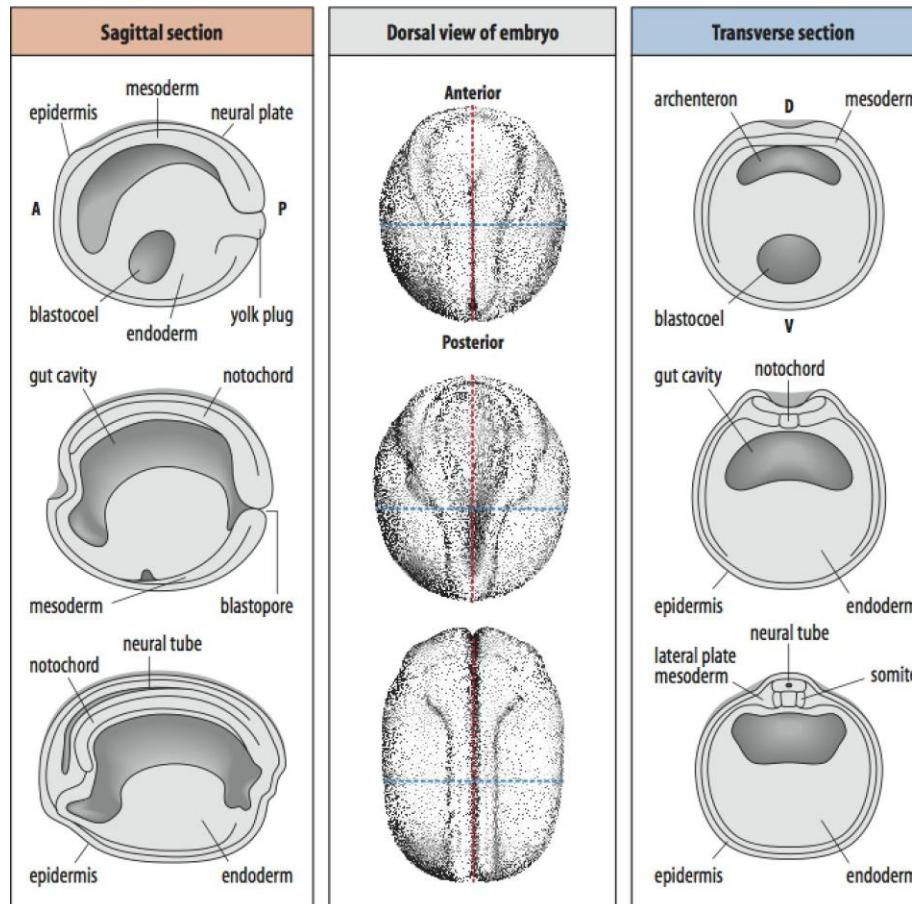


# Model organisms and developmental biology

仲寒冰

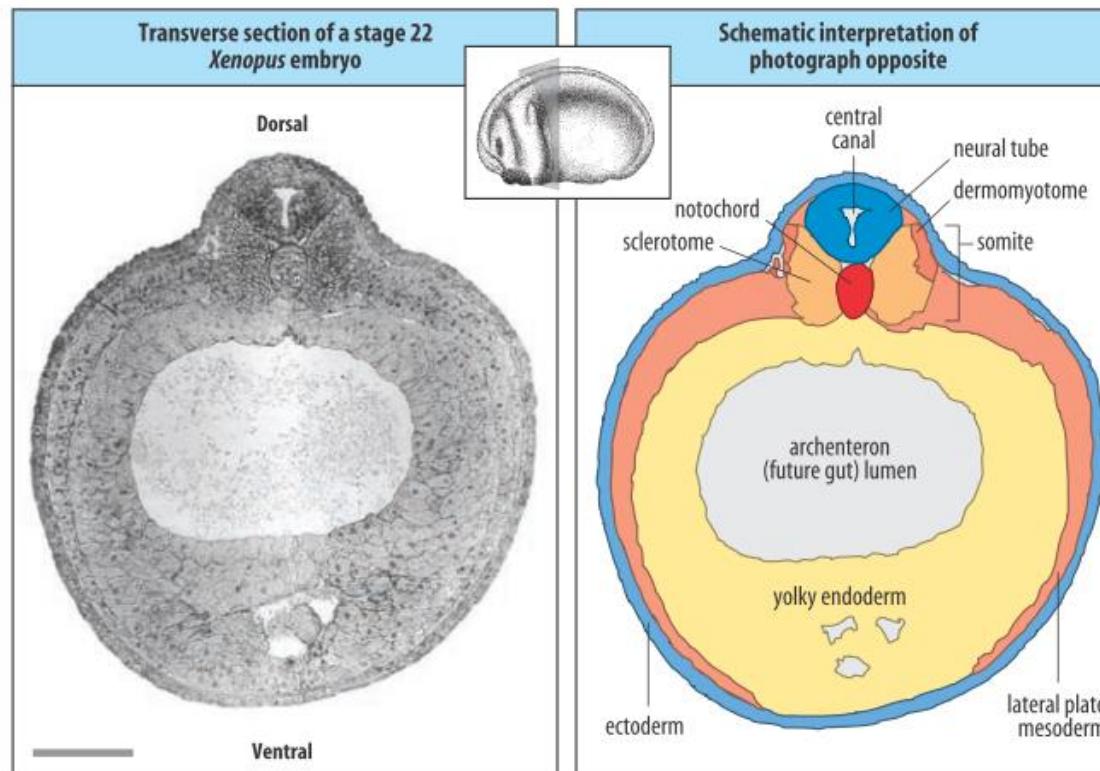
zhong.hb@sustc.edu.cn

# Neuralation in amphibians



Neuroectoderm = neural plate

# A cross-section through a *Xenopus* embryo



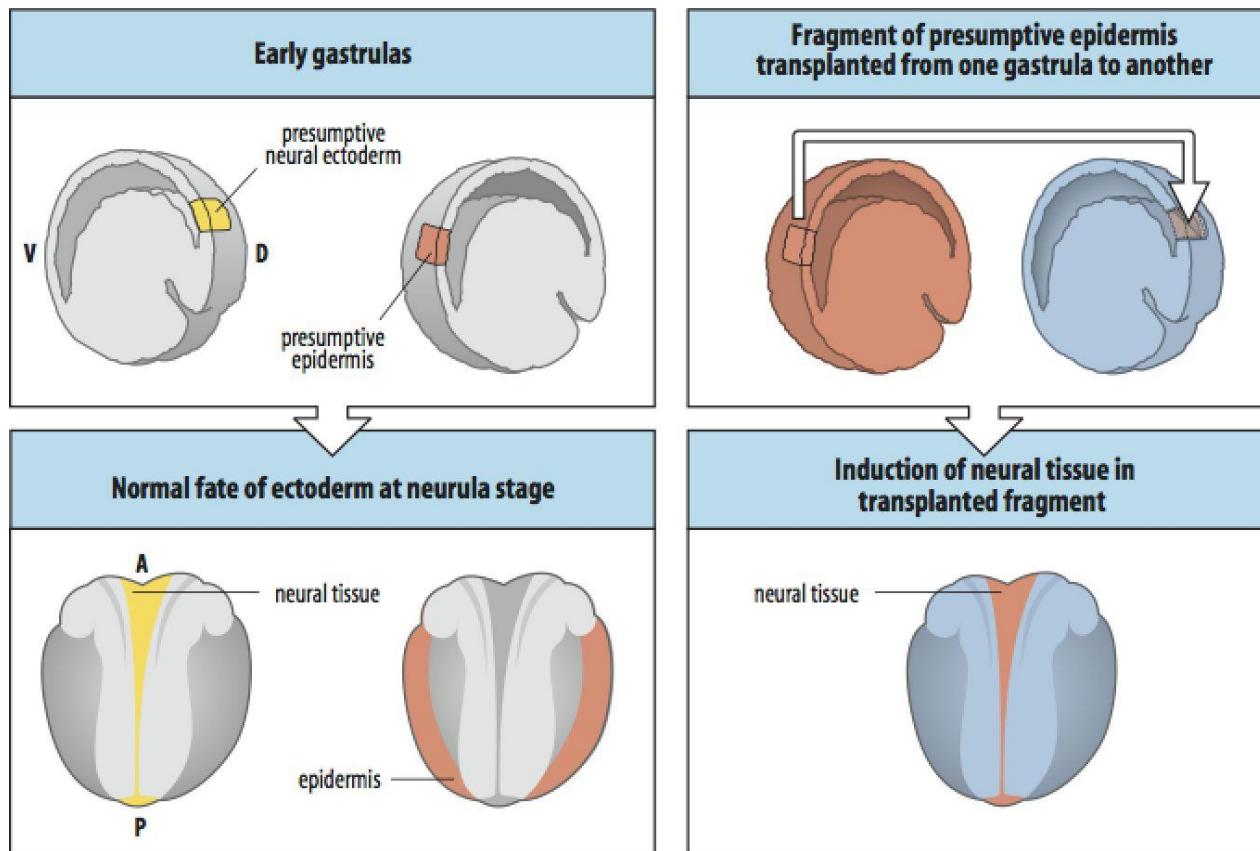
Sclerotome -> cartilage and bone.

Dermomyotome = dermo + myo -> dermis + muscle.

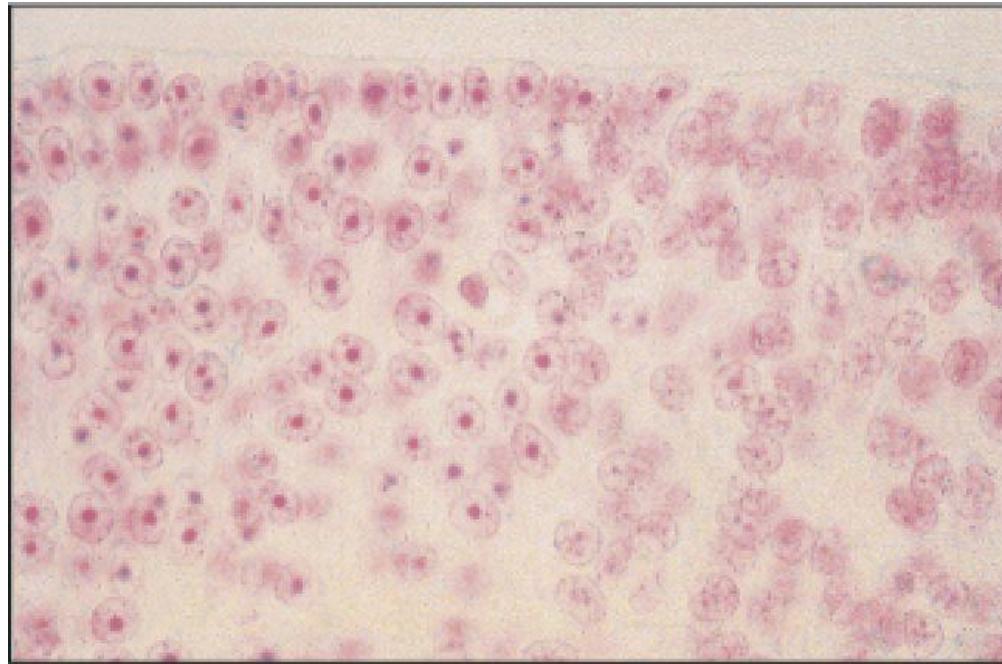
# What induces nervous system?

- The organizer region.
  - The Spemann organizer of amphibians.
  - The shield in zebrafish.
  - Hensen's node in the chick.
  - The equivalent node region in the mouse.
- They all can induce a complete body axis at an appropriate stage.

# The neural tissue is induced in the ectoderm

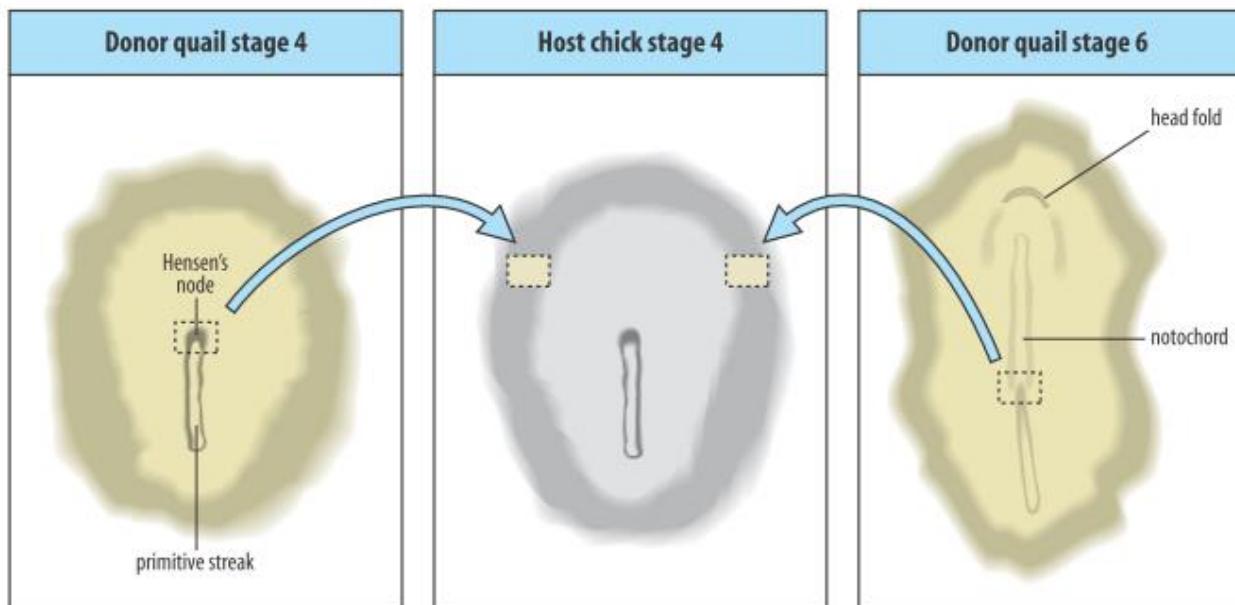


# Quail-chick chimeric tissue

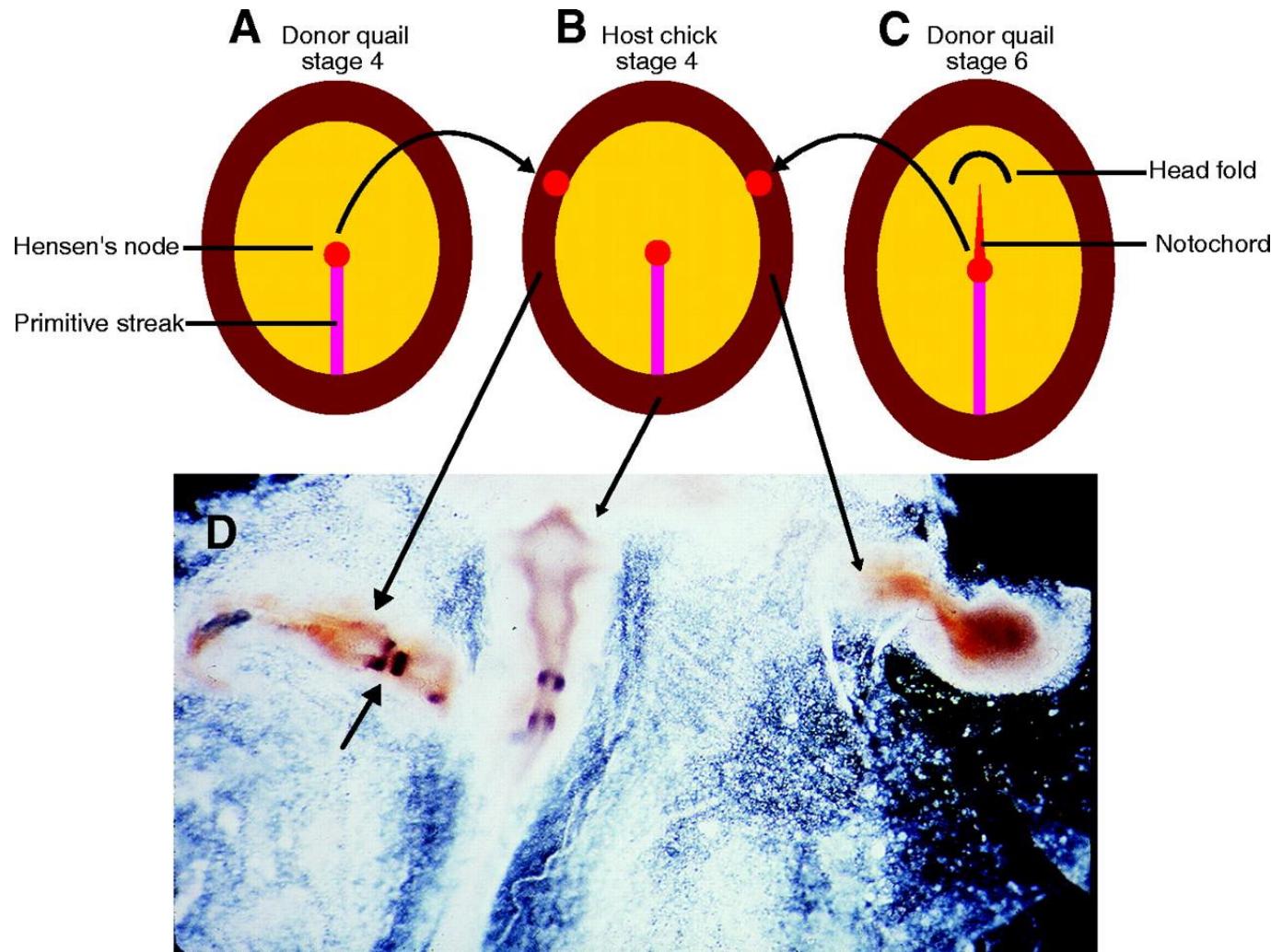


Left, quail. Right, chick.

# Hensen's node can induce a new axis in avian embryos

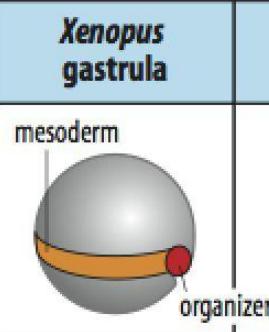
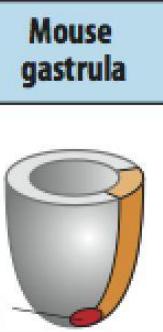


## Chick organizer graft experiments.

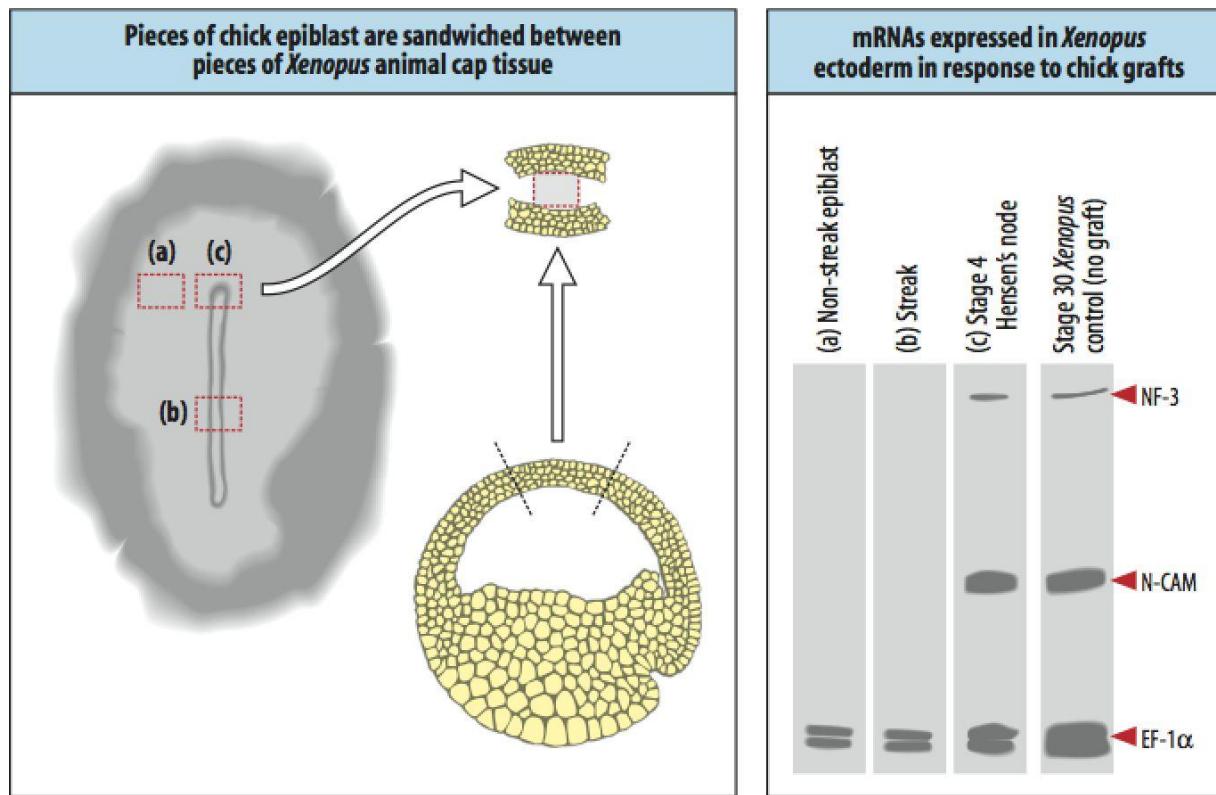


Stern C D Development 2005;132:2007-2021

# Genes expressed in Spemann organizer of *Xenopus* and in the node in the mouse

	<i>Xenopus</i> gastrula	Mouse gastrula
Genes encoding transcription factors	mesoderm	
		
		organizer
	Genes in organizer region	
Genes encoding transcription factors	<i>Brachyury</i>	<i>Brachyury</i>
	<i>goosecoid</i>	<i>goosecoid</i>
	<i>Xlim-1</i>	<i>Lim-1</i>
Genes encoding secreted proteins	<i>Xnr-3</i>	<i>Nodal</i>
	<i>chordin, Xnot2, noggin, Shh,</i>	<i>Shh</i>
	<i>Cerberus</i>	<i>Cerberus-related</i>

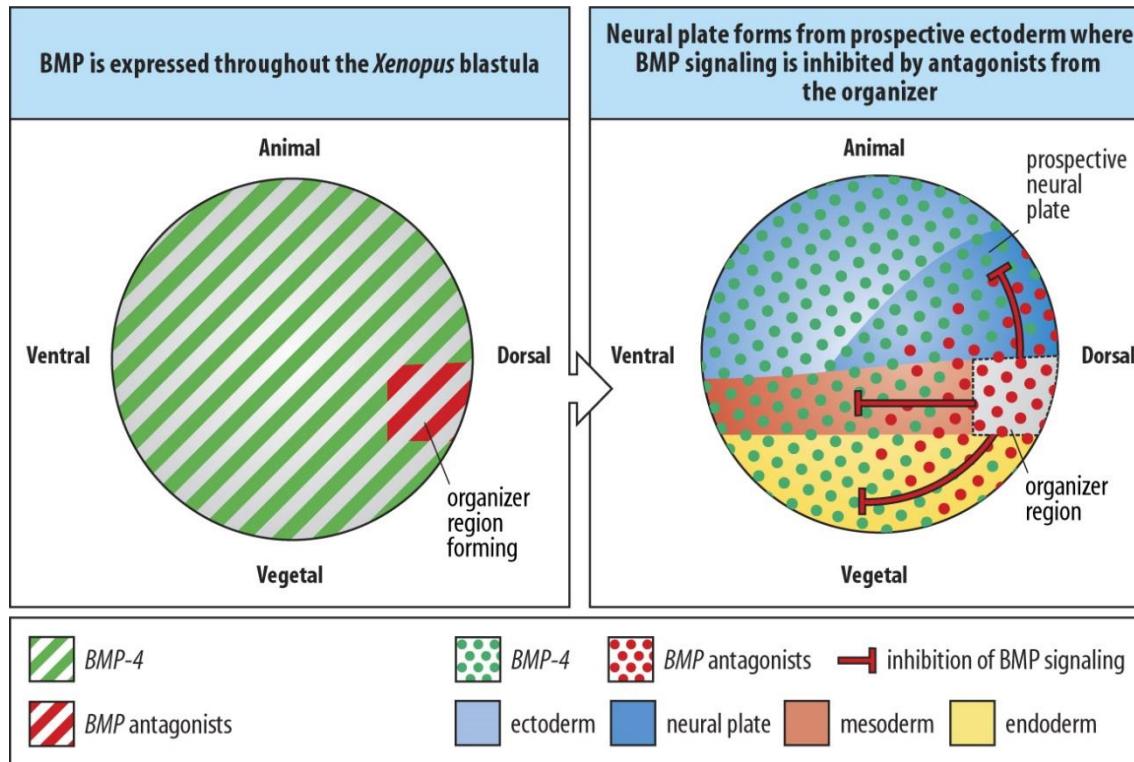
# Hensen's node from a chick embryo can induce gene expression characteristic of neural tissue in *Xenopus*



# A lesson in history

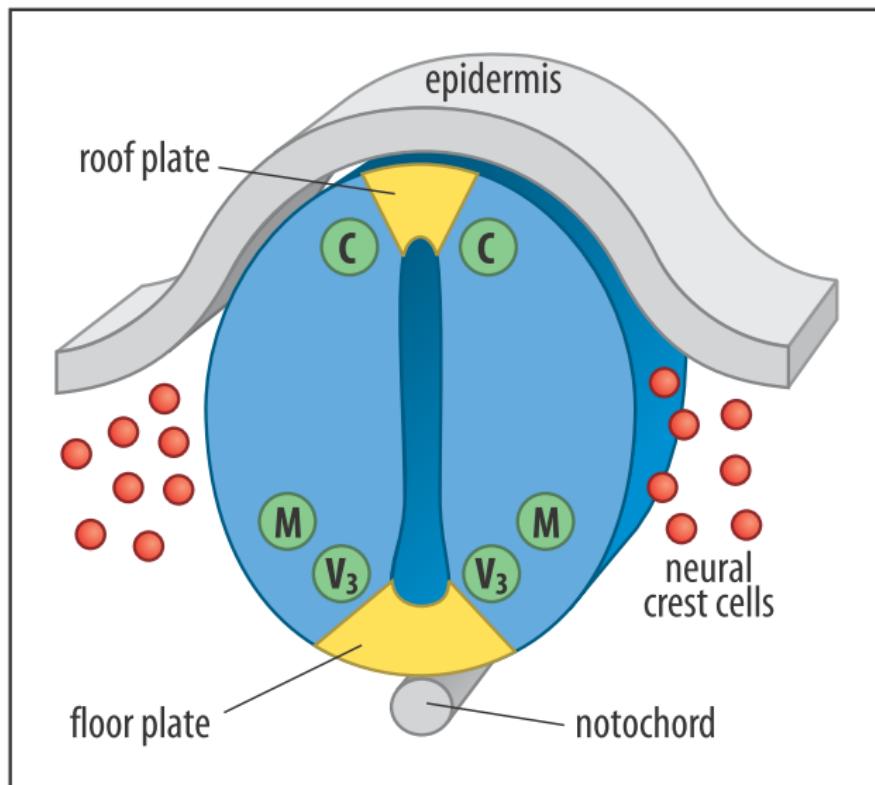
- In the 1930s and 1940s, an enormous amount of effort was devoted to isolate the signals (chemicals) involved in the neural induction in amphibians.
- A dead organizer region could still induce neural tissue.
- It seemed a large range of substances were capable of varying degrees of neural induction.
- Why? It turns out, the model animal salamander's ectoderm has a high propensity to develop into neural tissue on its own. *Xenopus*? Not!

# “Default” model for neural induction

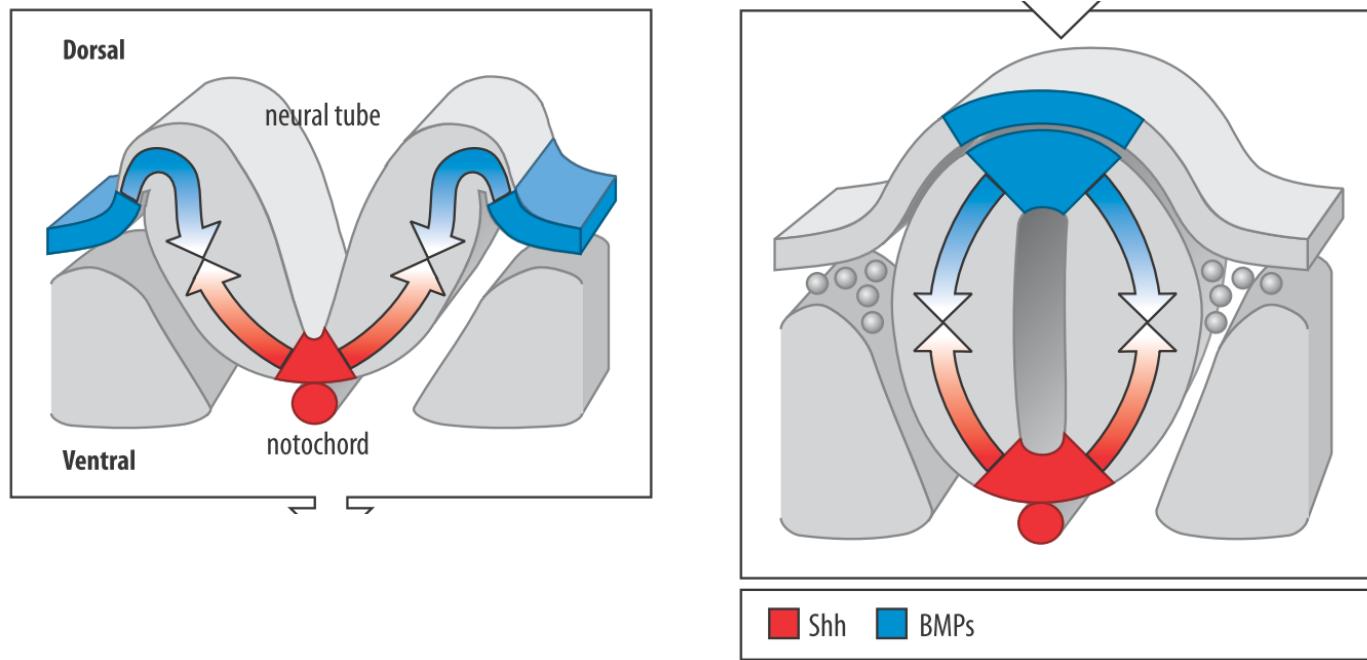


Noggin is the first key discovery.

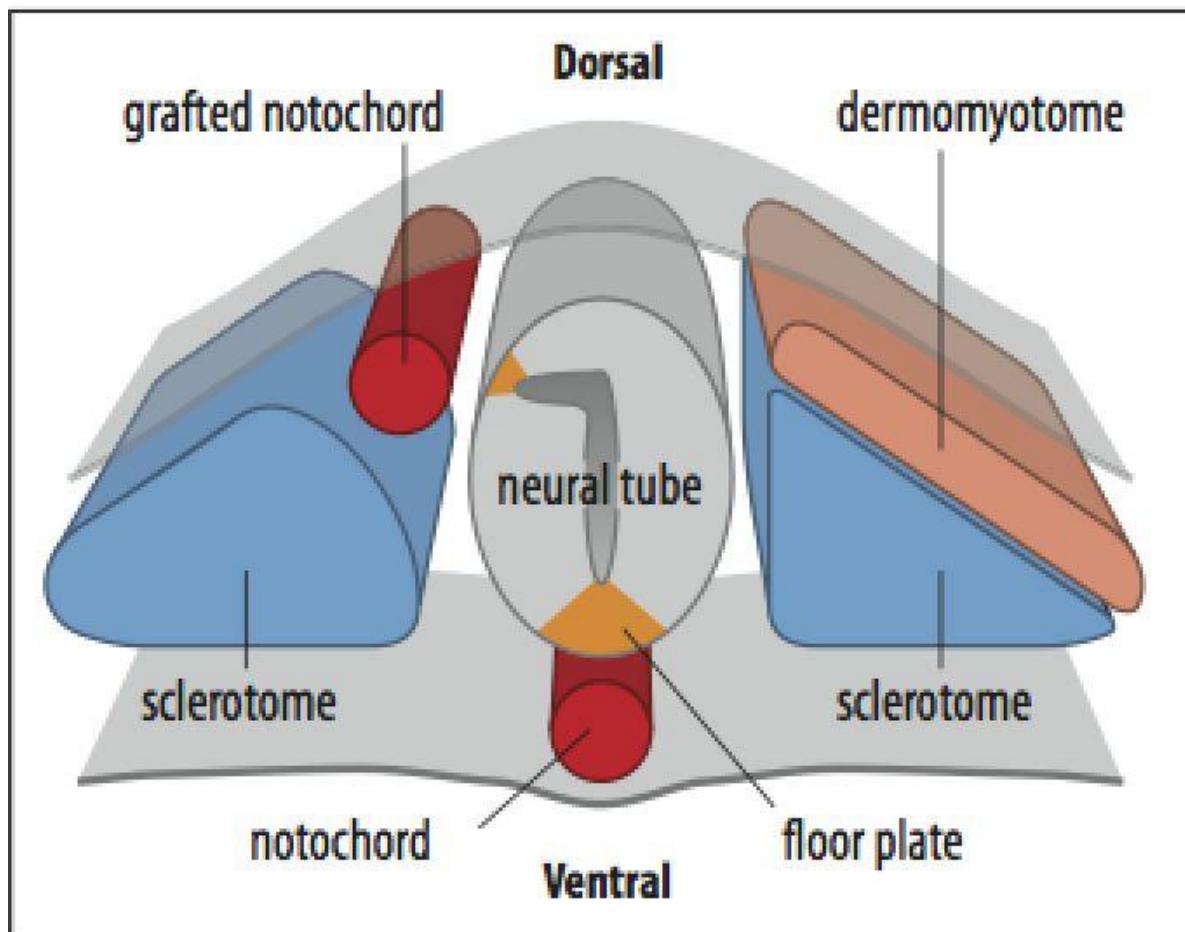
# Neural tube



# DV patterning needs both dorsal and ventral signals



# DV patterning needs both dorsal and ventral signals



The nervous system is the most complex of all the organ systems in animal

- The nervous system contains neurons and glia.
- In mammals, there are **billions** of neurons.
- There are **many hundreds** of different types of neurons.
- **Trillions** of synapses (connection).
- A single neuron in the central nervous system can receive as many as 100,000 different inputs.

## Two big projects

- Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative (USA)
- The Human Brain Project (European Union)



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## WHAT IS THE BRAIN INITIATIVE?

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is part of a new Presidential focus aimed at revolutionizing our understanding of the human brain. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. Long desired by researchers seeking new ways to treat, cure, and even prevent brain disorders, this picture will fill major gaps in our current knowledge and provide unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought.

### BRAIN Initiative Partners

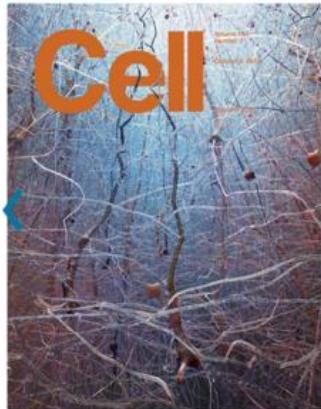
#### Federal

National Science Foundation (NSF)

Defense Sciences Office Solicitations (DARPA)

U.S. Food and Drug Administration (FDA)

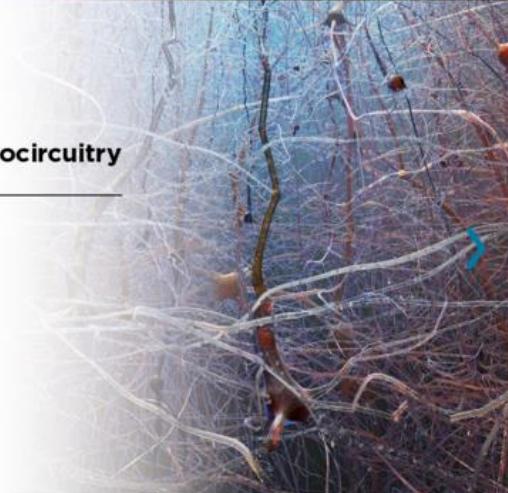
The Intelligence Advanced Research Projects  
Activity (IARPA)



## Reconstruction and simulation of neocortical microcircuitry

### CELL PUBLICATION

Published on 8<sup>th</sup> October 2015. The Blue Brain Project, the simulation core of the Human Brain Project, completed a first draft computer reconstruction of a piece of the neocortex.



[N Magazine releases V1.2.: A Special Summit Edition](#)

posted on 5 Nov 2015

[European Commission and Human Brain Project sign Framework Partnership Agreement](#)

[Science Highlights Year II](#)

posted on 26 Oct 2015



The Nobel Prize in Physiology or Medicine 1906  
Camillo Golgi, Santiago Ramón y Cajal

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# Santiago Ramón y Cajal - Biographical



Santiago Ramón y Cajal was born on May 1, 1852, at Petilla de Aragón, Spain. As a boy he was apprenticed first to a barber and then to a cobbler. He himself wished to be an artist - his gift for draughtsmanship is evident in his published works. His father, however, who was Professor of Applied Anatomy in the University of Saragossa, persuaded him to study medicine, which he did, chiefly under the direction of his father. (Later, he made drawings for an atlas of anatomy which his father was preparing, but which was never published.)

# 圣地亚哥·拉蒙-卡哈尔

 编辑

圣地亚哥·拉蒙-卡哈尔（[西班牙语](#)：Santiago Ramón y Cajal，1852年5月1日－1934年10月17日），[西班牙](#)病理学家、组织学家，神经学家。生于西班牙阿拉贡自治区，[1906年诺贝尔生理学或医学奖得主](#)。

中文名	圣地亚哥·拉蒙-卡哈尔	出生日期	1852年5月1日
外文名	Santiago Ramón y Cajal	逝世日期	1934年10月17日

## 目录

- [1 简介](#)
- [2 生平](#)
- [3 著作](#)

## 简介

 编辑

他对于大脑的微观结构研究是开创性的，被许多人认为是现代神经科学之父。他绘图技能出众，他的关于脑细胞的几百个插图至今用于教学。

## 生平

 编辑

拉蒙-卡哈尔是医师和解剖学讲师斯托·拉蒙（Justo Ramón）和安东尼·卡哈尔（Antonia Cajal）的儿子。孩提时期由于他不良行为和反专制的态度，被调到许多不同的学校。他的早熟和[叛逆](#)的一个极端的例子是在他11岁的时候，用自制的大炮摧毁城门，他也因此受到监禁。他是一个狂热的画家、艺术家和体操运动员。他曾作为鞋匠和理发师，他好斗的态度颇为知名。

拉蒙-卡哈尔于1873年从萨拉戈萨大学医学院毕业。通过考试后在西班牙军队担任医务人员。他参与了1874-75年到古巴的远



cajal 大炮



网页 图片 地图 视频 新闻 更多 ▾ 搜索工具

找到约 906 条结果 (用时 0.60 秒)

### 圣地亚哥·拉蒙·卡哈尔- 维基百科，自由的百科全书

<https://zh.wikipedia.org/zh-cn/圣地亚哥·拉蒙·卡哈尔> ▾

圣地亚哥·拉蒙·卡哈尔 (西班牙语: Santiago Ramón y Cajal, 1852年5月1 ... 他的早熟和叛逆的一个极端的例子是在他11岁的时候，用自制的**大炮**摧毁城门，他也因此 ...

### 圣地亚哥·拉蒙·卡哈尔\_百度百科

<baike.baidu.com/view/6799140.htm> ▾

圣地亚哥·拉蒙·卡哈尔 (西班牙语: Santiago Ramón y Cajal, 1852年5月1 ... 他的早熟和叛逆的一个极端的例子是在他11岁的时候，用自制的**大炮**摧毁城门，他也因此 ...

### Google Doodle 聖地亞哥·拉蒙·卡哈爾 (Santiago Ramón y ...

<zitolife.pixnet.net.../383573786-google-doodle-聖地亞哥...> ▾ 转为简体网页

2014年8月7日 - 聖地亞哥·拉蒙·卡哈爾 (西班牙語: Santiago Ramón y Cajal, 1852年5月1 ... 他的早熟和叛逆的一個極端的例子是在他11歲的時候，用自製的**大炮** ...

### 圣地亚哥·拉蒙·卡哈尔 - 超脑力教育网-脑力资讯

<www.9571.com.cn/MentalInfo.aspx?Mid=78> ▾

2013年12月3日 - 圣地亚哥·拉蒙·卡哈尔 (西班牙语: Santiago Ramón y Cajal, 1852年5月1 ... 他的早熟和叛逆的一个极端的例子是在他11岁的时候，用自制的**大炮** ...

### 聖地亞哥·拉蒙·卡哈爾- Wikiwand

<www.wikiwand.com/zh-tw/圣地亚哥·拉蒙·卡哈尔> ▾ 转为简体网页

聖地亞哥·拉蒙·卡哈爾 (西班牙語: Santiago Ramón y Cajal, 1852年5月1 ... 他的早熟和叛逆的一個極端的例子是在他11歲的時候，用自製的**大炮**摧毀城門，他也因此 ...

聖地亞哥·拉蒙·卡哈爾 台灣Wiki



cajal cannon



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### Santiago Ramón y Cajal - Wikipedia, the free encyclopedia

[https://en.wikipedia.org/wiki/Santiago\\_Ramón\\_y\\_Cajal](https://en.wikipedia.org/wiki/Santiago_Ramón_y_Cajal) ▾ 翻译此页

Santiago Ramón y **Cajal** (Spanish: [san'txajo rā'mon i ka'xal]; 1 May 1852 ... age of eleven for destroying his neighbor's yard gate with a homemade **cannon**.

### Explorer of the Human Brain: The Life of Santiago Ramon y ...

<https://www.questia.com/.../explorer-of-the-human-brain-the-lif...> - 翻译此页

Explorer of the Human Brain: The Life of Santiago Ramon y **Cajal** ... By Dorothy F. Cannon .... Ramon Y **Cajal**, Santiago, 1852-1934; Physicians--Biography ...

### Ramón y Cajal: Dorothy F. Cannon - Amazon.com

[www.amazon.com/Ramón-Cajal...F-Cannon/dp/B00FKR5C3I](http://www.amazon.com/Ramón-Cajal...F-Cannon/dp/B00FKR5C3I) - 翻译此页

Ramón y **Cajal** [Dorothy F. Cannon] on Amazon.com. \*FREE\* shipping on qualifying offers. Grijalbo. Barcelona. 1981. 21 cm. 253 p. Encuadernación en tapa ...

### Explorer of the Human Brain: The Life Santiago Ramon Y ...

[www.amazon.com/Explorer-Human-Brain.../B000JNUQDY](http://www.amazon.com/Explorer-Human-Brain.../B000JNUQDY) ▾ 翻译此页

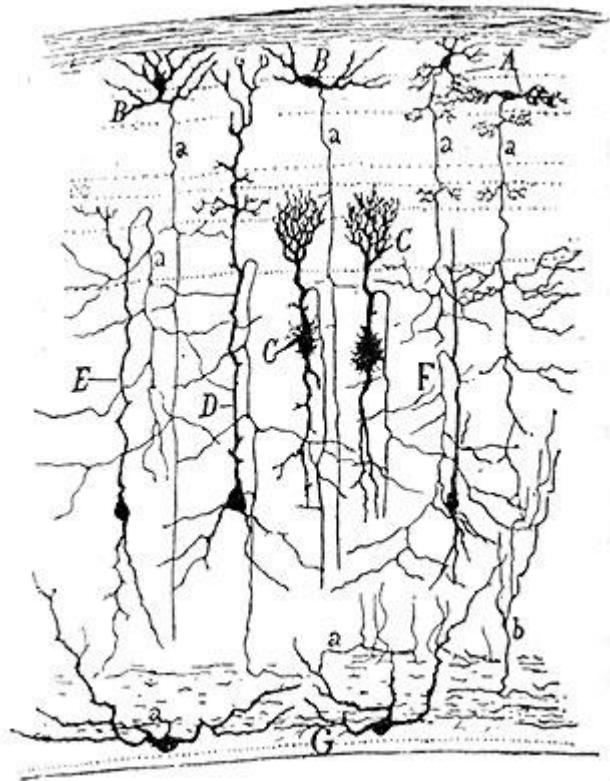
Explorer of the Human Brain: The Life Santiago Ramon Y **Cajal** (1852-1934) [Dorothy F. Cannon] on Amazon.com. \*FREE\* shipping on qualifying offers.

### Santiago Ramón y Cajal So what about the man...

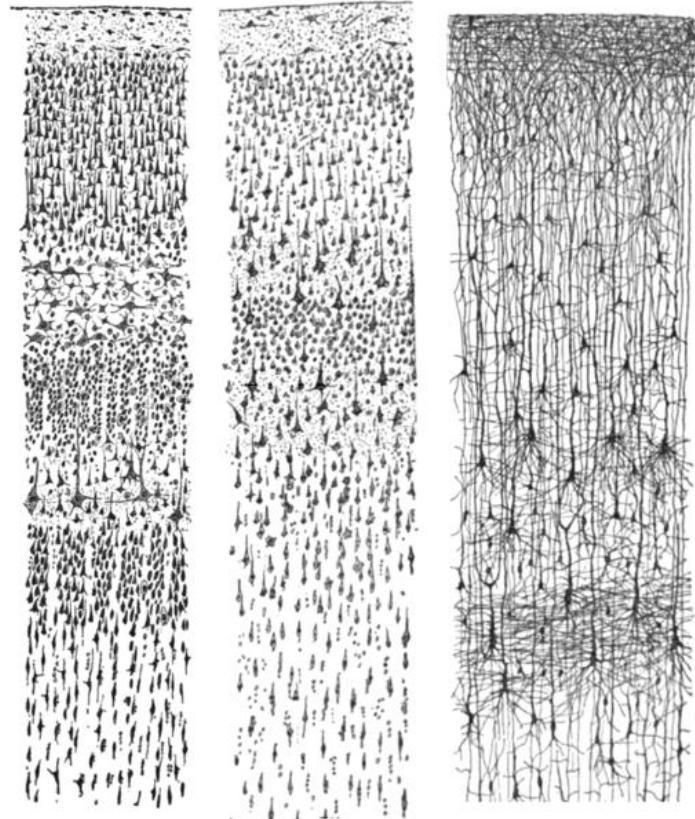
[neurolove.tumblr.com/.../santiago-ramón-y-cajal-so-what-abou...](http://neurolove.tumblr.com/.../santiago-ramón-y-cajal-so-what-abou...) ▾ 翻译此页

2012年5月14日 - ... for firing a homemade **cannon** at the town gate and destroying it (which I have to say, ... Ramón y **Cajal** did more than just draw them though.

[Santiago Ramón y Cajal WhoNamedIt](http://Santiago_Ramón_y_Cajal_WhoNamedIt) dictionary of



Drawing of a section through the optic tectum of a sparrow, from "Estructura de los centros nerviosos de las aves", Madrid, 1905.

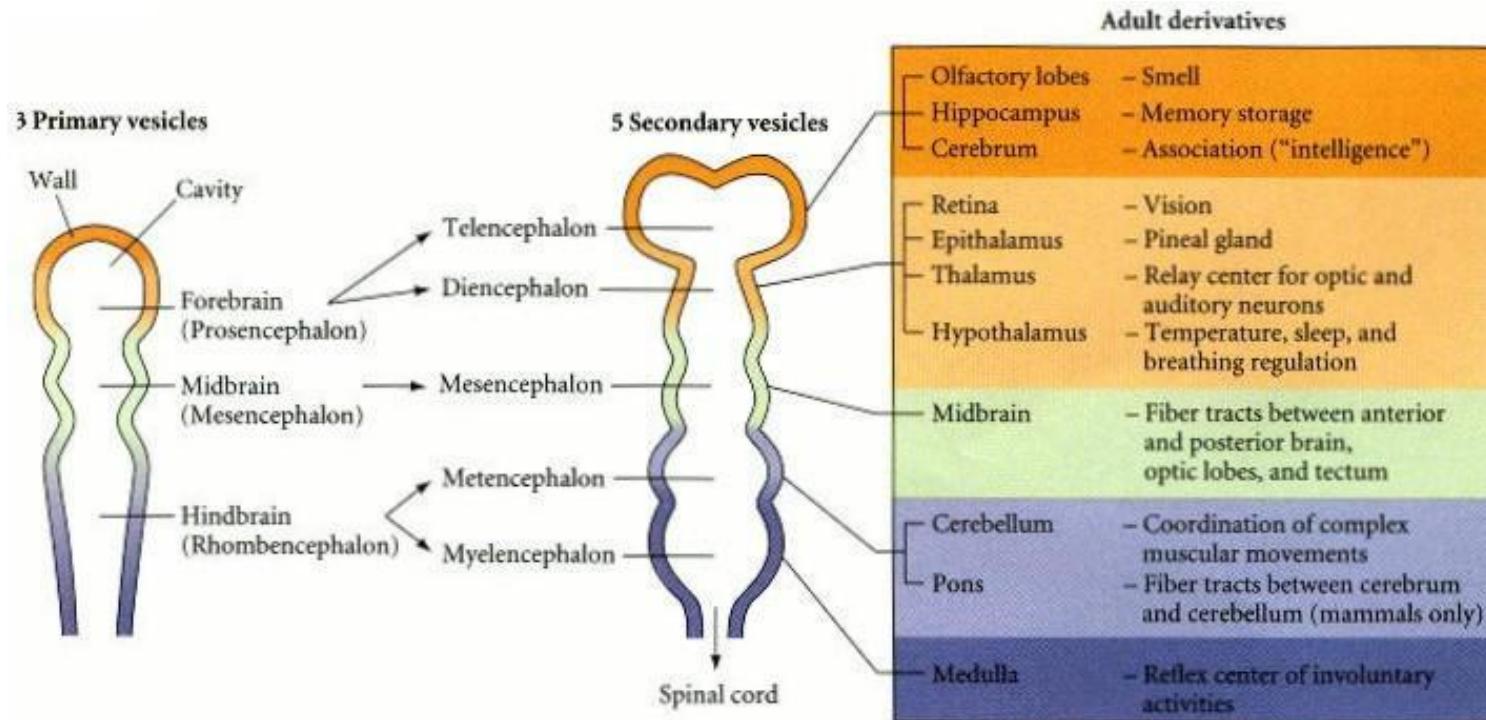


Drawn in 1899, taken from the book "Comparative study of the sensory areas of the human cortex

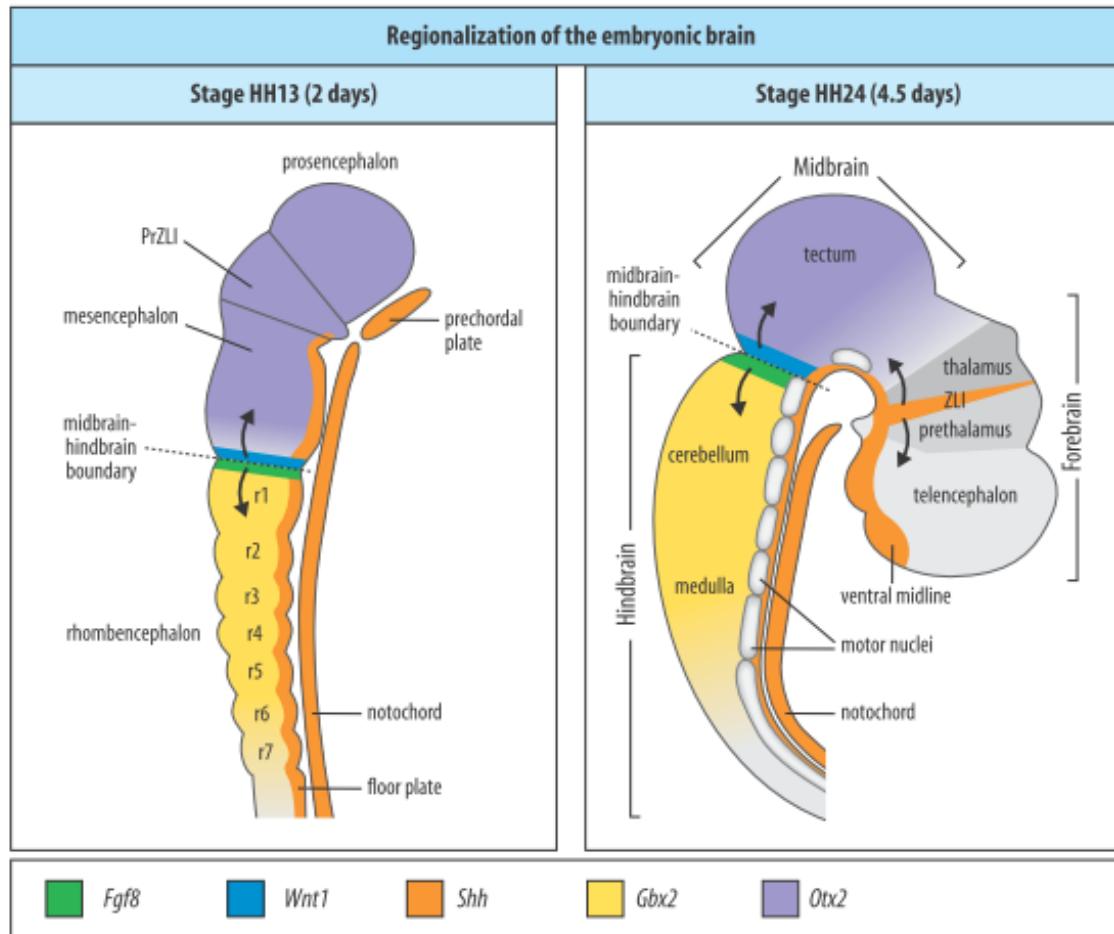
The overall process of nervous system development can be divided into four major stages

- The specification of neural cell (neuron or glial cell) identity;
- The migration of neurons and the outgrowth of axons to their targets;
- The formation of synapses with target cells, which can be other neurons, muscle or gland cells;
- The refinement of synaptic connections through the elimination of axon branches and cell death.

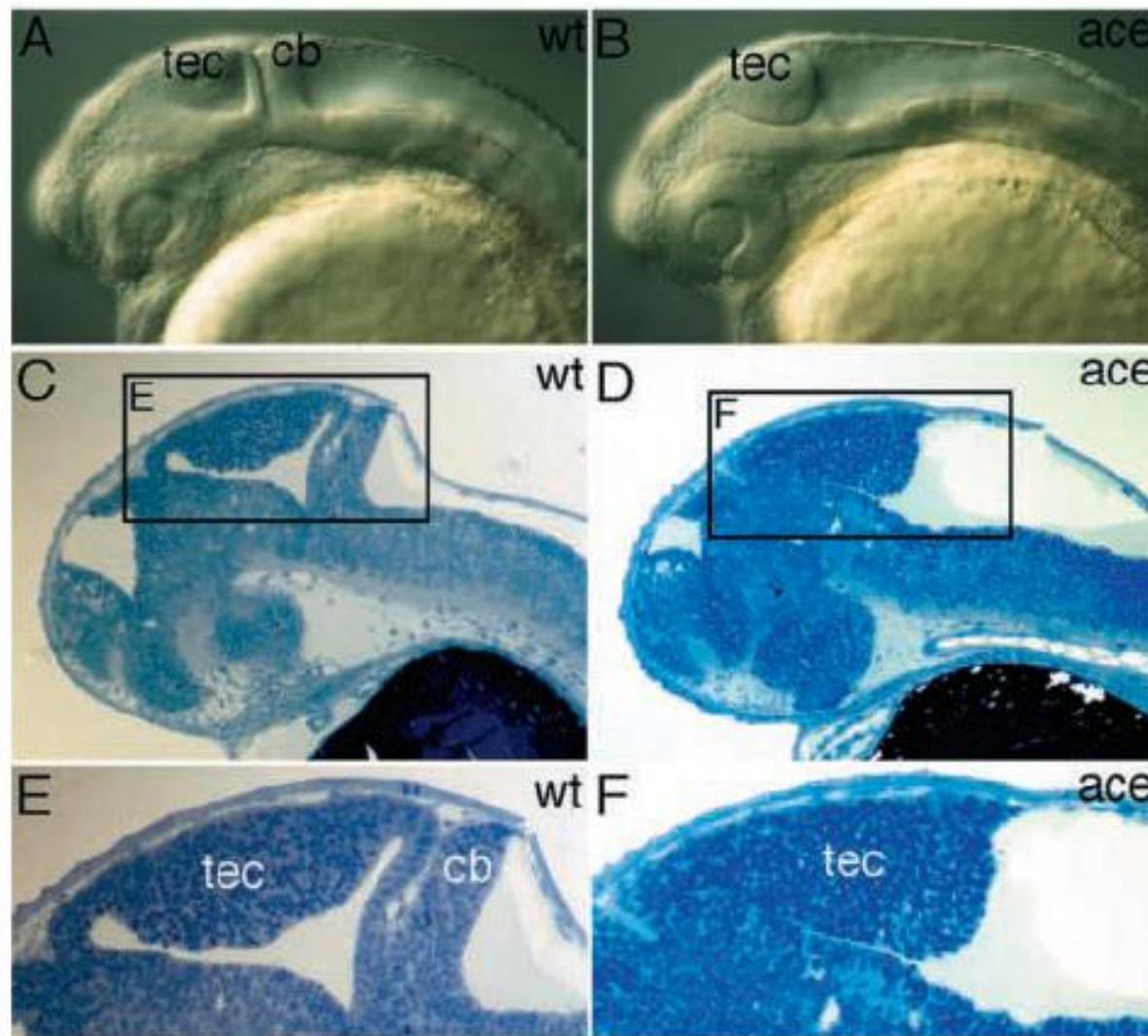
# Early human brain development



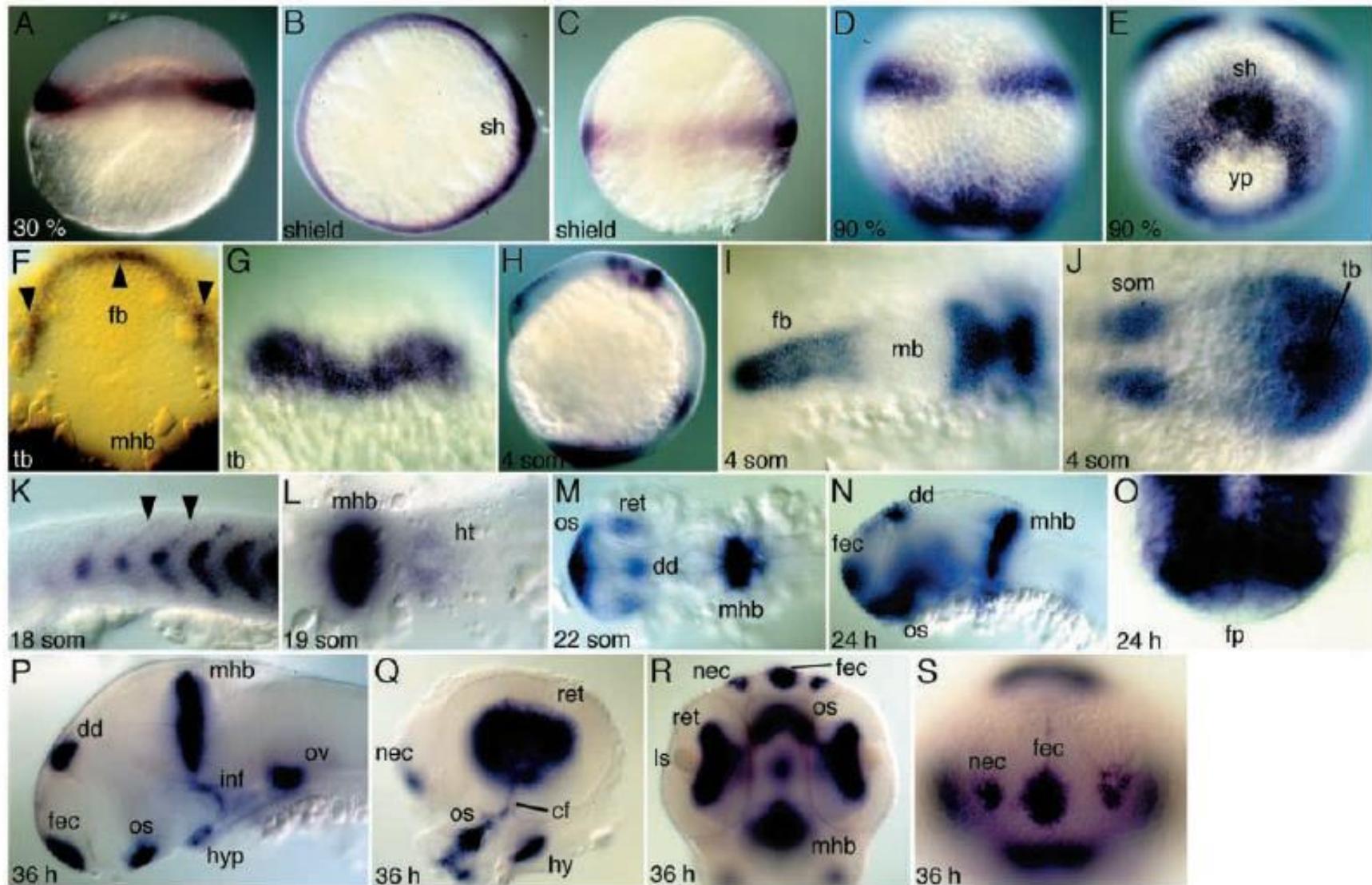
# Local signaling centers in the developing vertebrate brain



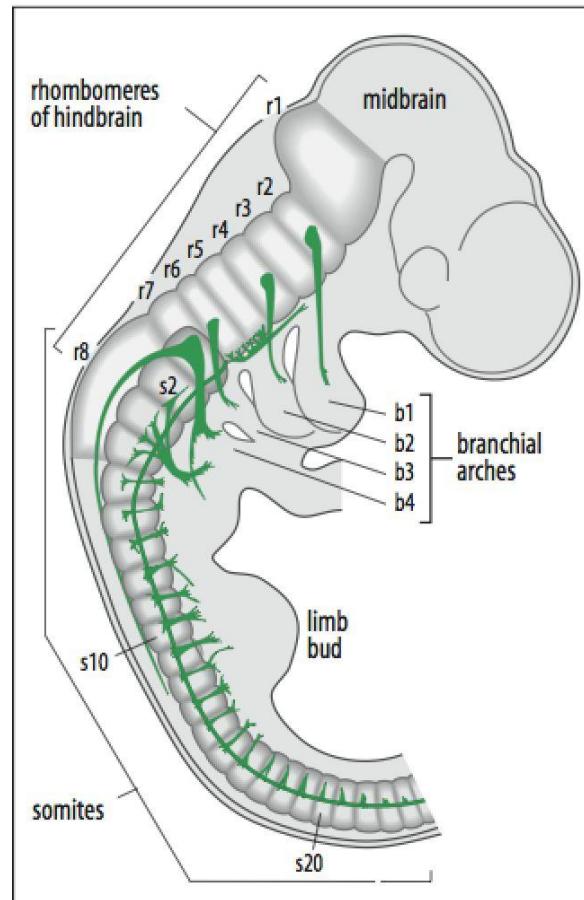
# Brain phenotype of *acerebellar* embryos



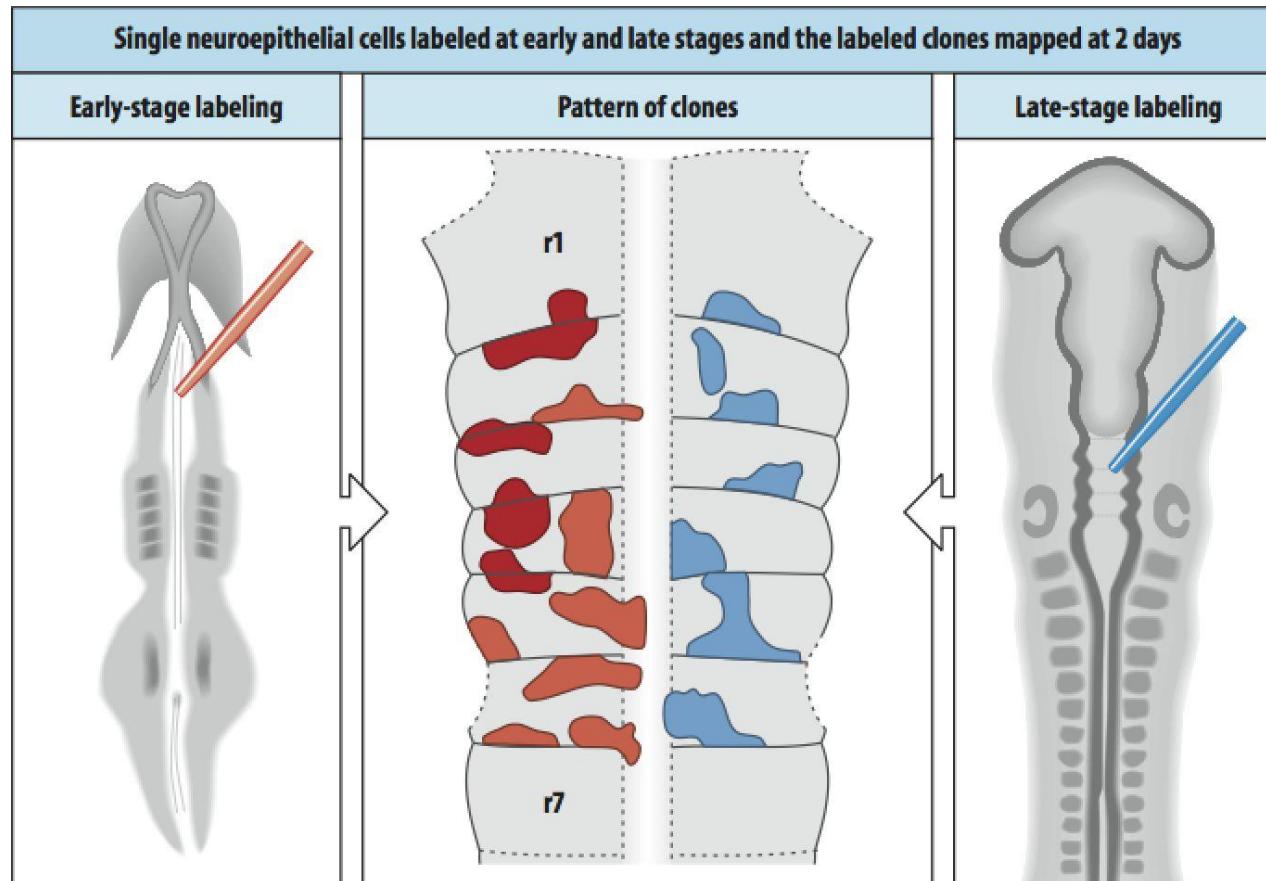
# Expression of *fgf8* in wild-type embryos



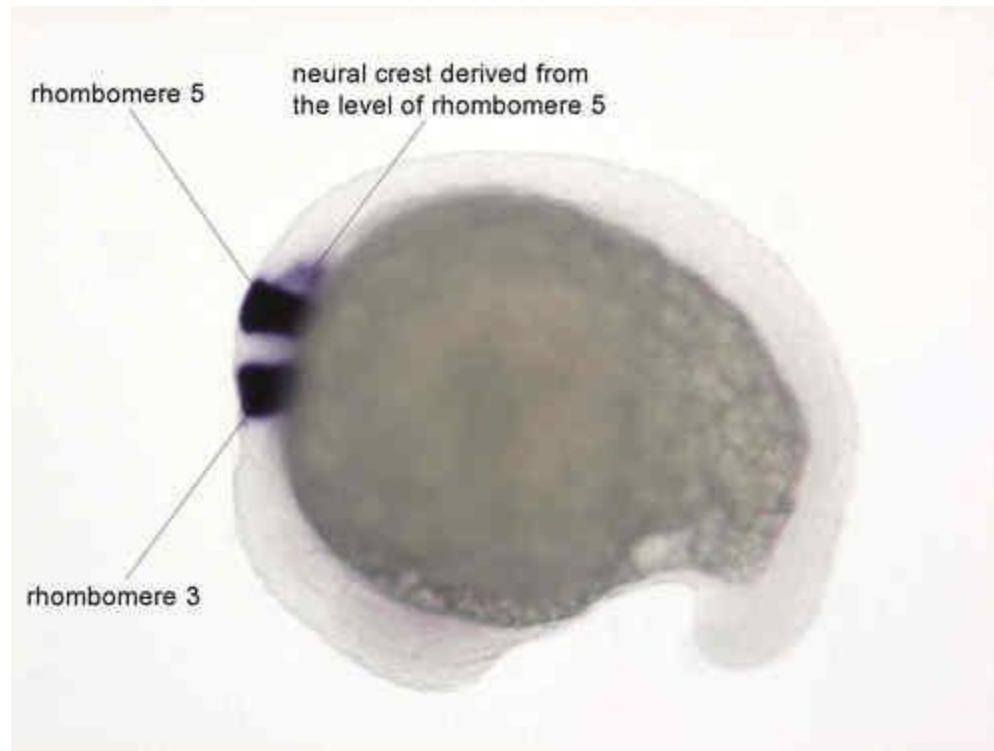
# The nervous system in a 3-day chick embryo (HH stage 18)

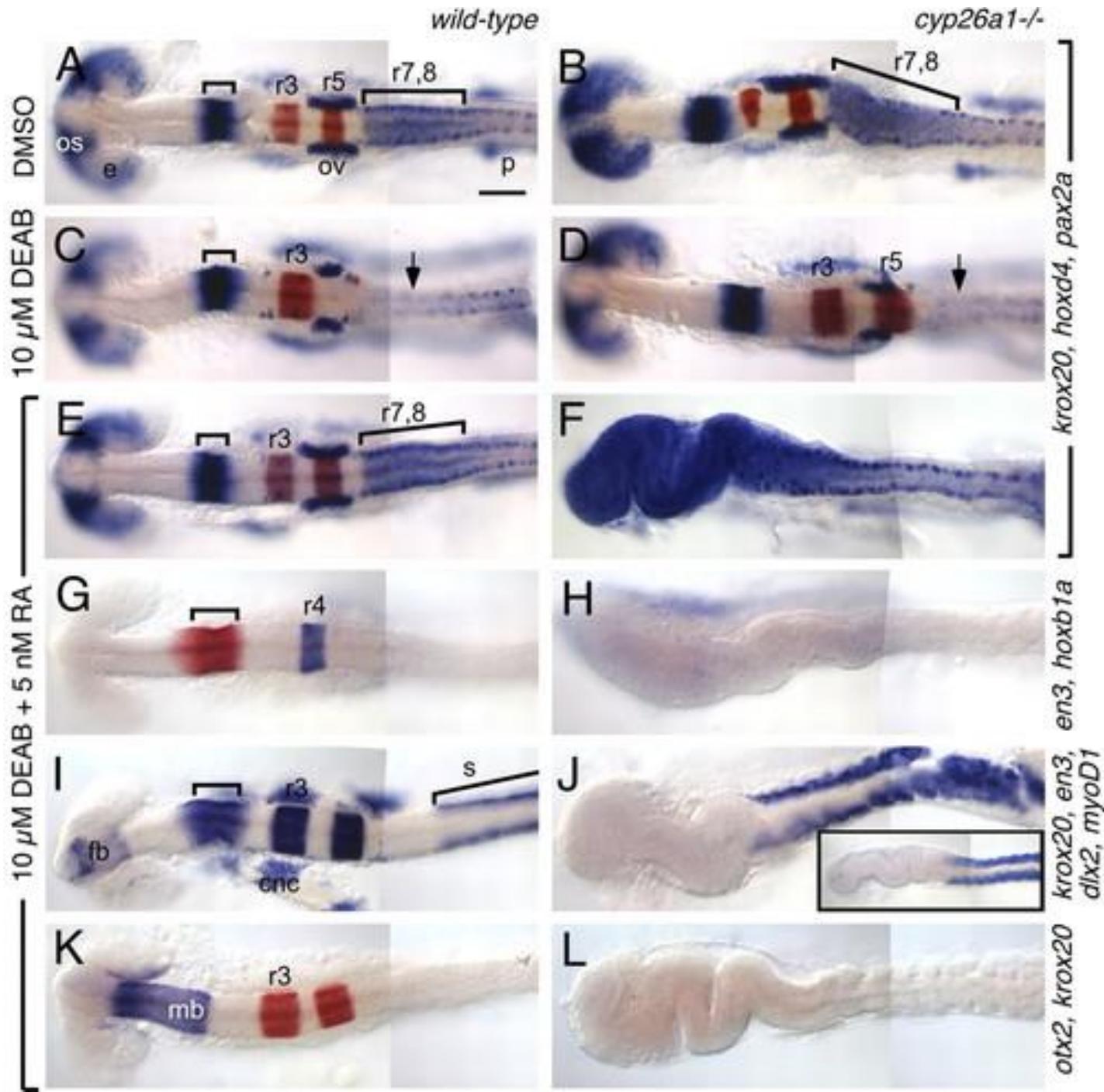


# Lineage restriction in rhombomeres of the embryonic chick hindbrain

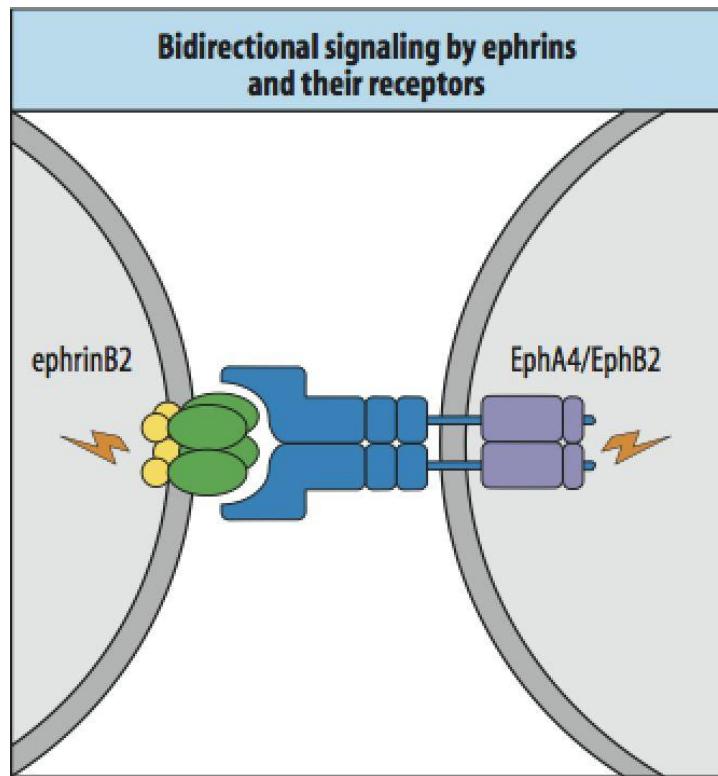


# Expression pattern of *krox20*

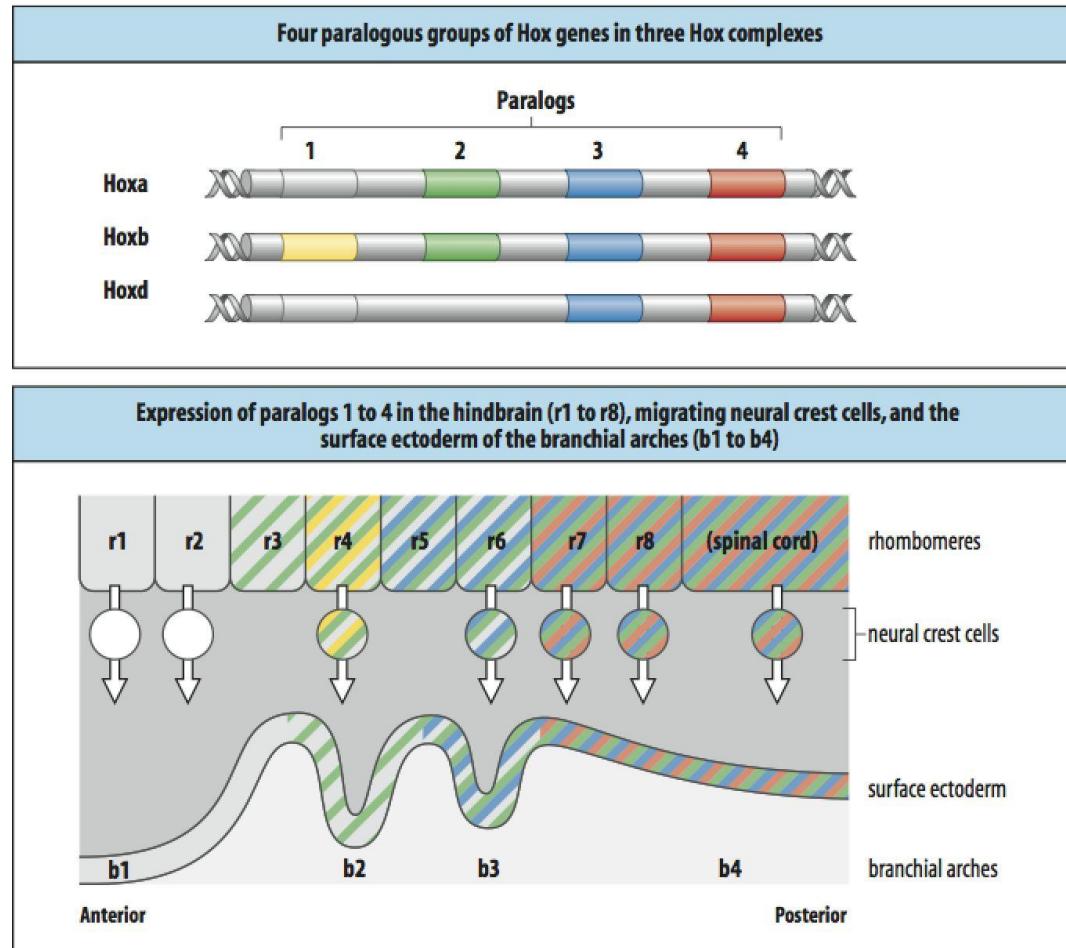




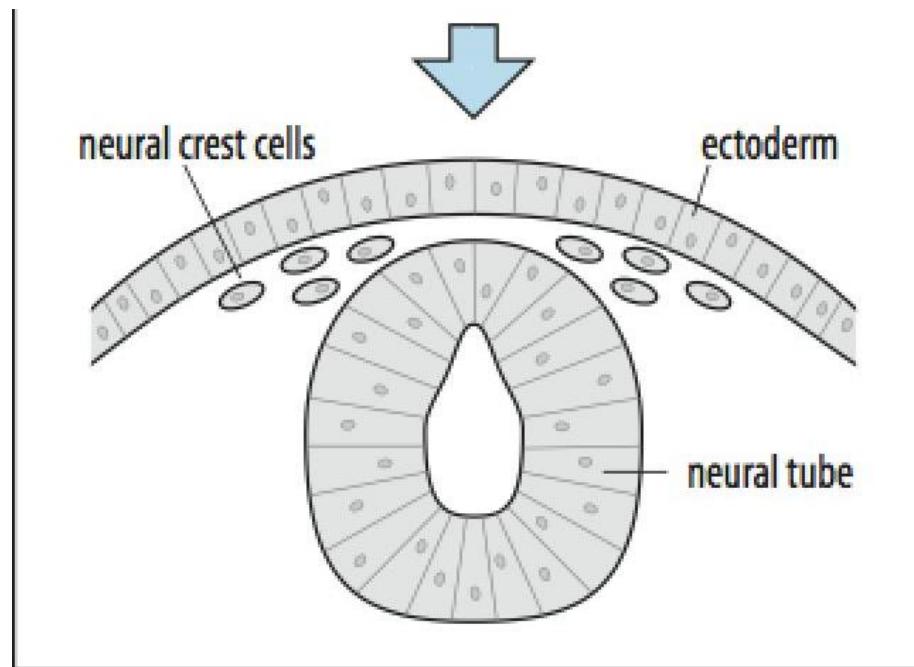
# Bidirectional signaling by ephrins and their receptors



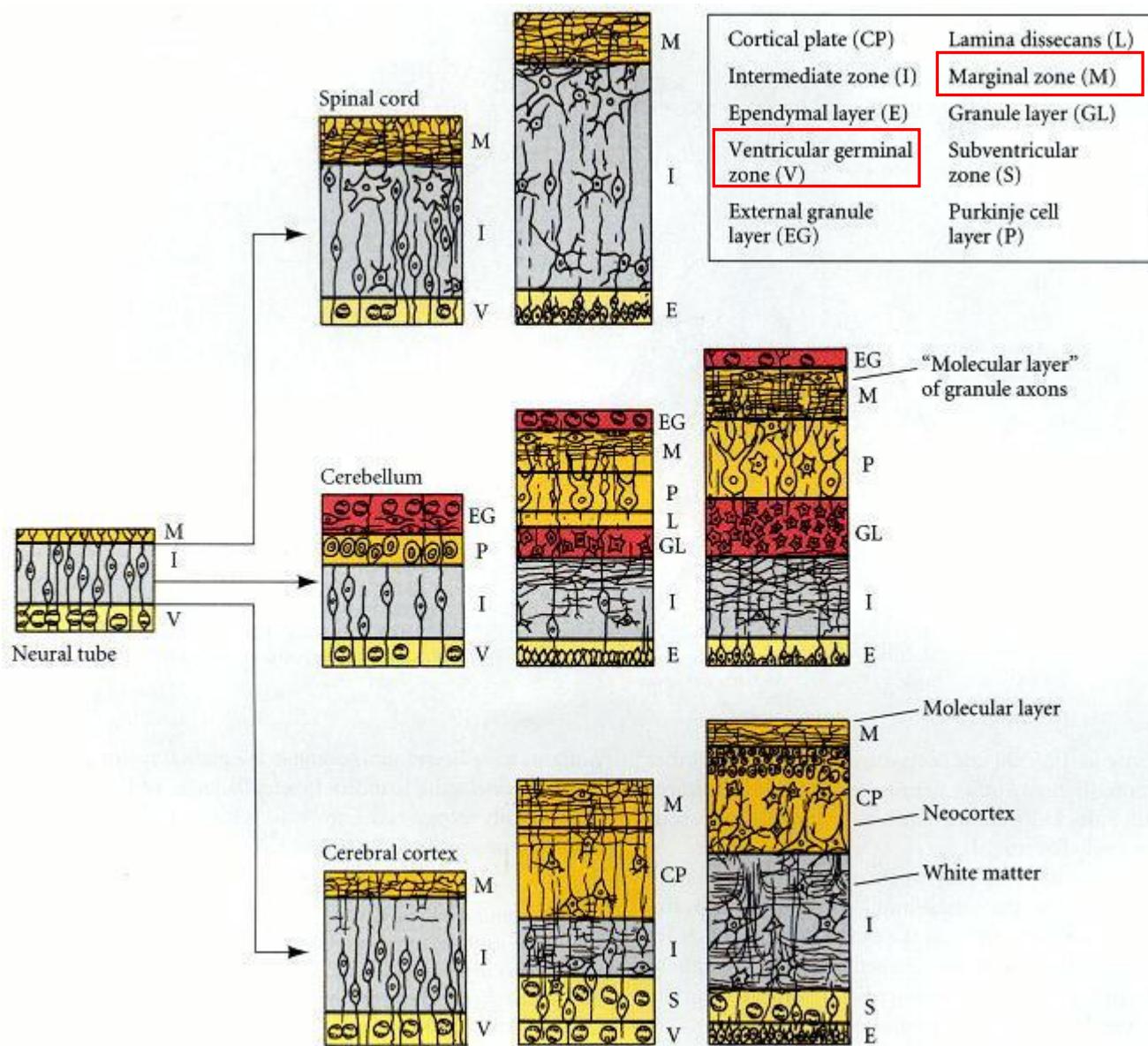
# Expression of Hox genes in the mouse embryonic hindbrain



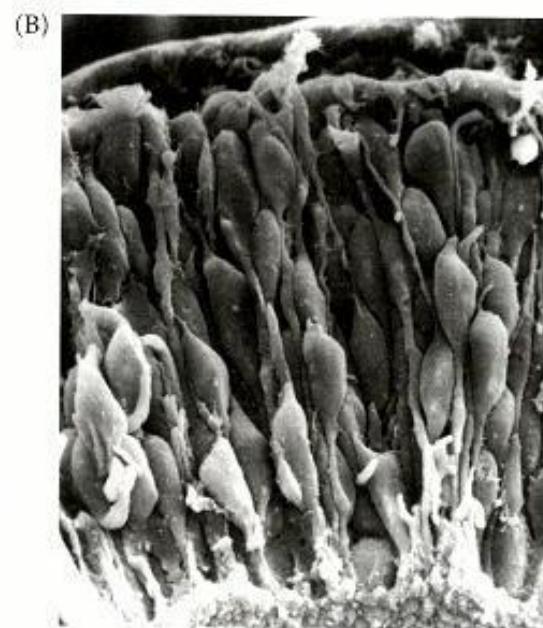
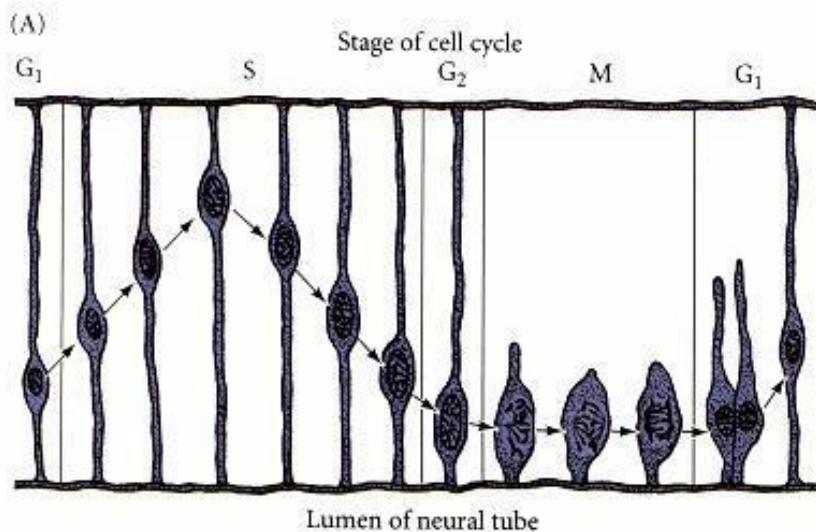
At the beginning, neural tube has a single layer of epithelium



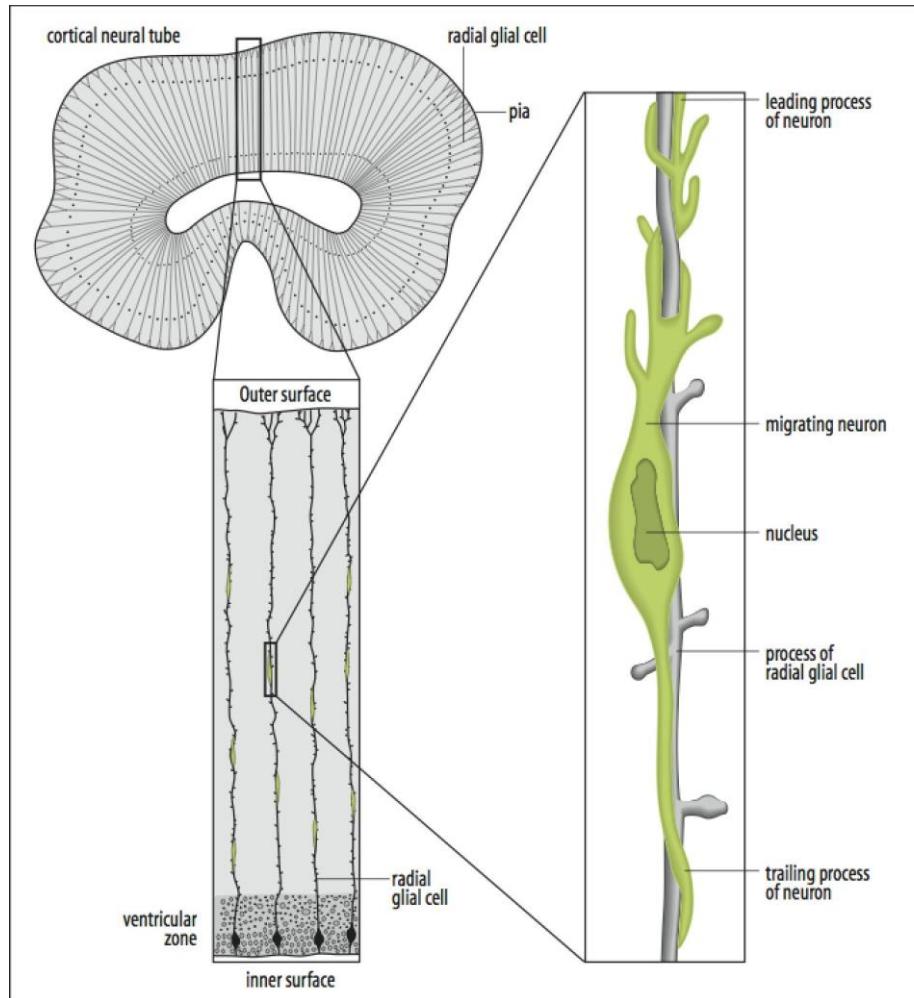
# Differentiation of the walls of the neural tube



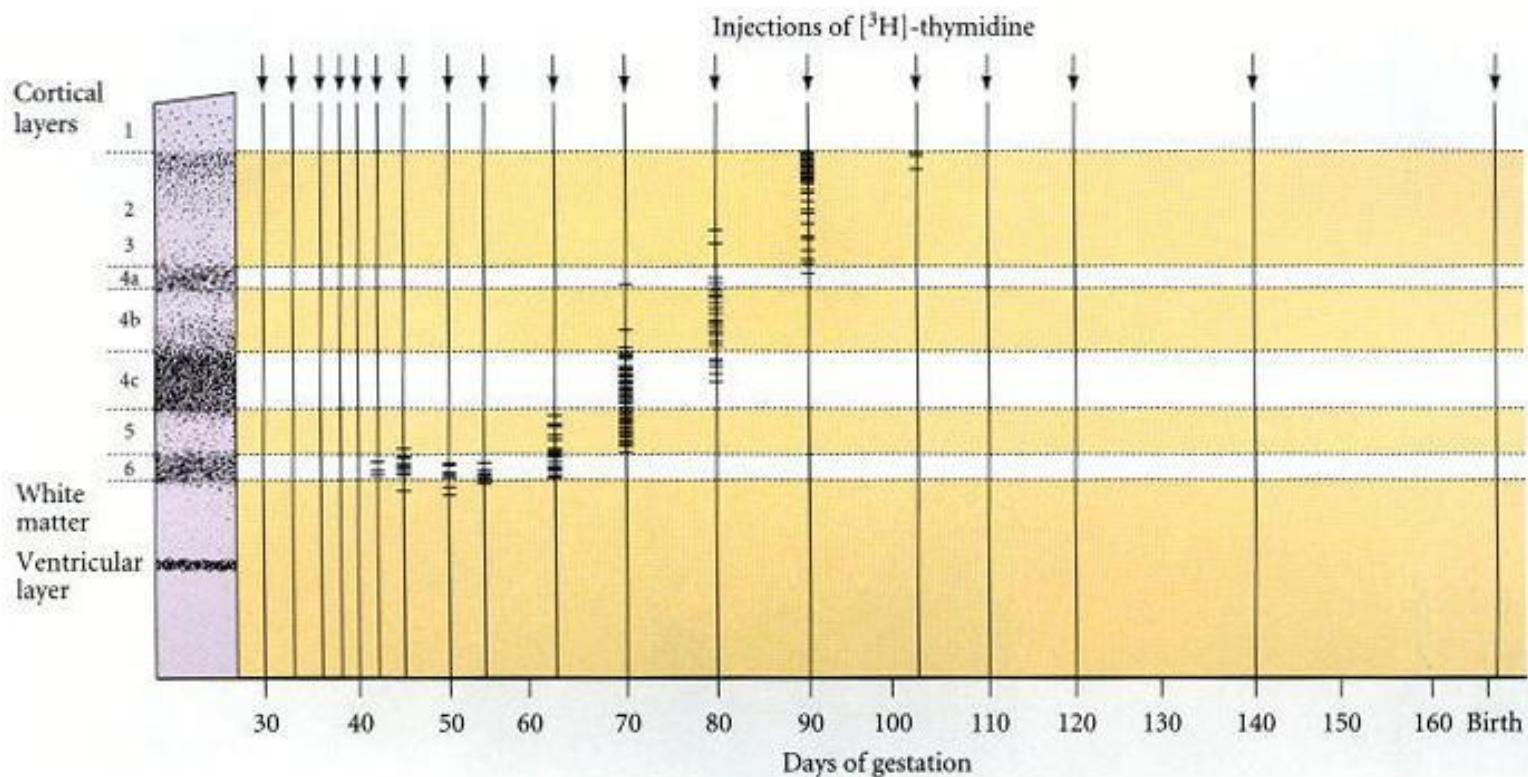
# The position of the nucleus in a neuroepithelial cell in cell cycle



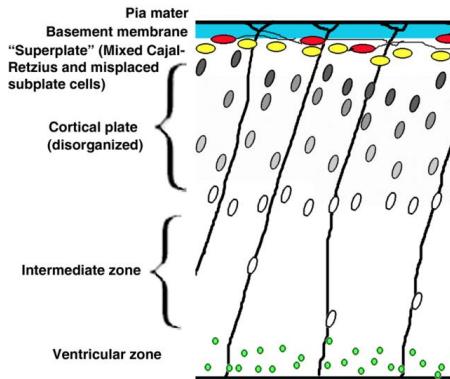
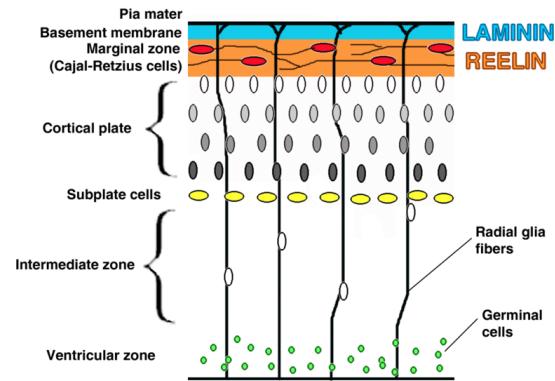
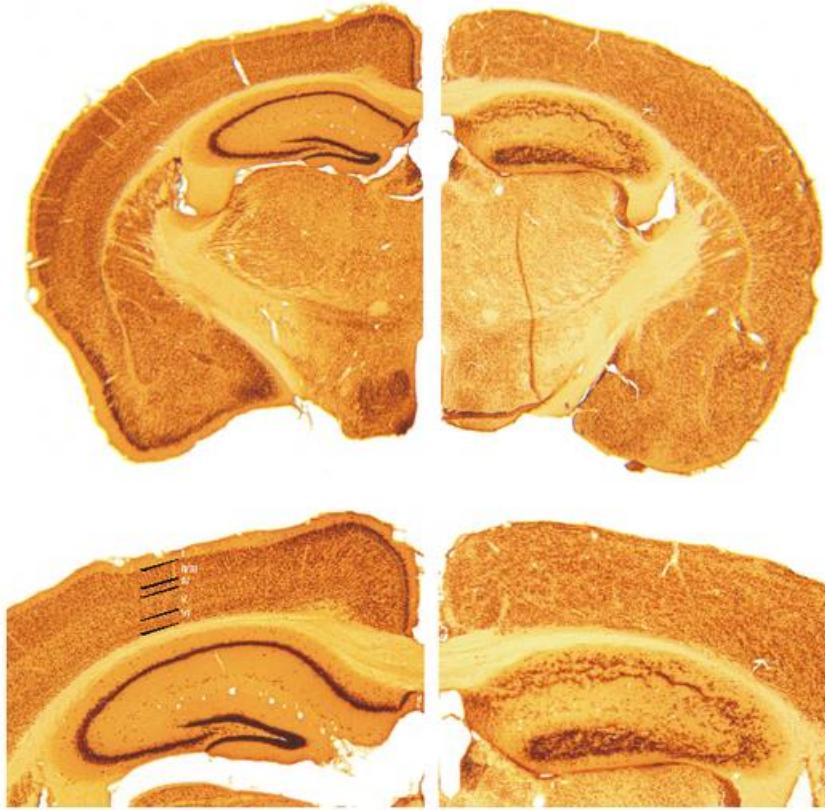
# Cortical neurons migrate along radial glial cells



# Timing the birth of cortical neurons

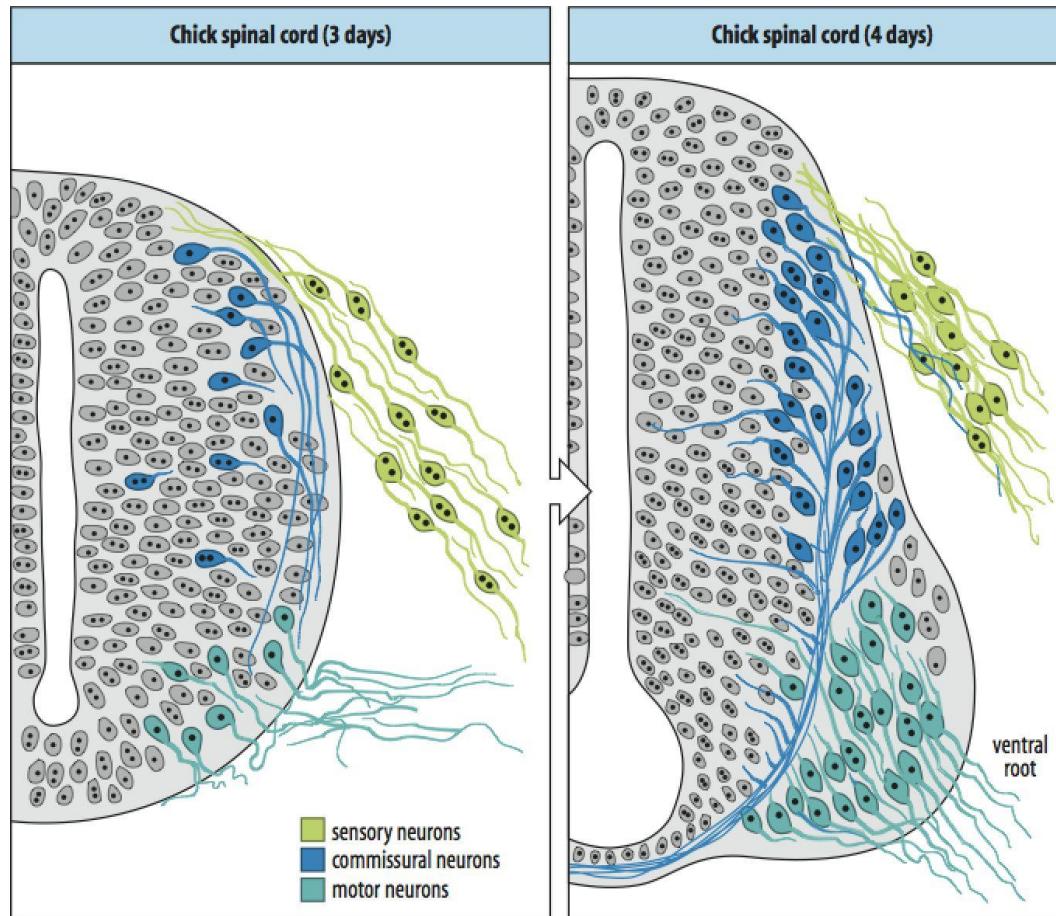


# Mouse *reeler* mutant

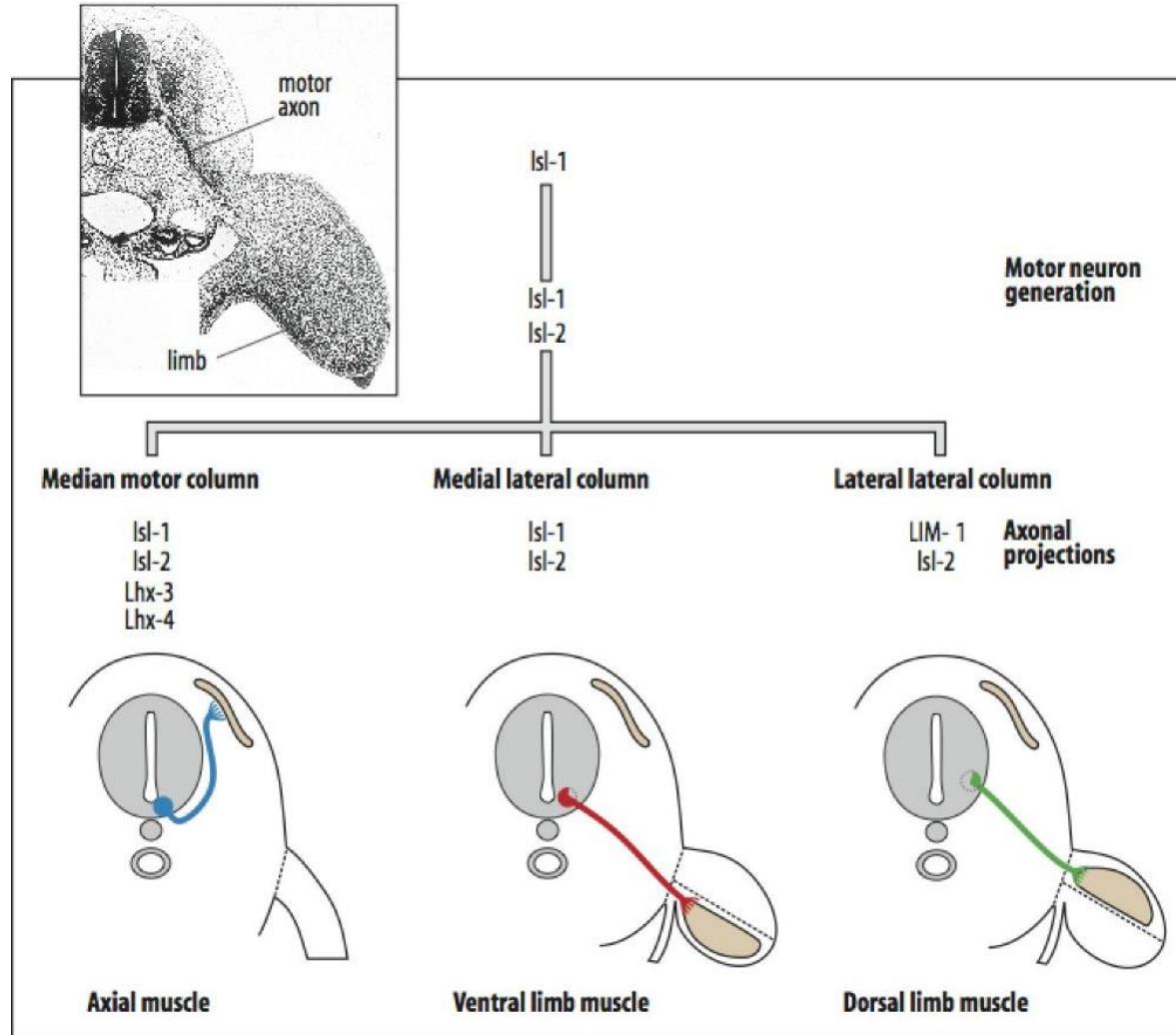


The gene *reelin* is an extracellular matrix molecule.

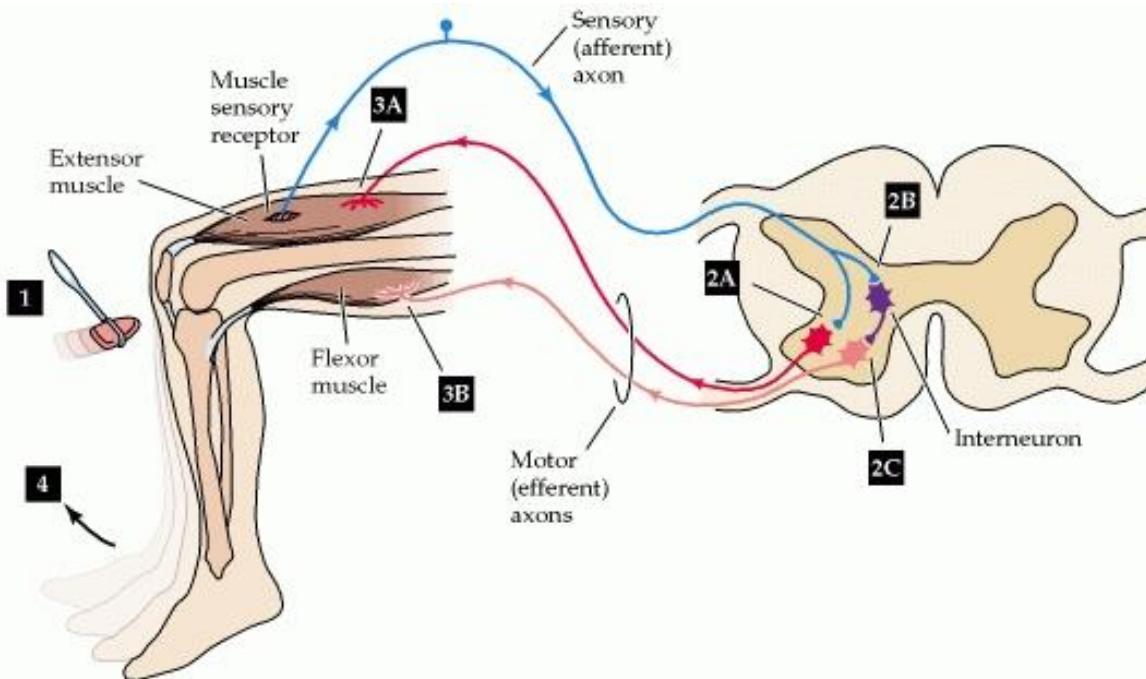
# Formation of sensory and motor neurons in the chick spinal cord



# Neurons in the chick spinal cord express different LIM homeodomain proteins

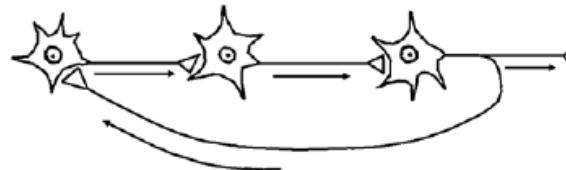
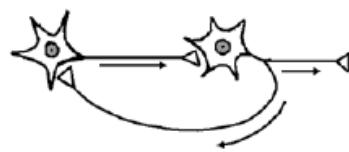
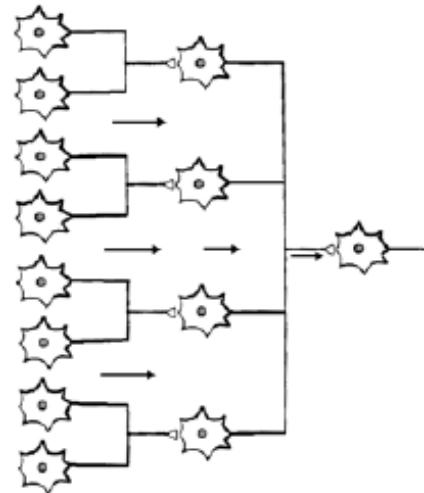
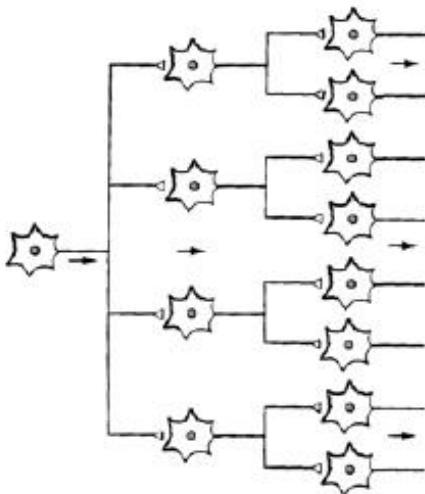


# Neural Circuits

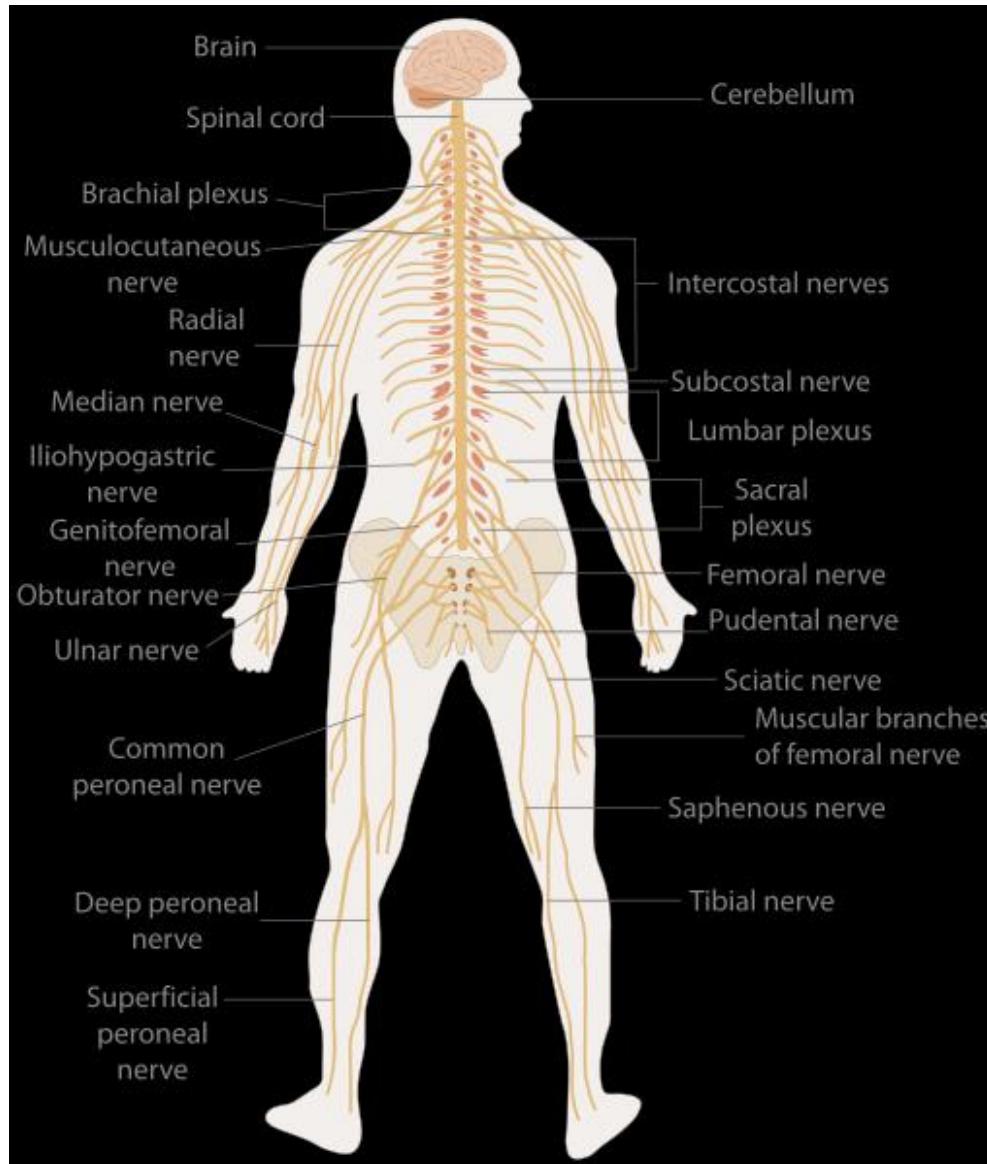


- 1 Hammer tap stretches tendon, which, in turn, stretches sensory receptors in leg extensor muscle
- 2 (A) Sensory neuron synapses with and excites motor neuron in the spinal cord  
(B) Sensory neuron also excites spinal interneuron  
(C) Interneuron synapse inhibits motor neuron to flexor muscles
- 3 (A) Motor neuron conducts action potential to synapses on extensor muscle fibers, causing contraction  
(B) Flexor muscle relaxes because the activity of its motor neurons has been inhibited
- 4 Leg extends

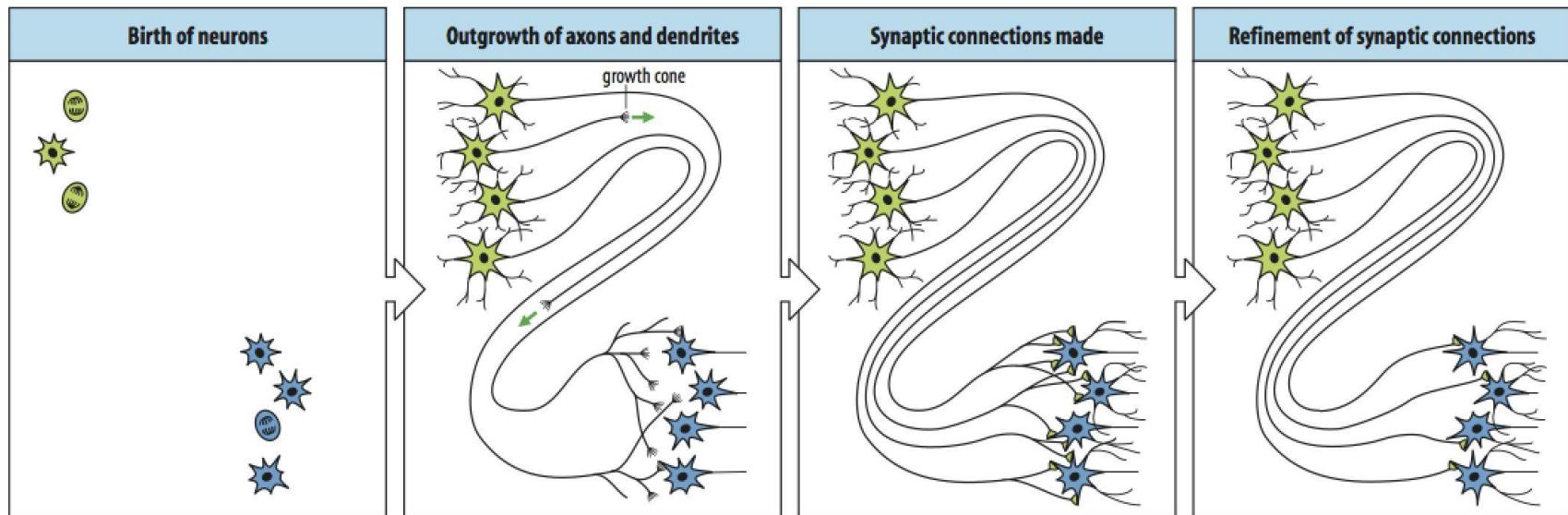
# Connections among neurons



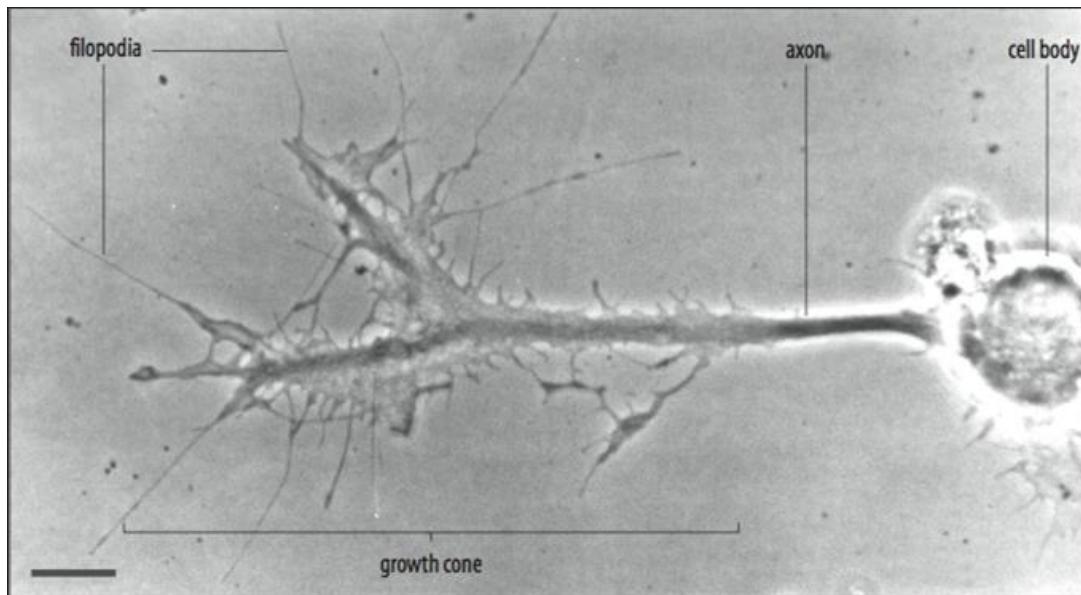
# Nerve system



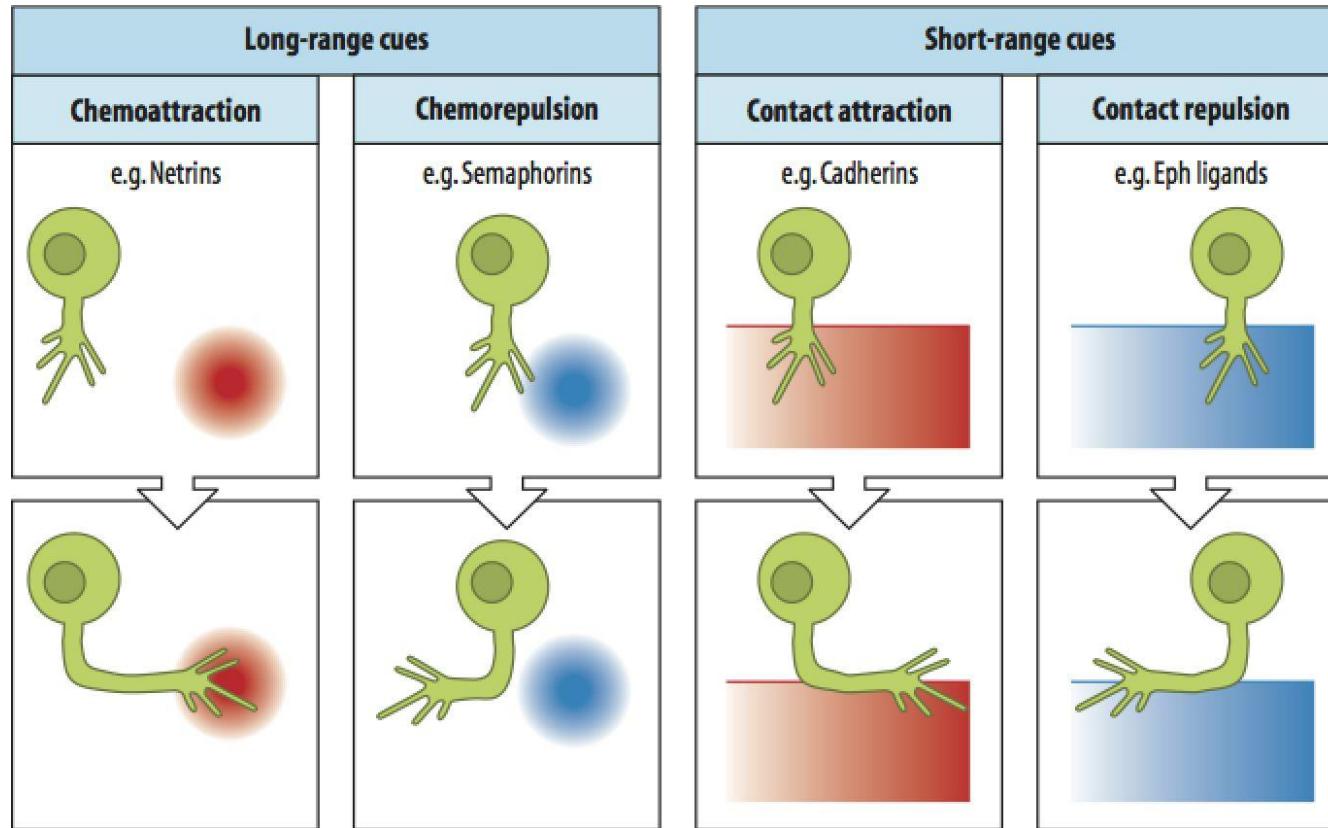
# Axon navigation / Axon guidance



# Axon growth cone



# Axon guidance mechanisms



# Both the Establishment and the Maintenance of Neuronal Polarity Require Active Mechanisms: Critical Roles of GSK-3 $\beta$ and Its Upstream Regulators

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bosomes (Caceres et al., 1986; Dotti and Banker, 1987;

Goslin et al., 1988; Kleiman et al., 1990; Steward, 2002).

How neuronal polarity forms remains an interesting and challenging question.

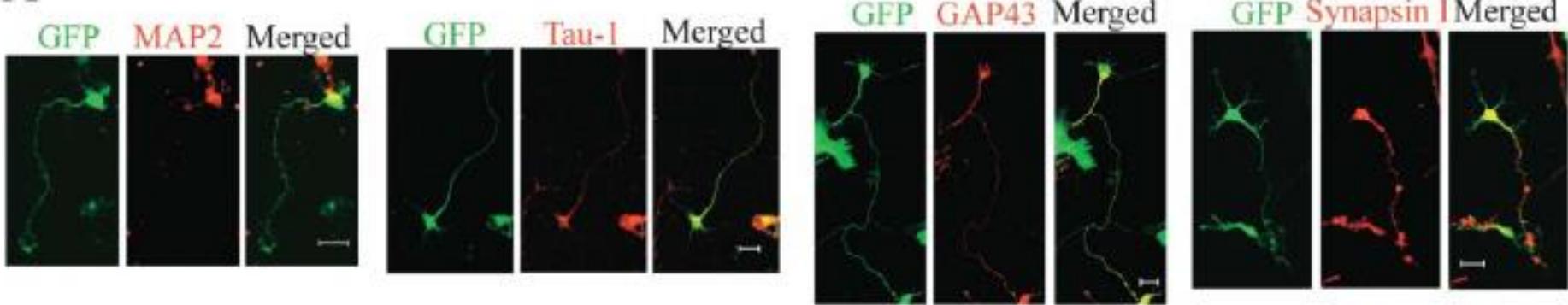
A well-established model for studying neuronal polarity is the pyramidal neurons from the mammalian hippocampus (Craig and Banker, 1994). Hippocampal neurons become polarized in successive steps (Banker and Cowan, 1977, 1979; Dotti and Banker, 1987). Shortly after culturing, a neuron extends lamellipodia around the soma (stage [st.] 1). It then extends several minor neurites in st. 2. At st. 3, one neurite is significantly longer and becomes the axon, whereas the others become dendrites. Experimental manipulations of neurite length can reset neurite competition (Dotti and Banker, 1987). Exposure of a neurite to extracellular adhesive molecules (Lein et al., 1992; Esch et al., 1999) or stimulation of a neurite by mechanical tension promotes neurite growth and favors axon formation (Lamoureux et al., 2002). Cytoskeleton dynamics has been implicated in breaking symmetry between stages 2 and 3 (Baas et al., 1988; Ahmad et al., 1994). Molecules affecting actin dynamics (Bradke and Dotti, 1999; but see also Ruthel and Hollenbeck, 2000) or microtubule (MT) dynamics such as the collapsin response mediator protein-2 (CRMP-2) (Inagaki et al., 2001; Fukata et al., 2002) regulate the formation of axon-dendrite polarity. The evolutionary conserved polarity complex composed of Par3/Par6/aPKC was first found in *C. elegans* for their roles in establishing the anterior-posterior polarity of the first blastomere. Par3/Par6, as well as two small GTPases CDC42 and Rap1B, have recently been implicated in the establishment of neuronal polarity in mammals (Shi et al., 2003; Nishimura et al., 2004b; Schwamborn and Puschel, 2004), though not in *Drosophila* (Rolls and Doe, 2004).

## Summary

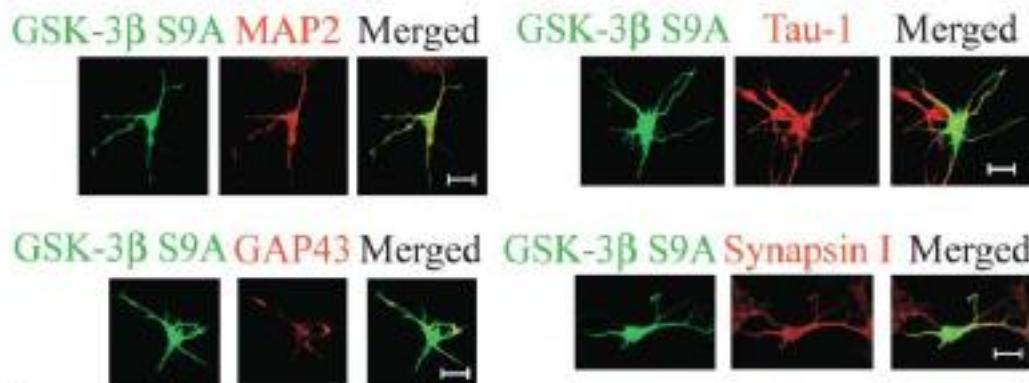
Axon-dendrite polarity is a cardinal feature of neuronal morphology essential for information flow. Here we report a differential distribution of GSK-3 $\beta$  activity in the axon versus the dendrites. A constitutively active GSK-3 $\beta$  mutant inhibited axon formation, whereas multiple axons formed from a single neuron when GSK-3 $\beta$  activity was reduced by pharmacological inhibitors, a peptide inhibitor, or siRNAs. An active mechanism for maintaining neuronal polarity was revealed by the conversion of preexisting dendrites into axons upon GSK-3 inhibition. Biochemical and functional data show that the Akt kinase and the PTEN phosphatase are upstream of GSK-3 $\beta$  in determining neuronal polarity. Our results demonstrate that there are active mechanisms for maintaining as well as es-

# Inhibition of Axon Formation by a Constitutively Active Form of GSK-3 $\beta$

A

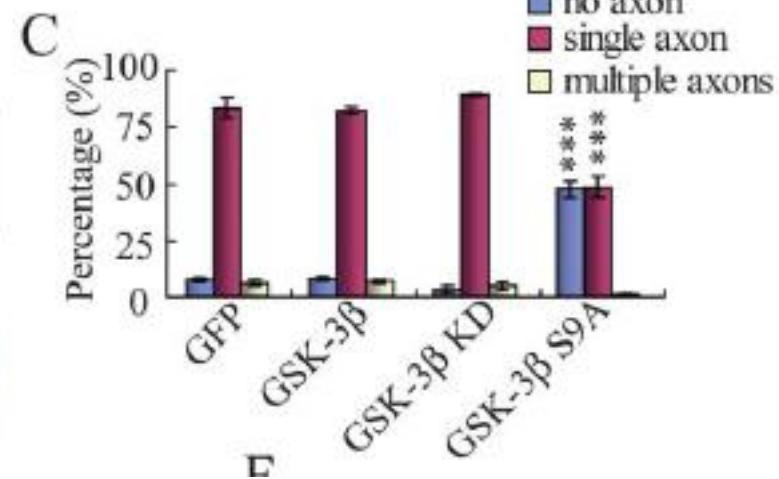


B

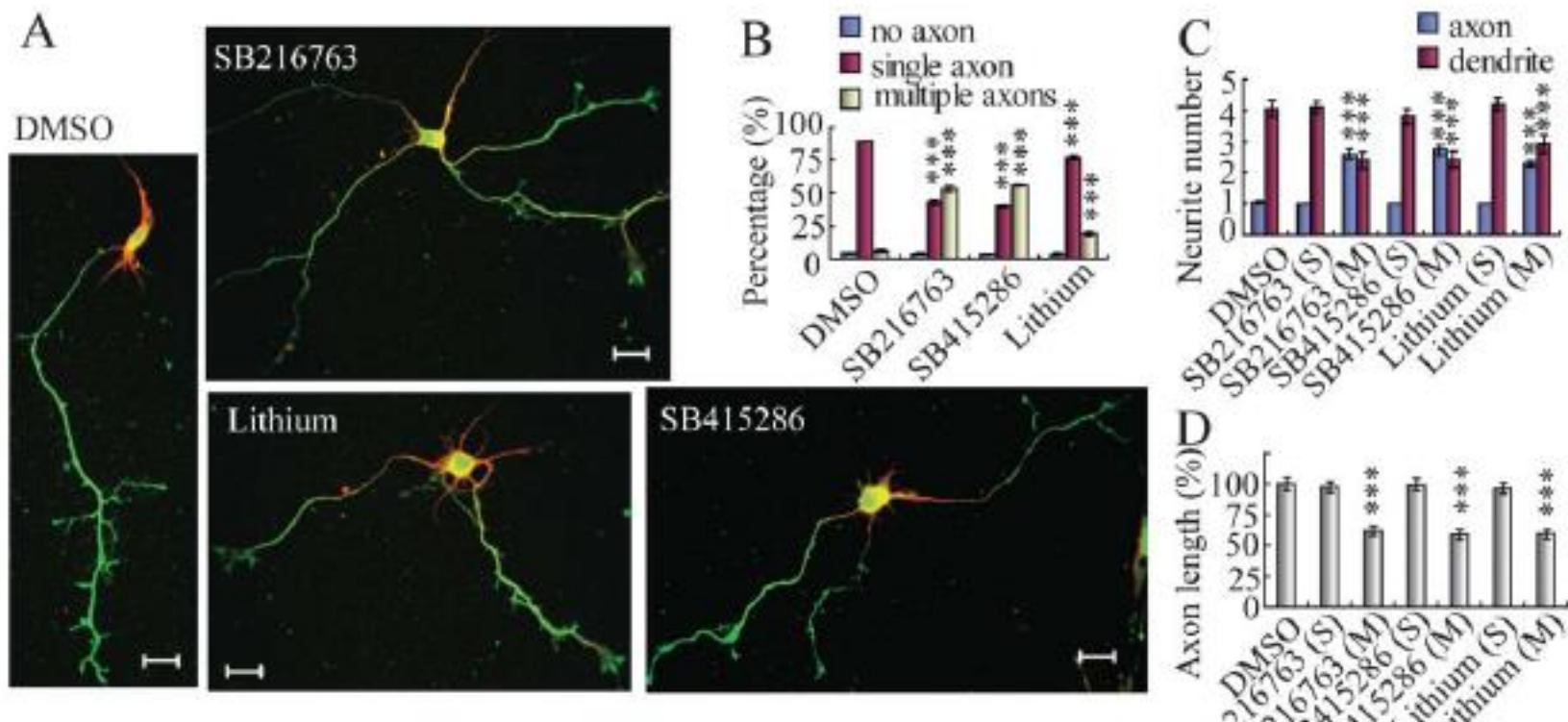


D

E

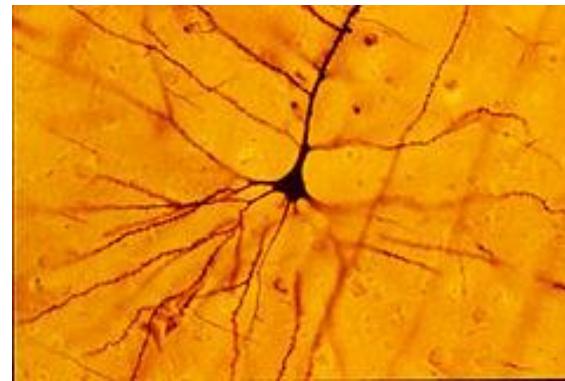
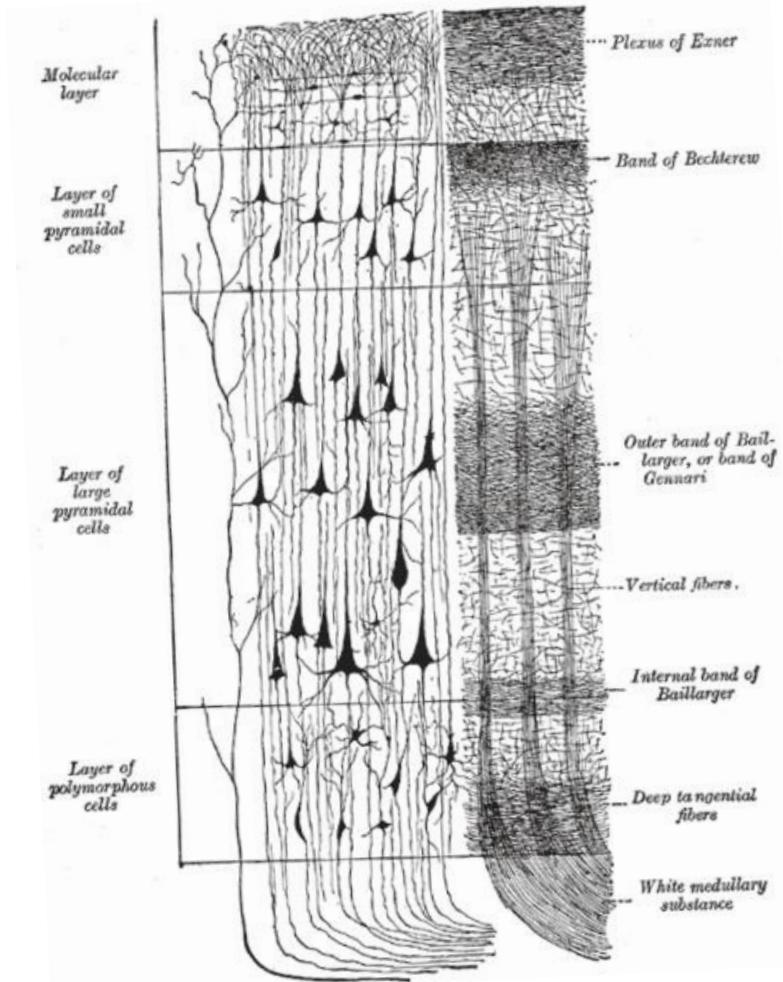


# Formation of Multiple Axons upon GSK-3 Inhibition by Pharmacological and Peptide Inhibitors



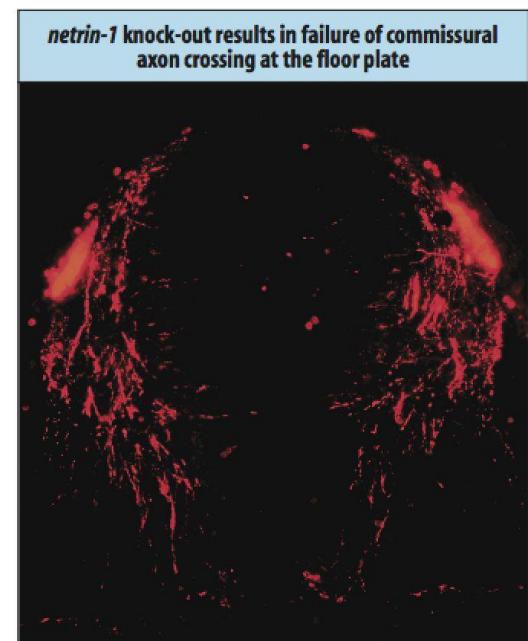
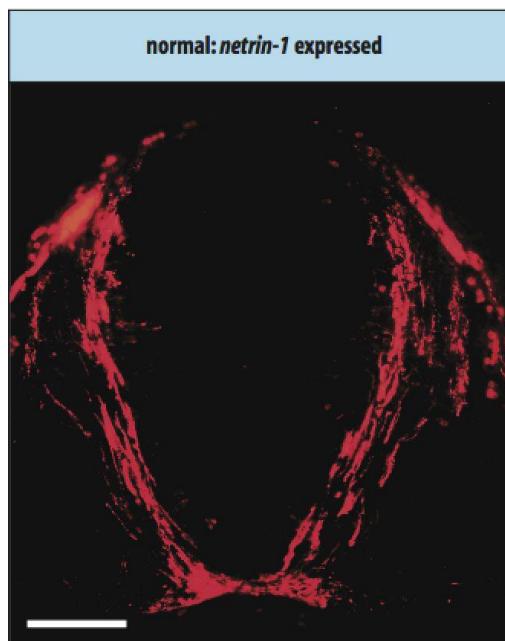
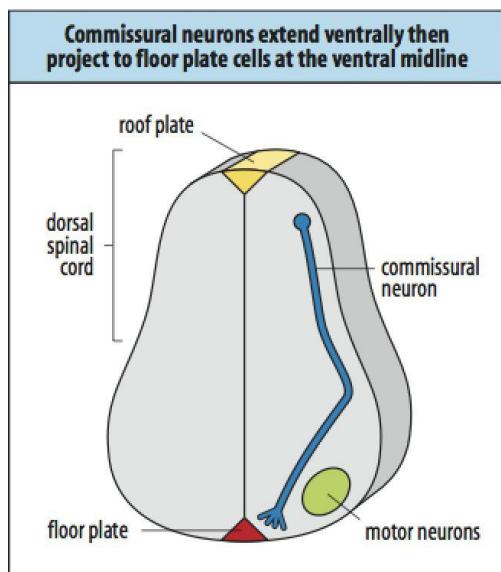
# The output of a cue also depends on the nature of a neuron

## Pyramidal neurons in the cortex

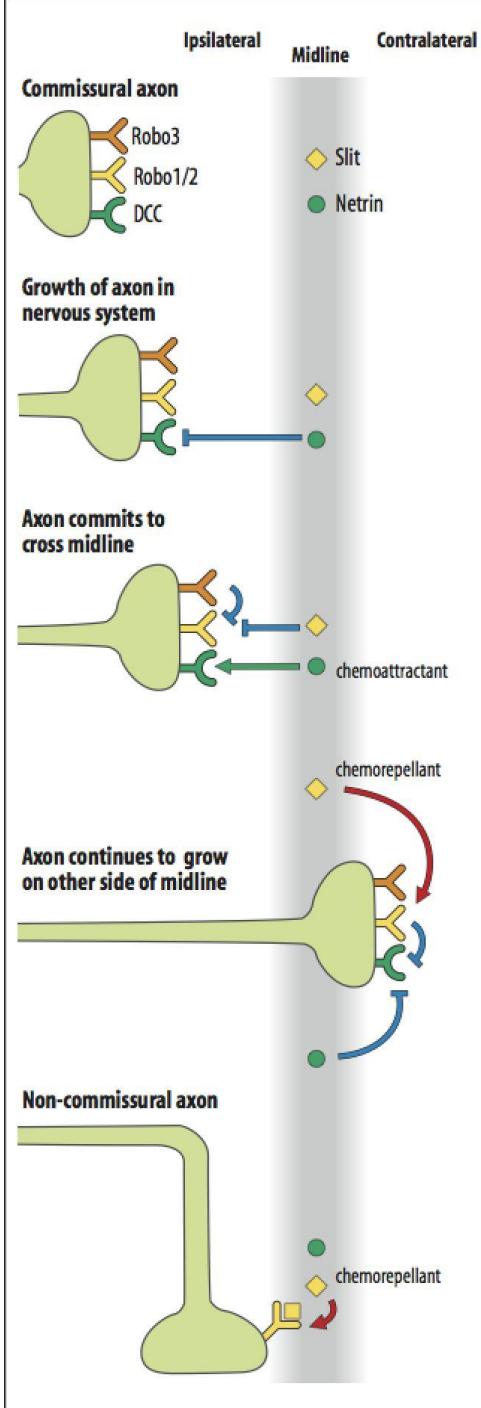


The apical dendrites of pyramidal neurons grow towards a source of semaphorin 3A, while their axons are repelled. It is due to the presence of guanylate cyclase in dendrites, but not in the axon.

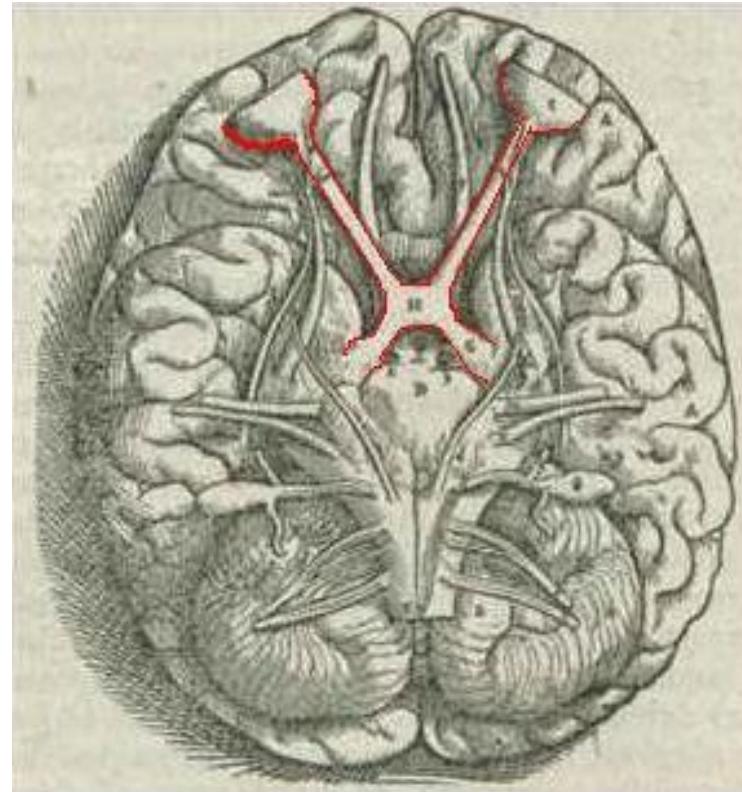
# Commissural axons, chemotaxis, and netrin



# Competition of chemo-attractant and chemo-repellent signals

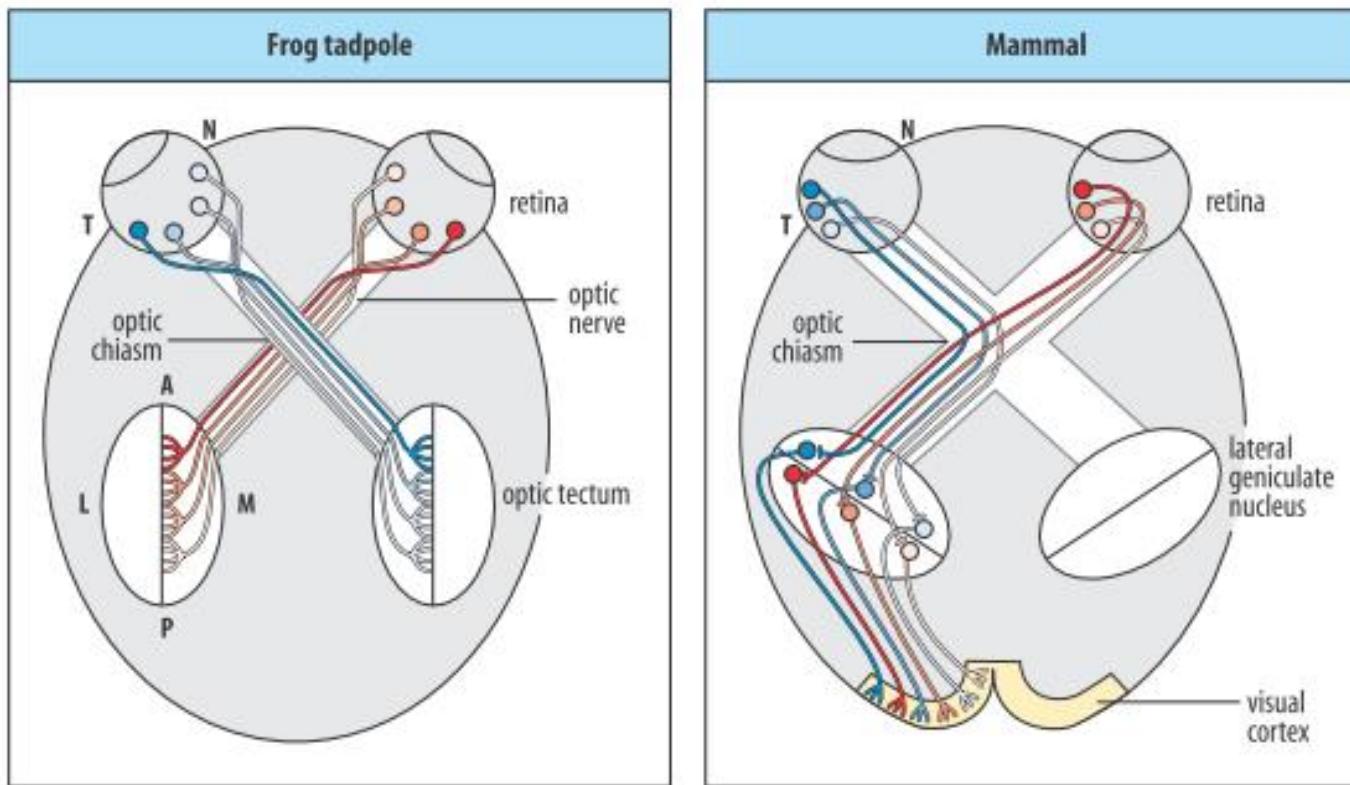


# Optic chiasm

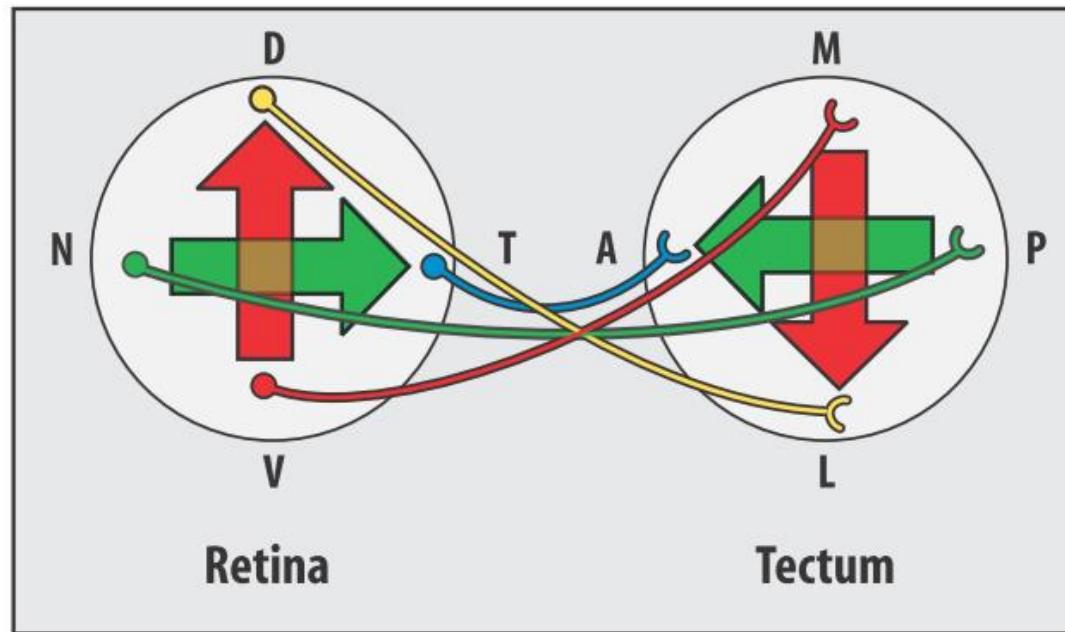


1543 image from [Andreas Vesalius' Fabrica](#)

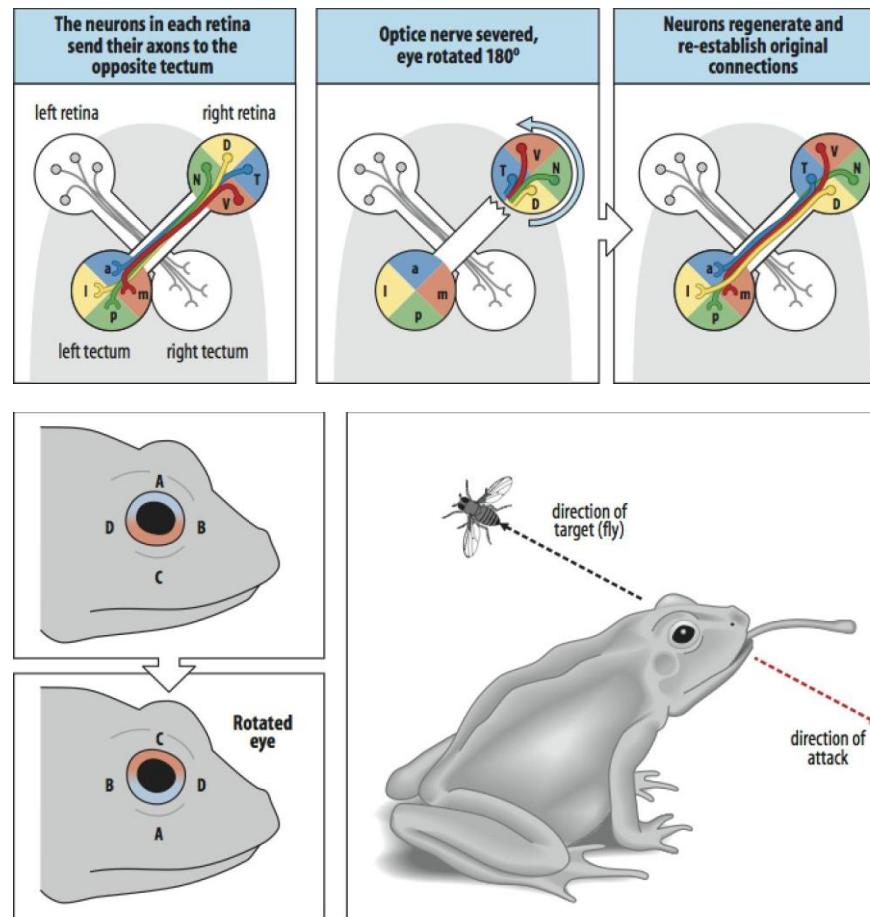
# Comparison of amphibian and mammalian visual systems



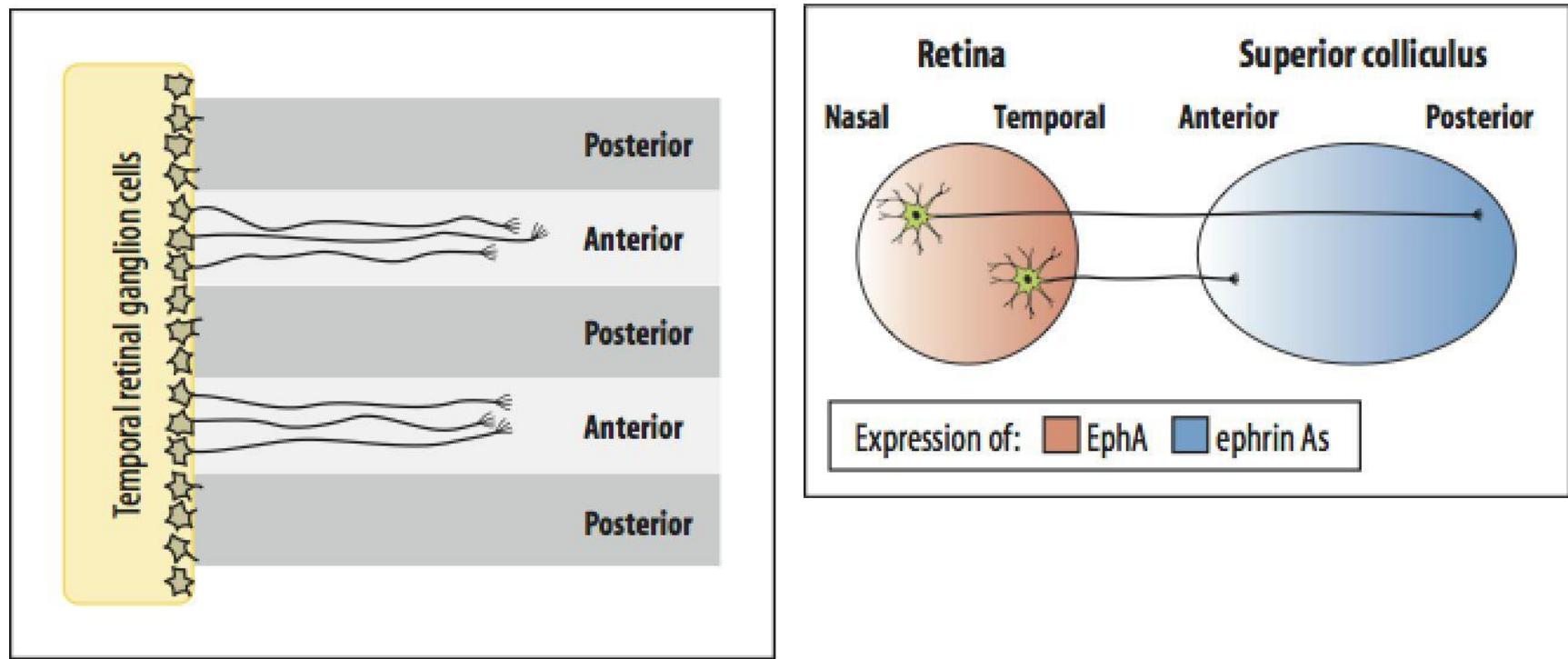
# The retina maps onto the tectum



# Retino-tectal connections in amphibians



# Choice of targets by retinal axons

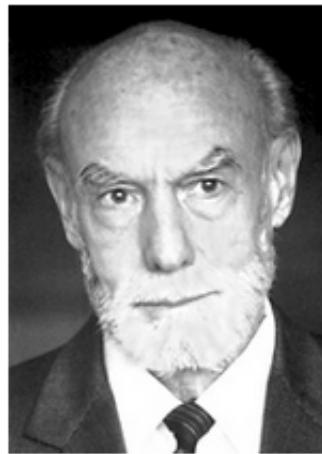




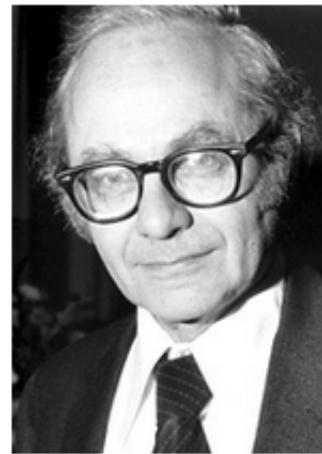
The Nobel Prize in Physiology or Medicine 1981  
Roger W. Sperry, David H. Hubel, Torsten N. Wiesel

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# The Nobel Prize in Physiology or Medicine 1981



Roger W. Sperry



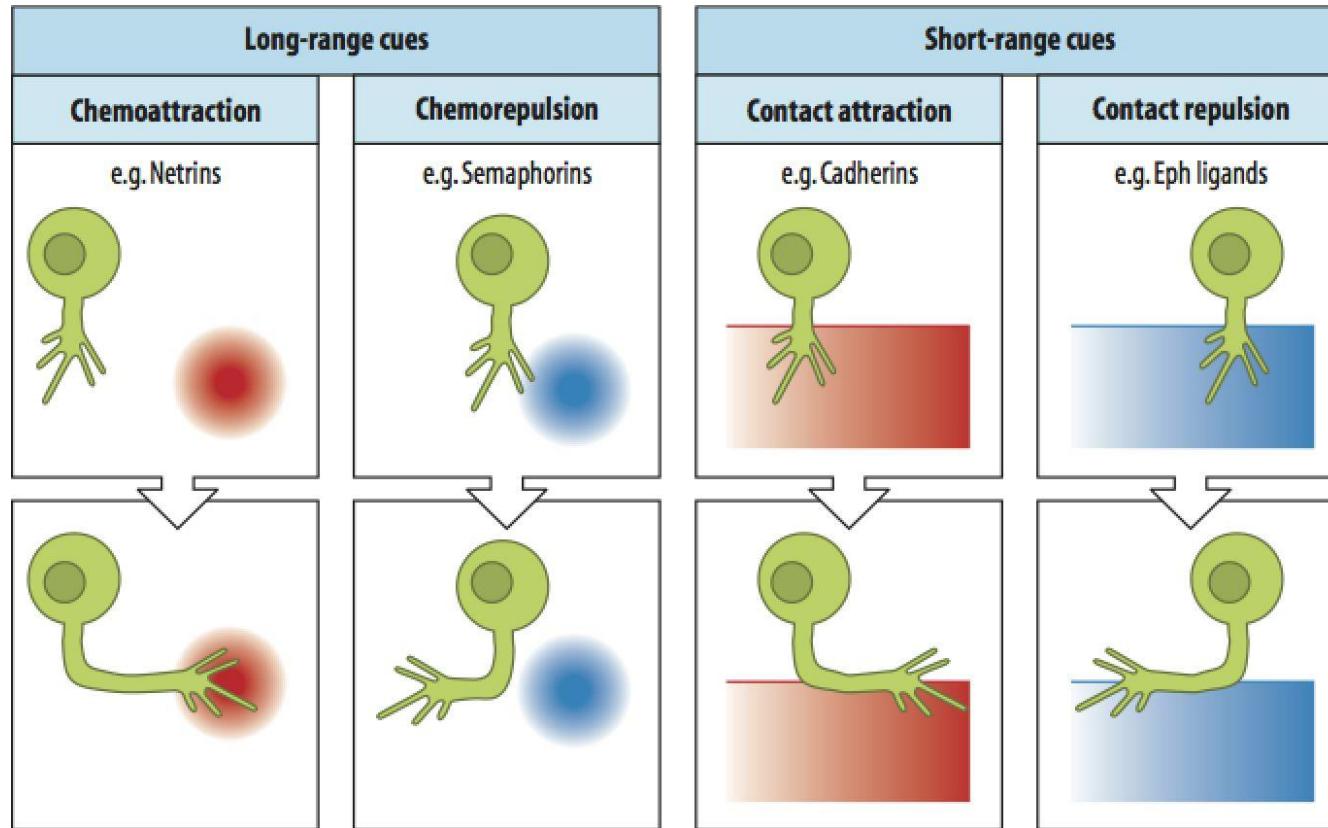
David H. Hubel



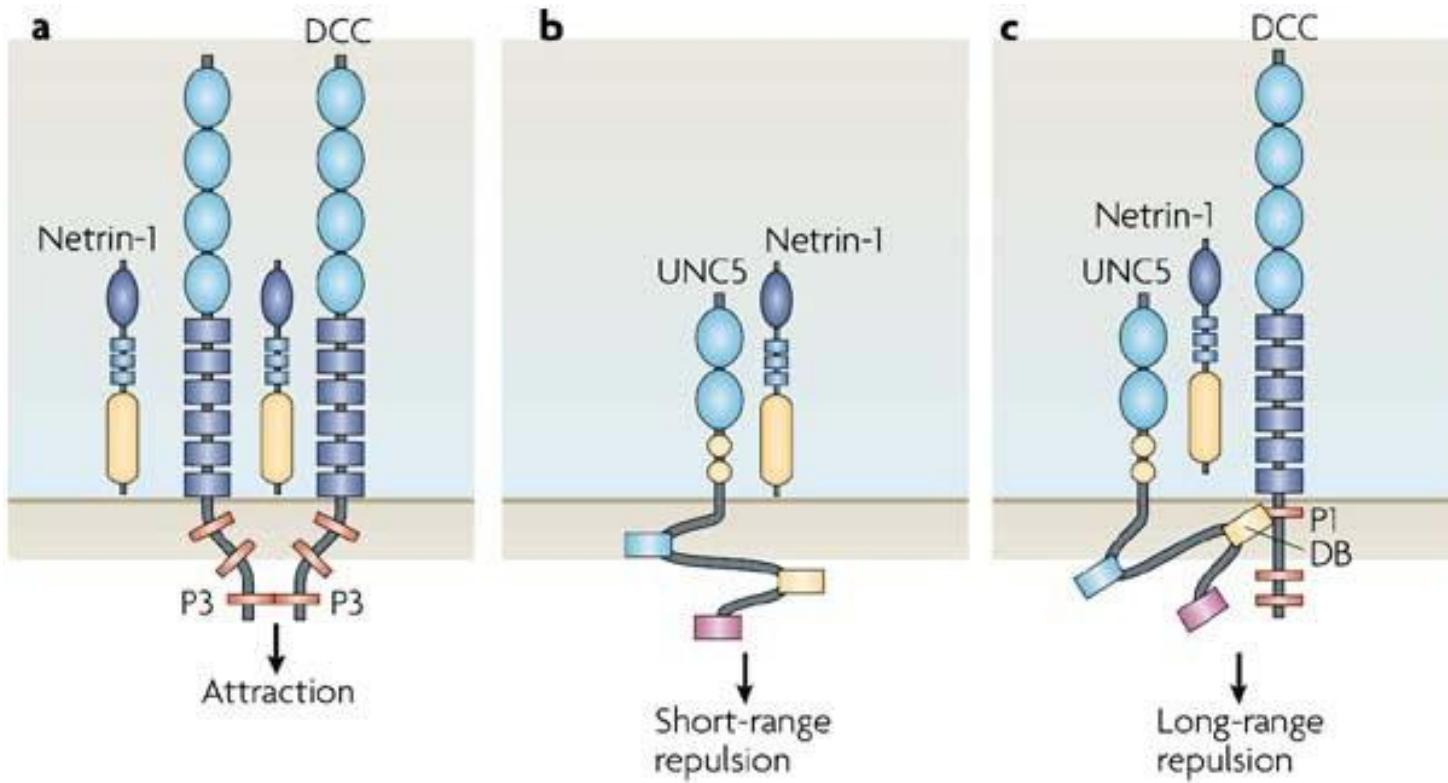
Torsten N. Wiesel

The Nobel Prize in Physiology or Medicine 1981 was divided, one half awarded to Roger W. Sperry *"for his discoveries concerning the functional specialization of the cerebral hemispheres"*, the other half jointly to David H. Hubel and Torsten N. Wiesel *"for their discoveries concerning information processing in the visual system"*.

# Axon guidance mechanisms



# Netrin pathway



Nature Reviews | Molecular Cell Biology

Named after the Sanskrit word *netr*, which means 'one who guides'.

# The Netrins Define a Family of Axon Outgrowth-Promoting Proteins Homologous to *C. elegans* UNC-6

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Michael J. Galko,\* Christine Mirzayan,\*  
Thomas M. Jessell,† and Marc Tessier-Lavigne\*

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San Francisco, California 94143-0452

†Howard Hughes Medical Institute

Center for Neurobiology and Behavior

Department of Biochemistry and Biophysics

Columbia University

New York, New York 10032

## Summary

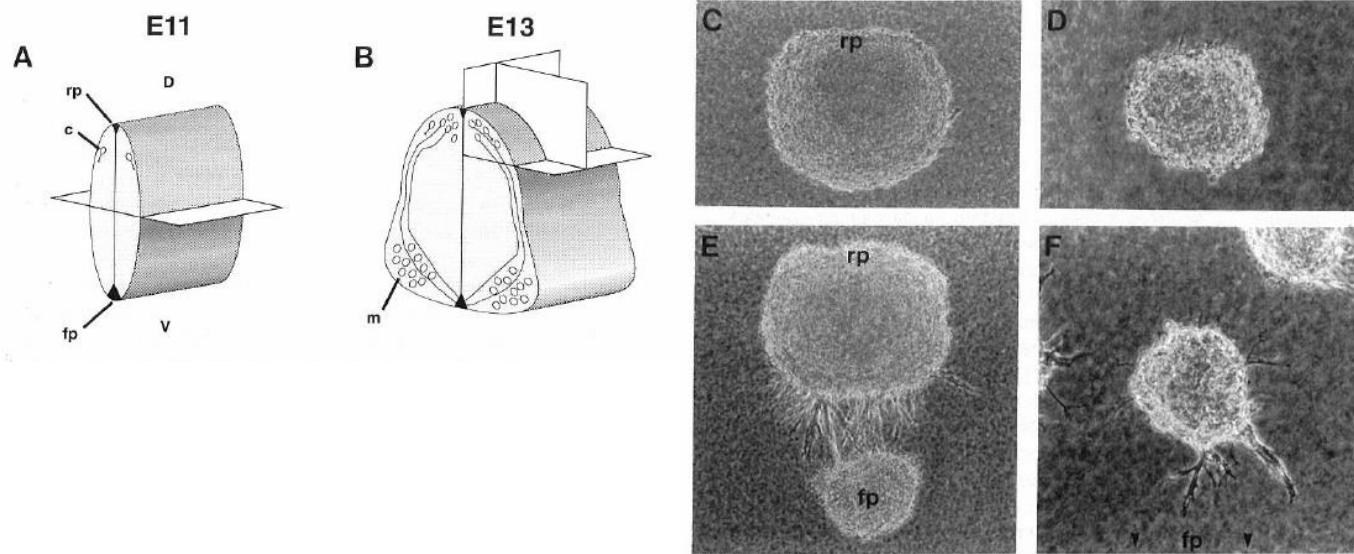
In vertebrates, commissural axons pioneer a circumferential pathway to the floor plate at the ventral midline of the embryonic spinal cord. Floor plate cells secrete a diffusible factor that promotes the outgrowth of commissural axons *in vitro*. We have purified from embryonic chick brain two proteins, netrin-1 and netrin-2, that each possess commissural axon outgrowth-promoting activity, and we have also identified a distinct activity that potentiates their effects. Cloning of cDNAs encoding the two netrins shows that they are homologous to UNC-6, a laminin-related protein required for the circumferential migration of cells and axons in *C. elegans*. This homology suggests that

culture (Gundersen and Barrett, 1979) but does not appear to be involved in guiding developing axons as they first grow to their targets (Davies, 1987) or in guiding regenerating axons *in vivo* (Diamond et al., 1992). Neurotransmitters can induce growth cone turning *in vitro* (Zheng et al., 1994), but their involvement in axon guidance *in vivo* remains to be established.

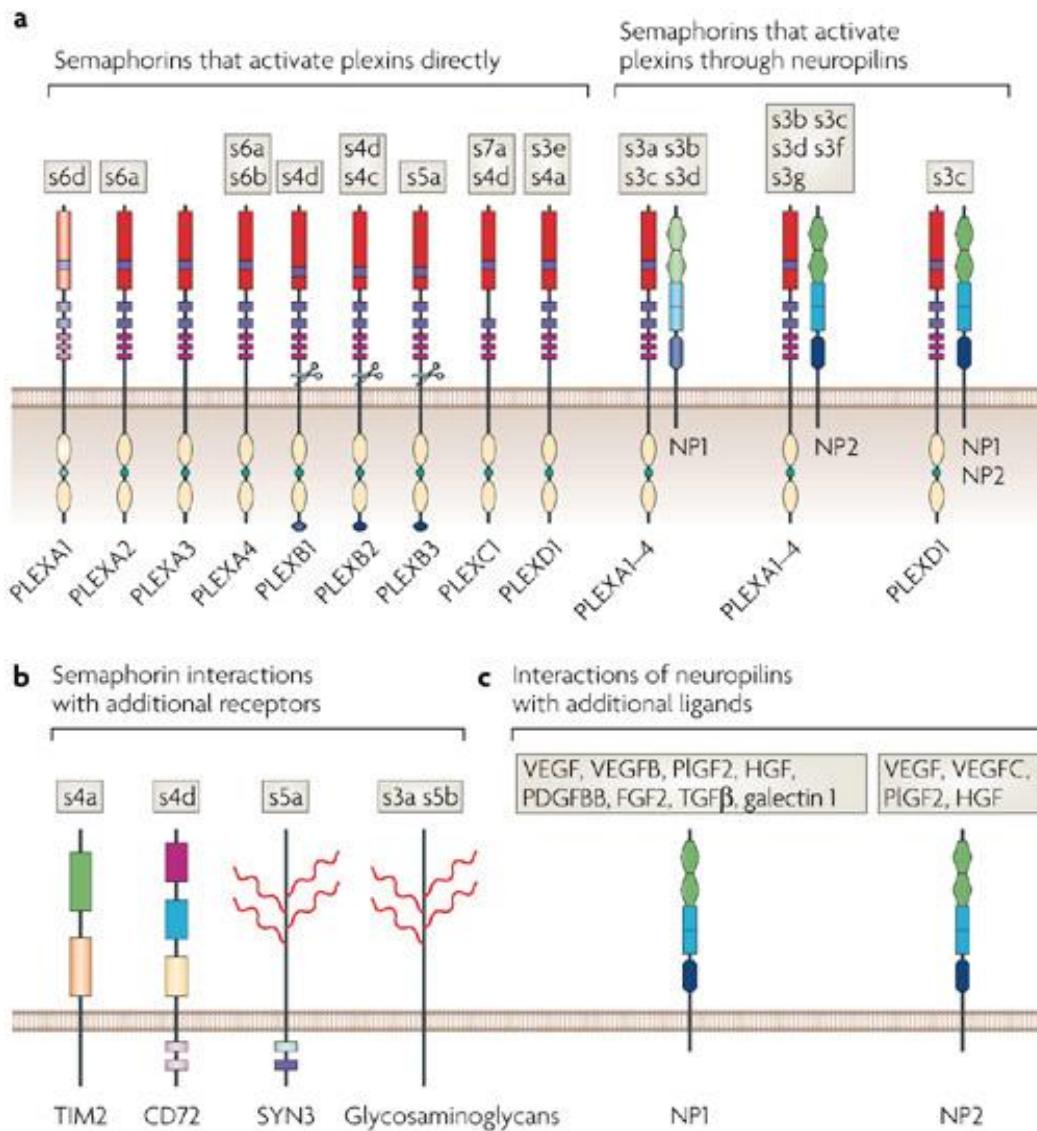
One region of the vertebrate central nervous system where evidence for the operation of chemotropic mechanisms has been obtained is the developing spinal cord. Commissural neurones that differentiate in the dorsal spinal cord extend axons along a stereotyped dorsoventral trajectory that leads them to the floor plate, an intermediate target at the ventral midline of the spinal cord (Ramón y Cajal, 1909; Holley, 1982; Wentworth, 1984; Dodd et al., 1988; Yaginuma et al., 1990). Experiments *in vitro* (Tessier-Lavigne et al., 1988; Placzek et al., 1990a) and *in vivo* (Weber, 1938; Placzek et al., 1990b; Yaginuma and Oppenheim, 1991) have demonstrated that the floor plate secretes a chemoattractant for developing commissural axons during the period that these axons grow to the floor plate, suggesting that chemotropism contributes to the ventral guidance of these axons to the floor plate during normal development.

Floor plate cells have two long-range effects on commissural axons *in vitro* (Tessier-Lavigne et al., 1988; Placzek et al., 1990a). First, they promote the outgrowth of these axons from explants of embryonic dorsal spinal cord into collagen gels. Second, they attract commissural axons by reorienting their growth within dorsal spinal cord explants. Both the outgrowth and the orienting effects of the floor

# Floor Plate Cells and Embryonic Brain Extract Elicit Commissural Axon Outgrowth from E11 and E13 Rat Dorsal Spinal Cord Explants



# Semaphorins



# Fasciclin IV: Sequence, Expression, and Function during Growth Cone Guidance in the Grasshopper Embryo

Alex L. Kolodkin,\*† David J. Matthes,\*†,  
Timothy P. O'Connor,† Nipam H. Patel,\*†‡  
Arie Admon,\* David Bentley,† and Corey S. Goodman\*†

\*Howard Hughes Medical Institute

†Division of Neurobiology

Department of Molecular and Cell Biology

Life Science Addition

University of California

Berkeley, California 94720

## Summary

Monoclonal antibody 6F8 was used to characterize and clone fasciclin IV, a new axonal glycoprotein in the grasshopper, and to study its function during growth cone guidance. Fasciclin IV is dynamically expressed on a subset of axon pathways in the developing CNS and on circumferential bands of epithelial cells in developing limb buds. One of these bands corresponds to the location where the growth cones of the Ti1 pioneer neurons make a characteristic turn while extending toward the CNS. Embryos cultured in the 6F8 antibody or Fah exhibit aberrant formation of this axon pathway. cDNA sequence analysis suggests that fasciclin IV has a signal sequence; long extracellular, transmembrane, and short cytoplasmic domains; and shows no homology with any protein in the available data bases. Thus, fasciclin IV appears to be a novel integral membrane protein that functions in growth cone guidance.

ance cues such as the limb bud epithelium, including particular regions of epithelium near segment borders, and another pair of neurons (e.g., Condic and Bentley, 1989a, 1989b; O'Connor et al., 1990). Guidance along an epithelium and its secreted extracellular matrix has also been observed in the developing wing imaginal disc of *Drosophila* (e.g., Blair et al., 1987). Nonneuronal cues are also important for the establishment of axon pathways in the developing insect CNS (Jacobs and Goodman, 1989; Klämbt et al., 1991). For example, glia provide guidance cues for the growth cones that pioneer one of the peripheral nerve roots in the grasshopper embryo (e.g., Bastiani and Goodman, 1986).

In contrast to the initial pioneers, most later growth cones in the developing insect CNS are followers, and they find themselves in an environment surrounded by the axons of earlier differentiating neurons. Experimental analysis reveals their ability to distinguish one bundle of axons, or fascicle, from another (called selective fasciculation), leading to the labeled pathway hypothesis (e.g., Raper et al., 1984; Bastiani et al., 1984, 1986; du Lac et al., 1986).

In an attempt to identify molecules involved in selective fasciculation, a series of monoclonal antibody (MAb) screens were conducted in both grasshopper and *Drosophila* to identify surface glycoproteins that are differentially expressed on subsets of axon pathways. Four surface glycoproteins were initially characterized (fasciclin I, fasciclin II, fasciclin III, and neuro-

# Fasciclin IV: Sequence, Expression, and Function during Growth Cone Guidance in the Grasshopper Embryo

Alex L. Kolodkin,\*† David J. Matthes,\*‡

Timothy P. O'Connell,\*‡ Arie Admon,\*

Arie Admon,\* David

\*Howard Hughes M

†Division of Neurol

Department of Mol

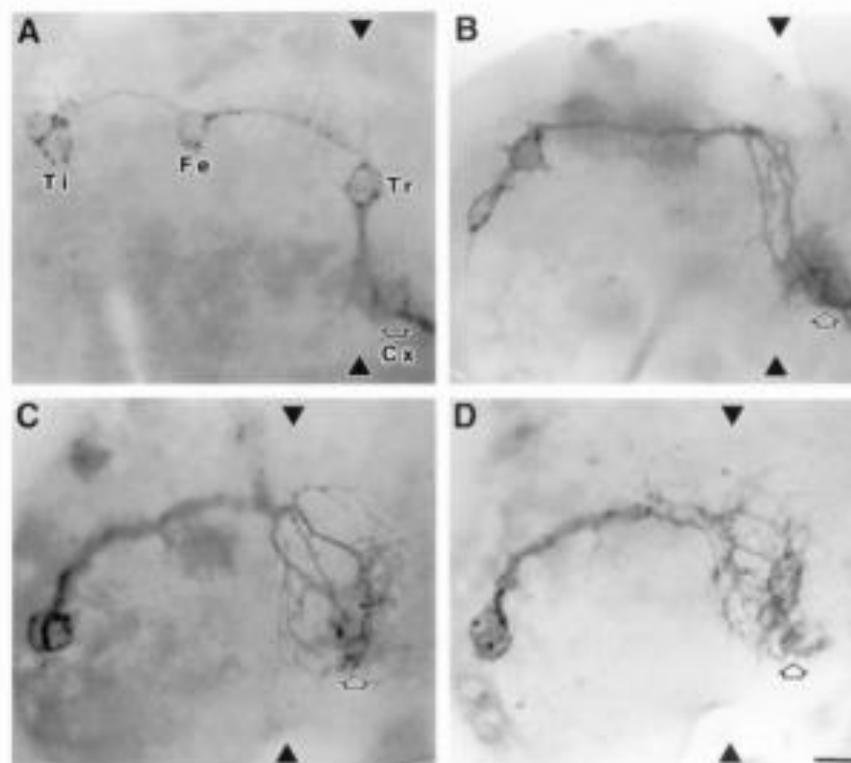
Life Science Additio

University of Califor

Berkeley, California

## Summary

Monoclonal antibody clone fasciclin IV, isolated from a grasshopper, and its function in growth cone guidance. Fasciclin IV is expressed on a subset of axon pathways that follow circumferential bands of guidance cues near segment borders (e.g., Condic and et al., 1990). Guided by these cues, the developing embryo forms a ring of neurons (e.g., Blair et al., 1989; Klämbt et al., 1989). Guidance cues for the ring of neurons include peripheral nerve fibers (e.g., Bastiani and



ance cues such as the limb bud epithelium, including

near segment borders (e.g., Condic and et al., 1990). Guided by these cues, the developing embryo forms a ring of neurons (e.g., Blair et al., 1989; Klämbt et al., 1989). Guidance cues for the ring of neurons include peripheral nerve fibers (e.g., Bastiani and

, most later growth cones are followers, and they follow the segmental arrangement surrounded by earlier forming neurons. Experimentally, it is difficult to distinguish one growth cone from another (called serial sectioning) because they share the same labeled pathway (Bastiani et al., 1984,

ules involved in selective guidance. Monoclonal antibody

(MAb) screens were conducted in both grasshopper and Drosophila to identify surface glycoproteins that are differentially expressed on subsets of axon pathways. Four surface glycoproteins were initially characterized (fasciclin I, fasciclin II, fasciclin III, and neuro-

# The semaphorin Genes Encode a Family of Transmembrane and Secreted Growth Cone Guidance Molecules

Alex L. Kolodkin, David J. Matthes,  
and Corey S. Goodman

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Division of Neurobiology  
Department of Molecular and Cell Biology  
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## Summary

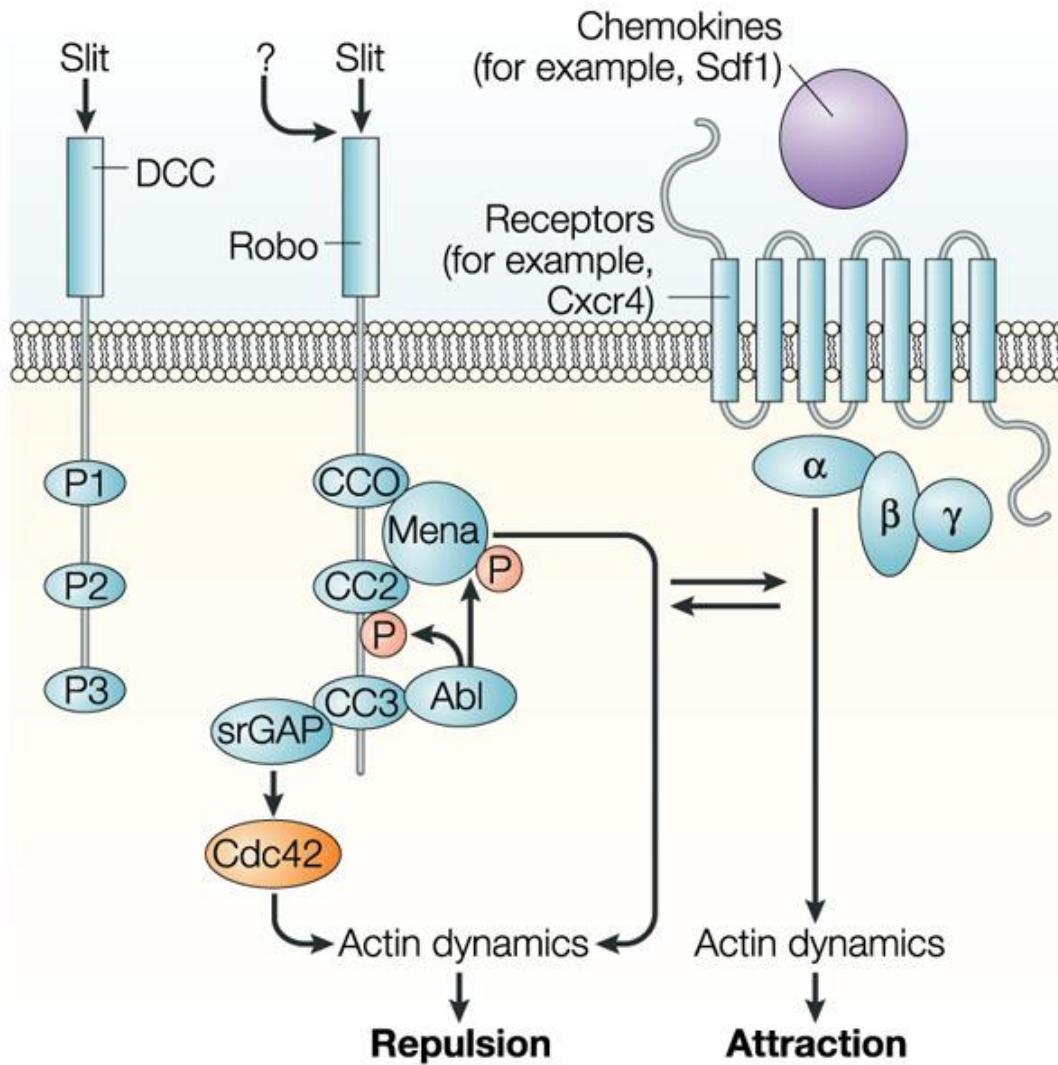
In addition to its expression on subsets of axons, grasshopper Semaphorin I (Sema I, previously called Fasciclin [Fas] IV) is expressed on an epithelial stripe in the limb bud, where it functions in the guidance of two sensory growth cones as they abruptly turn upon encountering this sema I boundary. We report here on the cloning and characterization of two *sema* genes in *Drosophila*, one in human, and the identification of two related viral sequences, all of which encode proteins with conserved Semaphorin domains. *Drosophila sema* (D-Sema) I is a transmembrane protein, while D-Sema II and human Sema III are putative secreted proteins that are similar to the recently reported chick collapsin. D-Sema I and D-Sema II are expressed by subsets of neurons and muscles. Genetic analysis in *Drosophila* reveals that *semal* is an essential gene that is required for both proper adult behavior and survival.

1991). The fifth gene encodes an axonal glycoprotein, initially called grasshopper Fasciclin (Fas) IV, that like the others is also expressed on a subset of axon pathways in the insect embryo (Kolodkin et al., 1992). However, Fas IV differs from the other four in a number of respects: it cannot mediate cell aggregation in vitro (suggesting that it is not a homophilic cell adhesion molecule), it is expressed as a guidance cue in the environment of the growth cone but is not expressed on the responding growth cone, and its sequence, when published in 1992, was novel. In addition to its expression on a subset of CNS axon pathways, Fas IV is also expressed on a stripe of epithelial cells in the embryonic limb bud, where it functions to help guide two sensory growth cones as they sharply turn upon encountering this Fas IV stripe (Figure 1; see Discussion) (Kolodkin et al., 1992).

Given the discovery reported here of a gene family encoding related transmembrane and secreted proteins and the differences between *fas*/IV and the other *fas* genes, all of which encode homophilic cell adhesion molecules, it seemed appropriate to rename this protein and the gene family to which it belongs. We call this initial grasshopper protein Semaphorin I (G-Sema I), and the family the Semaphorins, to denote their function as semaphores (or signals) for growth cone guidance.

In the present study, we have used a polymerase chain reaction-based (PCR-based) approach to clone two different *sema* genes in *Drosophila* and a related *sema* gene in humans. Based on the conserved amino acids in these sequences, we have also identified related sequences in

# Slit-robo



# Vertebrate Slit, a Secreted Ligand for the Transmembrane Protein Roundabout, Is a Repellent for Olfactory Bulb Axons

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Tanya Fagaly,\* Lijuan Zhou,\* Wenlin Yuan,‡  
Sophie Dupuis,† Zhi-hong Jiang,†  
William Nash,† Carrie Gick,† David M. Ornitz,‡  
Jane Y. Wu,†‡|| and Yi Rao\*†‡

\*Department of Anatomy and Neurobiology

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320 Yue-yang Road

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China

## Summary

The olfactory bulb plays a central role in olfactory information processing through its connections with both peripheral and cortical structures. Axons projecting from the olfactory bulb to the telencephalon are guided by a repulsive activity in the septum. The molecular nature of the repellent is not known. We report here the isolation of vertebrate homologs of the *Drosophila slit* gene and show that Slit protein binds to the transmembrane protein Roundabout (Robo). *Slit* is expressed in the septum whereas *Robo* is expressed in the olfactory bulb. Functionally, Slit acts as a chemorepellent for olfactory bulb axons. These results establish a ligand-receptor relationship between two molecules important for neural development, suggest

in the olfactory bulb. These secondary neurons project axons to olfactory cortical areas in the telencephalon including the anterior olfactory nucleus, the piriform cortex, the olfactory tubercle, the anterior cortical nucleus of the amygdala, the periamygdaloid cortex (also known as the posterolateral nucleus of the amygdala), and the lateral entorhinal cortex (Hinds, 1972; Hinds and Ruffett, 1973; Schwob and Price, 1984; Brunjes and Frazier, 1986; Saucier and Astic, 1986; Shepherd and Greer, 1990; Schoenfeld et al., 1994; Shipley et al., 1995; Mombaerts et al., 1996).

Although it is clear that the processing of olfactory information relies on precise connectivity among different parts of the olfactory system, our understanding of mechanisms underlying axon guidance in the olfactory system is quite limited. Recent studies have suggested roles for olfactory receptors and cell adhesion molecules in controlling axons projecting from the olfactory epithelium to the olfactory bulb (Wang et al., 1998; Yoshihara et al., 1997). By contrast, little is known at the molecular level about mechanisms guiding axons from the olfactory bulb to the cortex. Morphological studies have shown that axons of the olfactory bulb turn away from the midline, forming the lateral olfactory tract (LOT), and grow toward the olfactory cortex (Schwob and Price, 1984; Brunjes and Frazier, 1986; Shipley et al., 1995). In vitro explant studies have revealed that the septum at the midline of the telencephalon secretes a diffusible factor(s), which repels the projection axons of the olfactory bulb (Pini, 1993). The molecular nature of repulsive factor(s) in the septum has so far remained unknown.

The ventral midline of the neural tube can provide either attractive or repulsive guidance cues for axons, depending on the type and developmental history of the responding axons. Extensive studies have shown that

# Slit Is the Midline Repellent for the Robo Receptor in *Drosophila*

Thomas Kidd, Kimberly S. Bland,  
and Corey S. Goodman\*

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Department of Molecular and Cell Biology  
University of California, Berkeley  
Berkeley, California 94720

## Summary

Previous studies suggested that Roundabout (Robo) is a repulsive guidance receptor on growth cones that binds to an unknown midline ligand. Here we present genetic evidence that Slit is the midline Robo ligand; a companion paper presents biochemical evidence that Slit binds Robo. Slit is a large extracellular matrix protein expressed by midline glia. In *slit* mutants, growth cones enter the midline but never leave it; they abnormally continue to express high levels of Robo while at the midline. *slit* and *robo* display dosage-sensitive genetic interactions, indicating that they function in the same pathway. *slit* is also required for migration of muscle precursors away from the midline. Slit appears to function as a short-range repellent controlling axon crossing of the midline and as a long-range chemorepellent controlling mesoderm migration away from the midline.

together, these results suggest that Comm regulates Robo function by either controlling Robo levels or Robo signaling. Further analysis revealed that Comm controls Robo expression; increasing Comm leads to a reduction of Robo protein.

These studies led to the model that Robo is a repulsive guidance receptor for an unknown midline ligand and that Comm downregulates the levels of the Robo receptor on commissural axons (Kidd et al., 1998a, 1998b). We argued that this midline repellent is likely to function in a short-range fashion, since growth cones that express high levels of Robo do not necessarily extend away from the midline, but rather extend longitudinally close to the midline. One candidate ligand might be one of the two *Drosophila* Netrins that are expressed by midline glial cells (Harris et al., 1996; Mitchell et al., 1996). However, our unpublished genetic analysis led us to believe that the Netrins are not Robo ligands. What, then, is the midline Robo ligand?

We were also interested in answering a more general question. If the midline, with its expression of Netrins, is such an attractive place, with mirror-symmetric commissural axons from both sides extending toward and entering the midline, why do growth cones ever leave the midline? Why don't these growth cones fasciculate with their contralateral homolog and extend longitudinally along the midline? In a *robo* mutant, axons freely cross and recross the midline, but they do not stay at the

# Slit Proteins Bind Robo Receptors and Have an Evolutionarily Conserved Role in Repulsive Axon Guidance

Katja Brose,<sup>\*†</sup> Kimberly S. Bland,<sup>†‡</sup> Kuan Hong Wang,<sup>\*</sup> David Arnott,<sup>‡</sup> William Henzel,<sup>‡</sup> Corey S. Goodman,<sup>†</sup> Marc Tessier-Lavigne,<sup>\*§</sup> and Thomas Kidd<sup>†</sup>

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South San Francisco, California 94080

## Summary

Extending axons in the developing nervous system are guided in part by repulsive cues. Genetic analysis in *Drosophila*, reported in a companion to this paper, identifies the Slit protein as a candidate ligand for the repulsive guidance receptor Roundabout (Robo). Here we describe the characterization of three mammalian Slit homologs and show that the *Drosophila* Slit protein and at least one of the mammalian Slit proteins, Slit2, are proteolytically processed and show specific, high-affinity binding to Robo proteins. Furthermore, recombinant Slit2 can repel embryonic spinal motor axons in cell culture. These results support the hypothesis that Slit proteins have an evolutionarily conserved role in axon guidance as repulsive ligands for Robo receptors.

and vertebrates, midline cells also appear to express counterbalancing inhibitory cues that push axons away (reviewed in Tessier-Lavigne and Goodman, 1996). For instance, in vertebrates, ablation of the ventral midline, either surgically or genetically, results in a disruption of axon trajectories such that a proportion of axons that would normally cross now fail to and those that would normally not cross, now do so aberrantly (reviewed in Colamarino and Tessier-Lavigne, 1995). Experiments in chick embryos have provided further evidence that the ventral midline floor plate cells express a contact-dependent repellent cue whose activity is normally masked by the attractive cell adhesion molecule NrCAM (Stoeckli et al., 1997). In addition to being a source of attractants and repellents, the ventral midline is also able to alter an axon's ability to respond to these cues. For instance, upon crossing the floor plate, axons that were responsive to the floor plate-derived chemoattractant Netrin 1 prior to crossing are, after crossing, no longer able to respond to this cue (Shirasaki et al., 1998).

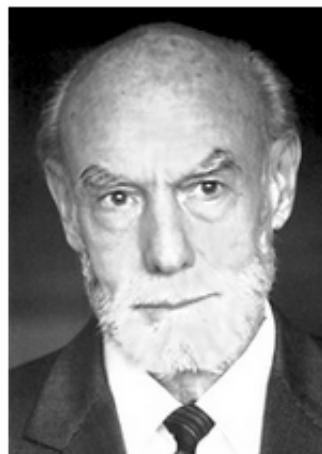
In *Drosophila*, the midline also appears to control growth cone properties. Thus, the Roundabout (Robo) receptor is downregulated on crossing axons at the midline, by a mechanism involving the Commissureless protein. After crossing the midline, Robo is again specifically upregulated, thus ensuring that these axons do not recross again (Seeger et al., 1993; Tear et al., 1996; Kidd et al., 1998a, 1998b). In *robo* loss-of-function mutants, axons cross and recross the midline inappropriately. Robo is highly conserved across species, both in sequence and apparent function (Kidd et al., 1998a; Zallen et al., 1998). In particular, in the rat spinal cord, Robo is expressed in a pattern consistent with a role in mediating guidance decisions at the floor plate (Kidd et al., 1998b).



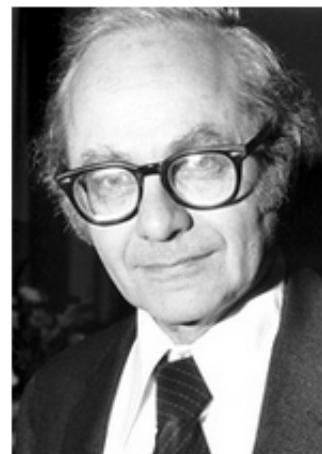
The Nobel Prize in Physiology or Medicine 1981  
Roger W. Sperry, David H. Hubel, Torsten N. Wiesel

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# The Nobel Prize in Physiology or Medicine 1981



Roger W. Sperry



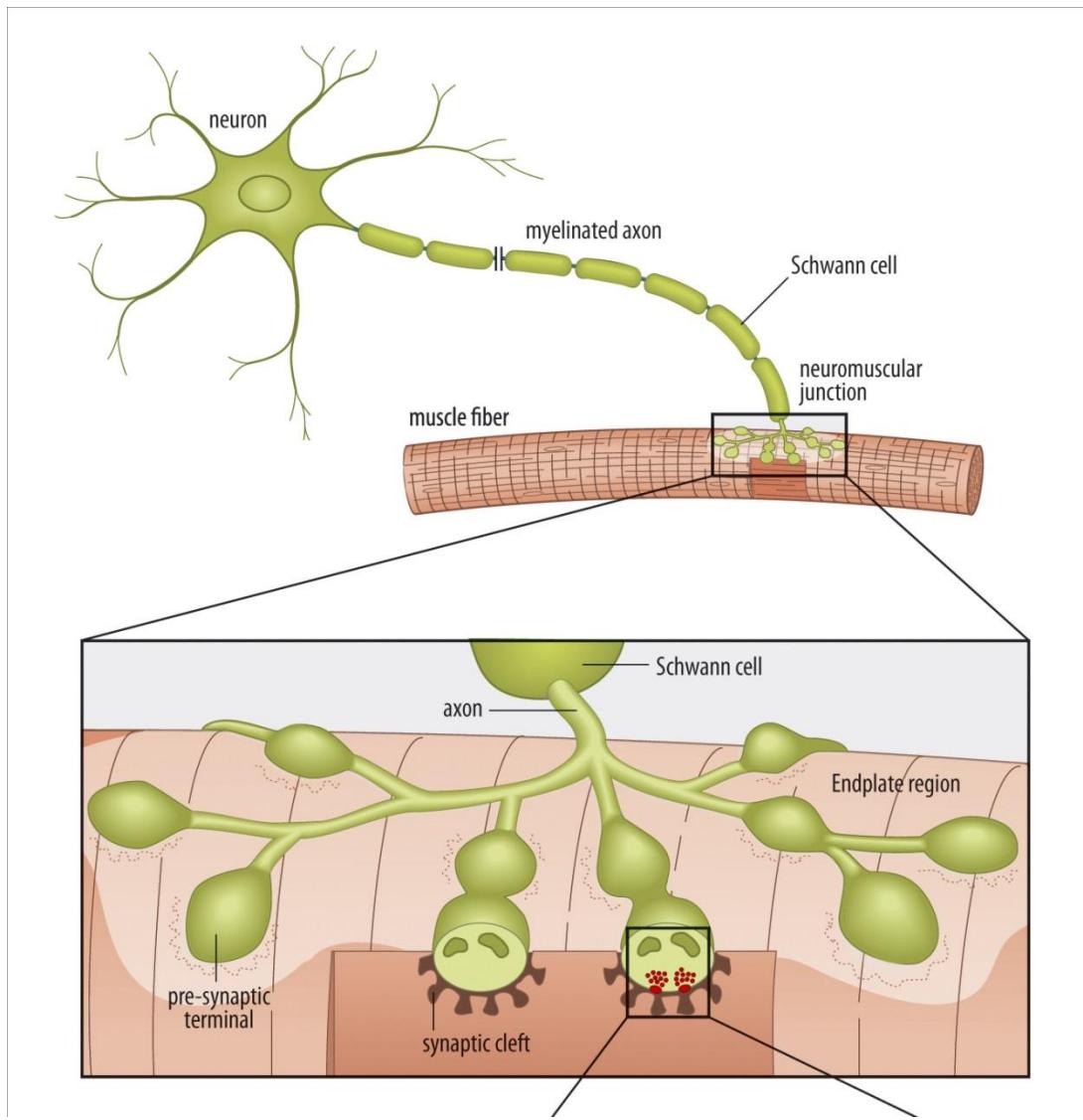
David H. Hubel



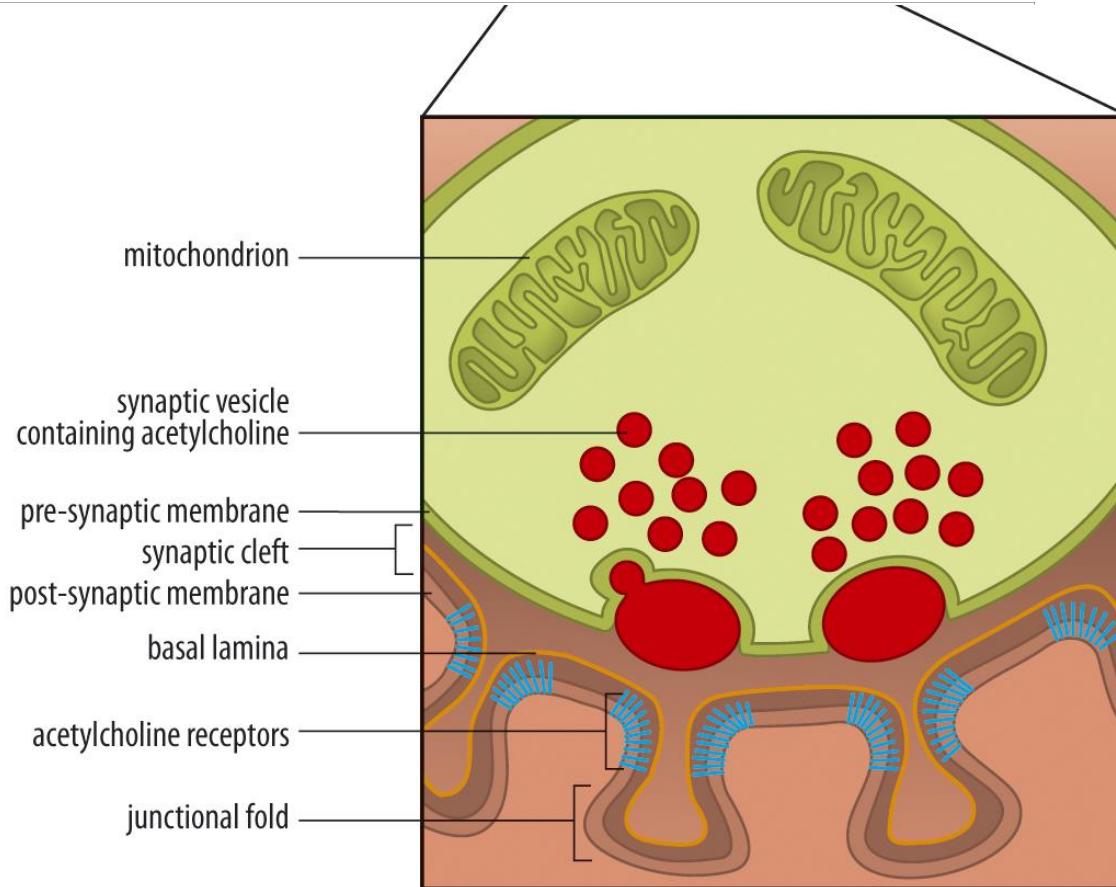
Torsten N. Wiesel

The Nobel Prize in Physiology or Medicine 1981 was divided, one half awarded to Roger W. Sperry *"for his discoveries concerning the functional specialization of the cerebral hemispheres"*, the other half jointly to David H. Hubel and Torsten N. Wiesel *"for their discoveries concerning information processing in the visual system"*.

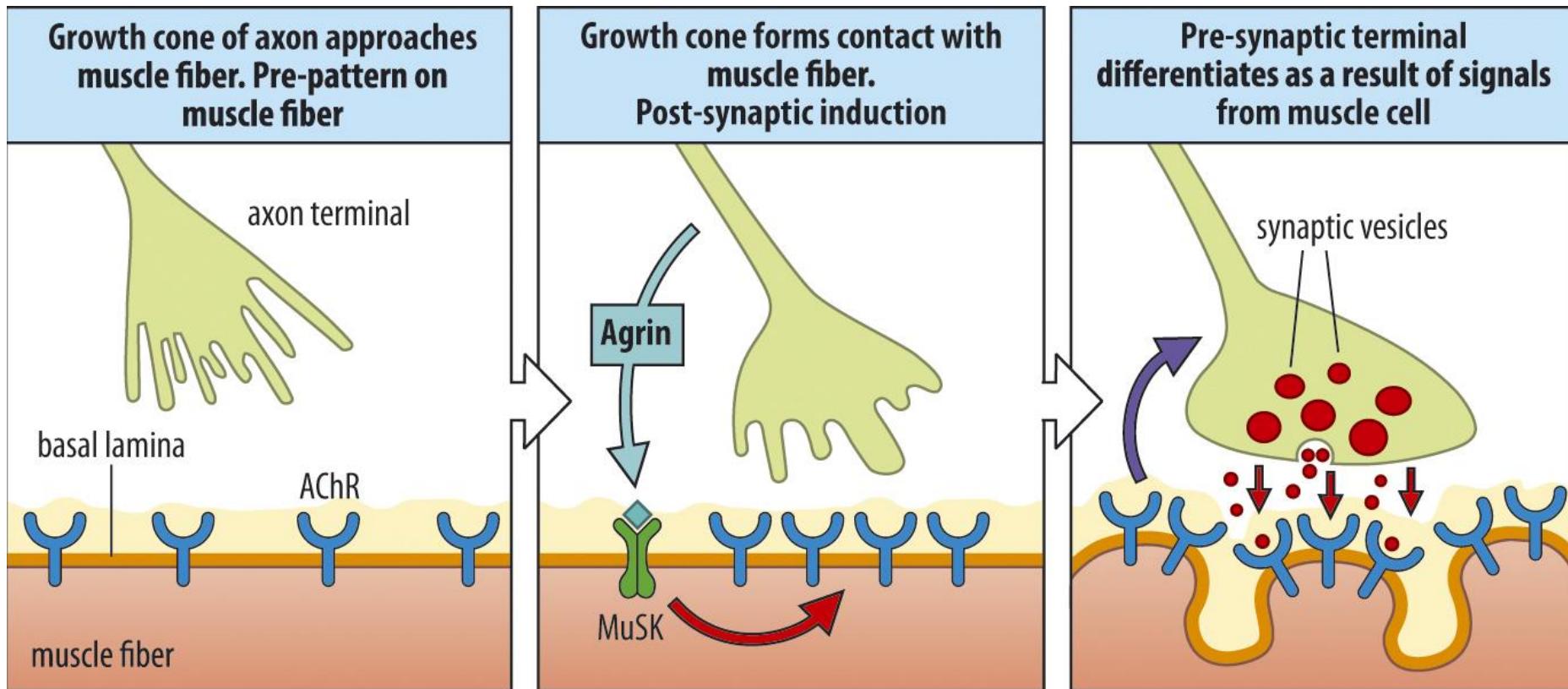
# Synapse formation and refinement



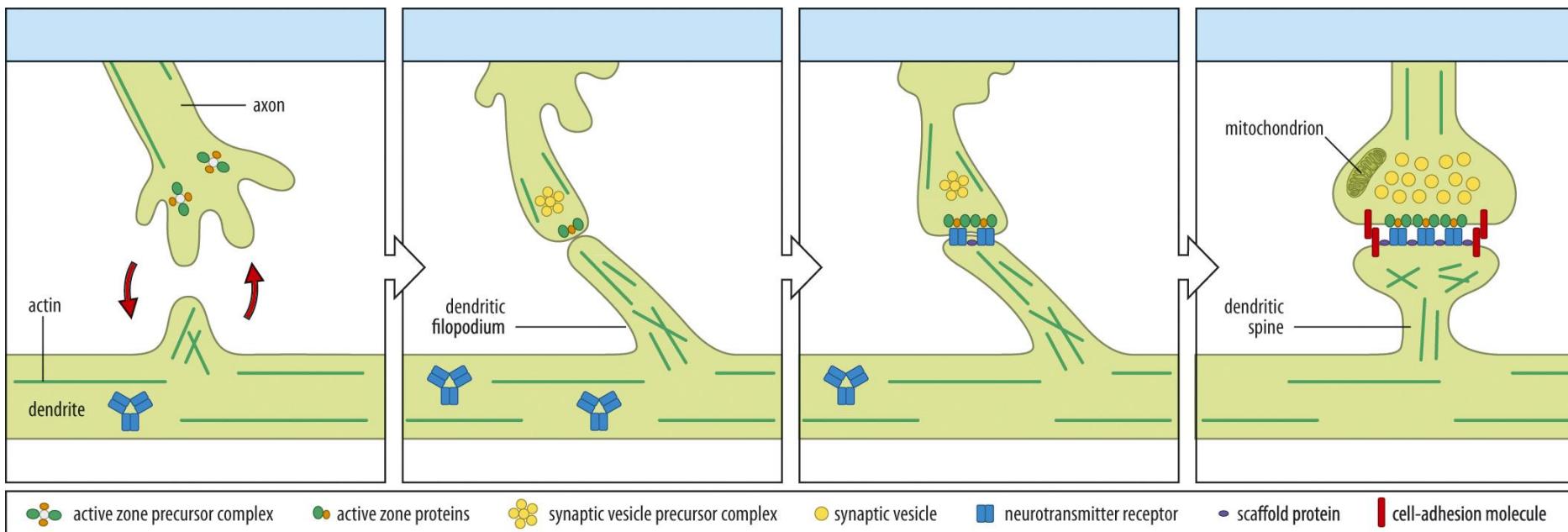
# Synapse formation and refinement



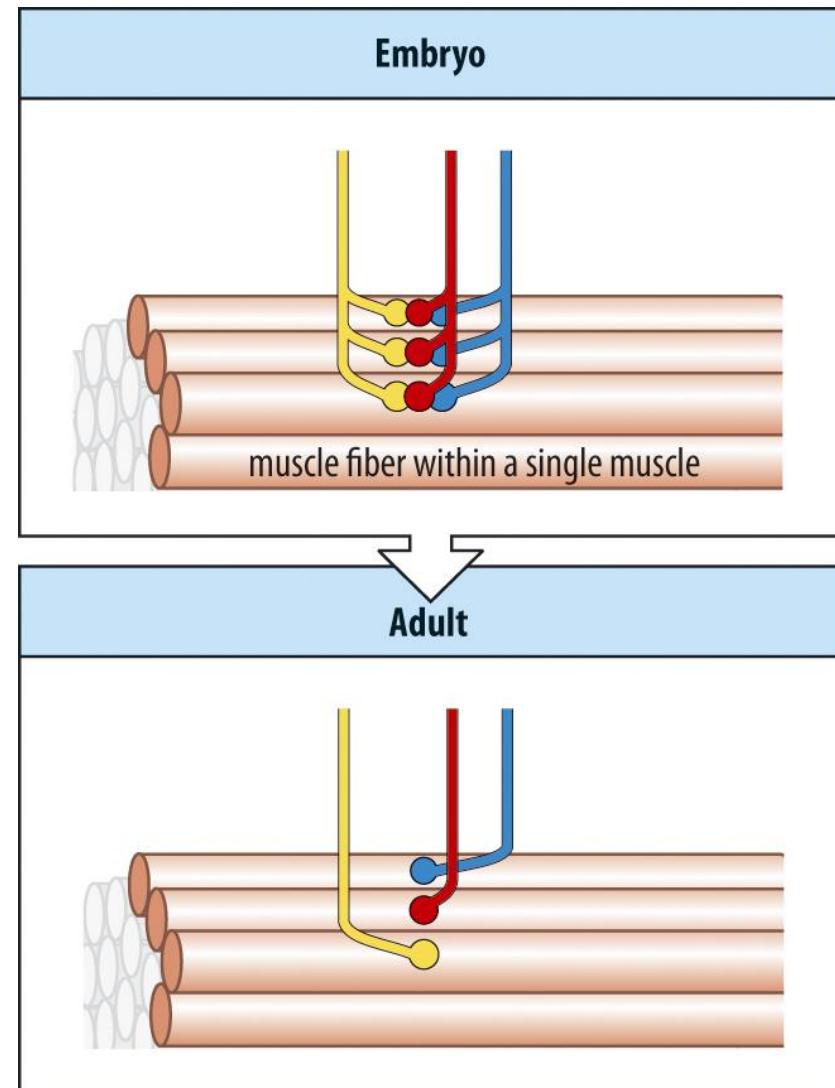
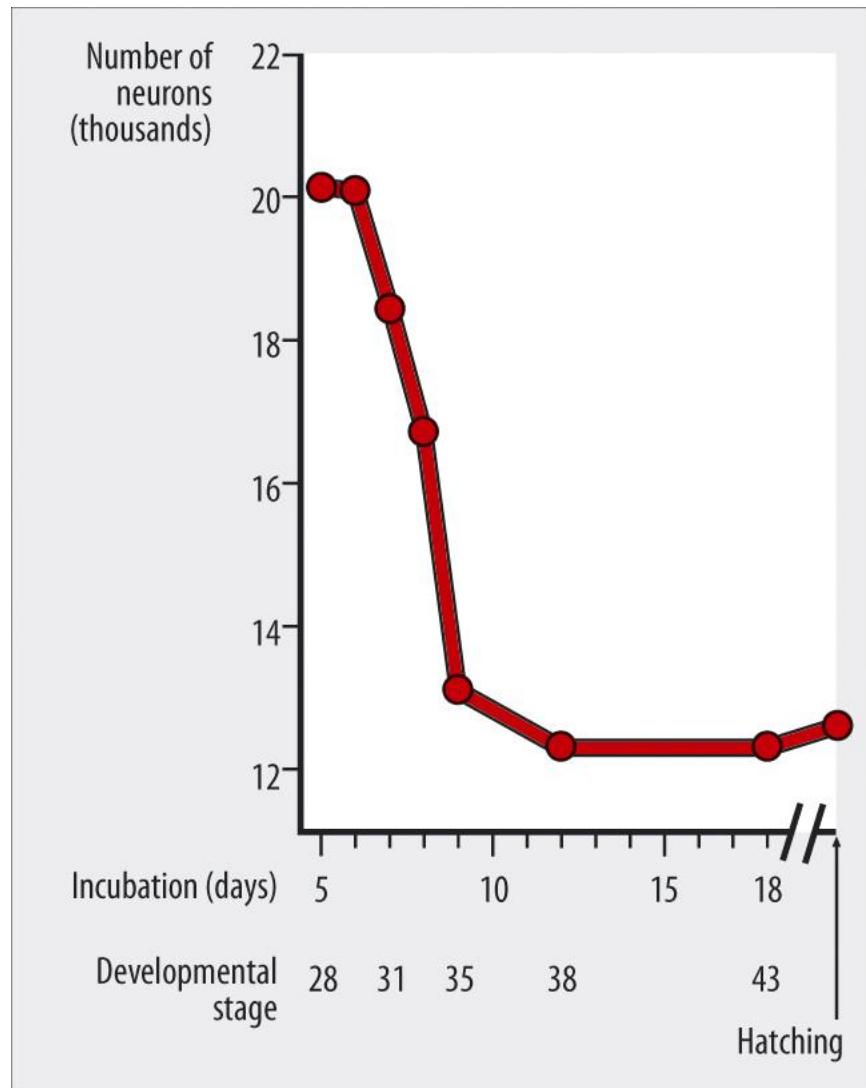
# Development of the neuromuscular junction



# Interneuronal synapse formation



# Many motor neurons die during normal development



# Why Do So Many Neurons Commit Suicide During Brain Development?

With a few notable exceptions, the roughly 100 billion neurons we have at birth are the only ones we'll ever have. Unlike skin and immune cells, which continuously self-renew, once a neuron has differentiated from its parent stem cell it will never divide again. Given this finite supply, why do so many neurons—more than half in some brain regions—kill themselves during embryonic brain development?

For roughly 50 years, many scientists

focused on a single explanation for this rampant cellular suicide. Their hypothesis was rooted in research on the peripheral nervous system, which connects the nerves of the brain and spinal cord to limbs, organs, and sensory systems. To survive in the developing brain, researchers thought, neurons must compete for limited quantities of a chemical “trophic” factor released by the targets they aim to innervate. Without this signal, the cells self-destruct in a pro-

cess known as programmed cell death, or apoptosis. Called the neurotrophic hypothesis, the concept neatly explained how an overabundance of neurons could attach where needed, or be culled.

“We were all carried away by this observation,” says neuroscientist Yves-Alain Barde of the University of Basel in Switzerland. Inspired by the discovery of nerve growth factor in the 1950s, a protein essential to the growth and survival of sensory and motor neurons in the peripheral nervous system, Barde hunted for a single “survival” molecule for neurons in

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- The first wave strikes down cells before they are fully differentiated neurons.
- A second wave of cell suicide occurs after neurons have begun to differentiate and extend their axons to make contact with other cells.

# The Apical Complex Couples Cell Fate and Cell Survival to Cerebral Cortical Development

Seonhee Kim,<sup>1,3,8</sup> Maria K. Lehtinen,<sup>1,8</sup> Alessandro Sessa,<sup>2</sup> Mauro W. Zappaterra,<sup>1</sup> Seo-Hee Cho,<sup>3</sup> Dilenny Gonzalez,<sup>1</sup> Brigid Boggan,<sup>3</sup> Christina A. Austin,<sup>1</sup> Jan Wijnholds,<sup>4</sup> Michael J. Gambello,<sup>5</sup> Jarema Malicki,<sup>6</sup> Anthony S. LaMantia,<sup>7</sup> Vania Broccoli,<sup>2,\*</sup> and Christopher A. Walsh<sup>1,\*</sup>

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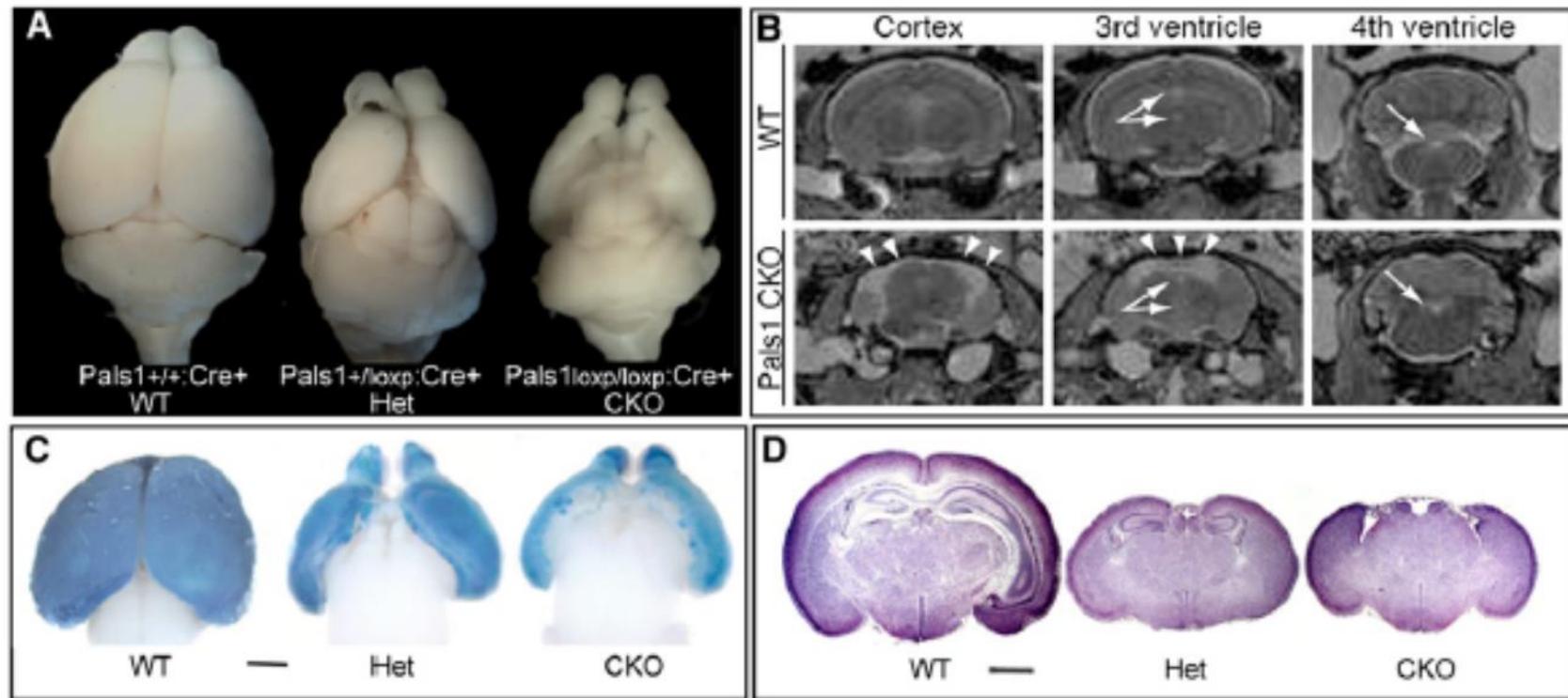
## SUMMARY

Cortical development depends upon tightly controlled cell fate and cell survival decisions that generate a functional neuronal population, but the coordination of these two processes is poorly understood. Here we show that conditional removal of a key apical complex protein, Pals1, causes premature withdrawal from the cell cycle, inducing excessive generation of early-born postmitotic neurons followed by surprisingly massive and rapid cell death, leading to the abrogation of virtually the entire cortical structure. Pals1 loss shows exquisite dosage sensitivity, so that heterozygote mutants show an intermediate phenotype on cell fate and cell death. Loss of Pals1 blocks essential cell survival signals, including the mammalian target of rapamycin (mTOR) pathway, while mTORC1 activation partially rescues Pals1 deficiency. These data highlight unexpected roles of the apical complex in Pals1 signaling and the molecular mechanisms that coordinate cell fate and cell survival.

nance of progenitors for later-born neurons (Caviness et al., 1995; Götz and Huttner, 2005; Takahashi et al., 1996). Two neural progenitor cell types are identified in the developing cortex. One is a radial neuroepithelial cell, with a cell body in the ventricular zone and an apical process that inserts into the ventricular lining, and a long, thin basal processes that reaches the pial surface at the outside of the brain (Anthony et al., 2004; Fishell and Kriegstein, 2003; Noctor et al., 2001, 2002; Tamamaki et al., 2001). These radial cells serve both as progenitors and migratory guides for newly born neurons. The other progenitor cell type is a more recently characterized basal progenitor, which localizes primarily to the subventricular zone (SVZ) and undergoes one or more cell divisions, typically symmetrically, to generate neurons in the cerebral cortex (Haubensak et al., 2004; Kowalczyk et al., 2009; Miyata et al., 2004; Noctor et al., 2004, 2008). Radial neuroepithelial progenitors form an epithelial structure with their apical, ventricular processes connected to adjoining cells by adherens junctions. Although considerable progress has been made in understanding the cellular events of radial glial progenitor cell division, the molecular control of cell fate decisions remains poorly understood.

# The Apical Complex Couples Cell Fate and Cell Survival to Cerebral Cortical Development

Seonhee Kim,<sup>1,3,8</sup> Maria K. Lehtinen,<sup>1,8</sup> Alessandro Sessa,<sup>2</sup> Mauro W. Zappaterra,<sup>1</sup> Seo-Hee Cho,<sup>3</sup> Dilenny Gonzalez,<sup>1</sup> Brigid Boggan,<sup>3</sup> Christina A. Austin,<sup>1</sup> Jan Wijnholds,<sup>4</sup> Michael J. Gambello,<sup>5</sup> Jarrema Malicki,<sup>6</sup> Anthony S. LaMantia,<sup>7</sup> Vania Broccoli,<sup>2,\*</sup> and Christopher A. Walsh<sup>1,\*</sup>



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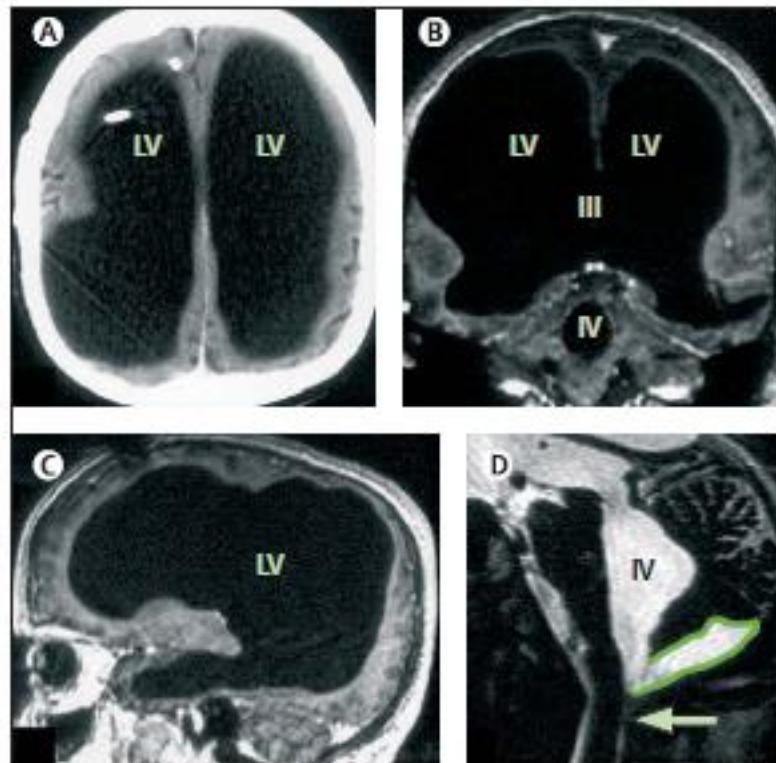
coupling of cell fate and cell survival during cerebral cortical development.

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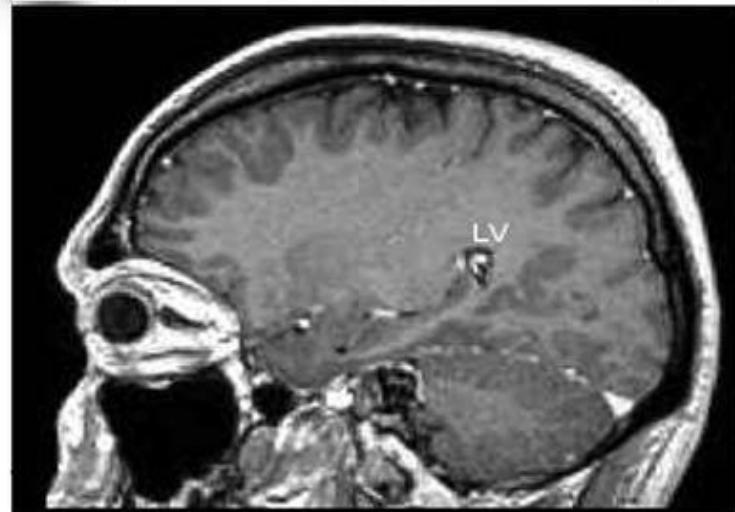
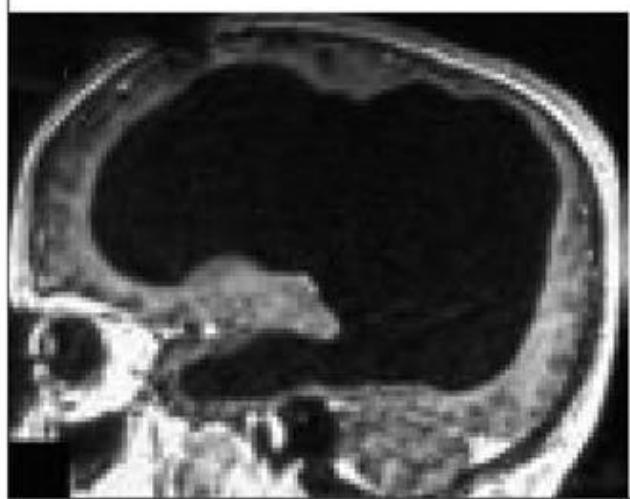
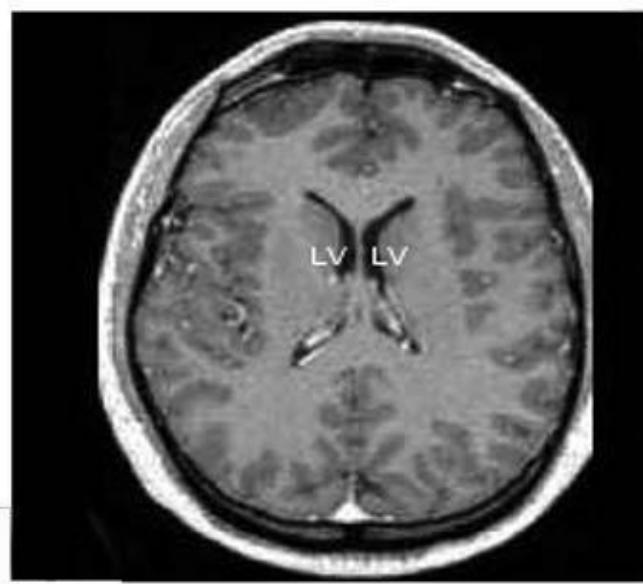
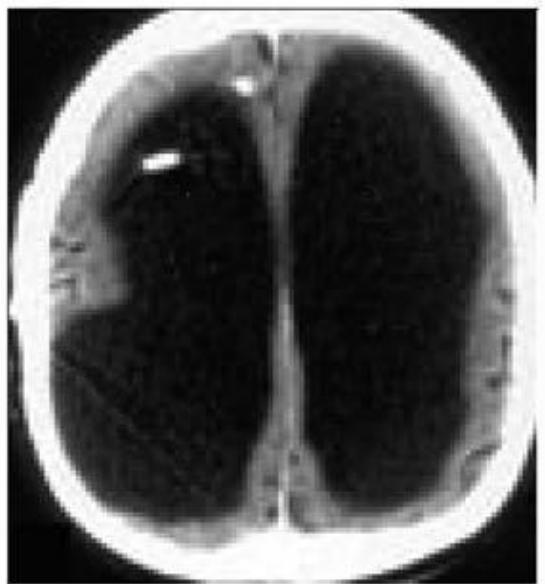
# Brain of a white-collar worker

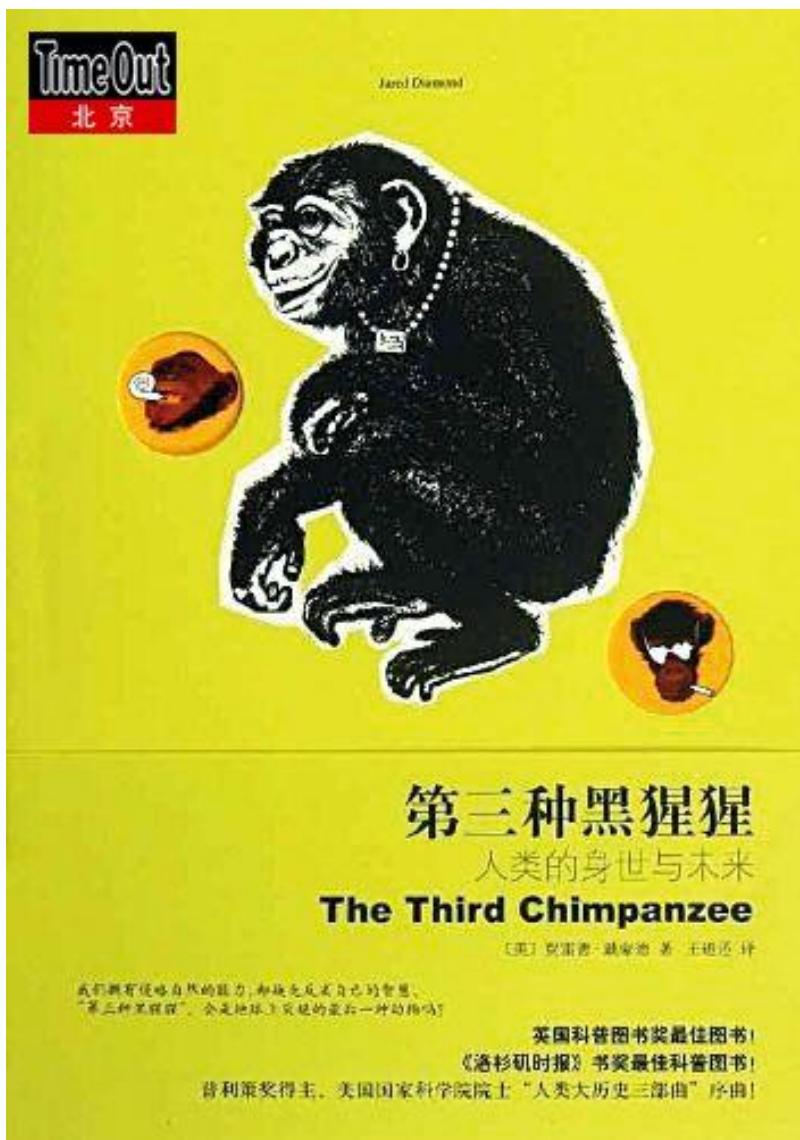
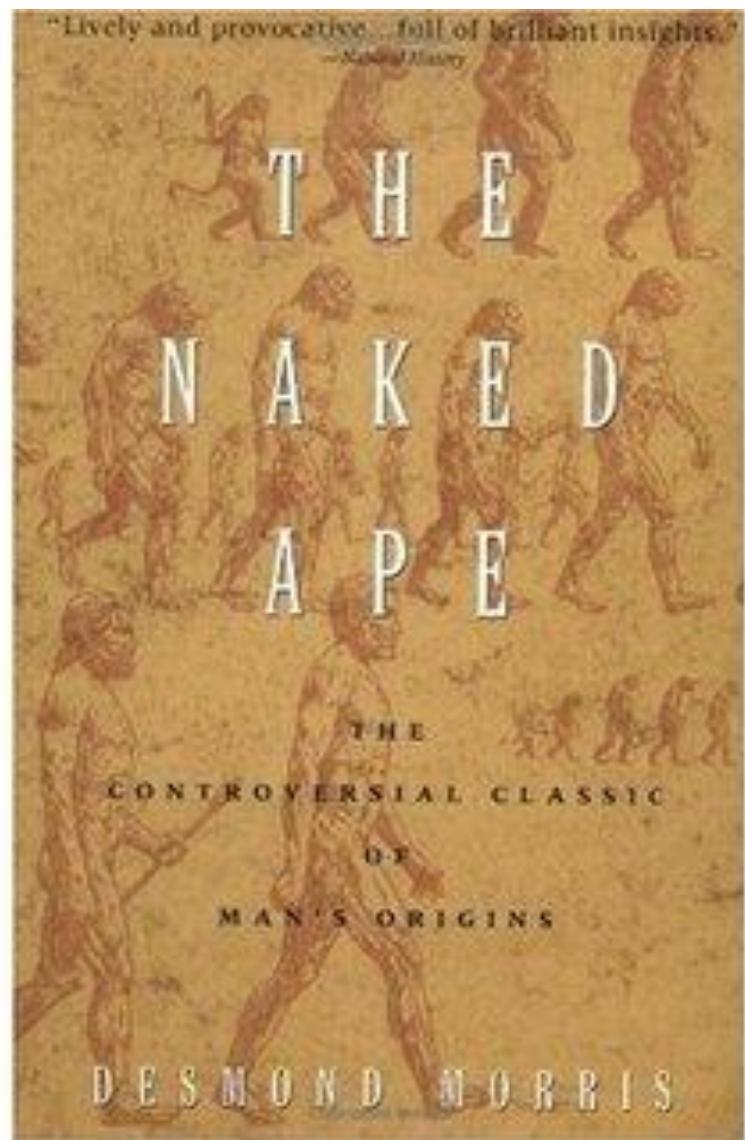
Lionel Feuillet, Henry Dufour, Jean Pelletier

A 44-year-old man presented with a 2-week history of mild left leg weakness. At the age of 6 months, he had undergone a ventriculoatrial shunt, because of postnatal hydrocephalus of unknown cause. When he was 14 years old, he developed ataxia and paresis of the left leg, which resolved entirely after shunt revision. His neurological development and medical history were otherwise normal. He was a married father of two children, and worked as a civil servant. On neuropsychological testing, he proved to have an intelligence quotient (IQ) of 75: his verbal IQ was 84, and his performance IQ 70. CT showed severe dilatation of the lateral ventricles (figure); MRI revealed massive enlargement of the lateral, third, and fourth ventricles, a very thin cortical mantle and a posterior fossa cyst. We diagnosed a non-communicating hydrocephalus, with probable stenosis of Magendie's foramen (figure). The leg weakness improved partly after neuro-endoscopic ventriculocisternostomy, but soon recurred; however, after a ventriculoperitoneal shunt was inserted, the findings on neurological examination became normal within a few weeks. The findings on neuropsychological testing and CT did not change.



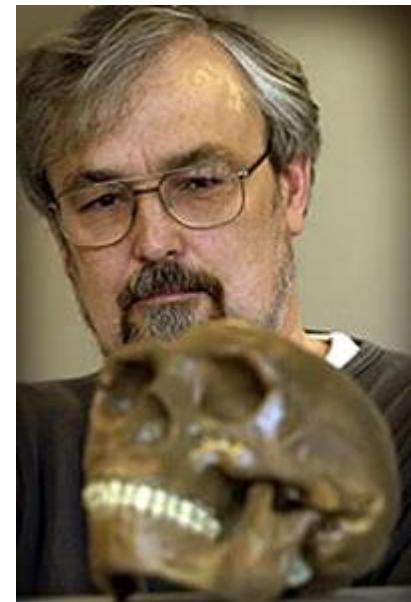
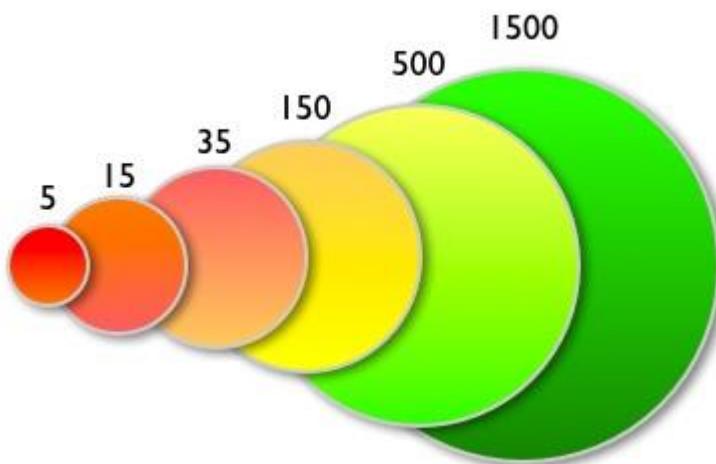
**Figure: Massive ventricular enlargement, in a patient with normal social functioning**  
(A) CT; (B, C) T1-weighted MRI, with gadolinium contrast; (D) T2-weighted MRI.  
LV—lateral ventricle. III—third ventricle. IV—fourth ventricle. A row—Magendie's foramen. The posterior fossa cyst is outlined in (D).





# Dunbar's number (邓巴数)

- Dunbar's number is a suggested cognitive limit (new cortex volume) to the number of people with whom one can maintain stable social relationships.



Robin Dunbar



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# Professor Robin Dunbar

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**There are over 13,000 Medieval deeds within Magdalen's archive, some dating back to the twelfth century.**

## Background

I attended Magdalen College School, Brackley, and then went to Magdalen College to read PPP (Psychology & Philosophy), graduating in 1969. After completing a PhD on the behavioural ecology of primates at Bristol University, I went to Cambridge on a SERC Advanced Research Fellowship (URF). I subsequently held research and teaching posts at Stockholm University (Zoology), University College London (Anthropology) and Liverpool University (Psychology and then Biology) before returning to Oxford in 2007. I am currently funded by a European Research Council Advanced grant as a Research Professor in the Department of Experimental Psychology.

R. I. M. Dunbar

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1991 and accepted 2 December  
1991

**Keywords:** behavioural ecology,  
grooming, brain size, body size,  
social intellect.

## **Neocortex size as a constraint on group size in primates**

Two general kinds of theory (one ecological and one social) have been advanced to explain the fact that primates have larger brains and greater cognitive abilities than other animals. Data on neocortex volume, group size and a number of behavioural ecology variables are used to test between the various theories. Group size is found to be a function of relative neocortical volume, but the ecological variables are not. This is interpreted as evidence in favour of the social intellect theory and against the ecological theories. It is suggested that the number of neocortical neurons limits the organism's information-processing capacity and that this then limits the number of relationships that an individual can monitor simultaneously. When a group's size exceeds this limit, it becomes unstable and begins to fragment. This then places an upper limit on the size of groups which any given species can maintain as cohesive social units through time. The data suggest that the information overload occurs in terms of the structure of relationships within tightly bonded grooming cliques rather than in terms of the total number of dyads within the group as a whole that an individual has to monitor. It thus appears that, among primates, large groups are created by welding together sets of smaller grooming cliques. One implication of these results is that, since the actual group size will be determined by the ecological characteristics of the habitat in any given case, species will only be able to invade habitats that require larger groups than their current limit if they evolve larger neocortices.

Thanks!



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## RESEARCH ARTICLE

### Ectopic eyes outside the head in *Xenopus* tadpoles provide sensory data for light-mediated learning

Douglas J. Blackiston and Michael Levin\*

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Medford, MA 02155, USA

\*Author for correspondence (michael.levin@tufts.edu)

#### SUMMARY

A major roadblock in the biomedical treatment of human sensory disorders, including blindness, has been an incomplete understanding of the nervous system and its ability to adapt to changes in sensory modality. Likewise, fundamental insight into the evolvability of complex functional anatomies requires understanding brain plasticity and the interaction between the nervous system and body architecture. While advances have been made in the generation of artificial and biological replacement components, the brain's ability to interpret sensory information arising from ectopic locations is not well understood. We report the use of eye primordia grafts to create ectopic eyes along the body axis of *Xenopus* tadpoles. These eyes are morphologically identical to native eyes and can be induced at caudal locations. Cell labeling studies reveal that eyes created in the tail send projections to the stomach and trunk. To assess function we performed light-mediated learning assays using an automated machine vision and environmental control system. The results demonstrate that ectopic eyes in the tail of *Xenopus* tadpoles could confer vision to the host. Thus ectopic visual organs were functional even when present at posterior locations. These data and protocols demonstrate the ability of vertebrate brains to interpret sensory input from ectopic structures and incorporate them into adaptive behavioral programs. This tractable new model for understanding the robust plasticity of the central nervous system has significant implications for regenerative medicine and sensory augmentation technology.

Key words: vision, behavior, memory, transplantation, innervation, plasticity, frog.

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