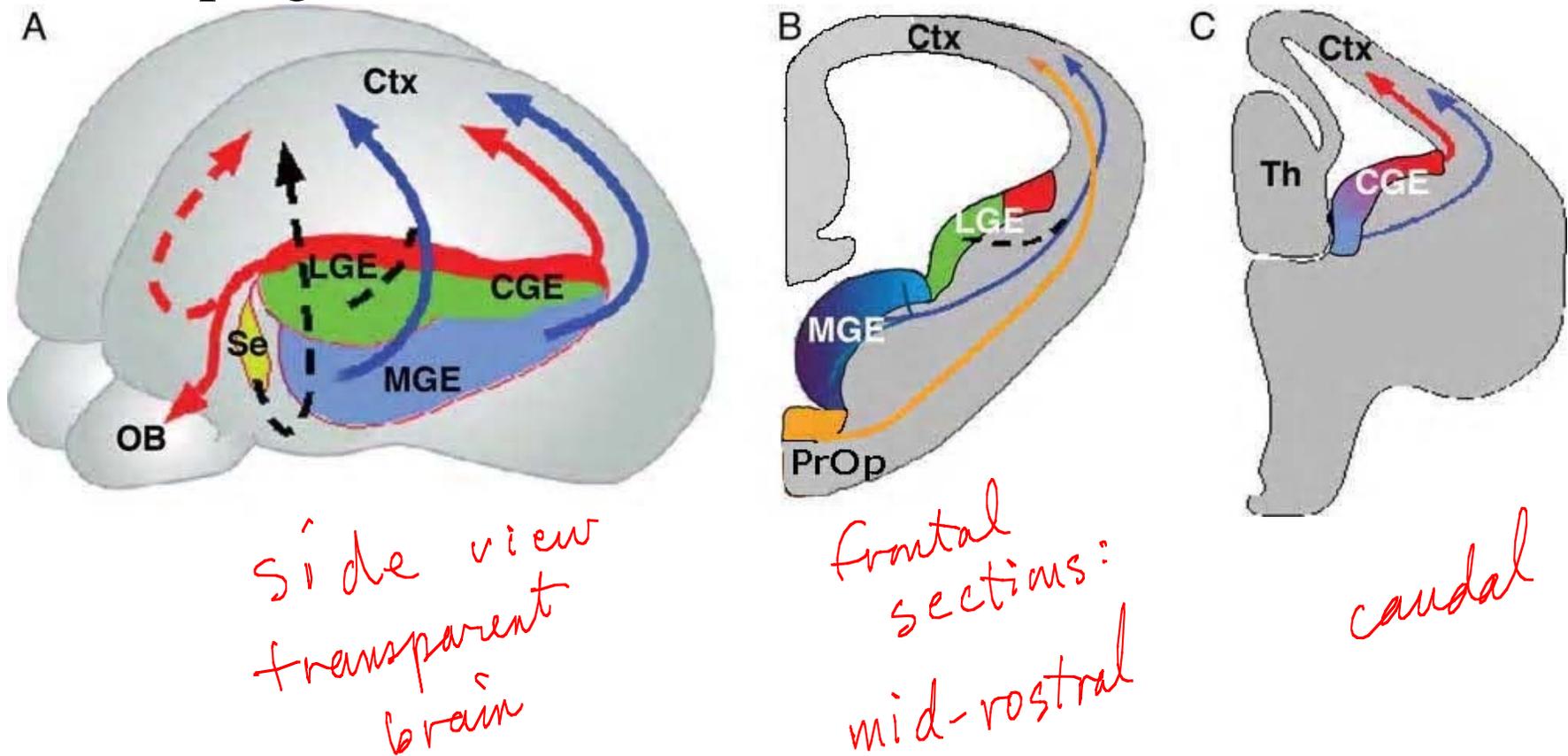


Image by MIT OpenCourseWare.

From a review published in 2011: Migrations of precursors of inhibitory interneurons in developing mouse brain



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 Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN: 9780262026734.

OB = olfactory bulb

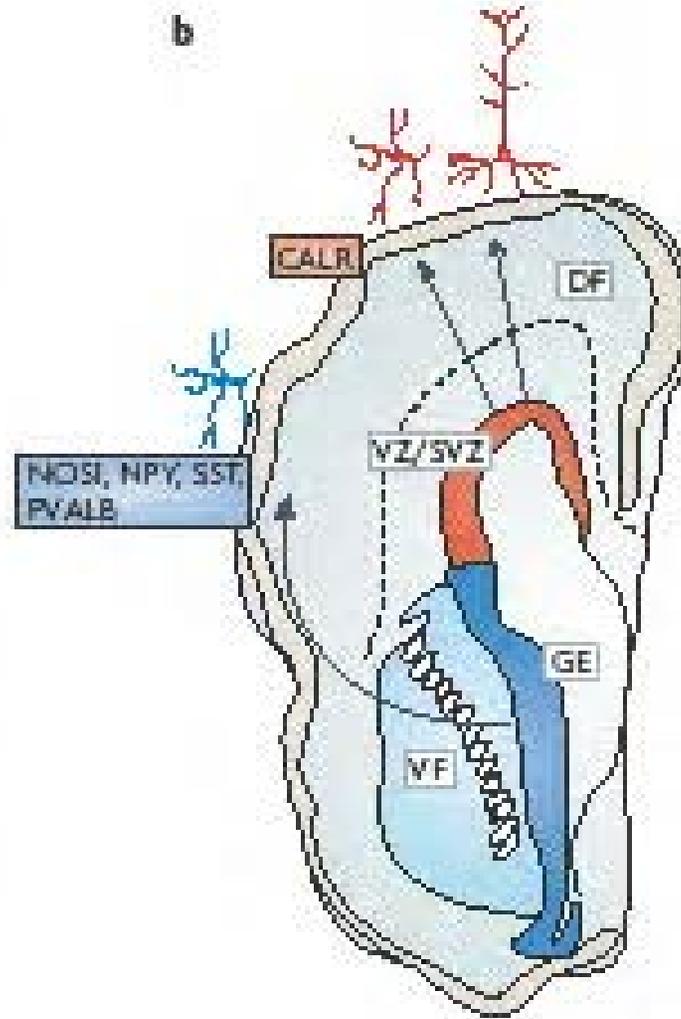
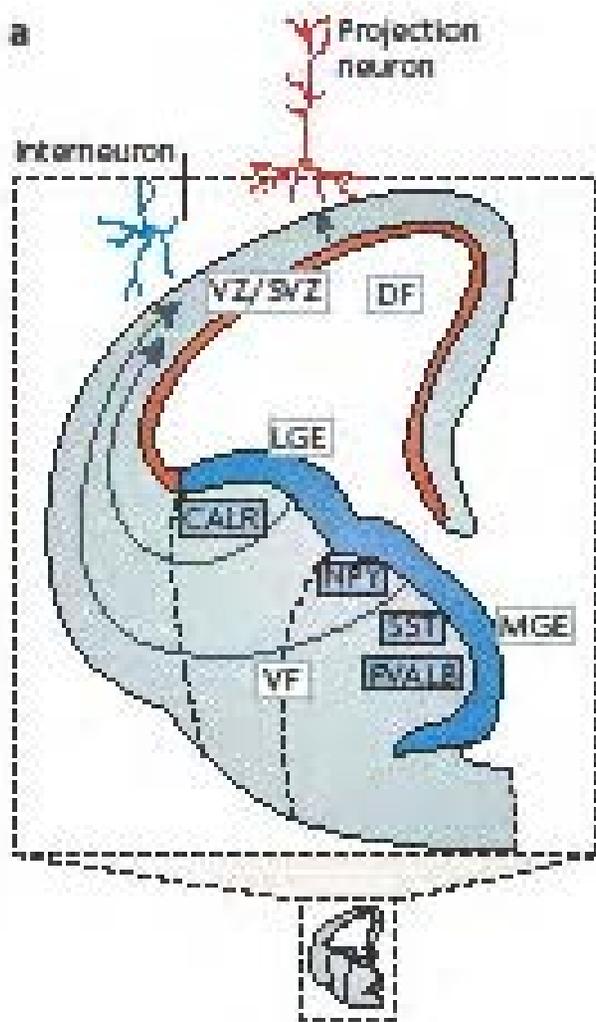
PrOp = preoptic area of hypothalamus

SE = septal area (anterior to thalamus)

MGE = medial ganglionic eminence of embryo

LGE = lateral ganglionic eminence of embryo

CGE = caudal ganglionic eminence of embryo



DF, VF = dorsal forebrain, ventral forebrain
VZ/SVZ = ventricular zone/ subventricular zone
GE = ganglionic eminence
LGE = lateral ganglionic eminence
MGE = medial ganglionic eminence
NOS1 = nitric oxide synthase 1
NPY = neuropeptide Y
SST = somatostatin
PVALB = parvalbumin
CALR = calretinin

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience.
 Source: Rakic, Pasko. "Evolution of the Neocortex: A Perspective from Developmental Biology." *Nature Reviews Neuroscience* 10, no. 10 (2009): 724-35. © 2009.

Fig 12-11
Rodent and human fetal forebrains are illustrated in frontal sections by Rakic (2009, his figure 5) at the peak of corticogenesis. Note that the rodent section is greatly enlarged compared with the human. **Ventricular zone: similar to ventricular zone of the developing spinal cord. It is much thicker in the striatal area, from which many neurons migrate, to become inhibitory interneurons.**

Next:

A major aspect of nervous system differentiation at the cellular level:

The growth, plasticity and regeneration of axons.

A sketch of the central nervous system and its origins

G. E. Schneider 2014

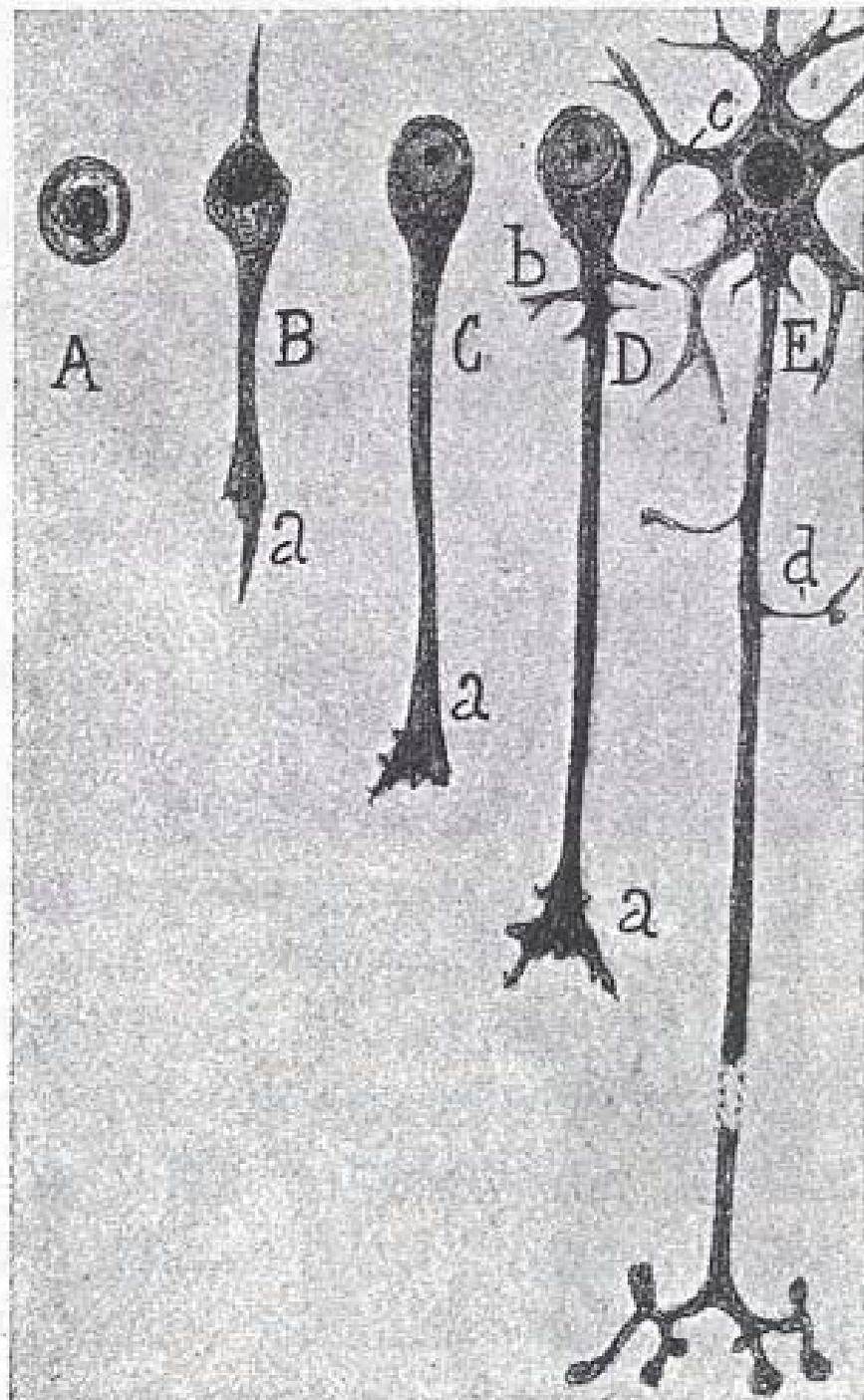
Part 5: Differentiation of the brain vesicles

MIT 9.14 Class 13

Growth of axons

Major stages of nervous system development

- **Proliferation** of cells
- **Migration** from birth places to destinations
- **Differentiation** of neurons and cell groups
 - **Growth of extensions (axons, dendrites, spines)**
 - Sculpting by branch loss and cell death
 - Maturation
- **Plasticity**



Nerve fiber development (Cajal)

How did he observe
such developmental
dynamics?

a = growth cone

Questions, chapter 13

1) Ramon y Cajal described the axonal growth cone from his Golgi studies of developing chicks and mammals. However, he never saw a living growth cone. How was this first accomplished, and by whom? *names in Q 3*

2) To see growth cones in histological material, methods other than the Golgi stain can be used. Give an example. *DiI, and other fluorescent markers.*

3) What technical advances in neuroembryology can attributed to Ross G. Harrison? How did Speidel's method differ from Harrison's?

4) Describe membrane incorporation in the growing axon.

*see books
Schneider,
Purves + Lichtman*

Growth of dendrites and axons

- The growth cone
 - Motile filopodia (plural of filopodium) containing actin filaments
- Selective adhesion by filopodial tips;
 - CAMs (cell adhesion molecules, like N-CAM)
 - Contraction of filopodia due to contractile proteins (mostly actin).

filopodium (from Purves & Lichtman): "Slender protoplasmic projection, arising from the growth cone of an axon or dendrite, that explores the local environment and adheres to a favorable substrate."

Axon of dorsal root ganglion cell from a chick embryo growing in tissue culture for 14 minutes

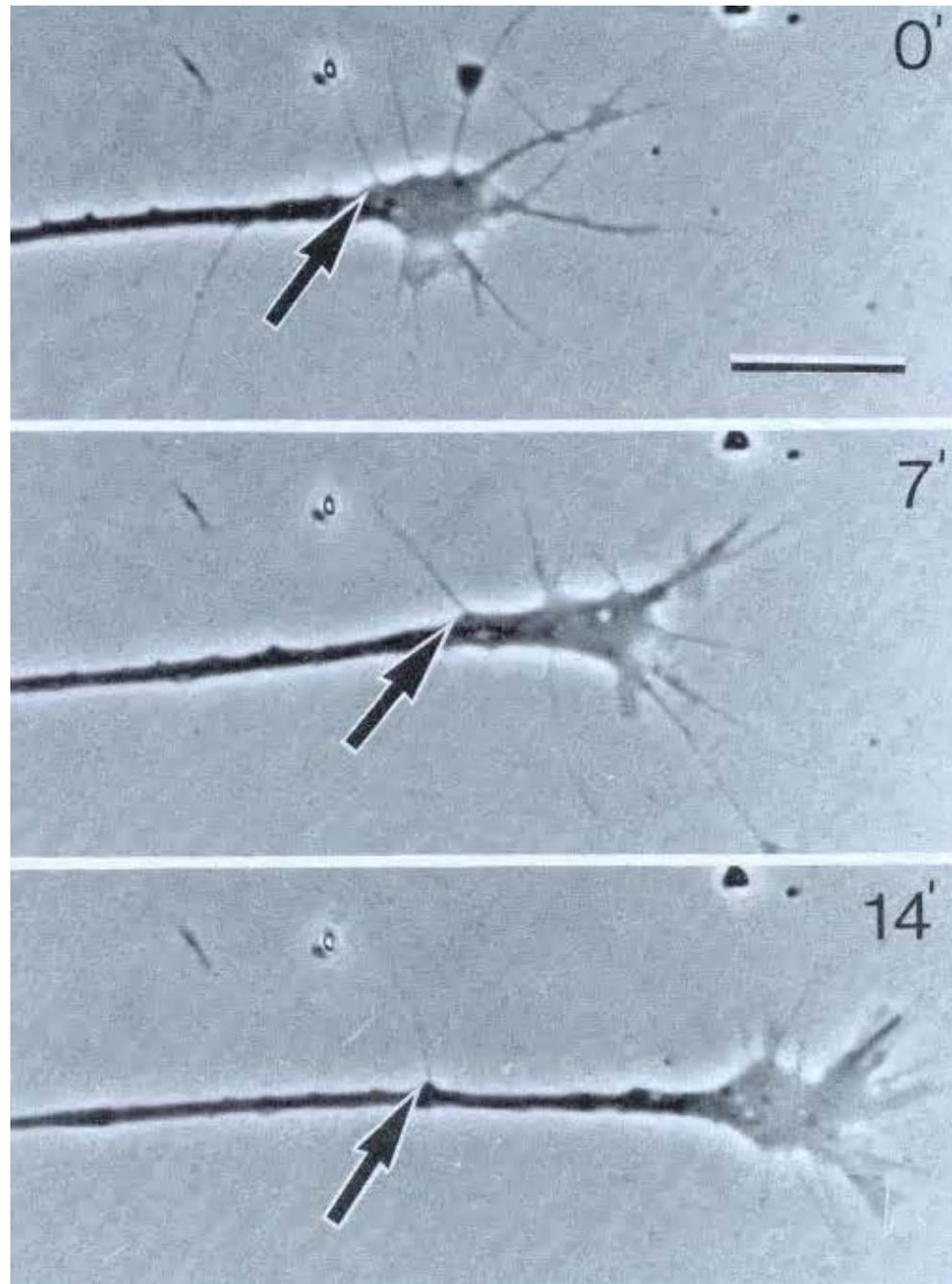
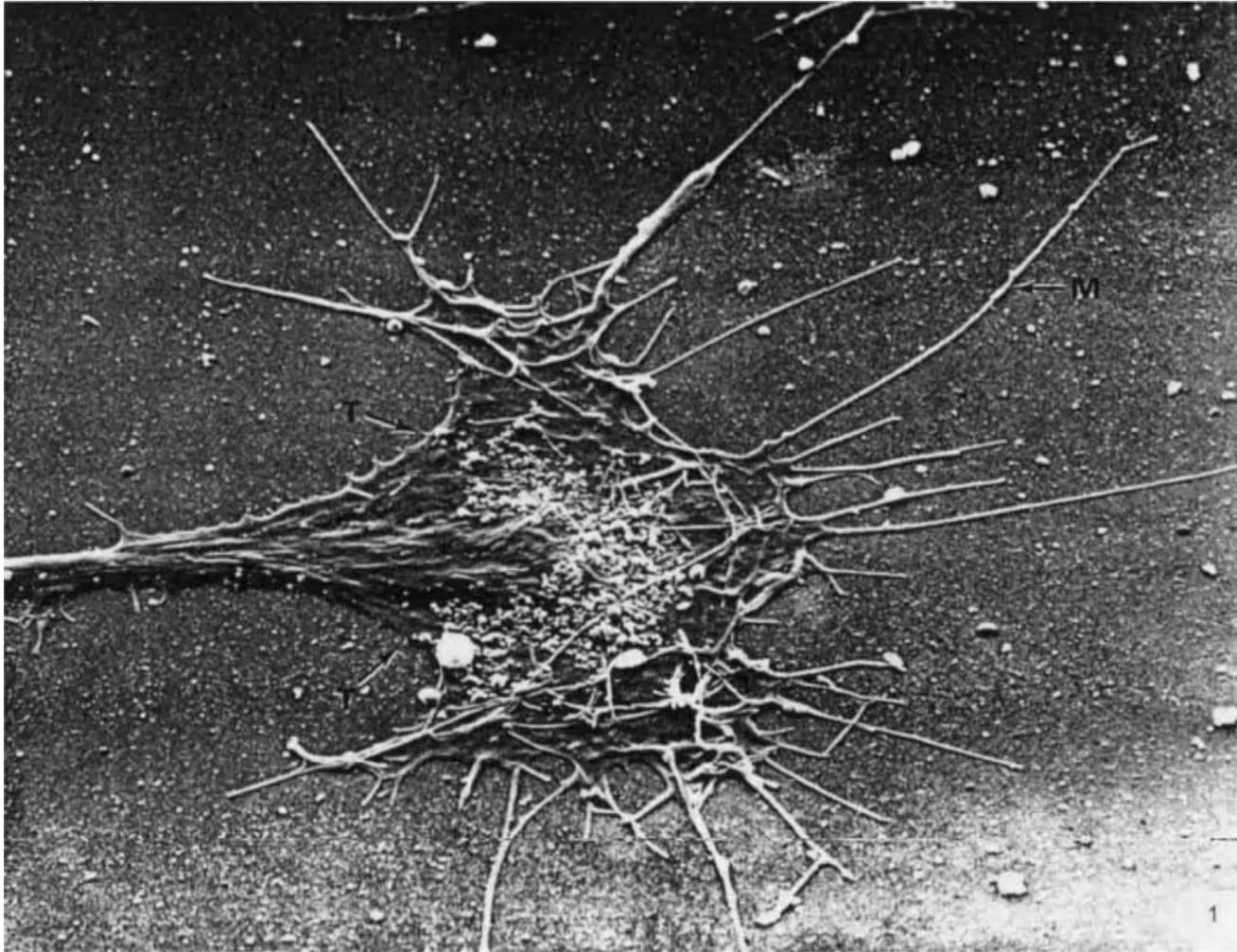


Fig 13-2b

Figure 13 of Bray, D., and K. Chapman. "Analysis of Microspike Movements on the Neuronal Growth Cone." *The Journal of Neuroscience* 5, no. 12 (1985): 3204-13. Available under Creative Commons BY-NC-SA.

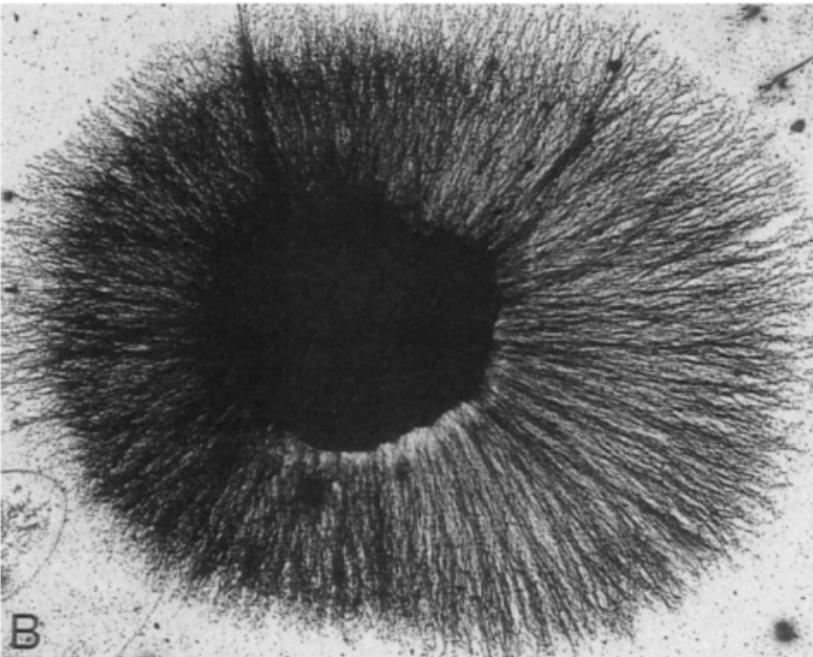
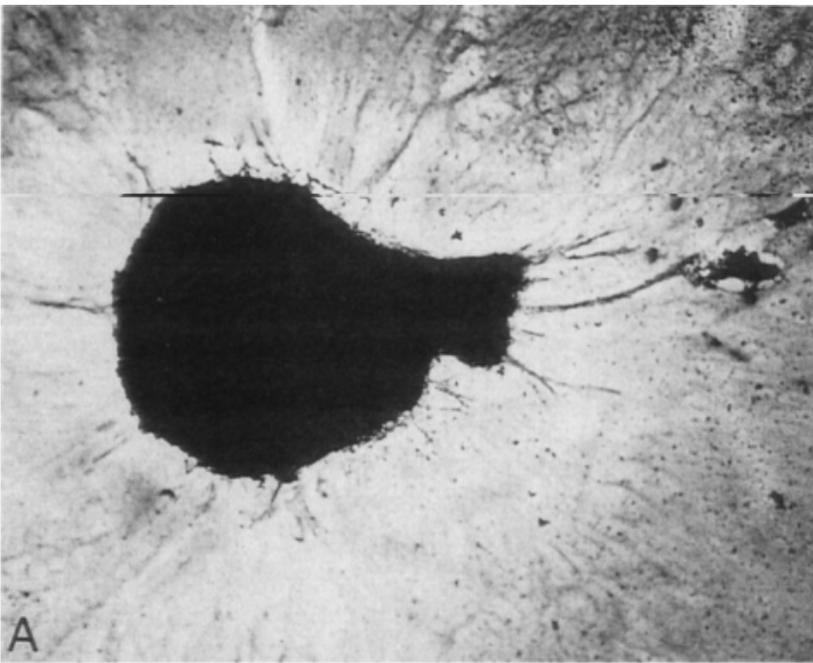
Axon growth cone, scanning e.m. picture



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Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN: 9780262026734.

From Wessells and Nuttall, 1978 (reproduced in Zigmond et al., 1999)



Growth of axons in tissue culture: NGF Assay

NEXT: Living growth cones
in tissue culture; growth
factors

Large growth cone in tissue culture, video clip

Video removed due to copyright restrictions.

Other videos can be found online

Growing axons in culture: chick retina and DRG (video clip)

Video removed due to copyright restrictions.

Three growth cones *in vitro* (video clip)

Video removed due to copyright restrictions.

Axonal growth cone of sympathetic ganglion neuron and fibroblast *in vitro* (video clip)

Video removed due to copyright restrictions.

Questions, chapter 13

- 5) Study the model of a growth cone depicted in figure 13.3. Describe the dynamics of axon growth using the concepts of fundamental cellular events named by Lewis Wolpert (chapter 8).

Adhesion by filopodial tips

Contraction of filopodia, pulling on the growth cone.

Growth of axon, by membrane addition at the active tip

Growth cone *model*

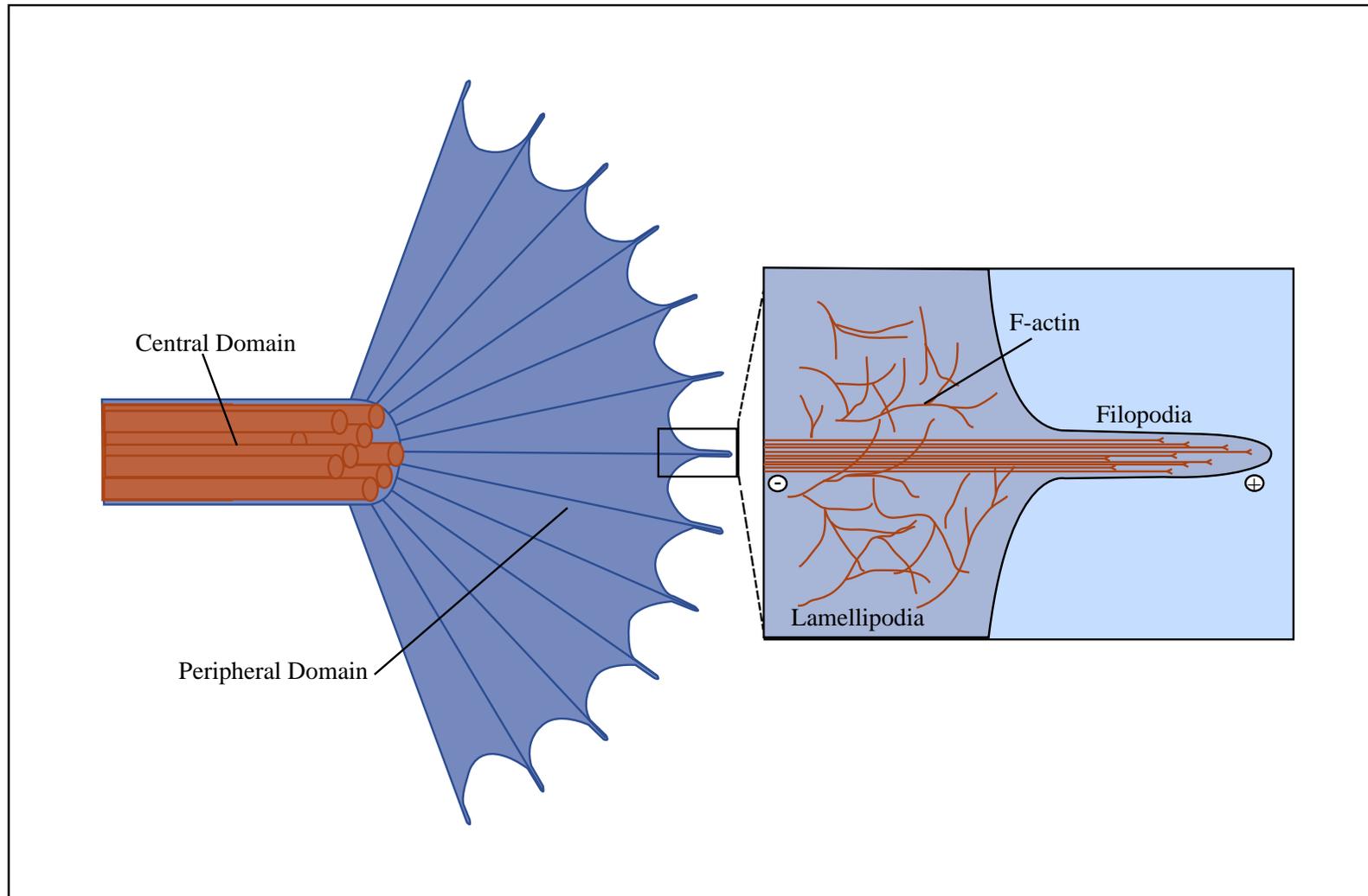


Image by MIT OpenCourseWare.

Singular terms (Latin):
Filopodium,
lamellipodium

Questions, chapter 13

- 6) The study of axonal growth was advanced by a discovery by Rita Levi-Montalcini and Victor Hamburger. Describe the discovery. What did it lead to?

They discovered the first chemical growth factor active in the growing nervous system.

Their factor (NGF) was the first in a family of growth factors. Other families were discovered later.

NGF = Nerve Growth Factor

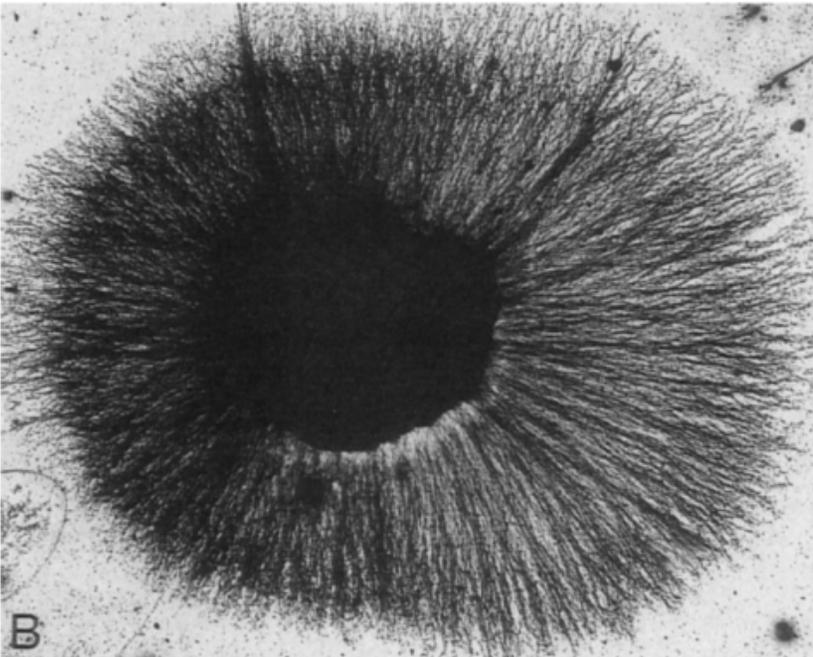
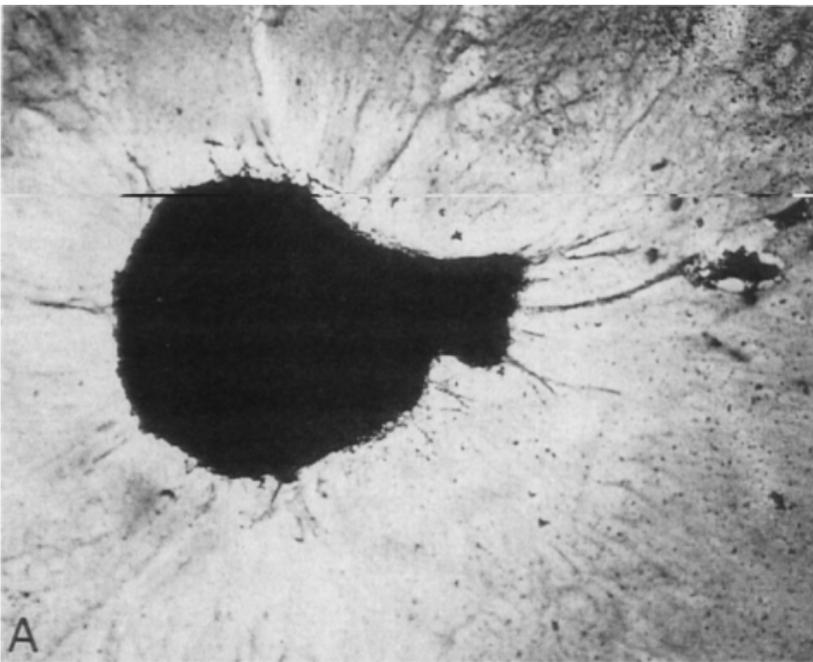
Using tissue culture for studies of neuronal growth:

NGF Assay

First developed by Rita Levi-Montalcini

“Neurotrophins”: a family of growth factors. NGF was the first.

[These will be discussed further later.]



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Questions, chapter 13

- 7) How do axons that originate in the distal part of the leg of a grasshopper appear to find their way to a central ganglion in a consistent pattern?
- 8) Can the same mechanisms explain the pattern of growth of the mammalian optic tract?

via "guidepost cells"

no

An experiment on the growth of sensory axons in the developing grasshopper leg

- How can the axons be observed?
- How does an axon find its way to its target ganglion?

From Bentley & Caudy ('83)

Reviewed by Purves & Lichtman ('85); Zigmond et al., '99.

Evidence for “Guidepost cells”

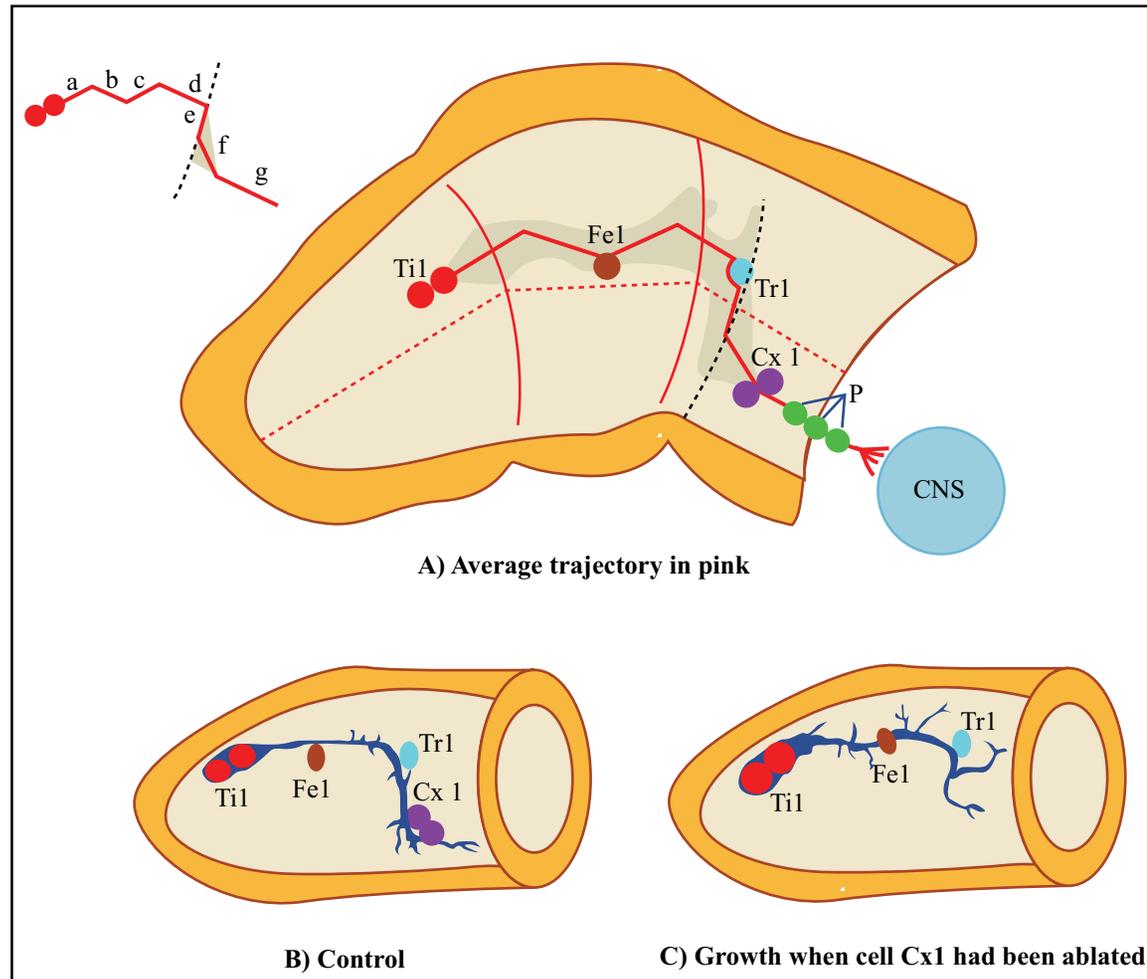


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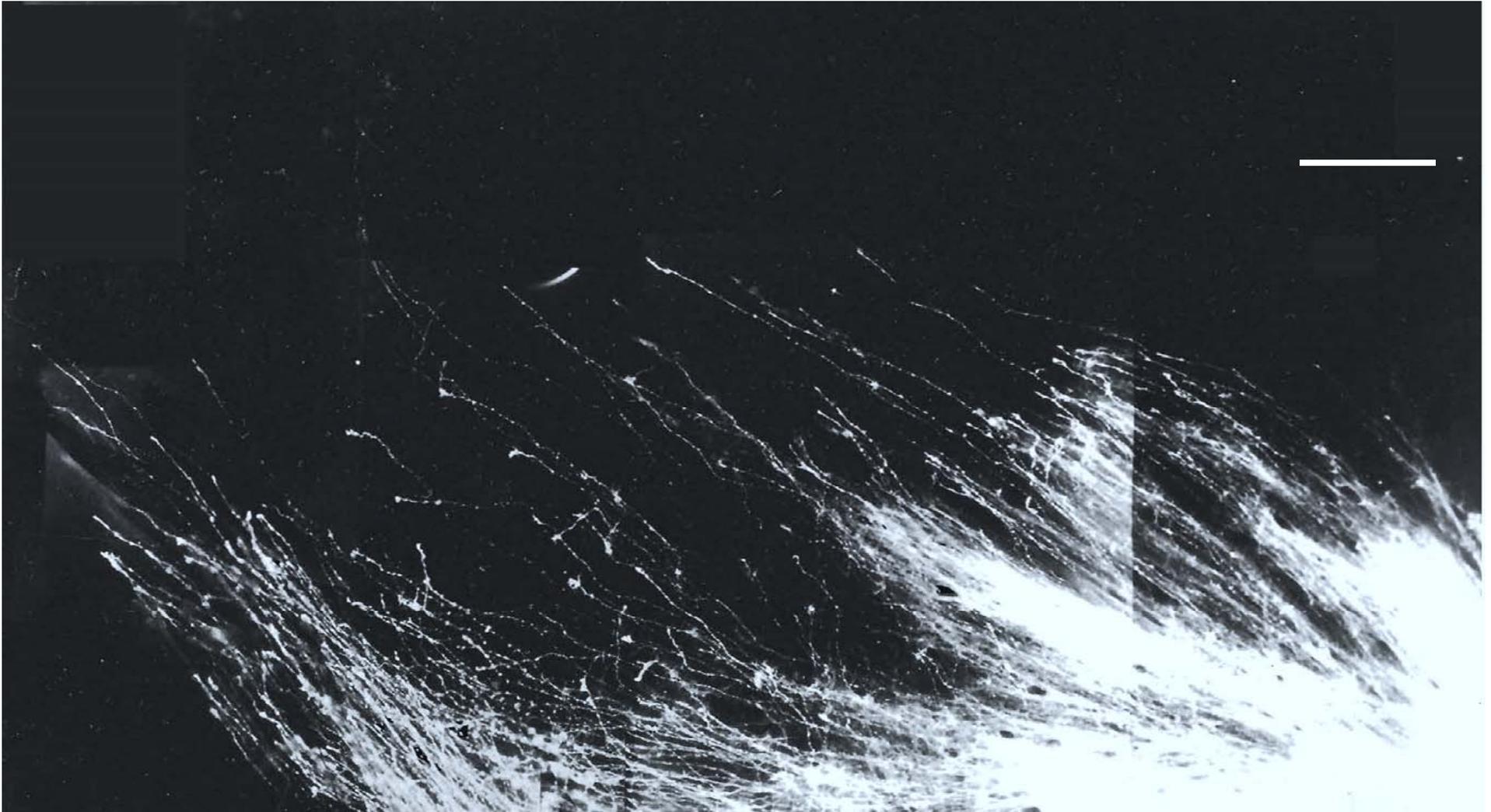
Grasshopper leg vs. mammalian optic tract

- **Grasshopper leg**

- *Pioneer axon*: The role of "guidepost cells" and long filopodia of growth cones of the primary sensory neurons in the epithelium.
- Later growing axons *follow* the first one.

- **Mammalian optic tract**

- What happens in the grasshopper leg is **not** what happens in the mammalian optic tract
- Later-growing axons do not grow along the surfaces of the earlier ones, but rather space themselves between them.



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Schneider, G. E. *Brain Structure and its Origins: In the Development and in Evolution of Behavior and the Mind*. MIT Press, 2014. ISBN: 9780262026734.

From Jhaveri S, Erzurumlu RS, Schneider GE (1996)

Fig 13-6

Questions, chapter 13

- 9) What is the major result in Hibbard's experiment on transplanted amphibian Mauthner cells?

What does it mean?

An experiment on specificity of axon growth

Hibbard's experiment and what it means

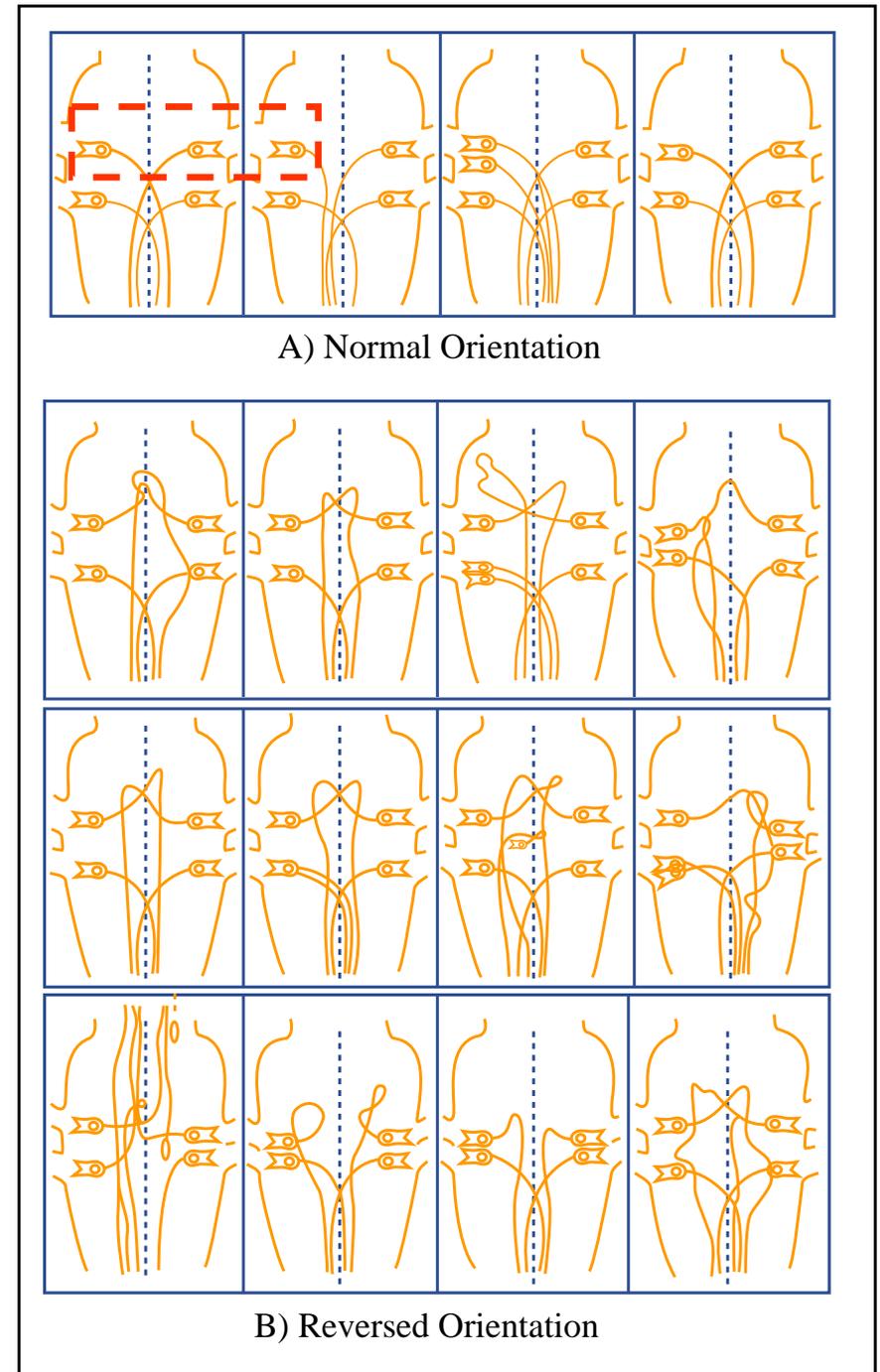
(reviewed by Purves & Lichtman, pp.118-119, and by Schneider)

Hibbard's experiment on transplanted amphibian Mauthner cells:

He used grafted medullary segments, placed just rostral to the normal position in either normal or reversed orientation (published in 1965).

Results indicate that cues in the tissue guide axons growing through it.

The Mauthner cell axons grow caudally. If the tissue where they begin growing is turned around 180 degrees, they start to grow rostrally until they encounter tissue outside the graft, then they reverse course.



Guidance Mechanisms for axon outgrowth:

Four mechanisms as seen in 1985

- **Stereotropism** *mechanical effects of surfaces axons grow on.*
- Galvanotropism
- Tropism based on **differential adhesion**
- **Chemotropism**
 - Membrane contact
 - Diffusible signals

(Purves & Lichtman, pp 119-129)

Questions, chapter 13

10) There is much evidence that chemical guidance is a major factor in the growth of axons. However, there are multiple types of chemical guidance, with involvement of many different molecular substances. Describe major types of chemical guidance.

next slides

Since the Purves & Lichtman review in 1985

Four types of chemical guidance have been distinguished. What are they? Figures depicting these four types have been frequently published.

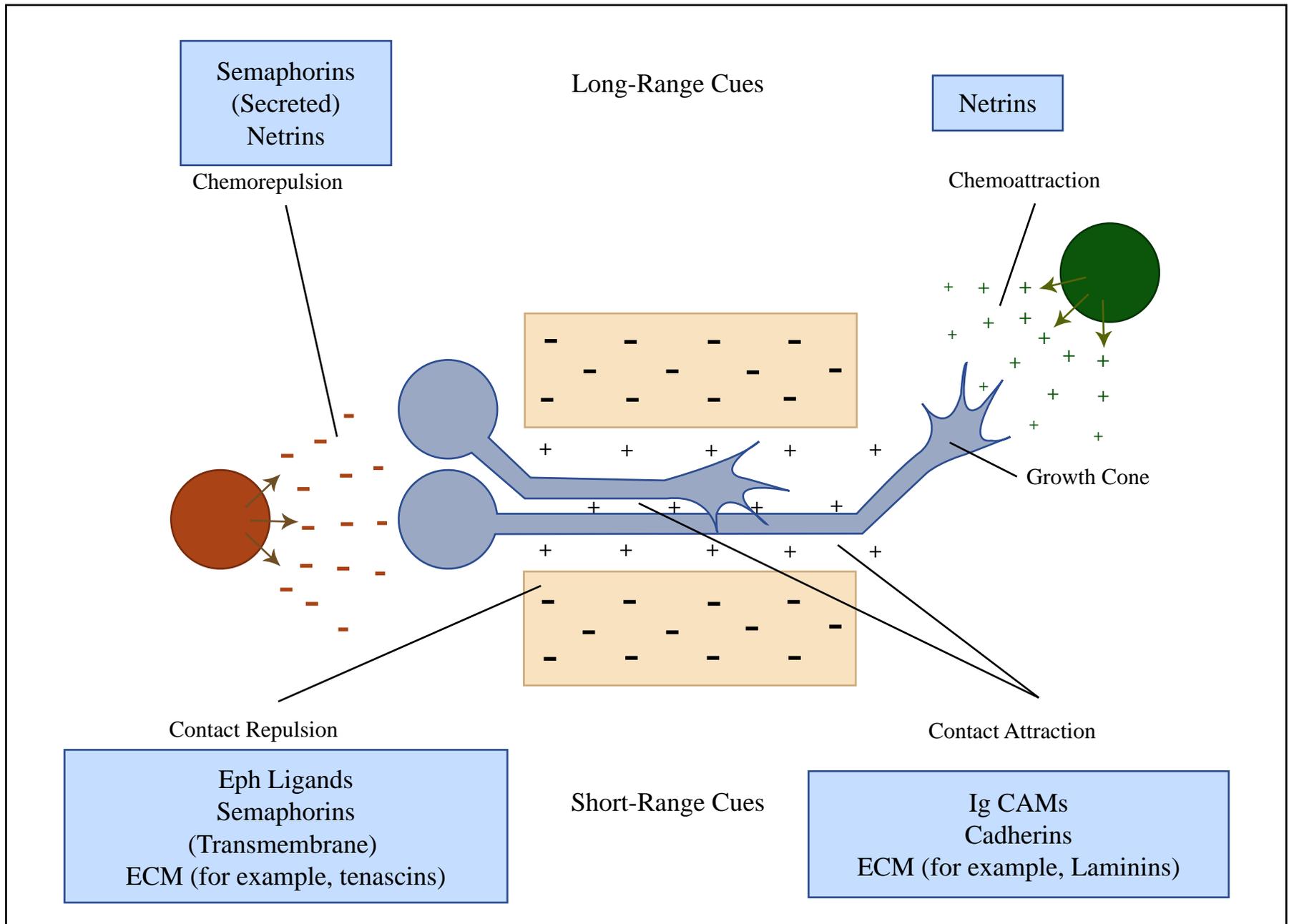


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Thus, chemical specificity depends on two different kinds of effects:

1. Attraction effects
2. Repulsion effects, or inhibition of growth

Each of these can involve one of two kinds of effect:

- a) Diffusing chemicals
- b) Contact

More detail:

Chemical specificity 1: attraction effects

- Cell-cell adhesion (CAMs; ECM molecules like the laminins and cadherins)
cell adhesion molecules extracellular matrix
- Growth factors:
 - Contact (Semaphorins)
slide 38-39
 - Diffusible (Netrins; NGF and other neurotrophins; other families of GFs)
slide 40

Chemical specificity 2: barriers; **inhibition** of growth

- Midline barriers
 - by contact repulsion, e.g., by certain proteoglycans secreted by midline radial glia *they block axons from crossing midline*
- Oligodendrocyte factors
 - A membrane protein, *Nogo*, which inhibits axon growth
- Secreted and transmembrane proteins (Semaphorins; neurotrophins and other GFs; ephrins)

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9.14 Brain Structure and Its Origins

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