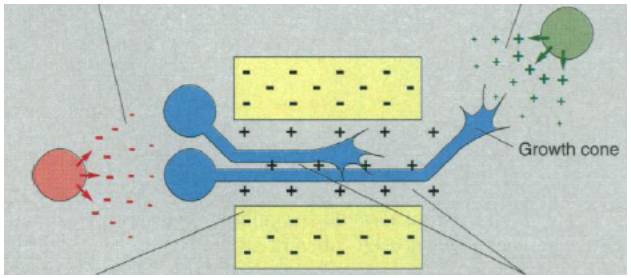
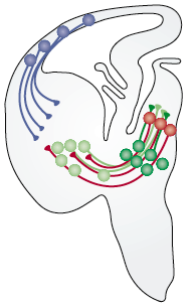
Development and evolution of connectivity

Development of connectivity

Mechanisms of axon guidance



Development of cortical and thalamocortical connections



Principles of evolution of connectivity

Epigenetic population mapping

Parcellation hypothesis

Connectional invasion and displacement hypothesis

Principles of network design

Development of connectivity

The Molecular Biology of Axon Guidance

Marc Tessier-Lavigne and Corey S. Goodman

Neuronal growth cones navigate over long distances along specific pathways to find their correct targets. The mechanisms and molecules that direct this pathfinding are the topics of this review. Growth cones appear to be guided by at least four different mechanisms: contact attraction, chemoattraction, contact repulsion, and chemorepulsion. Evidence is accumulating that these mechanisms act simultaneously and in a coordinated manner to direct pathfinding and that they are mediated by mechanistically and evolutionarily conserved ligand-receptor systems.

The remarkable feats of information-processing performed by the brain are determined to a large extent by the intricate network of connections between nerve cells (or neurons). The magnitude of the task involved in wiring the nervous system is staggering. In adult humans, each of over a trillion neurons makes connections with, on average, over a thousand target cells, in an intricate circuit whose precise pattern is essential for the proper functioning of the nervous system. How can this pattern be generated during embryogenesis with the necessary precision and reliability?

Neuronal connections form during embryonic development when each differentiating neuron sends out an axon, tipped at its leading edge by the growth cone, which migrates through the embryonic environment to its synaptic targets, laying down the extending axon in its wake (Fig. 1). Observations of developing axonal projections in vivo have revealed that axons extend to the vicinity of their appropriate target regions in a highly stereotyped and directed manner, making very few errors of navigation. They do so apparently by detecting molecular guidance cues presented by cells in the environment (*1*). Studies in the past two decades have provided a detailed understanding of the cellular interactions between growth cones and their surroundings that direct pathfinding, which we summarize in the first section of this review. Our understanding of the molecular biology of axon guidance is, however, much more fragmentary. Molecules implicated as guidance cues or as receptors for these cues are introduced in the second section. Many of these molecules have only recently been identified, and it seems likely that additional guidance cues and receptors remain to be discovered. Moreover, in most cases the precise guidance functions of candidate ligand-receptor systems in vivo are poorly understood. In the third section we discuss specific guidance decisions in which the roles played by some of these molecules are beginning to be defined. As will become apparent, despite the many gaps in our knowledge the picture that is starting to emerge is that pathfinding is directed by the coordinate action of multiple guidance forces that are mediated by mechanistically and evolutionarily conserved ligand-receptor systems. A considerable body of evidence supports these conclusions (*2*).

M. Tessier-Lavigne is in the Department of Anatomy, Howard Hughes Medical Institute, University of California, San Francisco, CA 94143, USA. C. S. Goodman is in the Department of Molecular and Cell Biology, Howard Hughes Medical Institute, University of California, Berkeley, CA 94720, USA.

Cellular Interactions That Guide Axons

The appearance that axons give of unerring navigation to their targets is all the more

This was state of the art in 1996 … but a lot has been done since then.
I will try to incorporate some more recent information and will give more up to date references.

Development of connectivity

Mechanisms of axon guidance – some definitions

- *Growth cone*: at the tip of an extending axon is a flattened, fan-shaped structure called a growth cone, with many long spikes that radiate outward

- *Molecular guidance cues*

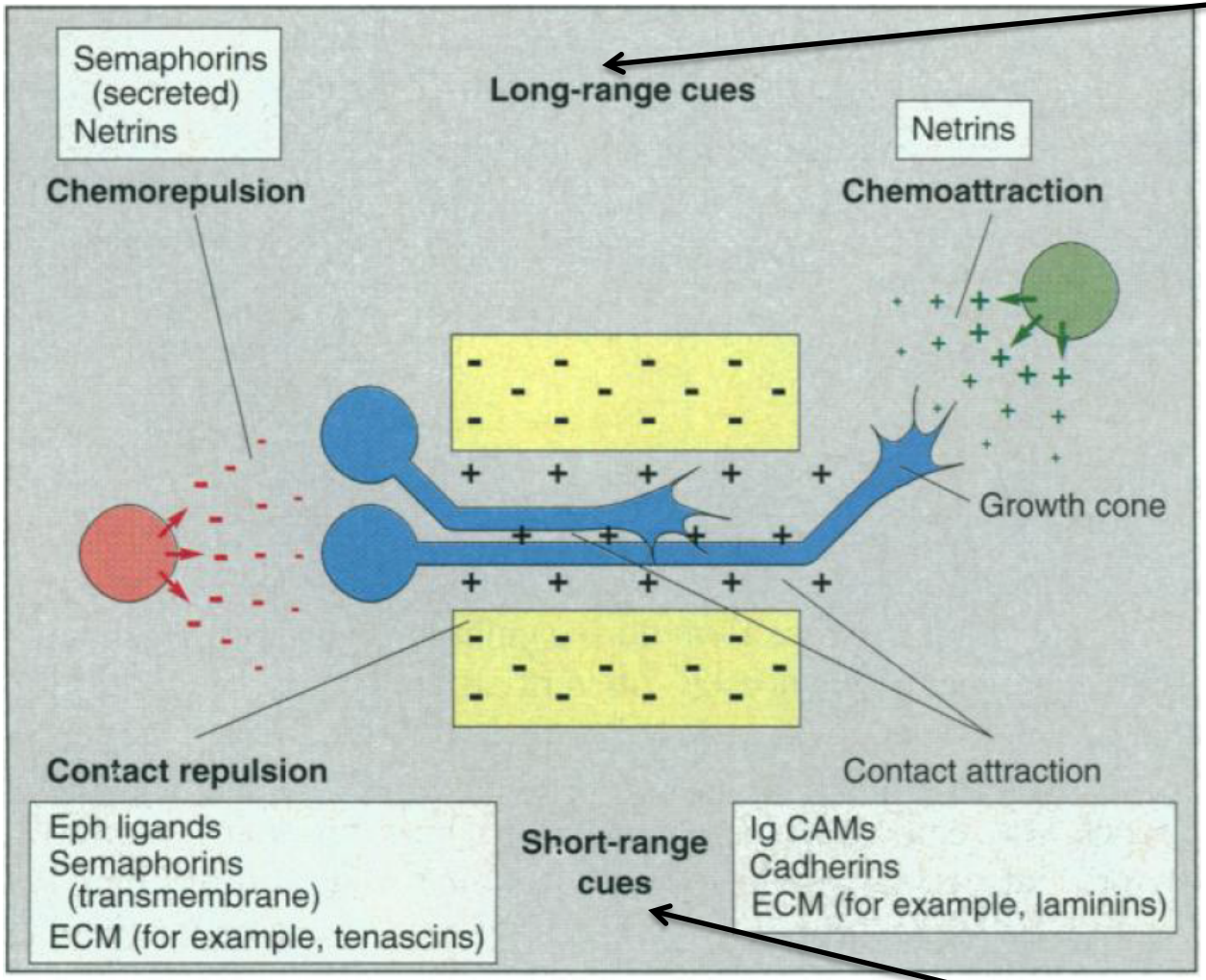
- *Intermediate targets*: small clusters of “guidepost cells’ or large groups of functionally specialized cells.

- *Stepwise process*

- *“Pioneer” axons*

- *Four guidance forces*: attractive and repulsive cues, which can be either short-range or long-range.

Development of connectivity



Cells secrete diffusible chemoattractant or chemorepulsion substances that attract or repel axons at a distance.

Short-range or contact-mediated mechanisms involving nondiffusible molecules.

Development of connectivity

For a more up to date reviews of these molecules, see:

REVIEW SCIENCE VOL 298 6 DECEMBER 2002

Molecular Mechanisms of Axon Guidance

Barry J. Dickson

Mechanisms and Molecules of Neuronal Wiring: A Primer

2011

Alex L. Kolodkin[1] and Marc Tessier-Lavigne[2]

- Four major families of guidance cues ("canonical" guidance-cues):
    - (1) Netrins
    - (2) Slits
    - (3) Semaphorins
    - (4) Ephrins
- Morphogens and growth factors
- Cell-adhesion molecules of the immunoglobulin and cadherin super families

Development of connectivity

Some general principles

(1) Axons are guided through the combined operation of four guidance mechanisms (short- and long-range attraction, and short- and long-range repulsion).

(2) Multifunctional nature of guidance cues.

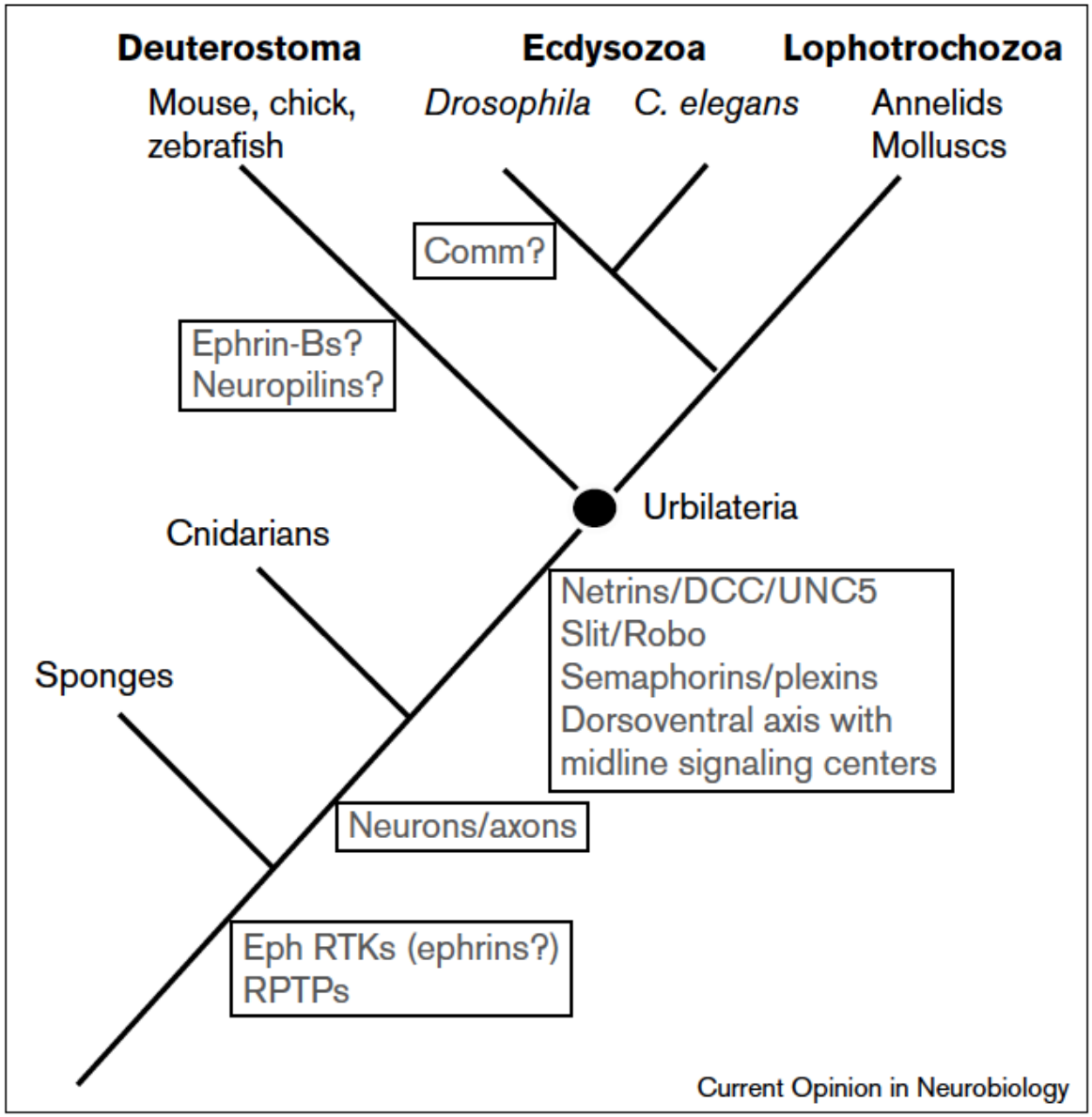
(3) These mechanisms appear to operate in all types of decisions: linear growth, sharp turns, axons fasciculation and defasciculation, and target invasion and selection.

(4) The four guidance mechanisms are mechanistically related and phylogenetically conserved. There are parallels between pathfinding events in nematodes, insects, and vertebrates.

(5) There is redundancy of guidance cues.

(6) A single growth cone may respond to the same cue in different ways at different points along its “journey”.

Chisholm & Tessier-Levigne 1999

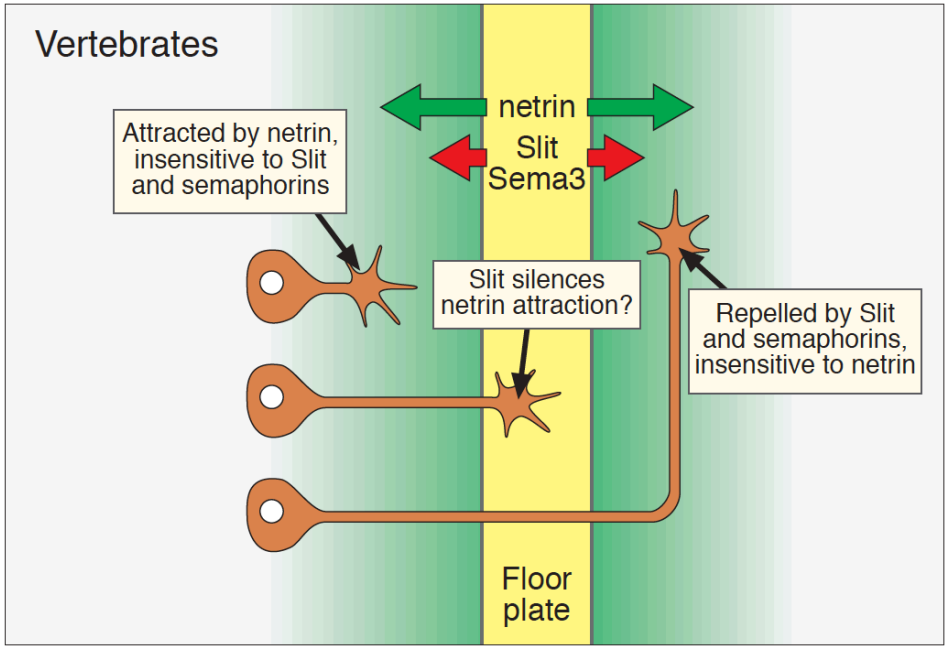


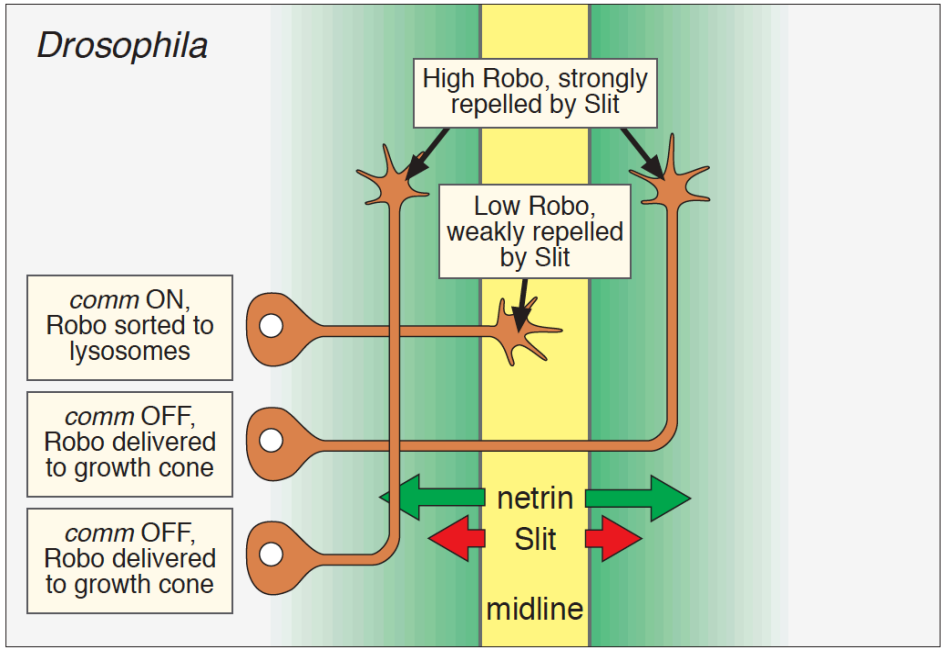
Development of connectivity

Example 1: Long-range guidance to and from the midline & local guidance at midline

- Axons that link the two sides of the nervous system project toward and across the midline, forming axon commissures.

- Long-range cheomoattractants emanating from the midline – the netrins.

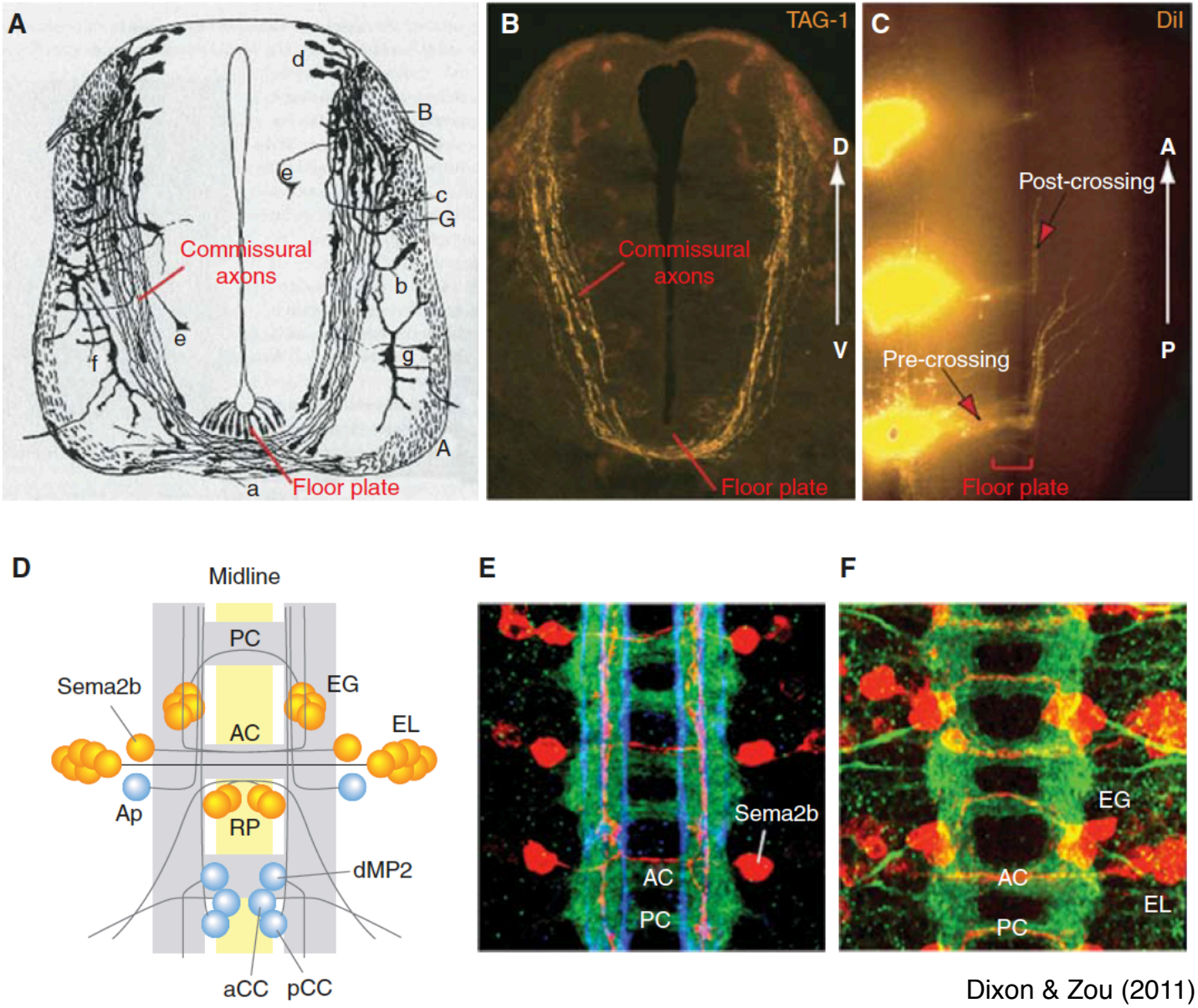




Dixon (2002)

For a more recent review, see Dixon & Zou (2011)

Development of connections

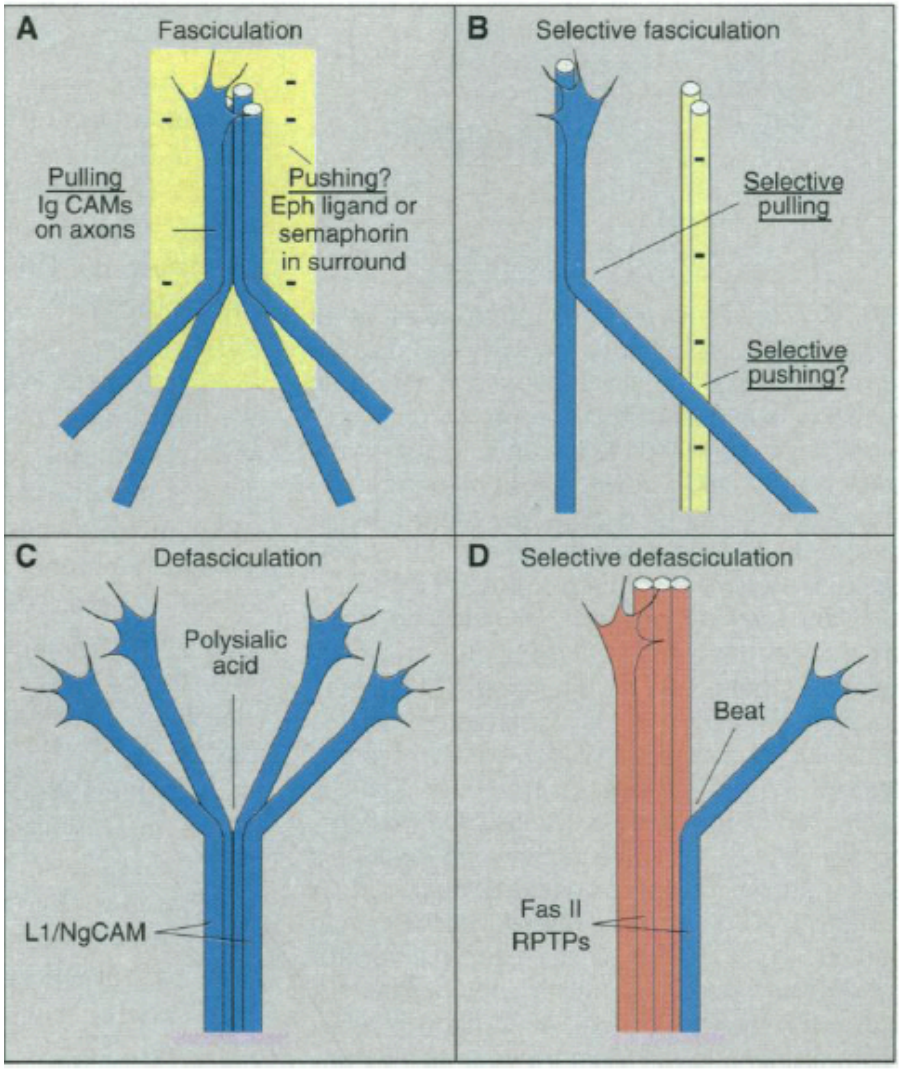


Dixon & Zou (2011)

Development of connectivity

Example 2: Regulation of axon fasciculation

- Growth cones often extend along the surface of other axons in axon fascicles to initiate the next leg of their trajectory.



Development of connectivity

Example 3: Target selection

- **Invading the target region** is regulated by both pathway- and target- derived cues: -

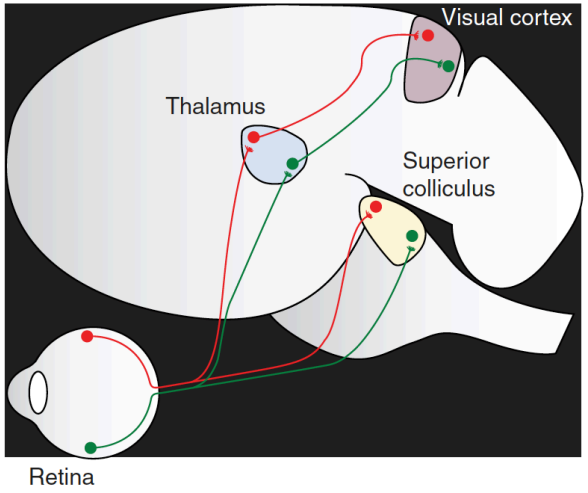
(1) 'Upward" gradient mechanisms: target invasion can be regulated by members of the nerve growth factor family of neurotrophins.

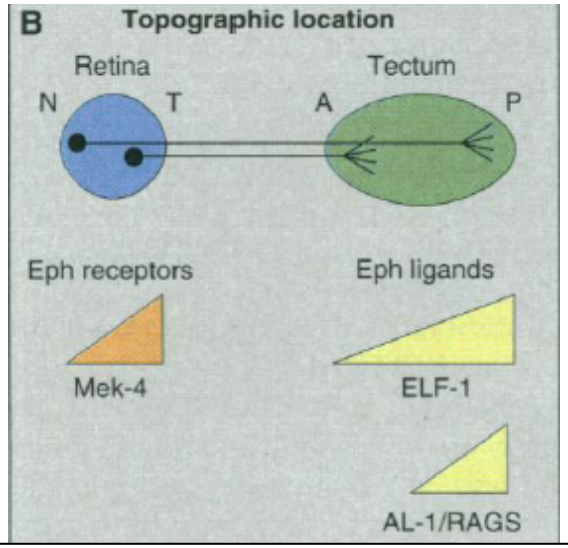
(2) "Downward" gradient mechanisms: axons "skirt" the target.

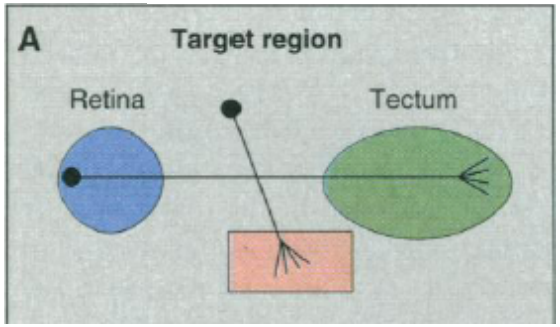
- **Generating topographic projections**: Topographically organized patterns of neuronal connections, in which neighboring neurons project to to neighboring sites in the target, occur throughout the nervous system. – the connections from retina to optic tectum/superior colliculus are the leading model (next slides)

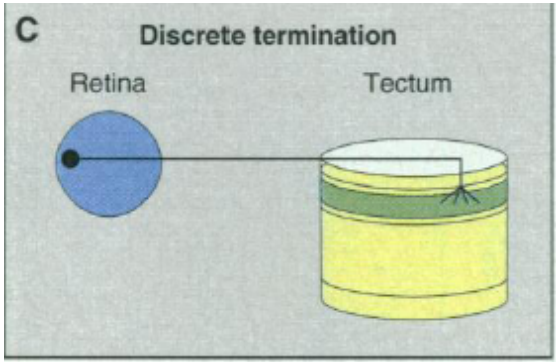
- **Selecting discrete targets**: After reaching their topographically appropriate sites retinal axons turn to seek their appropriate laminar termination site within the tectum, presumably in response to laminar-specific guidance cues.

Development of connectivity









Sperry's (1963) chemoaffinity hypothesis

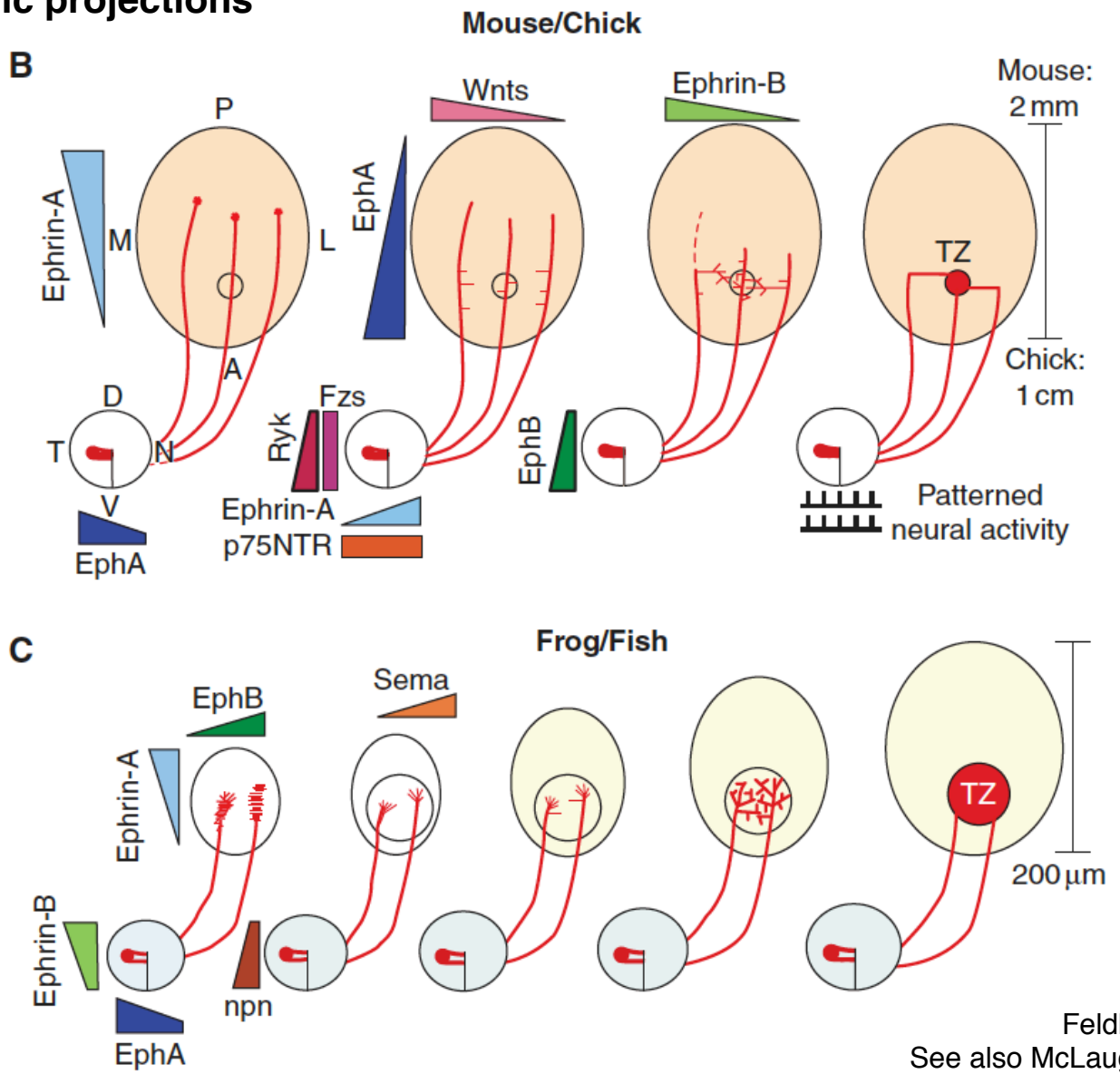
-The molecular tags on projecting axons and their target cells are distributed in complementary gradients that mark corresponding points in both the projecting and target neural populations.

- Each point in optic tectum has a unique molecular address determined by the graded distribution of the topographic guidance molecules along its two axes.

- Each retinal ganglion cell has a unique profile of receptors for those molecules that would result in a position-dependent, differential response to them by axons.

Development of connectivity

Topographic projections

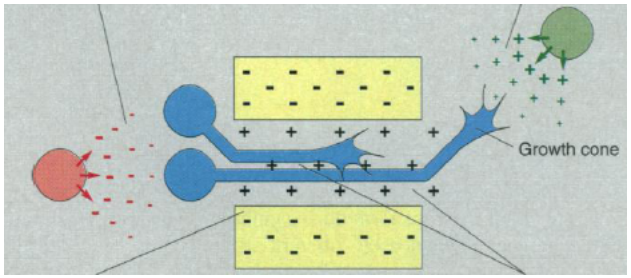


Feldheim & O'Leary (2011)
See also McLaughlin & O'Leary (2005)

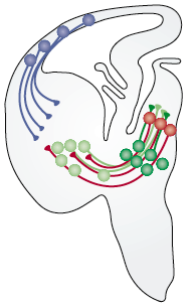
Development and evolution of connectivity

Development of connectivity

Mechanisms of axon guidance



Development of cortical and thalamocortical connections



Principles of evolution of connectivity

Epigenetic population mapping

Parcellation hypothesis

Connectional invasion and displacement hypothesis

Principles of network design

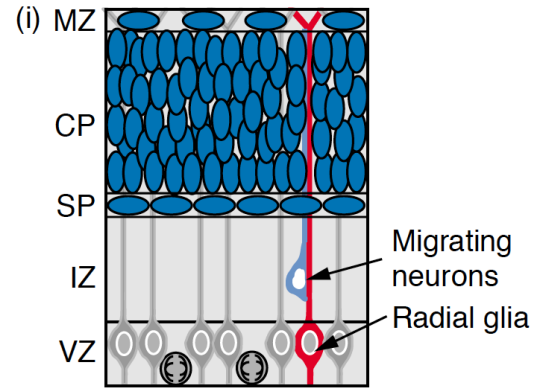
Development of connections

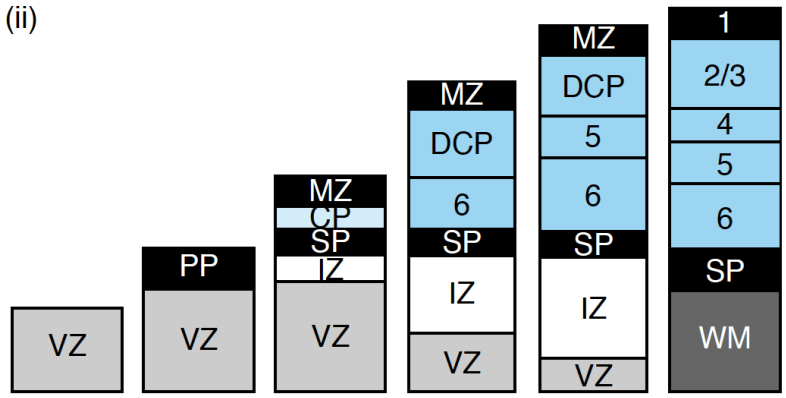
THALAMOCORTICAL DEVELOPMENT: HOW ARE WE GOING TO GET THERE?

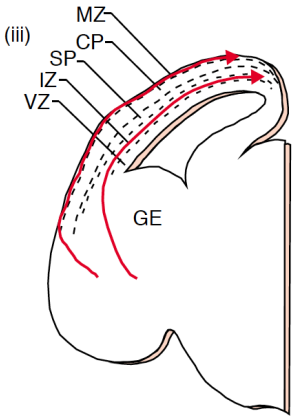
Guillermina López-Bendito and Zoltán Molnár

The arealization of the mammalian cortex is believed to be controlled by a combination of intrinsic factors that are expressed in the cortex, and external signals, some of which are mediated through thalamic input. Recent studies on transgenic mice have identified families of molecules that are involved in thalamic axon growth, pathfinding and cortical target selection, and we are beginning to understand how thalamic projections impose cytoarchitectonic differentiation on the developing cortex. By unravelling these mechanisms further, we should be able to increase our understanding of the principles of cortical organization.

O'Leary & Nakagawa, 2002







REVIEW

1. Most neocortical neurons, including all projection neurons are generated within **ventricular zone** (**VZ**) and subventricular zone (SVZ — between VZ and IZ – intermediate zone) in the lateral ventricle.

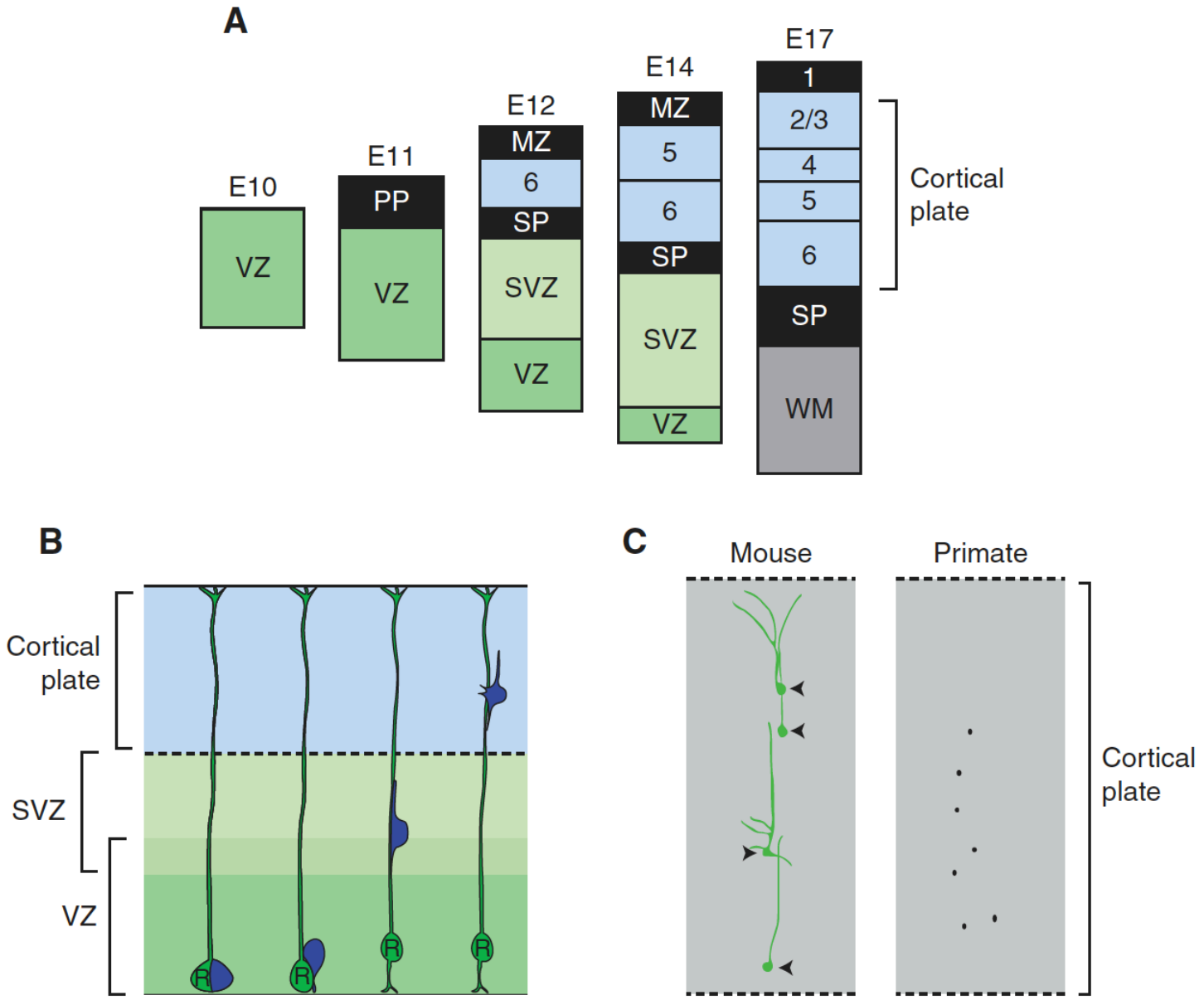
2. The first postmitotic neurons accumulate on the top of VZ, forming the **preplate** (**PP**), positioned just beneath the pial surface.

3. Neurons subsequently generated in the VZ migrate along **radial glia**, aggregate within the PP, and form the **cortical plate** (**CP**), which splits the PP into a superficial **marginal zone (MZ**) and a **deep subplate** (**SP**).

4. The CP gradually differentiates in a deep to superficial pattern, forming layers 6 though 2 of the adult neocortex.

5. The MZ contains Cajal-Retzius neurons that express reelin, a large sectreted protein required for radial migration of CP neurons and their formation of layers.

6. The SP contains local and long-distance projection neurons, proposed to serve a number of critical roles in cortical development, among them the pioneering of the internal capsule and the formation of major input and output projections paths between the cortex and the rest of the central nervous system.

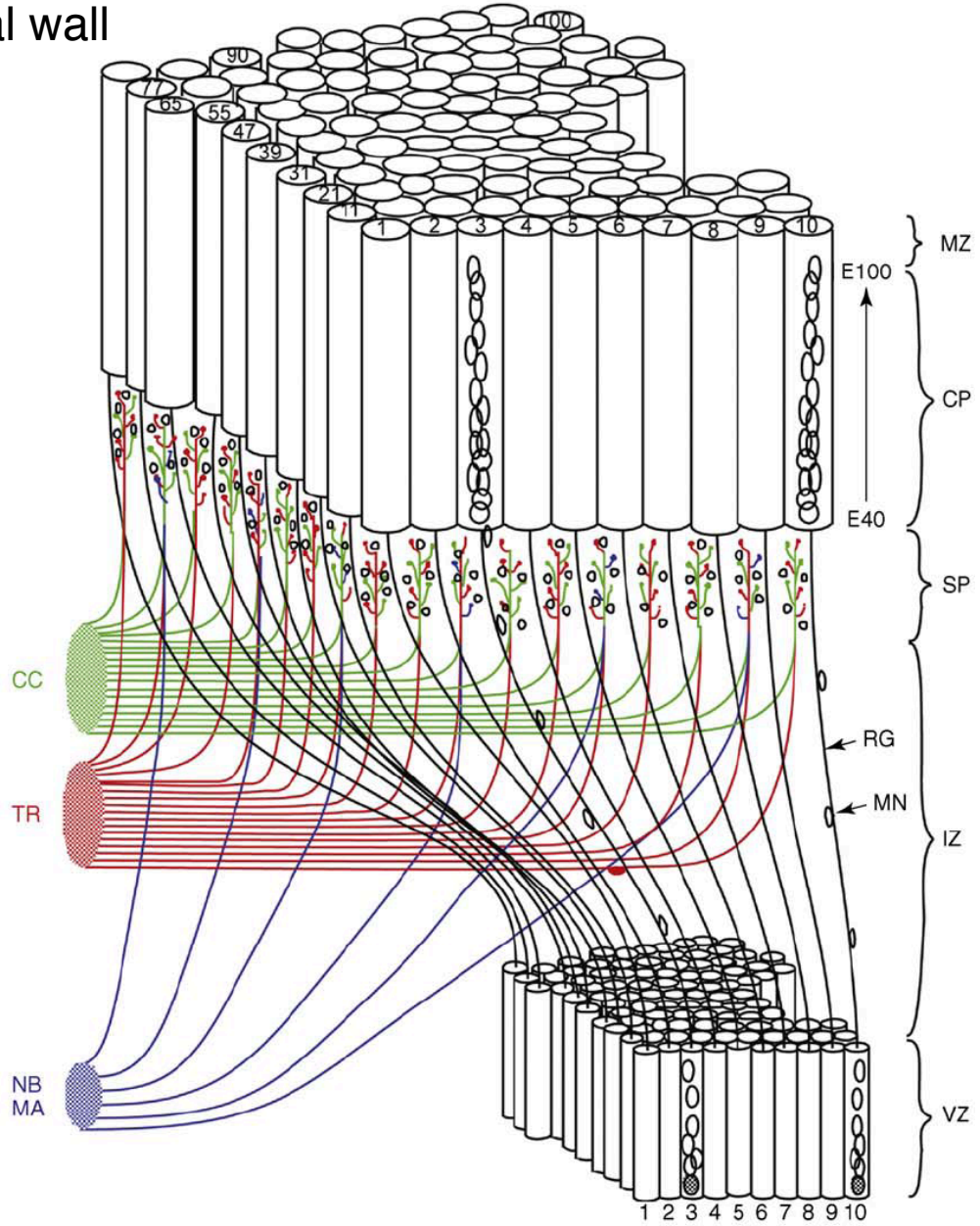

A
E10
VZ
E11
PP
VZ
E12
MZ
6
SP
SVZ
VZ
E14
MZ
5
6
SP
SVZ
VZ
E17
1
2/3
4
5
6
SP
WM
Cortical plate
B
Cortical plate
SVZ
VZ
R
R
R
R
C
Mouse
Primate
Cortical plate

Rakic et al, 2009

Monkey fetal cerebral wall

CC: Cortico-cortical connection

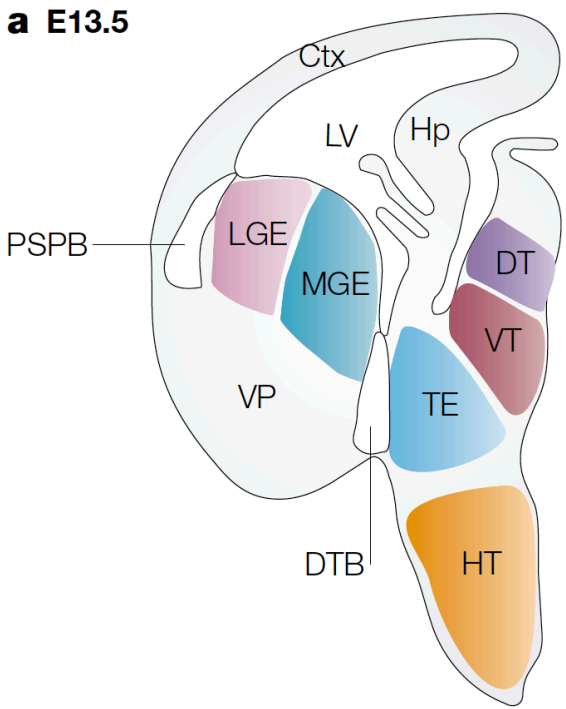
TR: thalamic radiation

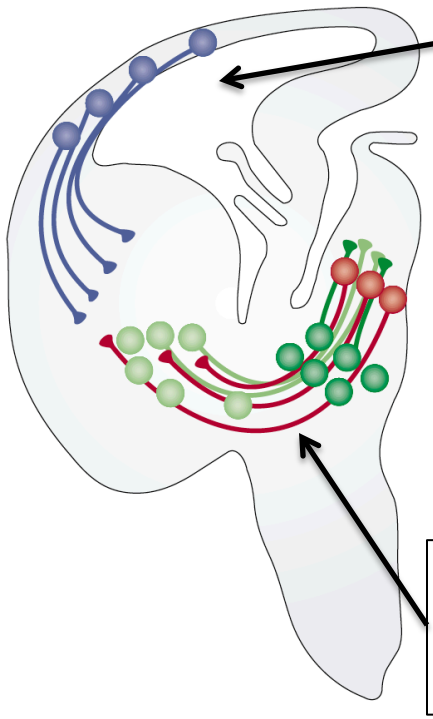


http://rakiclab.med.yale.edu/research/index.aspx

Development of connections

- Thalamus and cortex develop synchronously.
- Most thalamic neurons in the rat are born between embryonic day (E) 13 and E19.
- Second and third week of gestation: neocortex and dorsal thalamus start to link each other through reciprocal connections.



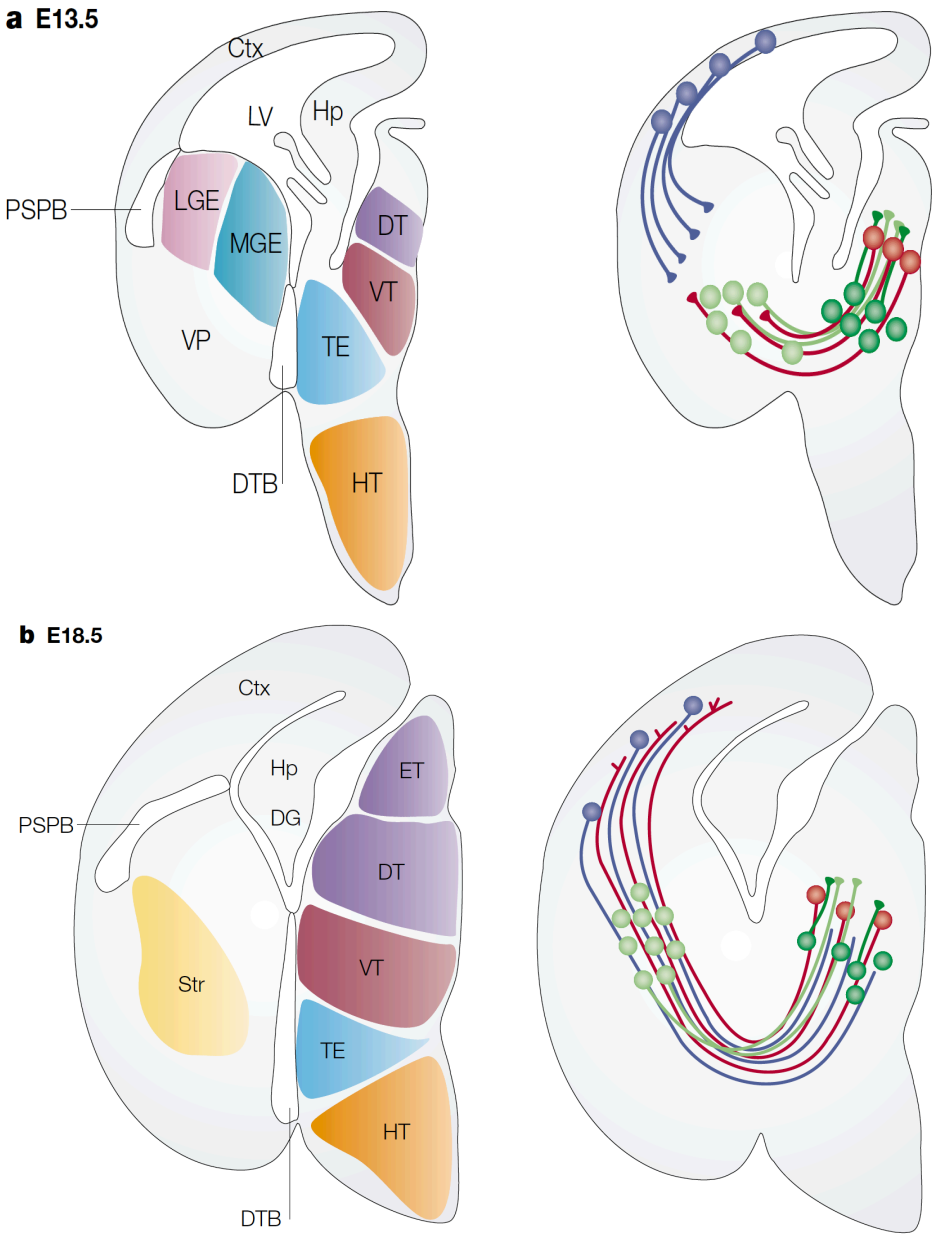


Corticofugal Axons (blue lines)

Thalamocortical Axons (red lines)

Emerging boundary zones with distinct molecular properties:
- DTB – diencephalic-telencephalic boundary
- PSPB – pallial-subpallial boundary

Development of connections



Development of connections

Factors that affect the growth of thalamocortical axons:

(1) Guidance molecules in the thalamocortical pathway — see slide

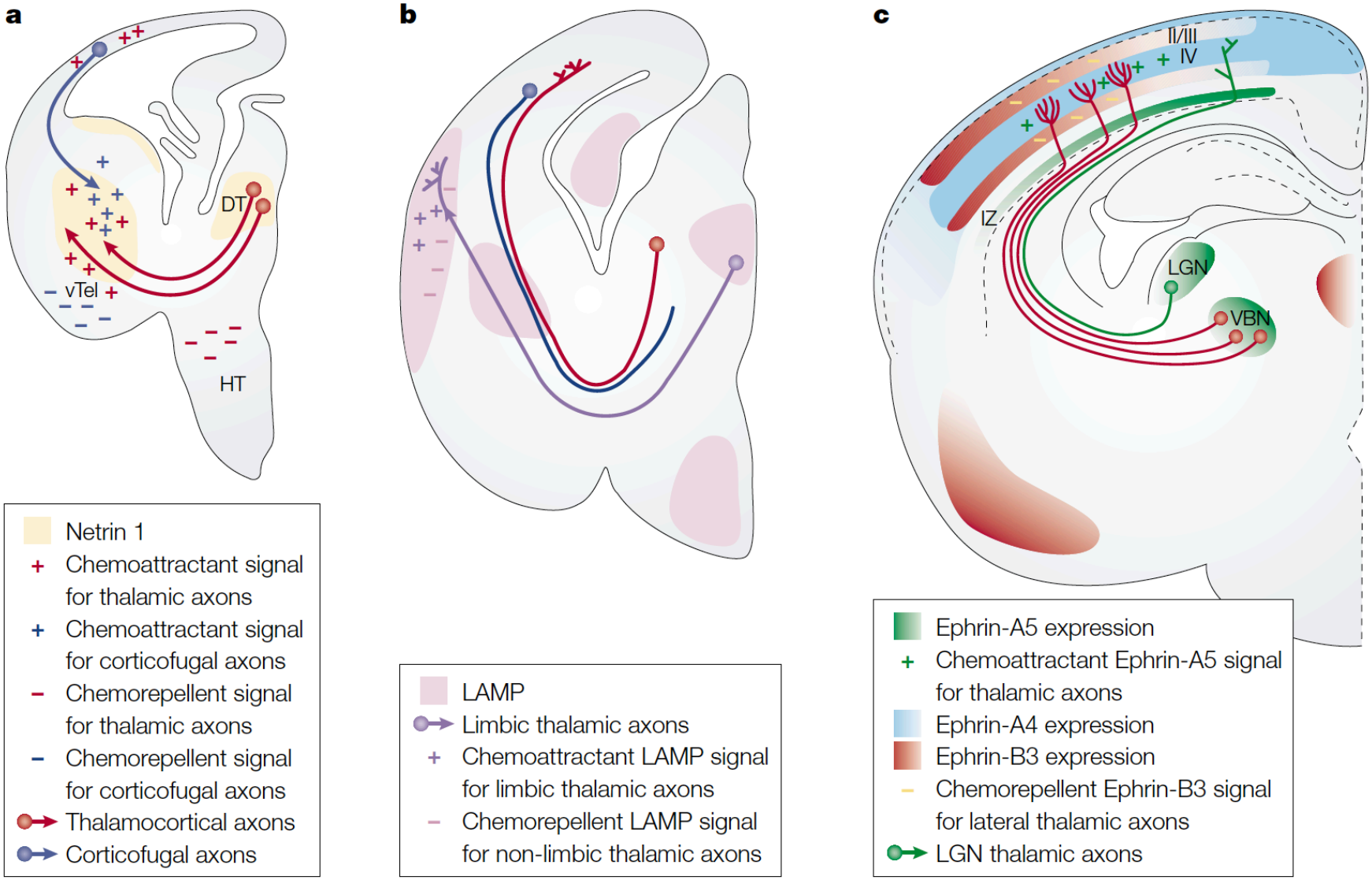
(2) Forebrain patterning and transcription factors — see slide

(3) Interactions with other cells and fibers

(4) Interactions between thalamic and cortical axons —" handshake hypothesis"

Development of connections

(1) Guidance molecules in the thalamocortical pathway

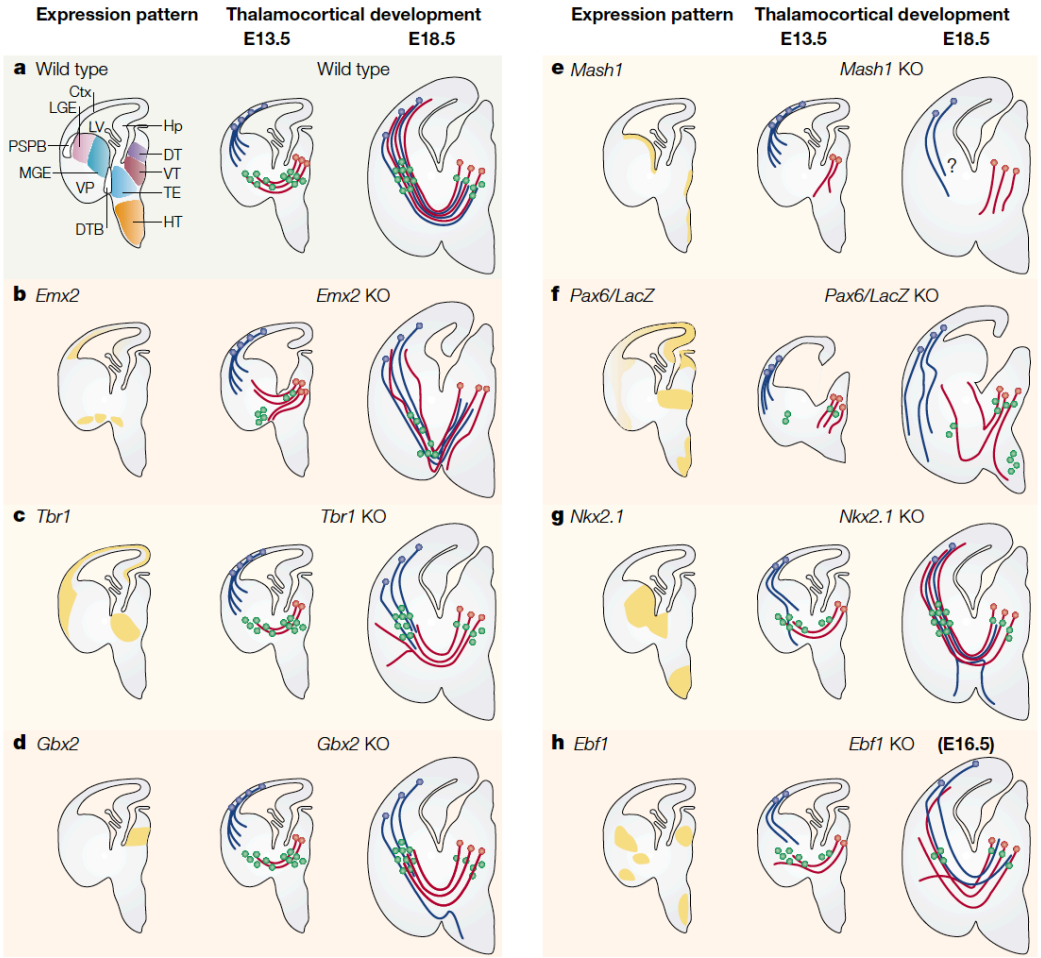


Development of connections

(2) Forebrain patterning and thalamocortical development

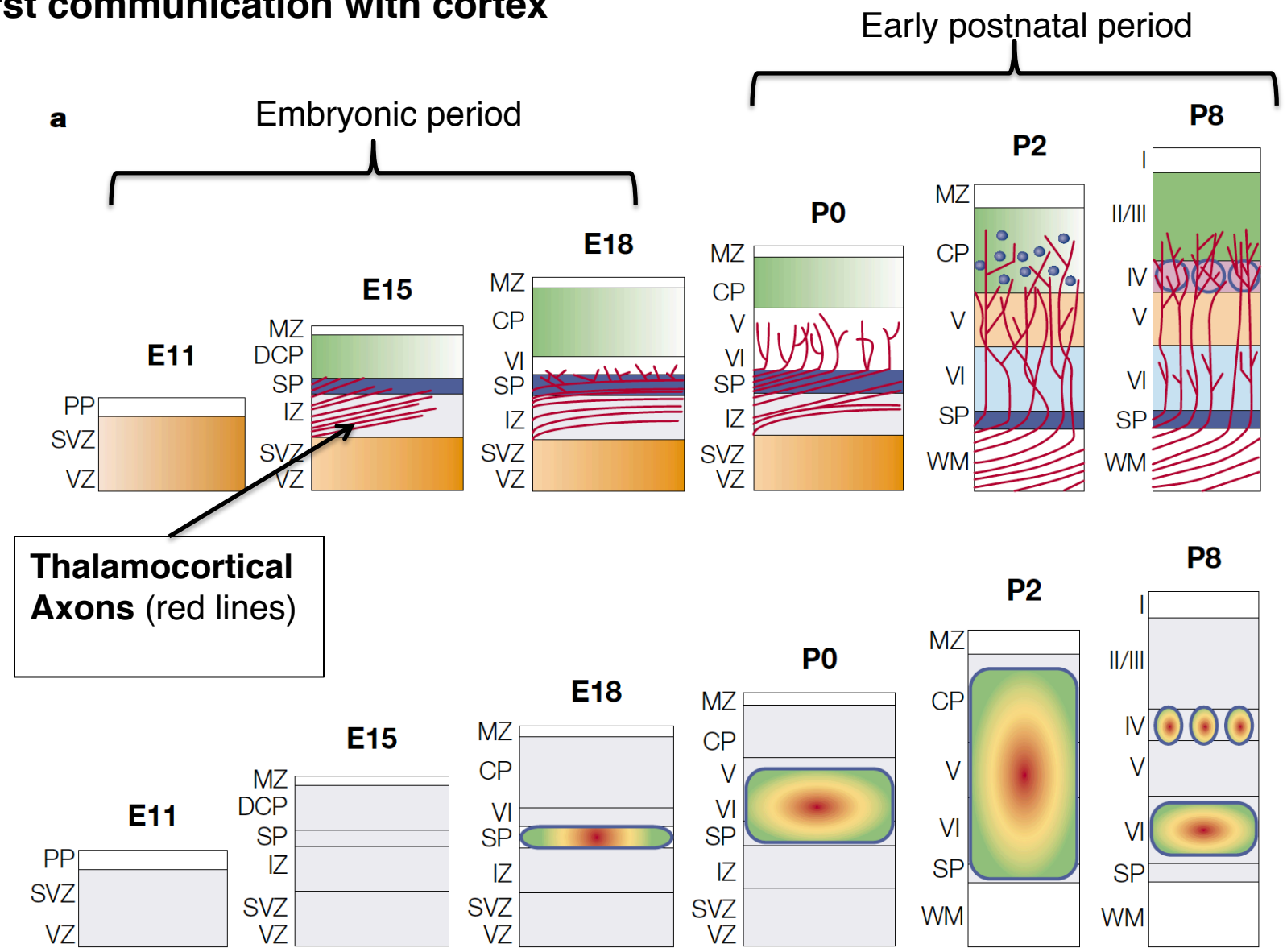
- Guidance molecules that modulate pathfinding of thalamocortical axons are in turn controlled by regulatory genes and transcription factors in the forebrain.

- Mutants lacking transcription factors that are expressed along the axons' rote of navigation cause abnormalities of thalamocortical development.



Development of connections

First communication with cortex



Development of connections

Do thalamocortical axons contribute to cortical patterning?

- The initial expression of region-specific and lamina-specific markers is probably independent of thalamic innervation.

- But the differentiation of many of the anatomical features that distinguish different cortical areas depends to a large extent on the input of thalamocortical axons.

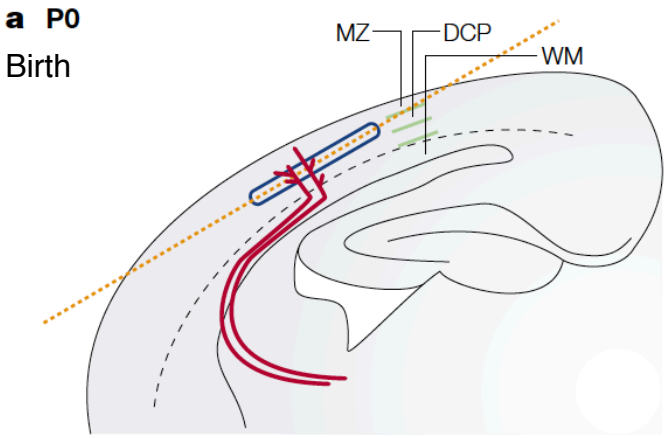
- Cortical regionalization is initially created by the graded expression of various genes, and thalamic input controls the later stages of area subdivision through activity-dependent or independent mechanisms.

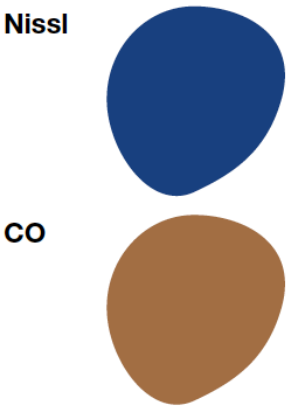
- But there is also some evidence that thalamic afferents release a diffusable factor that promotes proliferation of neurons and glia by cortical VZ – Dehay et al. (2001)

Development of connections

Do thalamocortical axons contribute to cortical patterning?

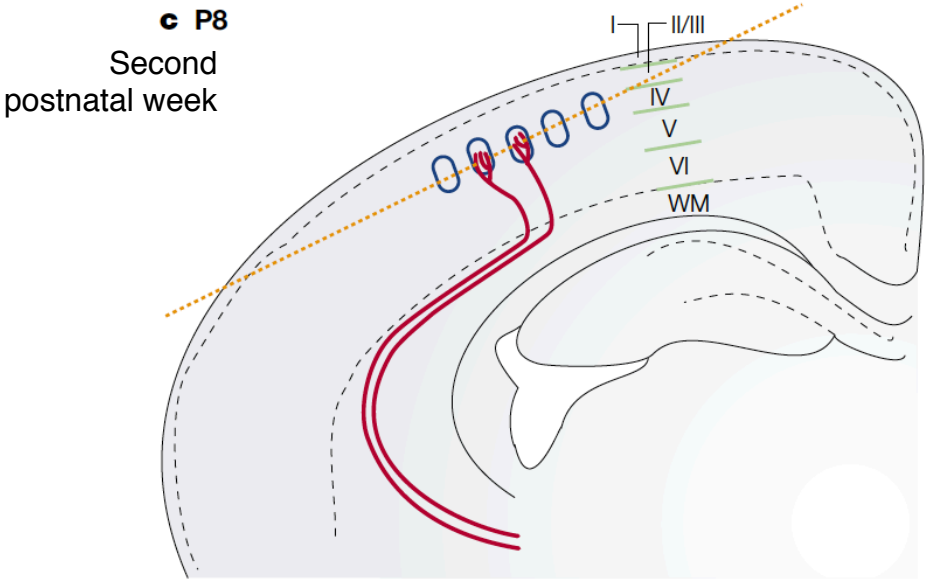
Somatosensory cortex of rodents - BARREL cortex

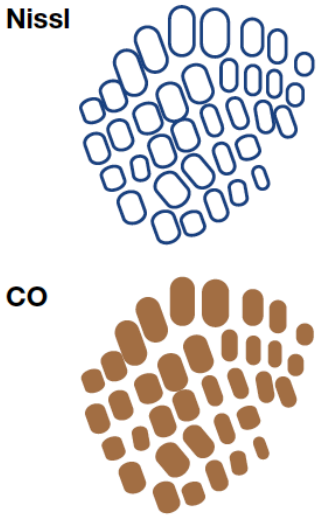




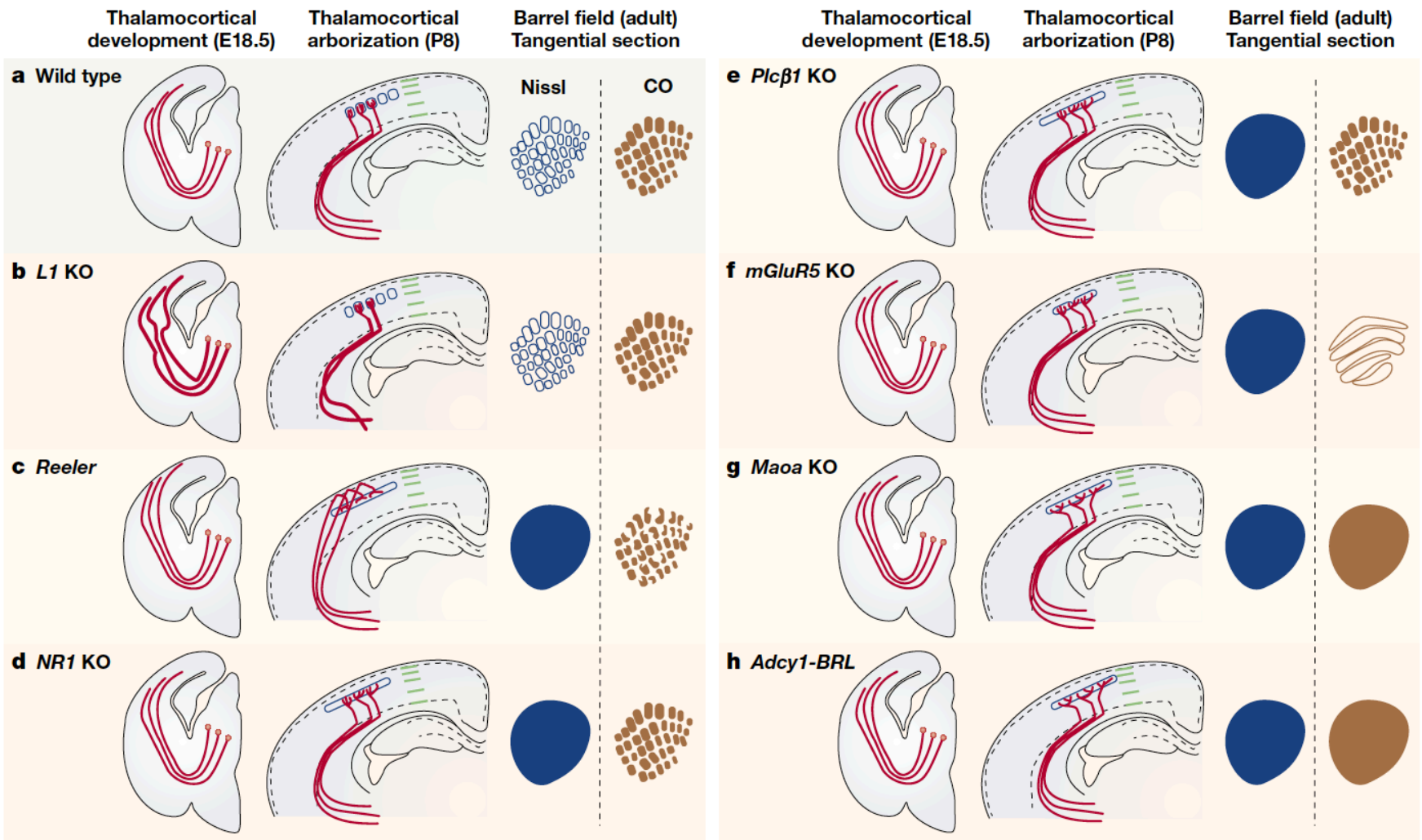
Cells in layer IV shown through Nissl staining.

Dendrites in layer IV shown through cytochrome oxidase (CO) staining.



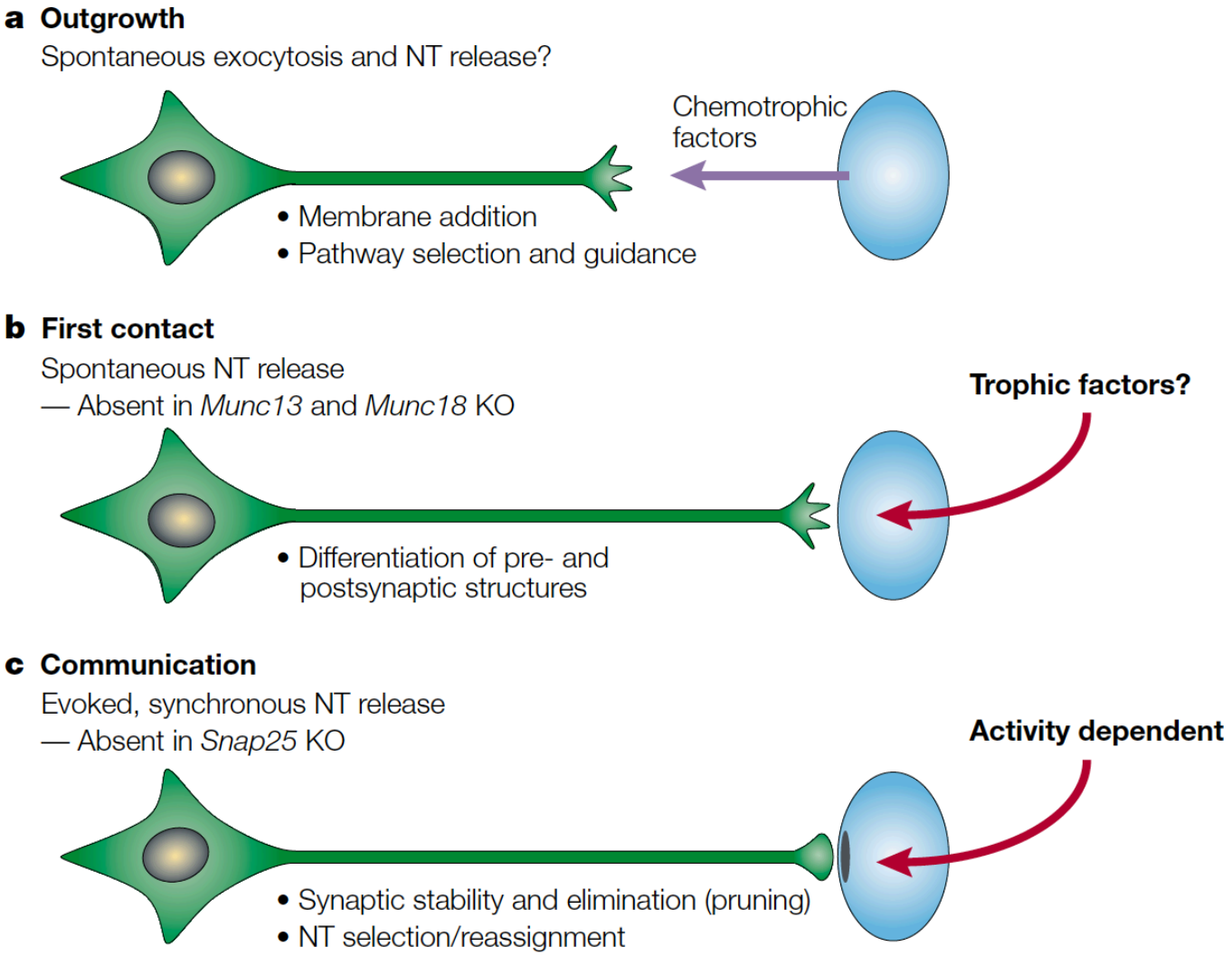


Development of connections



Development of connections

Does neural activity play a part in thalamocortical development?



Development of connections

More readings:

Review

Trends in Neurosciences Vol.32 No.5

Cell PRESS

Decision by division: making cortical maps

Pasko Rakic, Albert E. Ayoub, Joshua J. Breunig and Martin H. Dominguez

Annu. Rev. Neurosci. 1994. 17:185–218

THE SUBPLATE, A TRANSIENT NEOCORTICAL STRUCTURE: Its Role in the Development of Connections between Thalamus and Cortex

Karen L. Allendoerfer

Neuron

Article

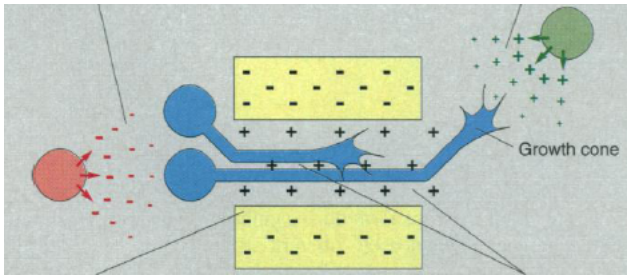
Slit2 Activity in the Migration of Guidepost Neurons Shapes Thalamic Projections during Development and Evolution

Franck Bielle,[1,2,3] Paula Marcos-Mondejar,[4,9] Maryama Keita,[1,2,3,9] Caroline Mailhes,[1,2,3] Catherine Verney,[5,6] Kim Nguyen Ba-Charvet,[7] Marc Tessier-Lavigne,[8] Guillermina Lopez-Bendito,[4] and Sonia Garel[1,2,3,*]

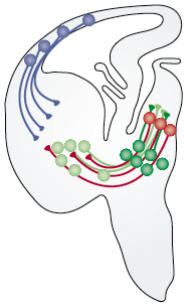
Development and evolution of connectivity

Development of connectivity

Mechanisms of axon guidance



Development of cortical and thalamocortical connections



Principles of evolution of connectivity

Epigenetic population mapping

Parcellation hypothesis

Connectional invasion and displacement hypothesis

Principles of network design

Evolution of connectivity

Striedter 2005

Epigenetic population mapping – Katz and Lasek 1978

- Most brain regions contain 20-80% more neurons at the end of neurogenesis than in adulthood. The excess is eliminated by naturally occurring cell death.

- Motor neuron loss is regulated, at least in part, by the amount of target issue that is available for innervation.

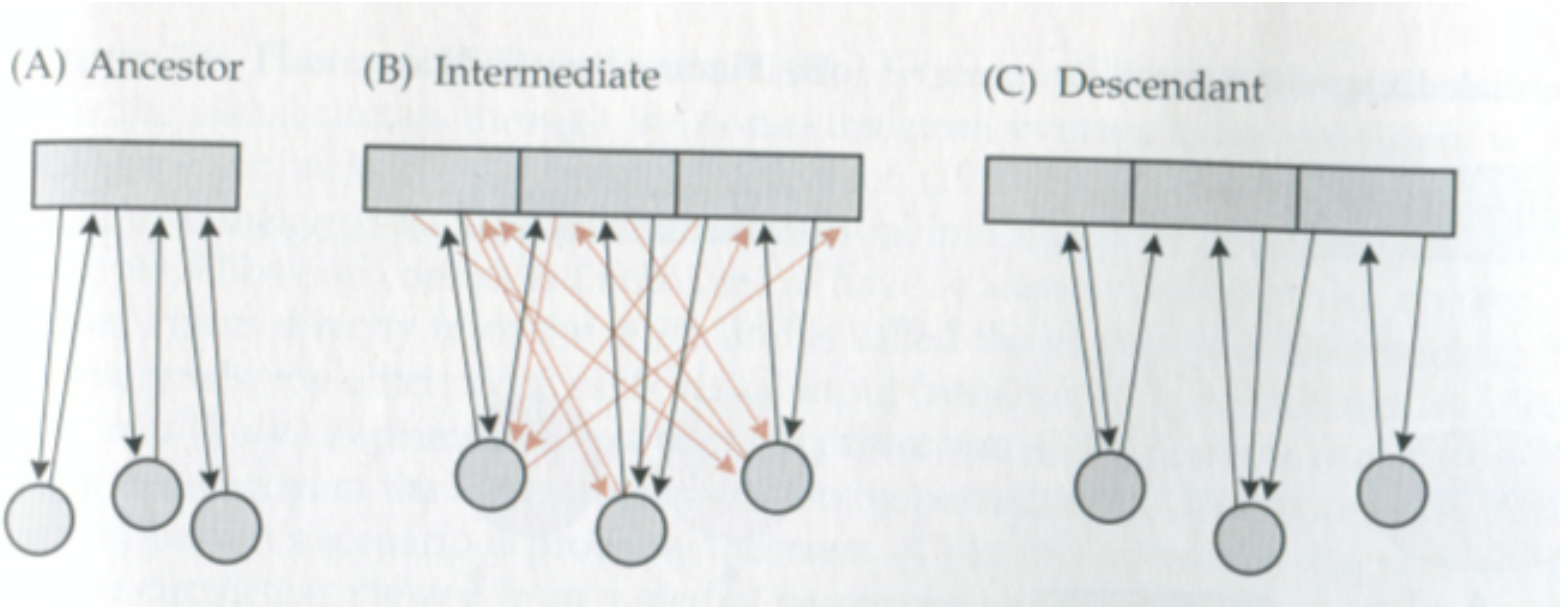
- Developing motor neurons compete with one another for some “trophic factor” that is produced by muscle fibers, taken up by the axon, and required for neuron’s survival. As a result for this competition for trophic support, the number of projection neurons is effectively matched to the number of available target cells.

Evolution of connectivity

Striedter 2005

Parcellation hypothesis – Ebbesson 1980

- “Nervous system becomes more complex by a process of parcellation that involves the selective loss of connections of the newly formed daughter aggregates and subsystems”.



Evolution of connectivity

Striedter 2005

Connectional invasion

- Evolution of projections to unusual targets, i.e., phylogenetic appearance of projections to targets that did not ancestrally receive homologous inputs

- Connectional invasion has occurred repeatedly as brains evolved.

- Deacon (1990) – displacement hypothesis: connectional invasion generally occurs when a brain region becomes disproportionately large in evolution.

Evolution of connectivity

EXUBERANCE IN THE DEVELOPMENT OF CORTICAL NETWORKS

Giorgio M. Innocenti and David J. Price‡*

NATURE REVIEWS | NEUROSCIENCE
VOLUME 6 | DECEMBER 2005 | 955

Evolution of connectivity

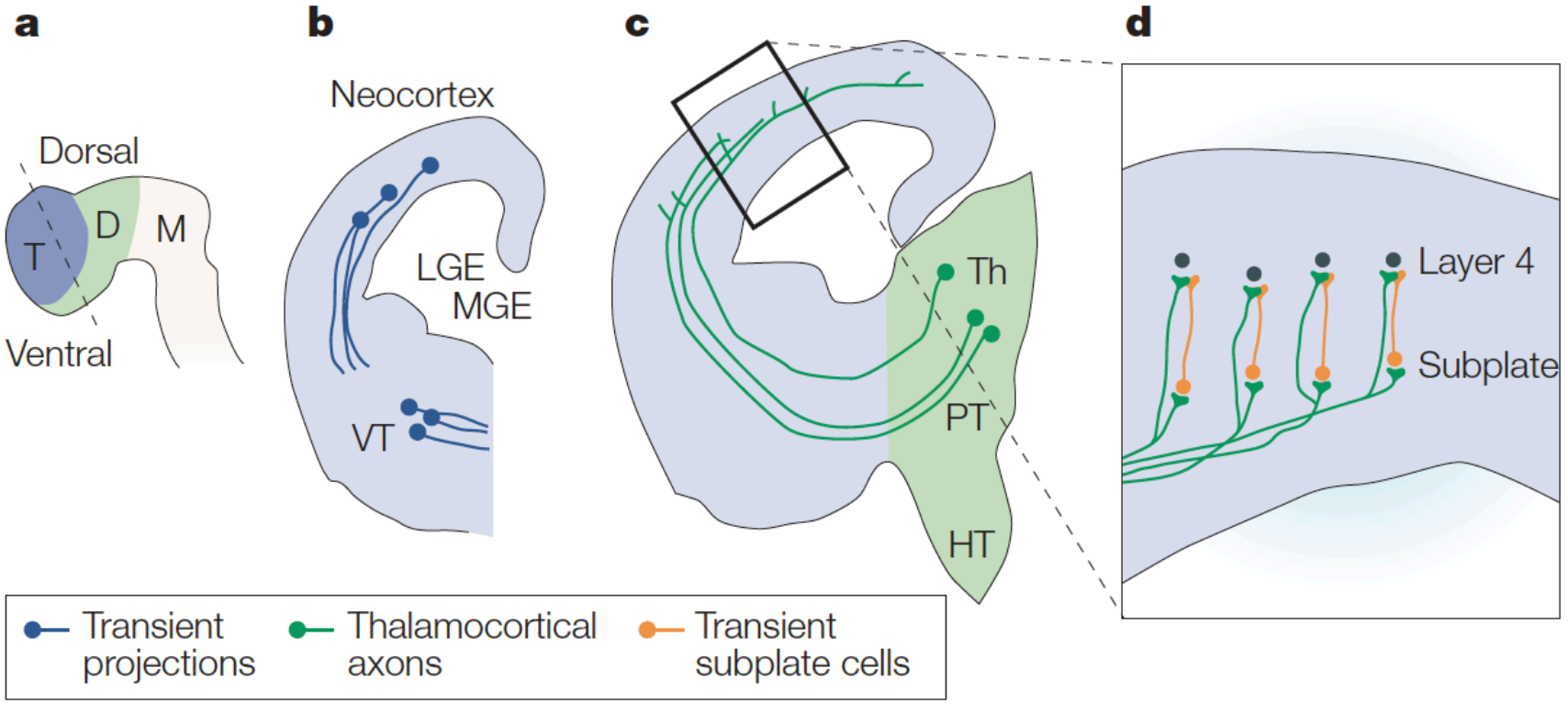
Developmental exuberance

- Exuberant development of connections: overproduction of axons, axonal branches and synapses, followed by selection

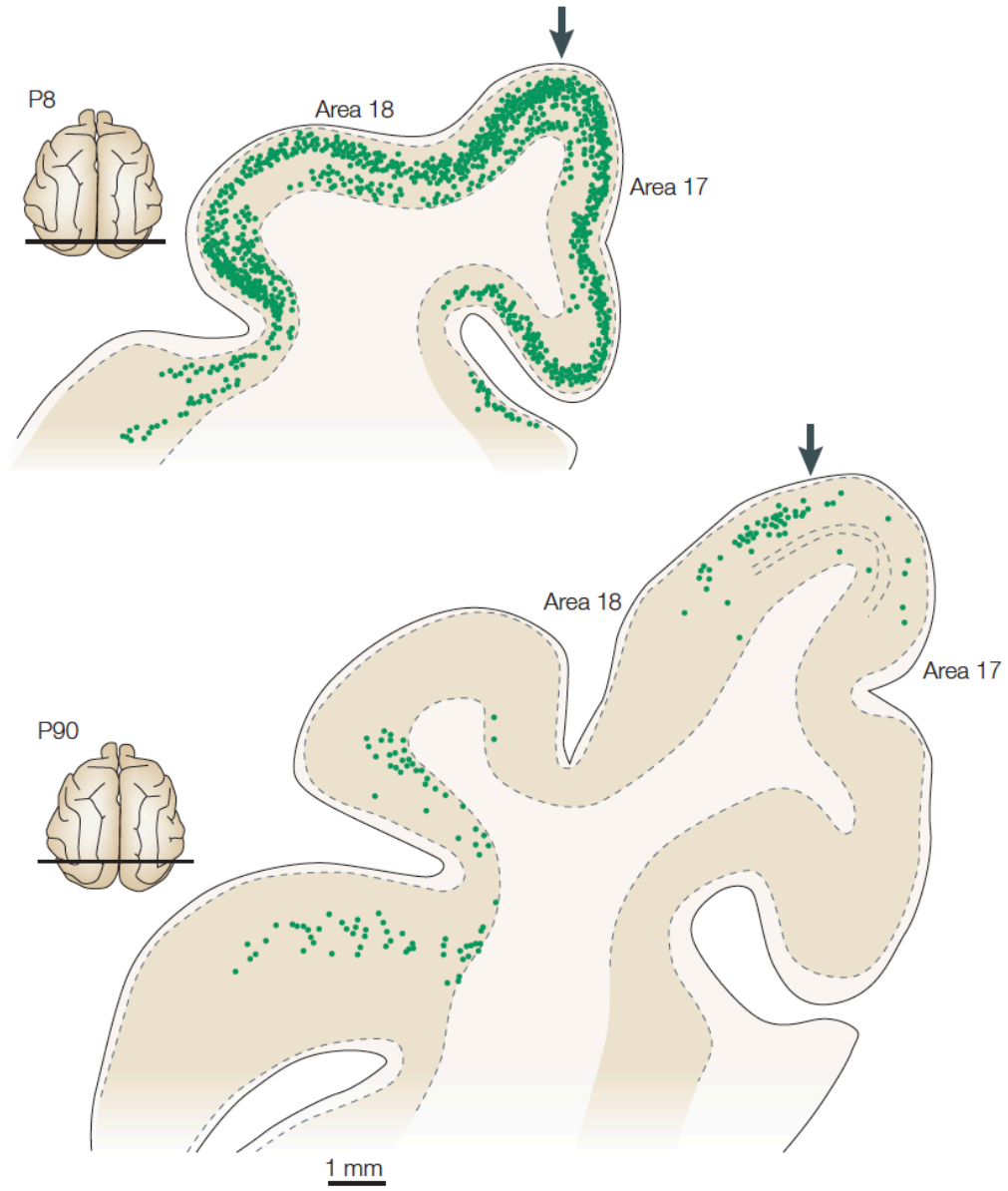
- Macroscopic exuberance: formation of transient projections between macroscopic brain parts.

- Microscopic exuberance: formation of transient structures that are involved in communication between neurons within a restricted cortical territory.

Evolution of connectivity



Evolution of connectivity



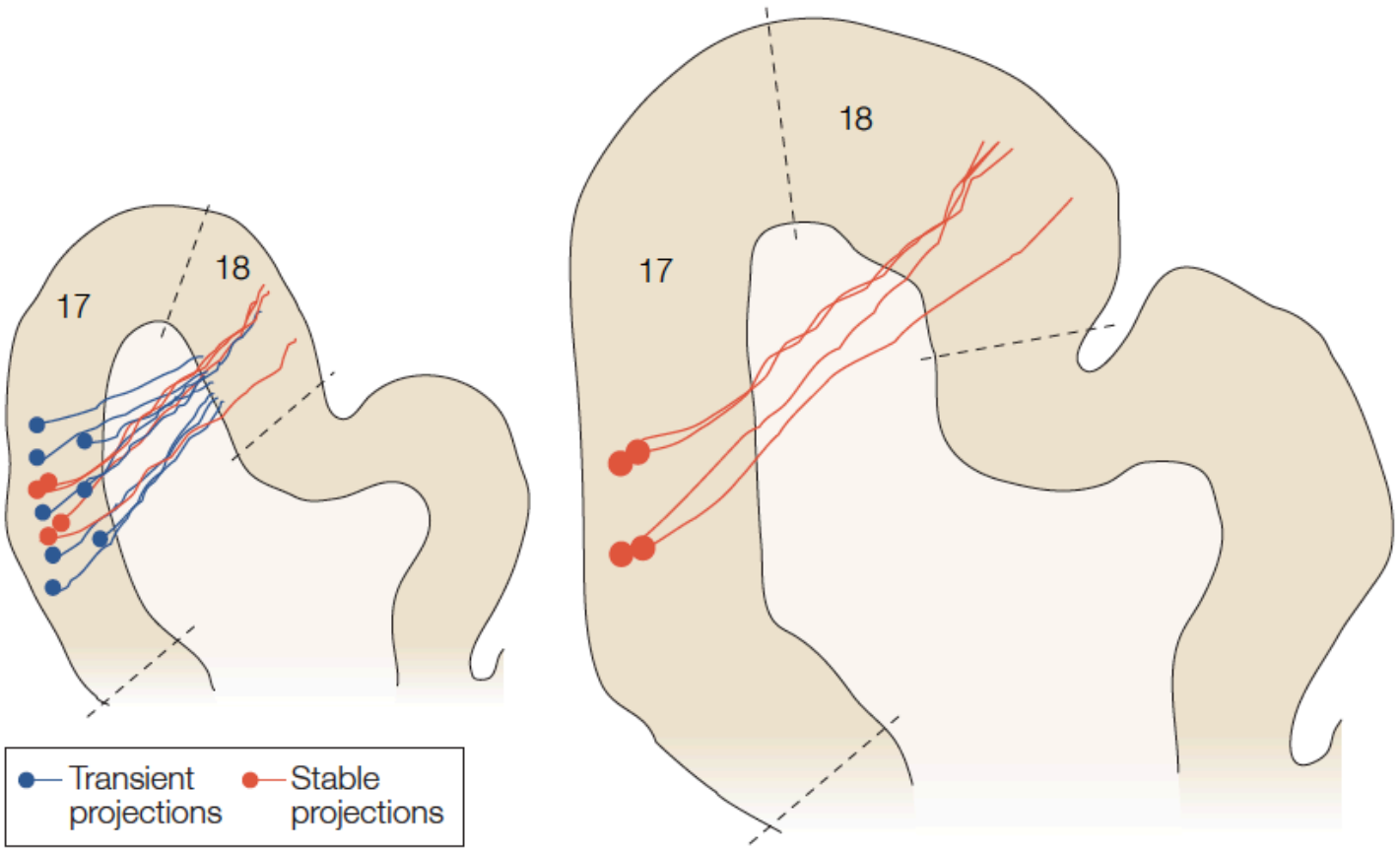
Evolution of connectivity

Functions of exuberant connections

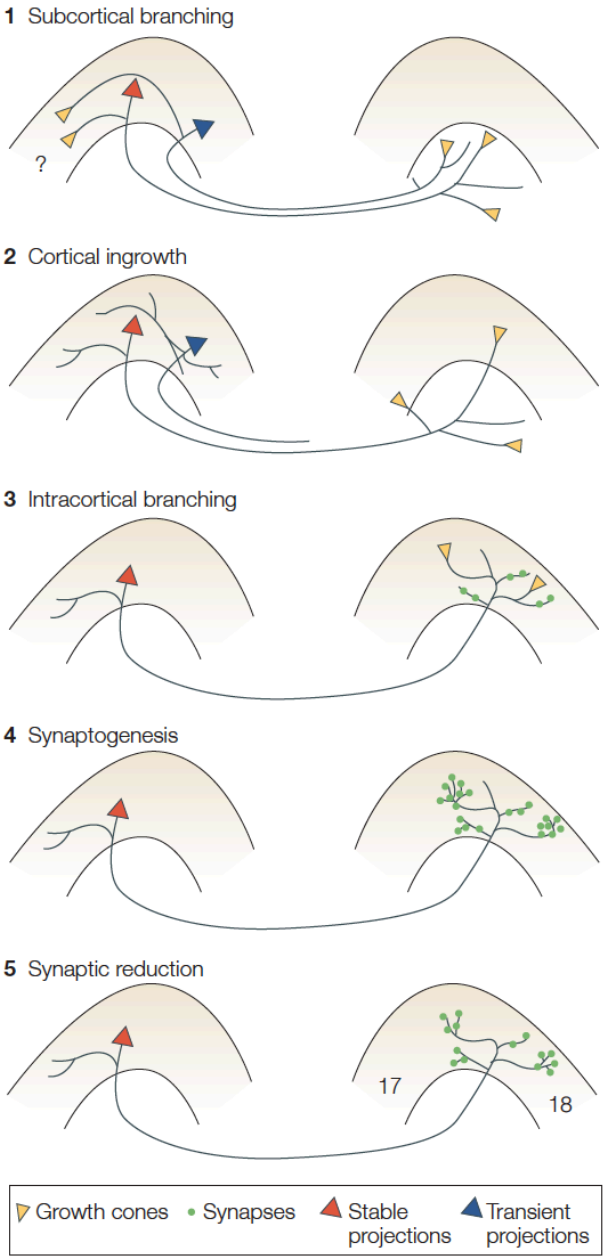
- Construction of cortical circuitry – case of thalamocortical development

- Provide a high degree of flexibility in the formation of cortical circuits — important for evolution?

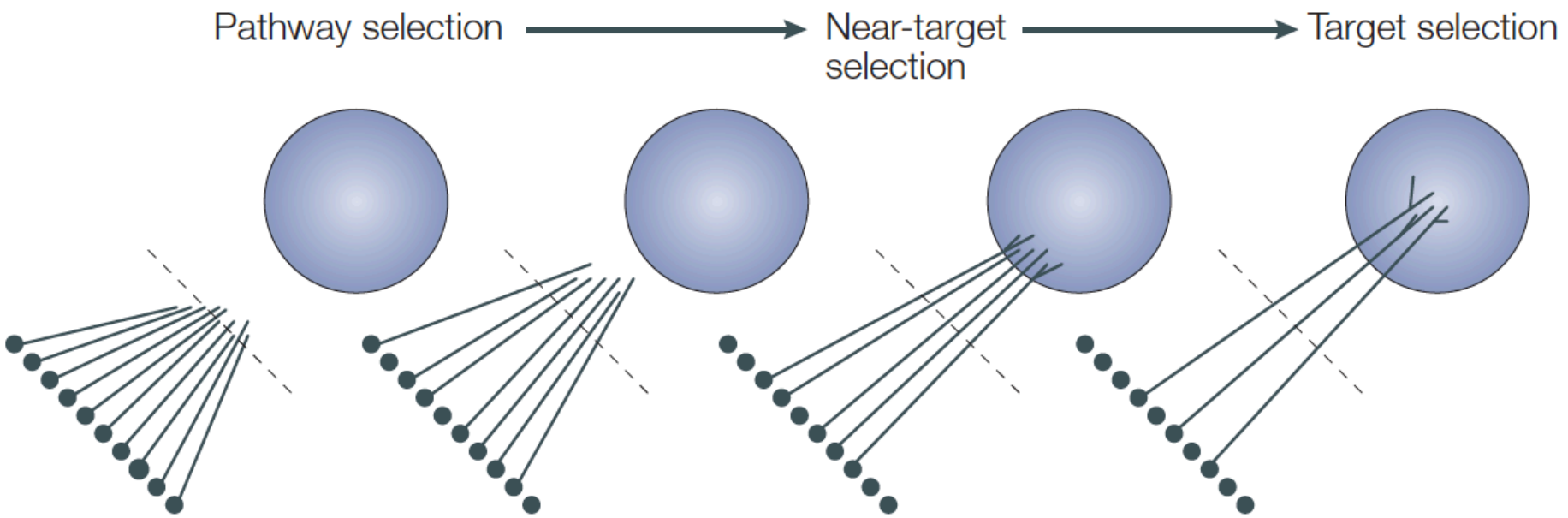
Evolution of connectivity



Evolution of connectivity



Evolution of connectivity



Evolution of connectivity

Factors that affect axonal selection

(1) Input from the periphery

(2) Axon-axonal competition

(3) Thyroid hormones, alcohol syndrome

(4) Markers of targets for persistent innervation

Evolution of connectivity

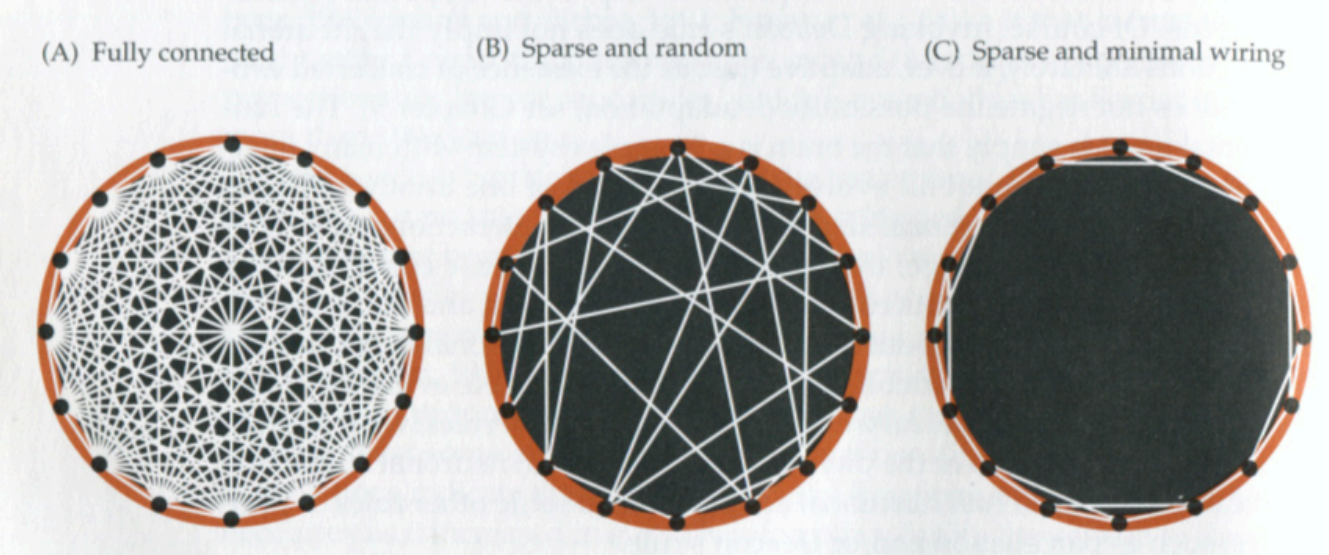
Striedter 2005

General principles of network design

- The number of connections in a fully interconnected network increase exponentially with neuron number, which means that such networks quickly become axon dominated as they increase in size – Deacon 1990, Ringo 1991.

- Real brains do not scale like that. The average neuron in real brains projects to roughly the same number of other neurons, no matter how large the brain – this helps to keep down the metabolic and physical costs of axonal "wiring". Therefore, real brains become sparsely interconnected as they increase in size.

- Minimum-wire principle: connections lengths are minimized.



Evolution of connectivity

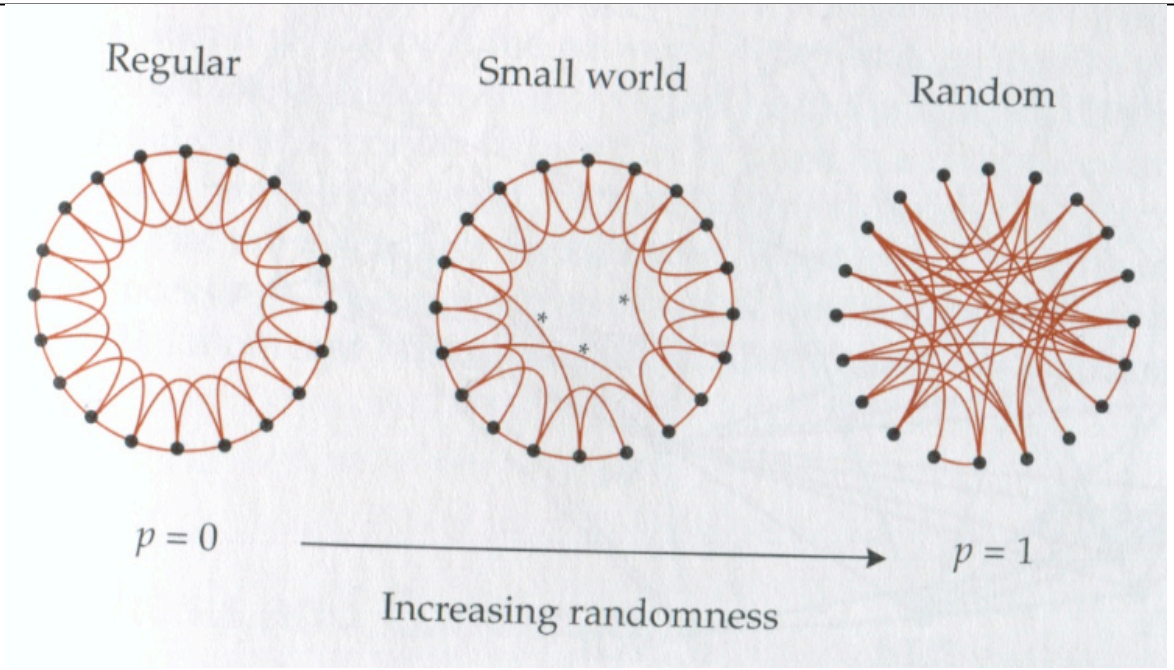
Striedter 2005

General principles of network design

- Problem: a network's average "degrees of separation" increases as connection lengths are minimized.

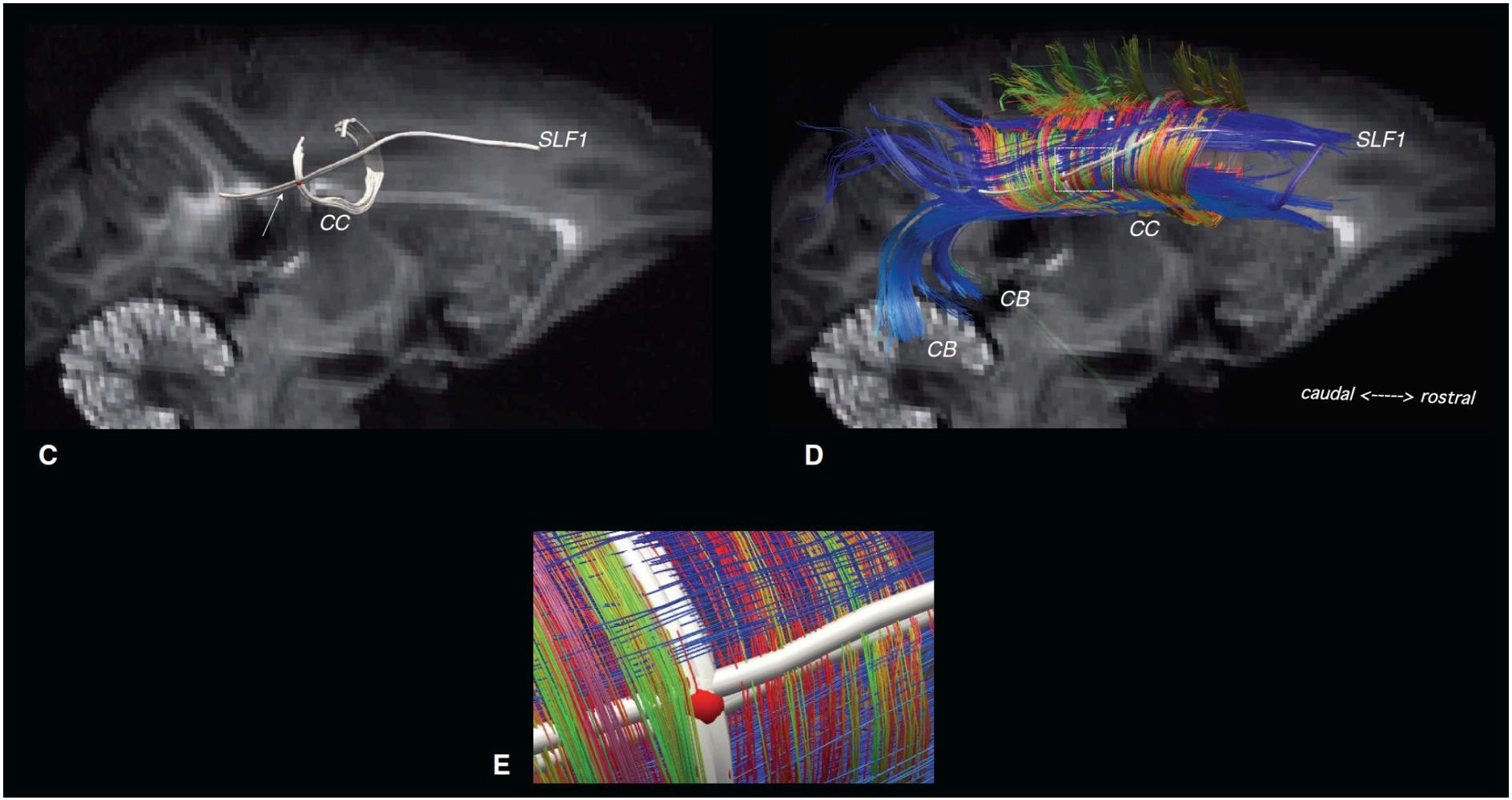
- Answer: not all connections are minimized— "small-world architecture".

- Visual cortex as small world architecture: Young(1992), Sporns et al. (2000) – did anyone go to the presentation?

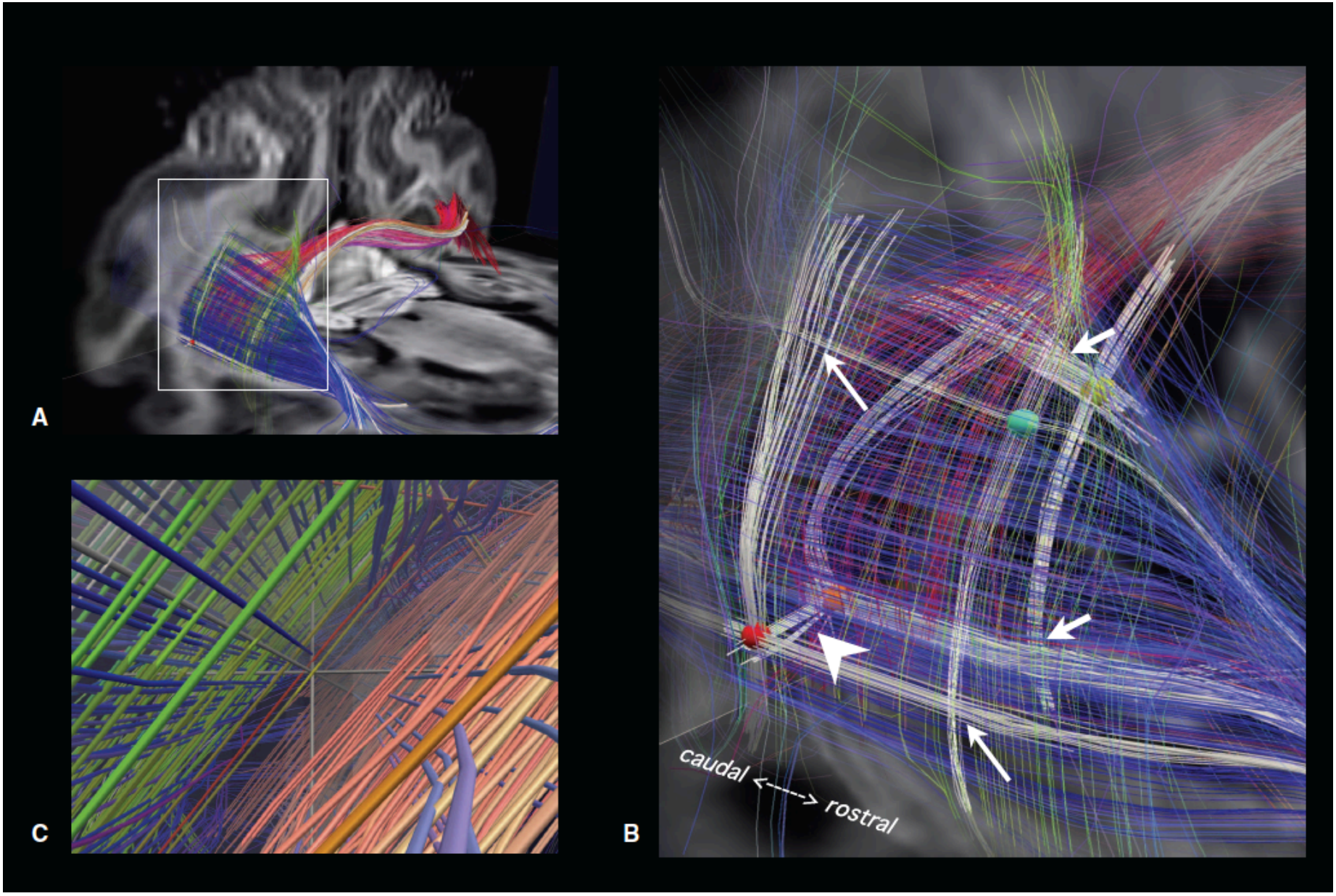


Extras

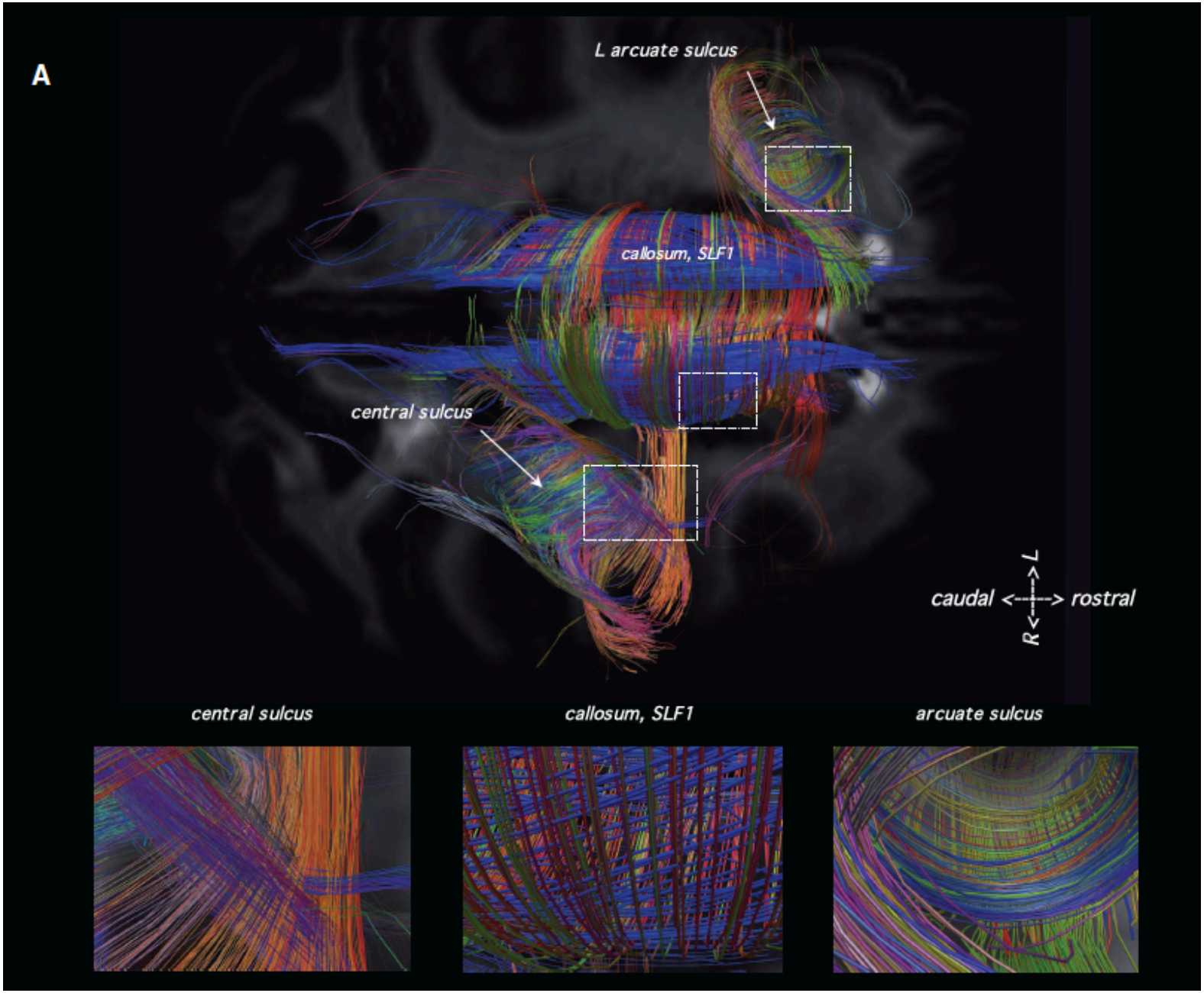
The Geometric Structure of the Brain Fiber Pathways
Van J. Wedeen *et al.*
Science **335**, 1628 (2012);
DOI: 10.1126/science.1215280



Extras



Extras


A
L arcuate sulcus
callosum, SLF1
central sulcus
caudal <---> rostral
L
R
central sulcus
callosum, SLF1
arcuate sulcus