Genetic guidance, development and plasticity of the brain

GDP1

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Learning objectives

- Know the main stages and mechanisms of the development of the nervous system and the human brain. In particular:
    - Neuronal migration
    - Regionalisation of the cortex
    - Activity-dependent patterning.
- Understand the respective roles of genetic and environmental factors in brain development.
- Understand the notion and the basic mechanisms of a critical period.
- Know the different types of brain plasticity, examples of both extreme cases of plasticity and limitations of plasticity.
- Obtain a general idea of the complexity of all the factors involved.

Outline of the course

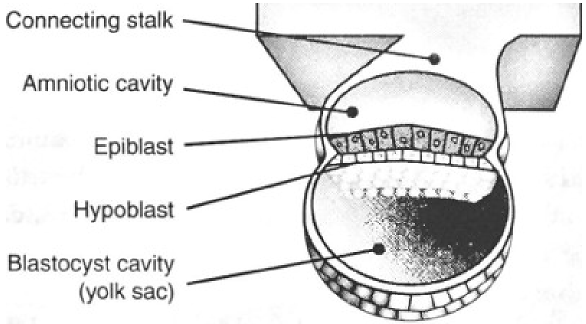
- *Morphogenesis*: from a single cell to a complex brain
- *Genetic guidance*: the brain development results from dynamic processes that are highly constrained genetically
- *Plasticity*: the brain development is also an adaptive process

Morphogenesis: from a single cell to a complex brain

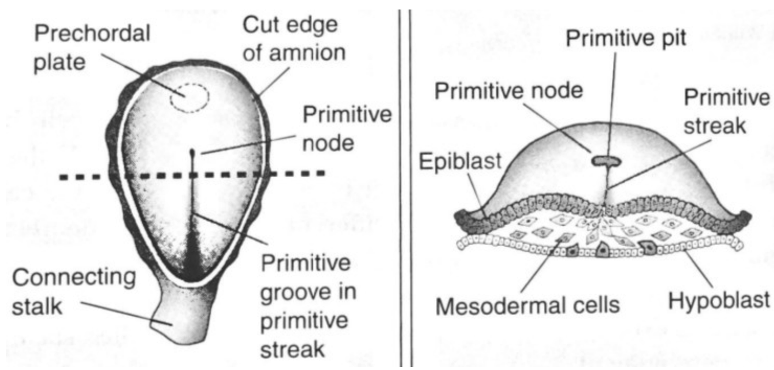
- Formation of the neural plate
- Formation of the neural tube
- Differentiation of cephalic vesicles
- Expansion of the telencephalon / diencephalon
- Characteristics of the adult brain

Morphogenesis – Formation of the neural plate 1/2

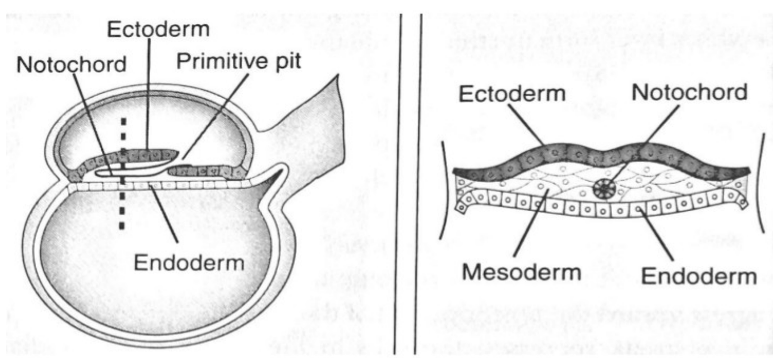
Gastrulation stage (E14 - E18): differentiation of three progetinor cell lines and specification of the three major spatial axis



E13: end of the blastula state. The epiblast contains embryonic stem cells, and the other parts will differentiate into extra-embryonic structures (placenta, etc.).



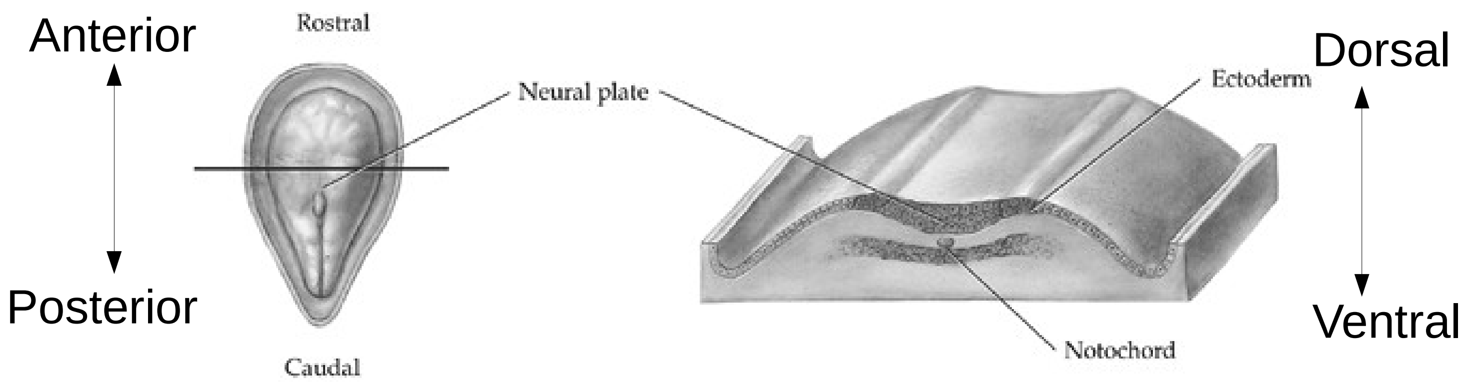
E14: The gastrulation begins with intense cell migration. This migration is organized around a primitive streak and pit that define the anterio-posterior axis and the dorso-ventral axis.

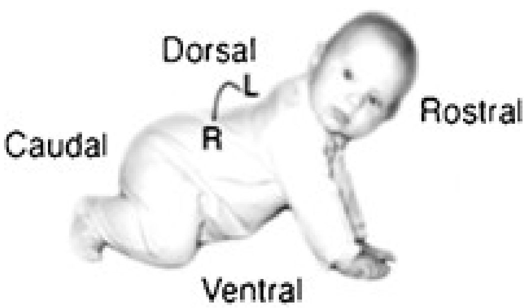


E18: The migration results into three layers.
Ectoderm → Neural tissue, epidermal tissue
Mesoderm → bones, muscles, vascular system, gonads
Endoderm → gastrointestinal and respiratory tracts

Morphogenesis – Formation of the neural plate 2/2

Neural induction: neural progenitors are induced in the ectoderm



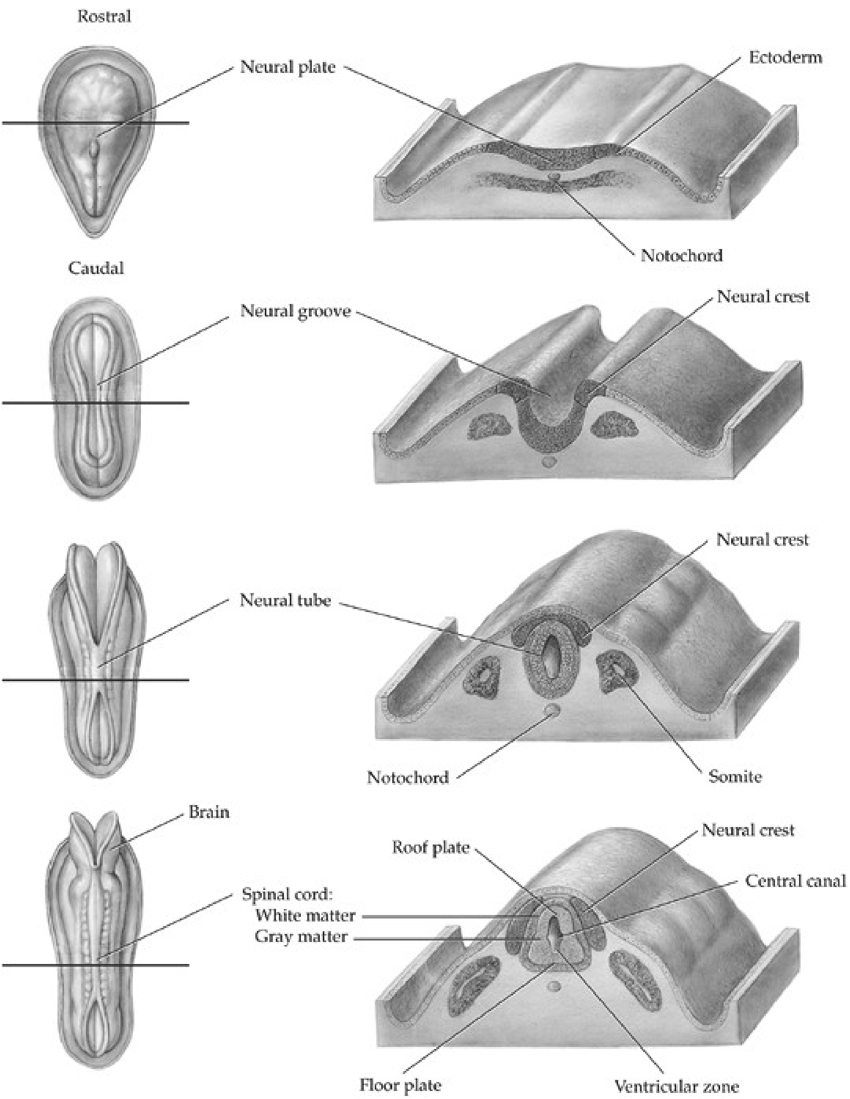


The cell migration beneath the ectoderm results in a gradient of molecules that induces neural progenitor cells, organized around two axis:

- antero-posterior (= rostro-caudal)
- dorso-ventral
- and hence: left-right

Morphogenesis

The neurulation stage: formation of the neural tube



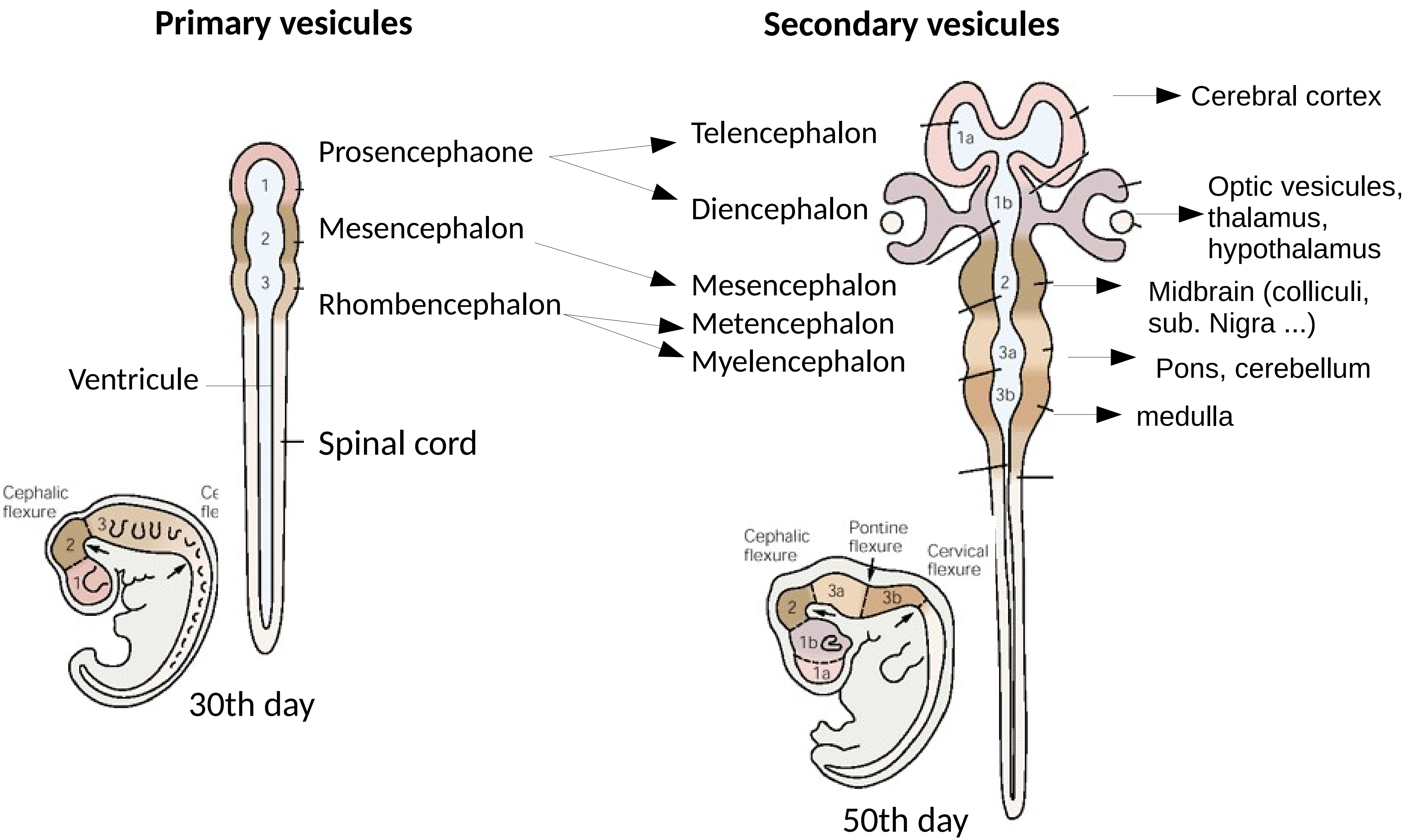
Step 1: shaping of the neural plate (E18)
Elongation of the embryo

Step 2: bending of the neural plate (E19)
Elevation of two neural folds by actin contraction (the cellular “skeleton”) and selective cell death (apoptosis)

Step 3: closure of the neural tube (E19)
In mammals, there is a multisite closure.

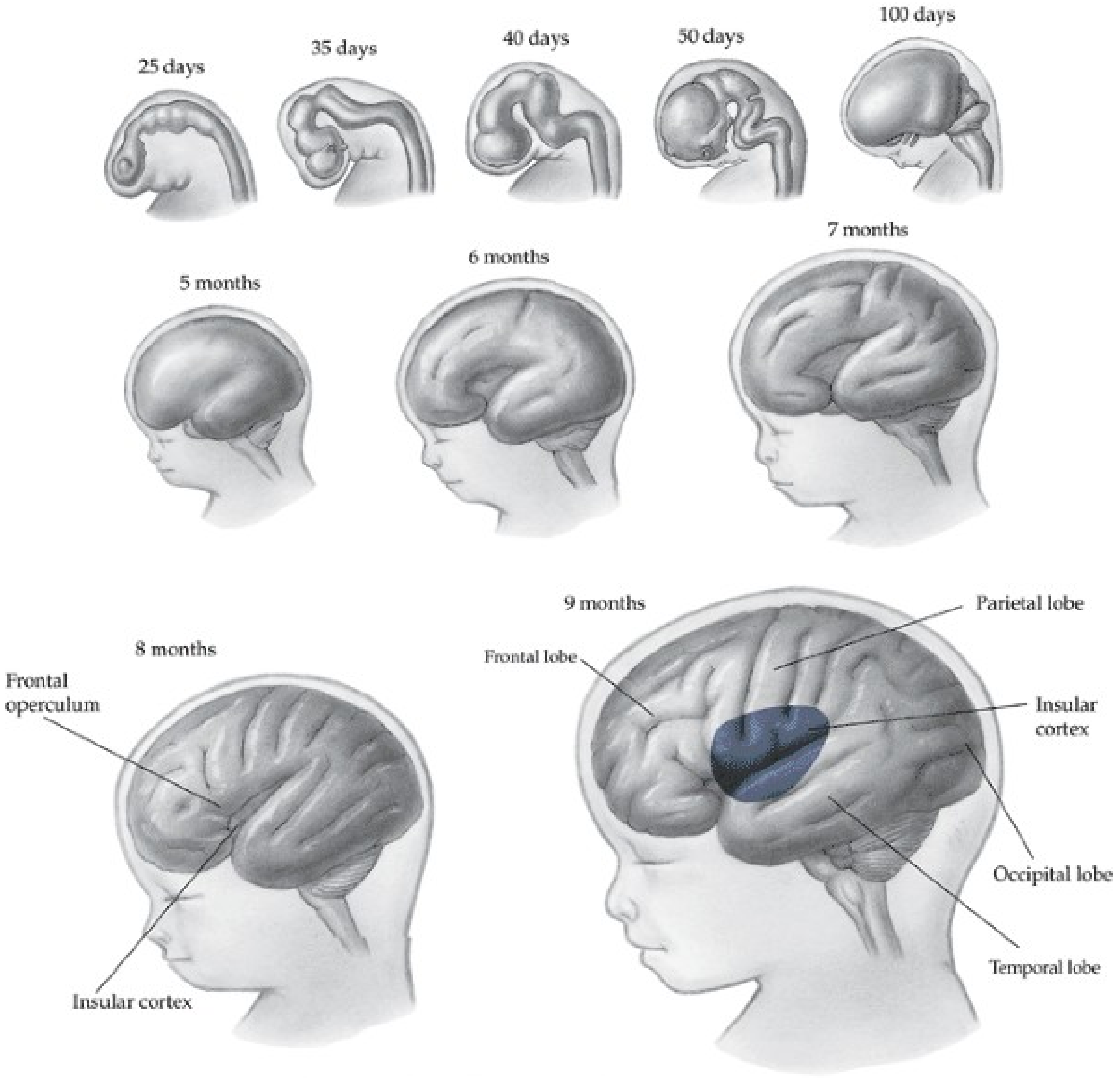
Step 4: fusion (E25 E28)
The anterior neuropore and then the posterior neuropore close, forming a hole (ventricule).
The size of the embryo is 3 to 5 mm long;

Morphogenesis
Differentiation of cephalic vesicles



Morphogenesis: from a single cell to a complex brain

Expansion of the telencephalon / diencephalon

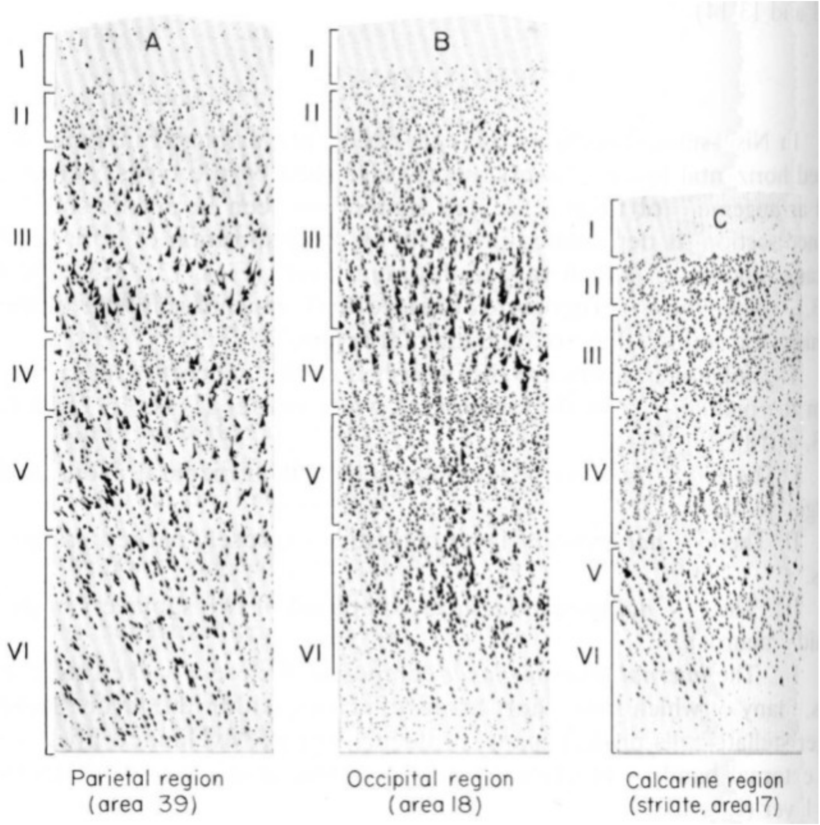


There is a curvilinear development of the dorso-ventral axis in primates (e.g. compared to rodents)

Morphogenesis: from a single cell to a complex brain

Characteristics of the adult brain

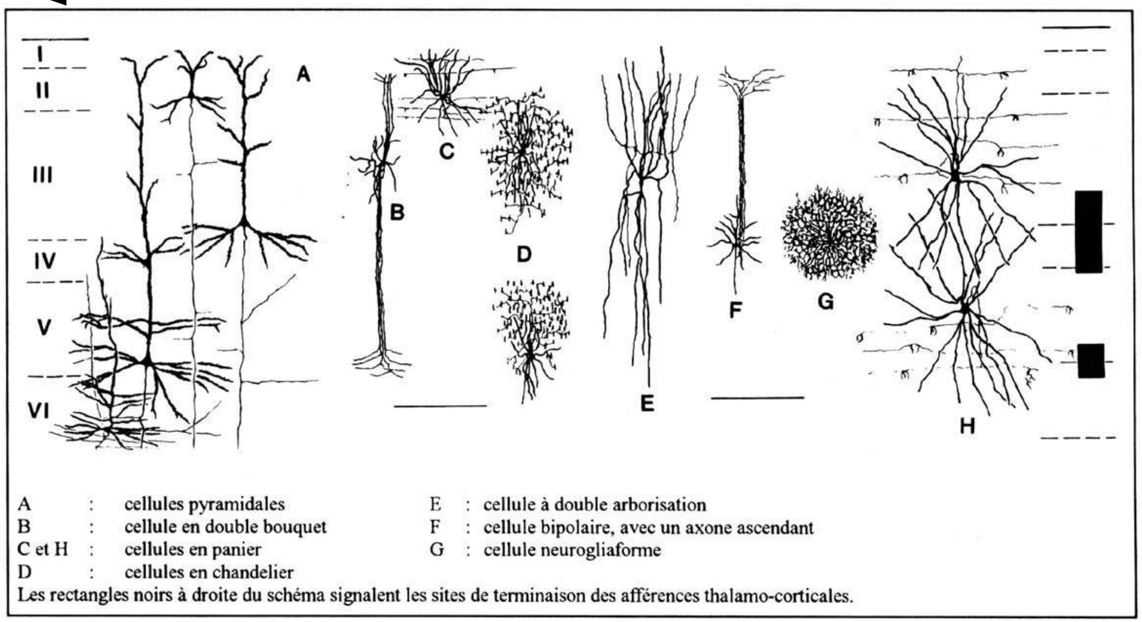
The neocortex has a laminar organization



Morphogenesis: from a single cell to a complex brain
Characteristics of the adult brain

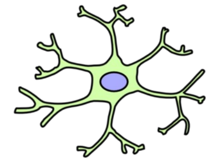
The neocortex is made of various cell types

Excitatory (80%)   Inhibitory (20% of neurons)

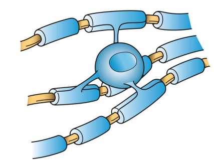


Les principaux types de neurones corticaux (d'après Hendry et Jones, 1981).

NB: more inhibitory interneurons in primates than in other animals

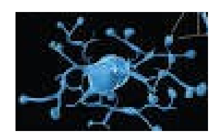


Astrocytes



Oligodendrocyte

(also derive from the ectoderm)



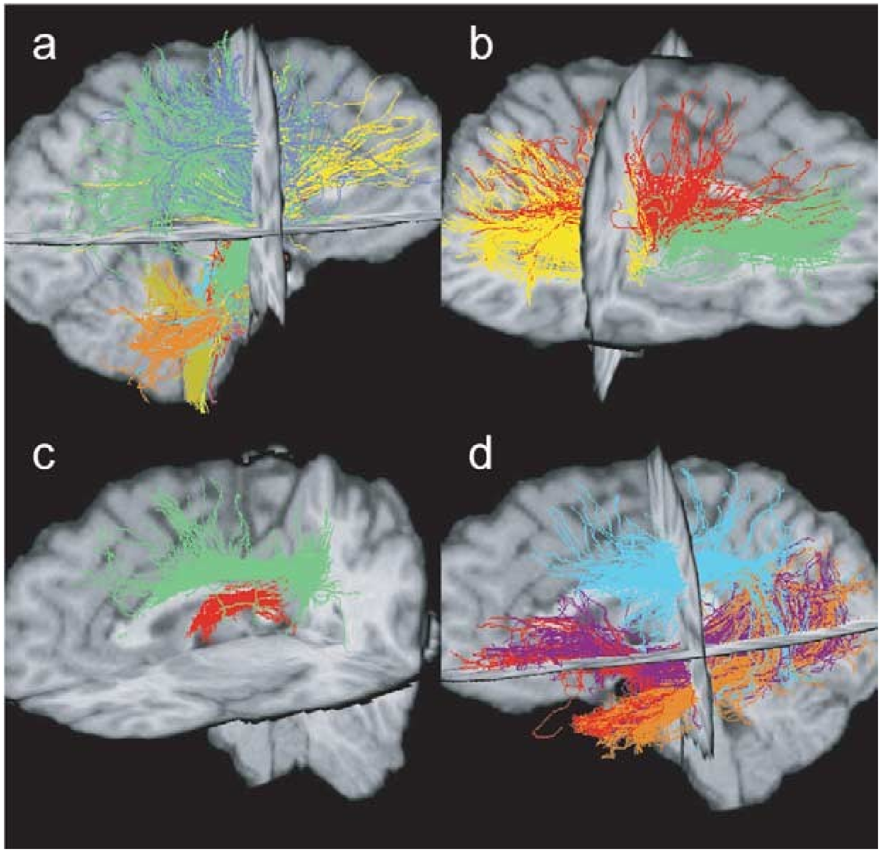
Microglia

Blood vessels

(derive from the mesoderm)

Morphogenesis: from a single cell to a complex brain
Characteristics of the adult brain

Different brain regions are connected by major communication pathways that are preserved between individuals, with layer specific connections



Hagmann, 2003, NeuroImage

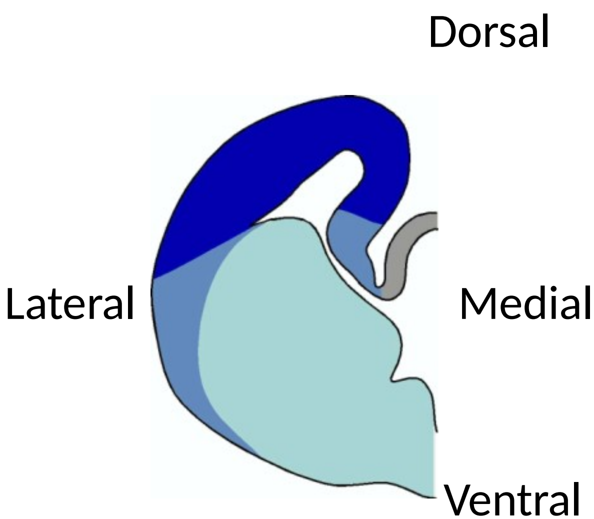
Genetic guidance: the brain development results from dynamic processes that are highly constrained genetically

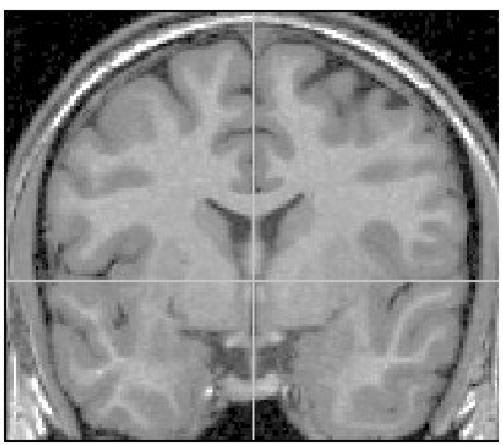
The developing cortex growths with cell divisions. New cells have to be set at the right place and to undergo a specific fate (differentiation).

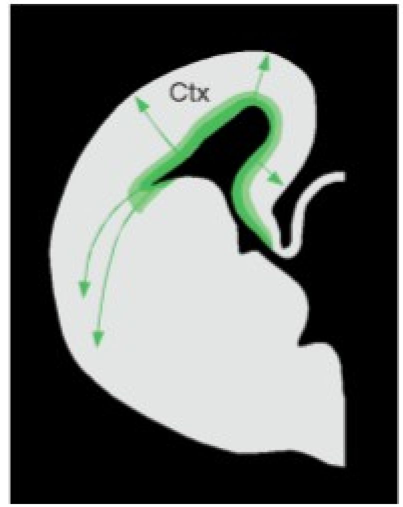
- Neuronal proliferation and migration
- Differentiation:
  - Genetic patterning
  - Activity-dependent patterning

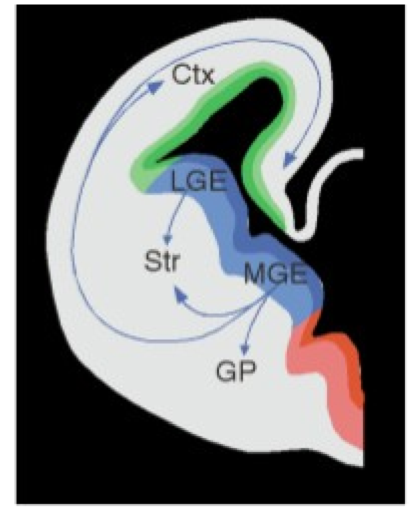
Genetic guidance

Expansion of the telencephalon: migration of projection neurons and interneurons from distinct origins









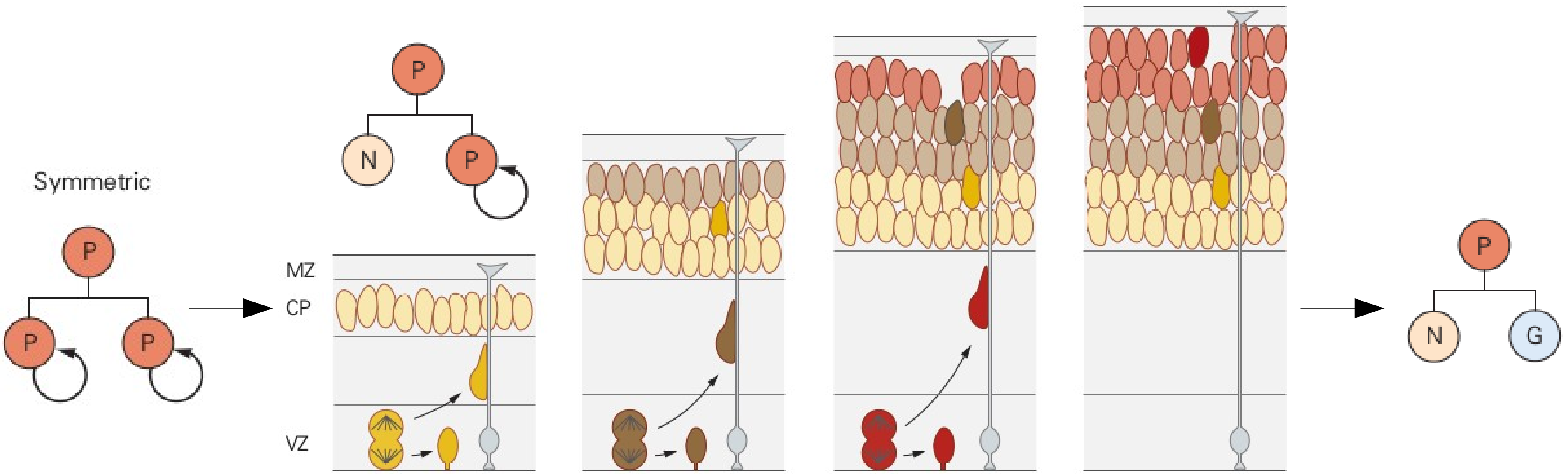
Excitatory projection neurons originates from the ventricular zone and migrate radially (max 2 cm)

Inhibitory inter-neurons originates from the ganglionic eminence and migrate tangiatially (max 15 cm)

Genetic guidance

The radial unit hypothesis of cortical layers

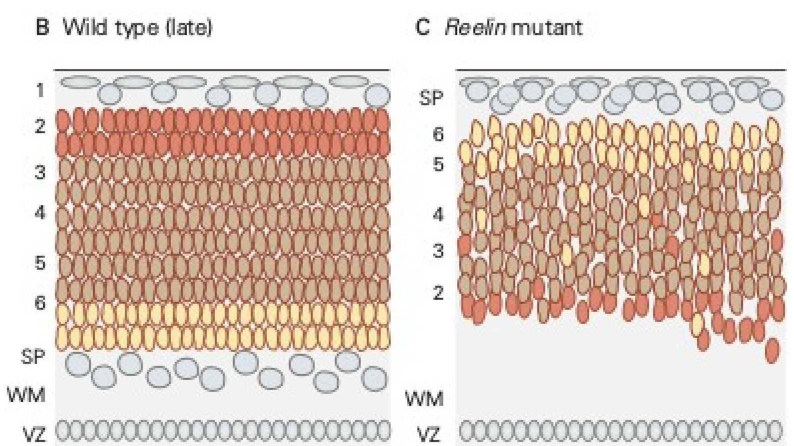
Proliferation and migration follows an inside-out spatio-temporal sequence



Symmetric divisions: increase the pool of neural progenitors

Asymmetric divisions. The apical cell contains lots of Notch that enable response to external signals and differentiation. In the basal cell, lots of Numb block Notch and differentiation.
20 10^9 neurons are produced, with a peak of 200 000/min in the human neocortex!
Migration of daughter cells along radial glial cells that serve as a scaffold.

In late development: glial cells are produced.

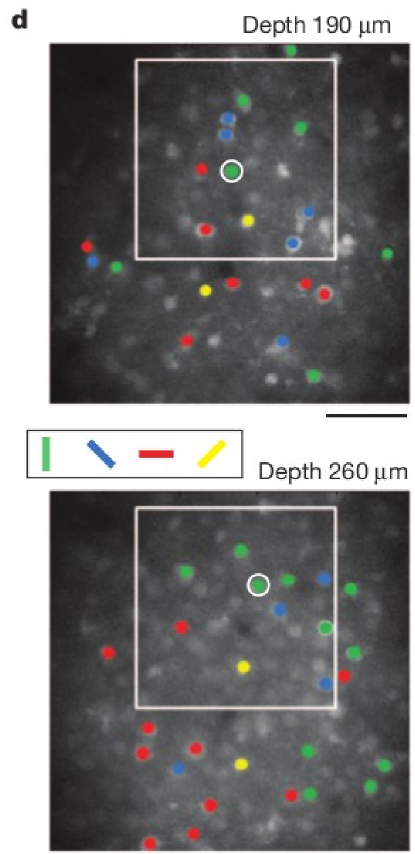


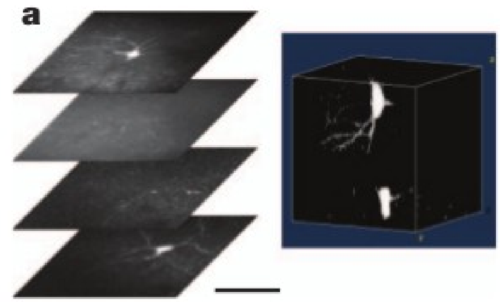
The inside-out development (newer neurons go on top) depends on Reelin, produced by Cajal-Retzius cells (in the MZ).

Genetic guidance

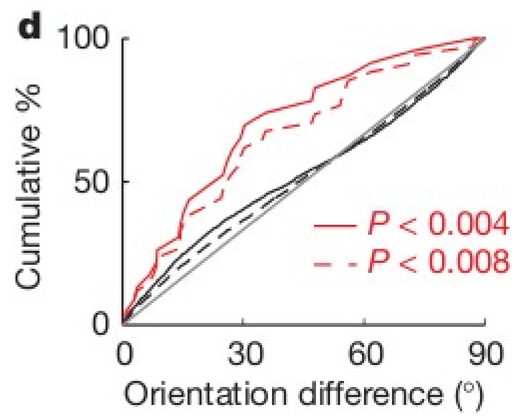
From ontogeny to function: the emergence of cortical columns

To sister cells (circled) at two level of a column





Labeling of sister cells (injection at E15 to tag radial clones



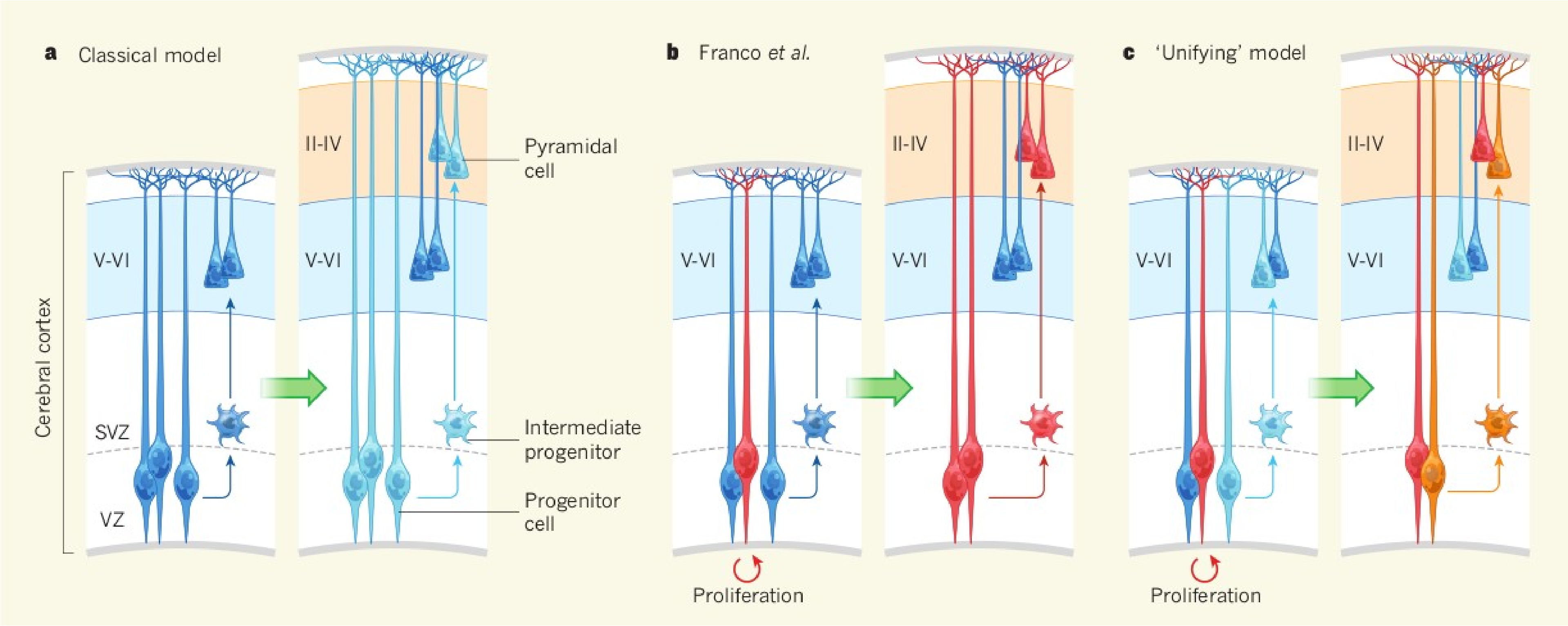
Pair of sister cells (red) show more similar tuning than non-sister pair (black)

Li 2012 Nature

=> The radial development could endow columns with a functional specificity

Genetic guidance

The radial unit hypothesis is debated: neurons in different layers of a cortical column may not be clonally related

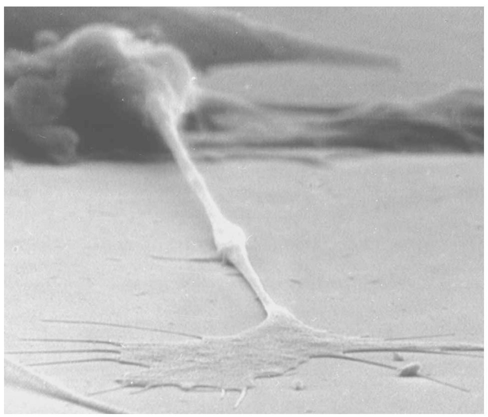


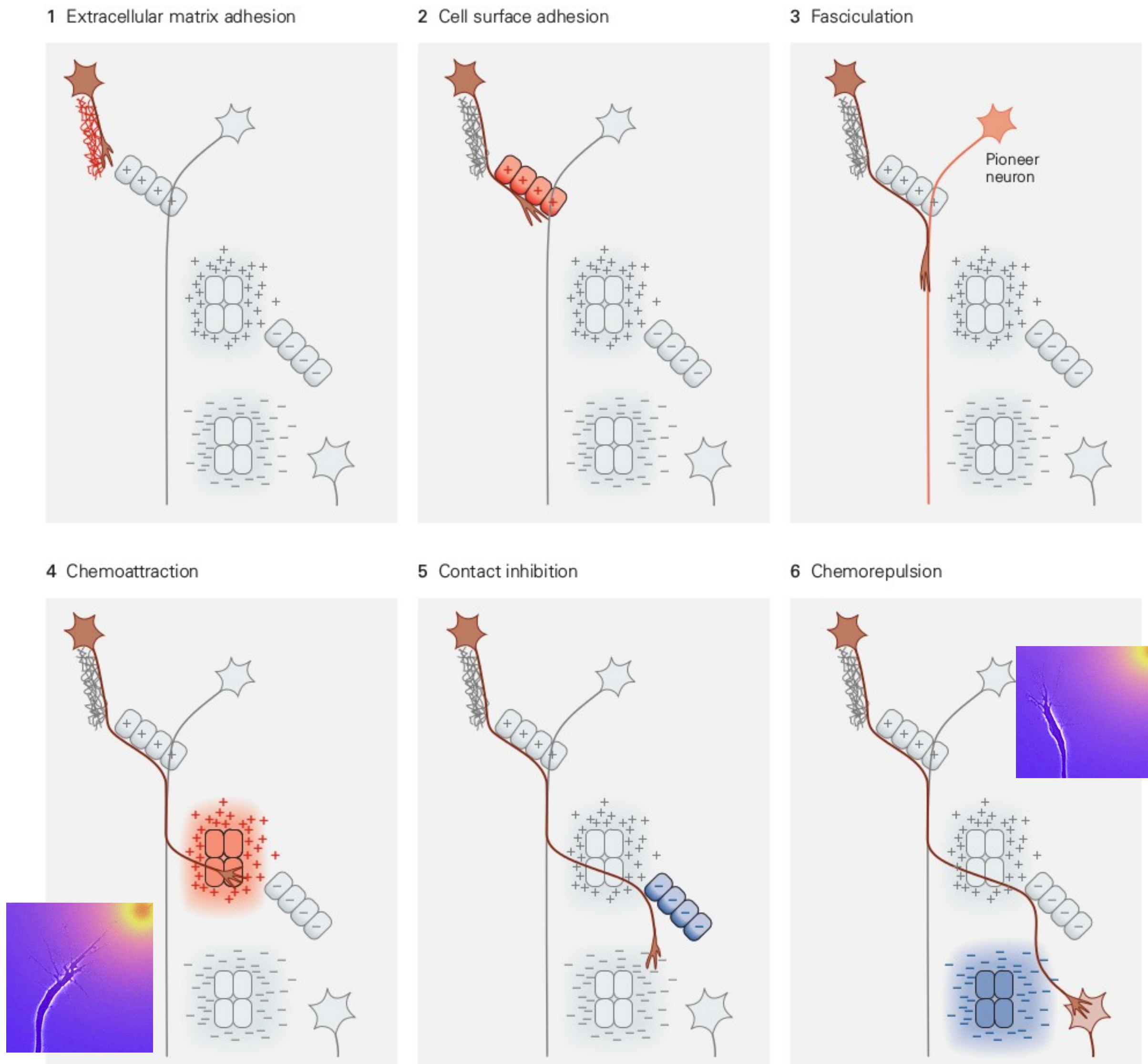
Study by Franco Science 2012, reported by Marin Nature 2012

Genetic guidance

The extension of neuronal connections is guided by many interactions

Growth cone of a neuron:
anchor and sampling of cue.

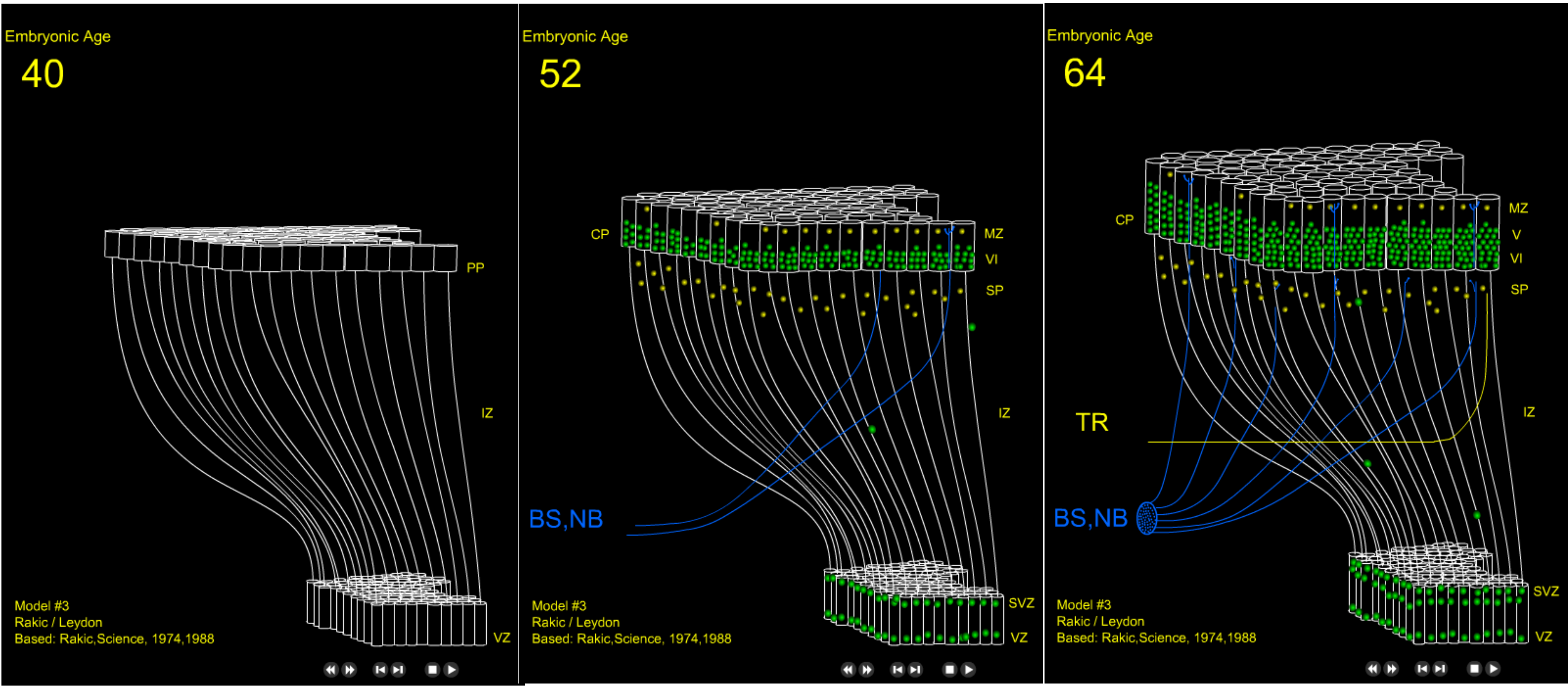




Genetic guidance

Setting the component: the radial unit hypothesis of cortical layers

A precisely orchestrated, protracted spatiotemporal sequence of interactions



Interactions in the subplate (a transient structure) establish early patterns of connectivity in the brain.

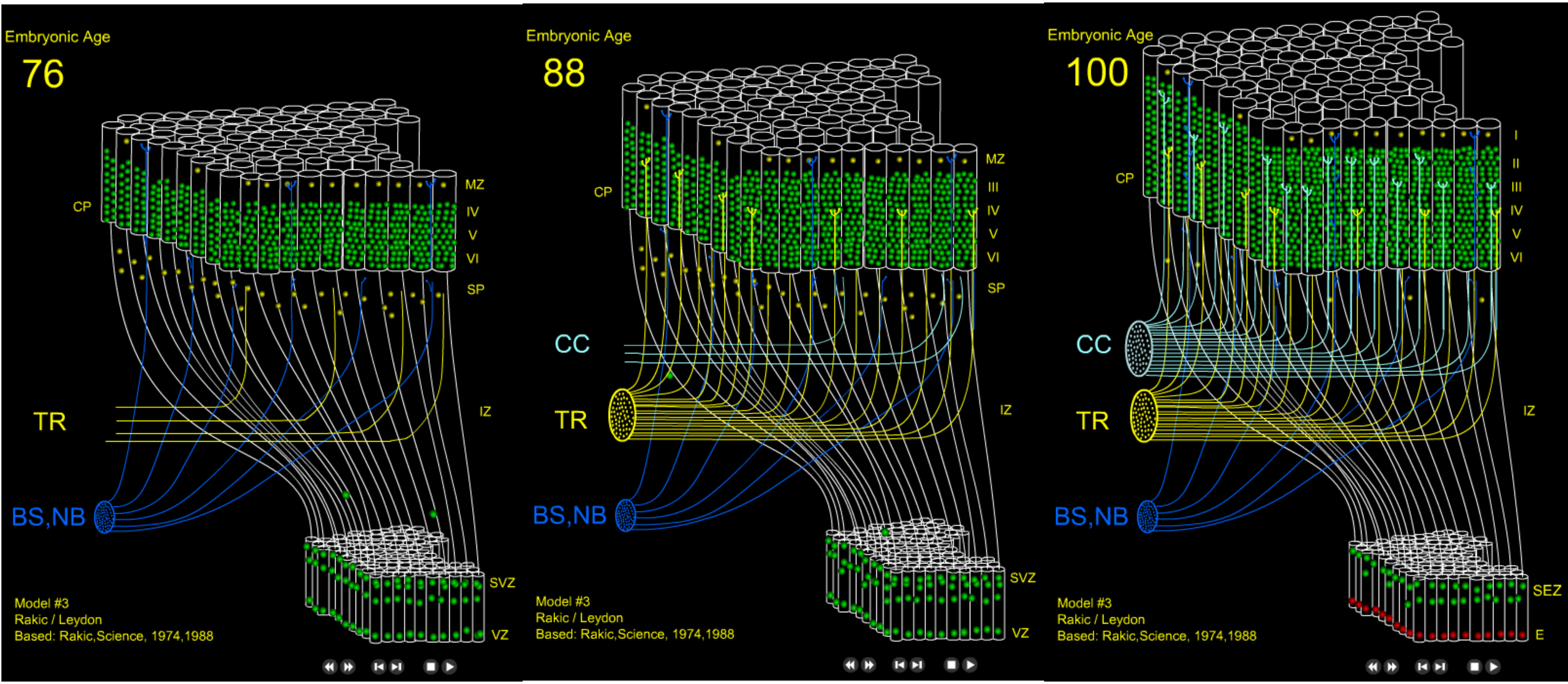
Thalamic connections remains in the subplate
→ interactions for thalamic / L4 connections
→ pioneering projection for later L5-6 / thalamic connections.

http://rakiclab.med.yale.edu/pages/radialMigration.php
Based on Rakic 1988 Science (primates)

Genetic guidance

The radial unit hypothesis of cortical layers

A precisely orchestrated, protracted spatiotemporal sequence of interactions



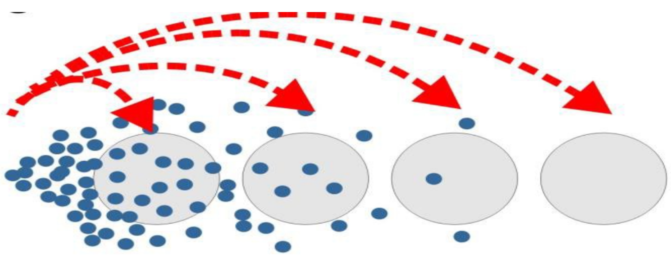
TR: thalamic radiation
NB, MA: basal ganglia & monoamine projection
CC: inter-hemispheric connection (corpus callosum)

SV: ventricular zone
IZ: intermediate zone
SP: subplate
MZ: marginal zone

Genetic guidance

Differentiation: notion of morphogen and patterning

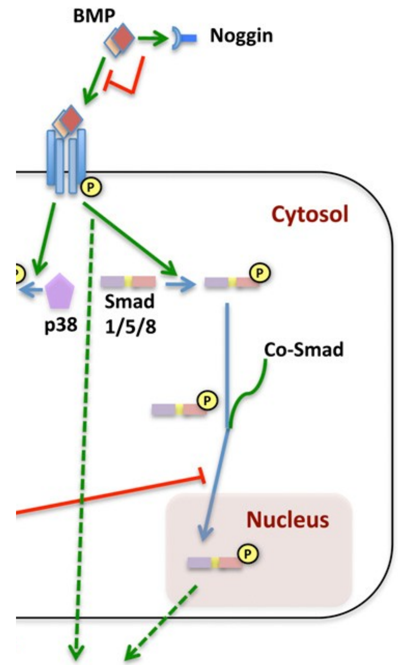
Morphogens diffusion



Gradients of secreted molecules generate a positional information.

If these molecules constrain genetic expression (transcription factor, mRNA silencing, …) and induce cellular differentiation, then the gradient results into a genetic patterning, i.e. a region-specific genetic expression.

Such molecules are called “morphogens”.

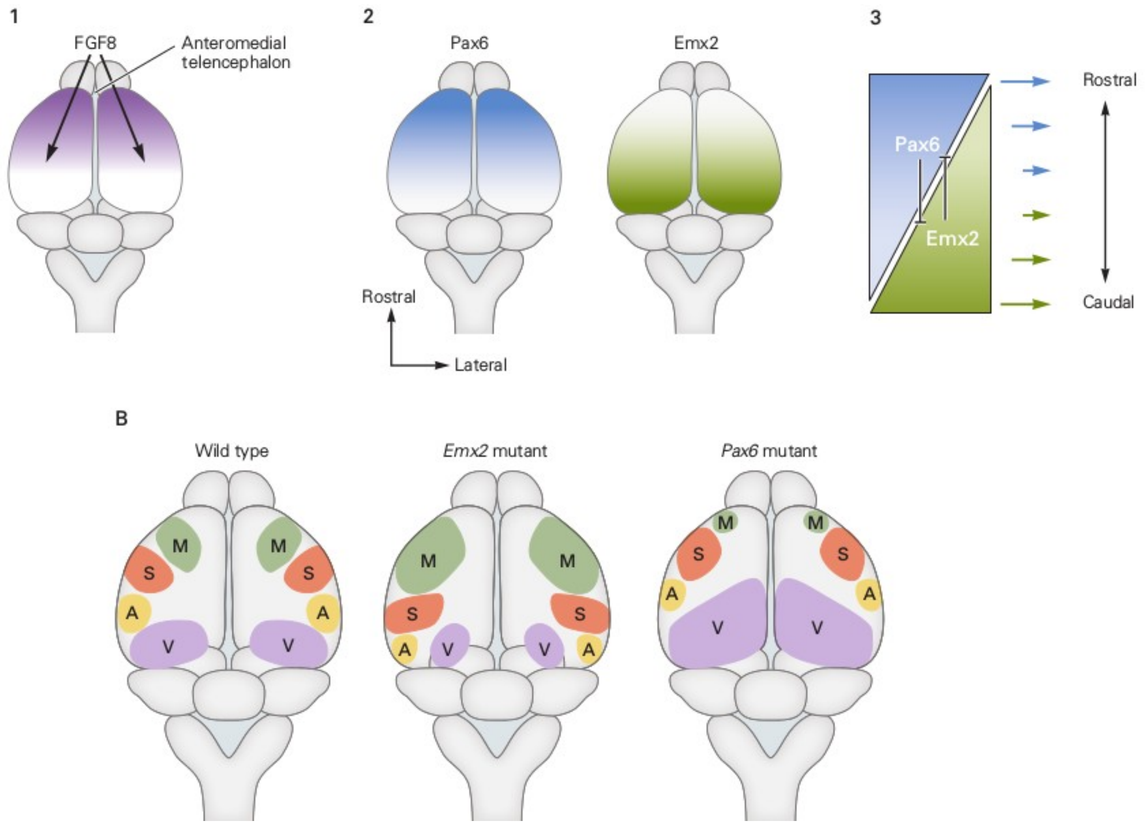


The effects of a morphogen depend on
- its concentration
- the intracellular signaling cascade (which is local and dynamic).

The patterning is thus a complex emergent property.

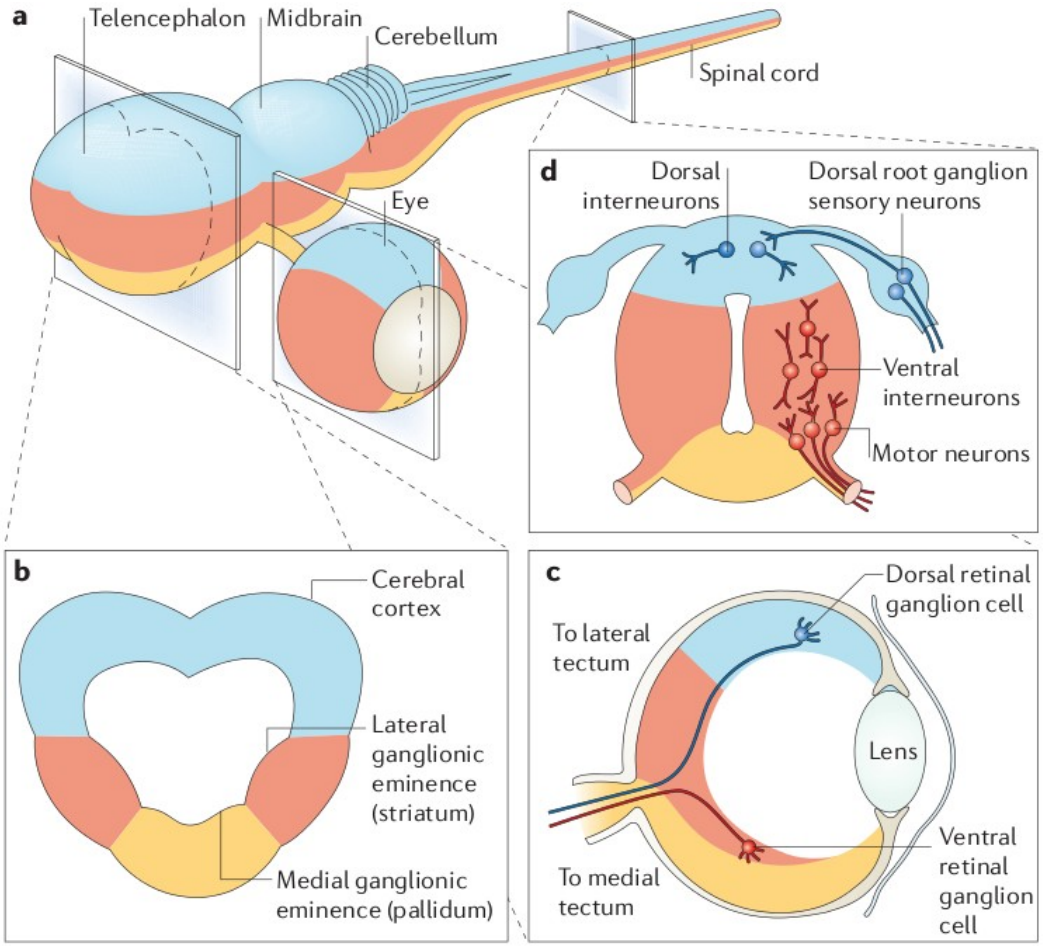
Genetic guidance

Example: genetic guidance of the antero-posterior regionalization

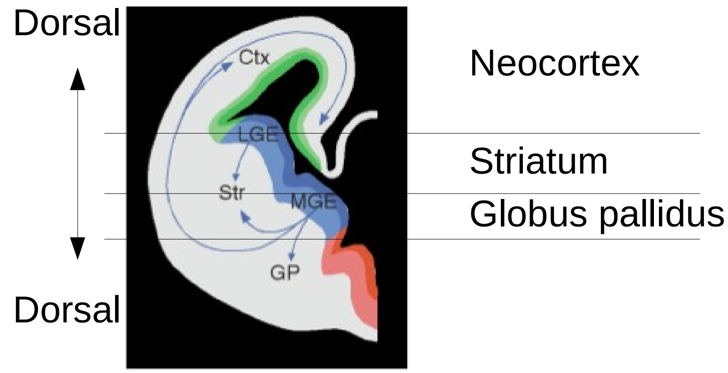


Genetic guidance

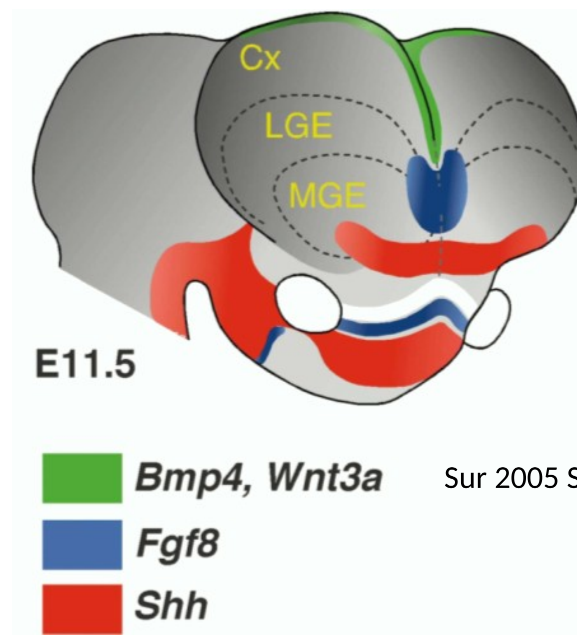
Example: genetic guidance of the dorso-ventral regionalization



Lupo 2006 NNR



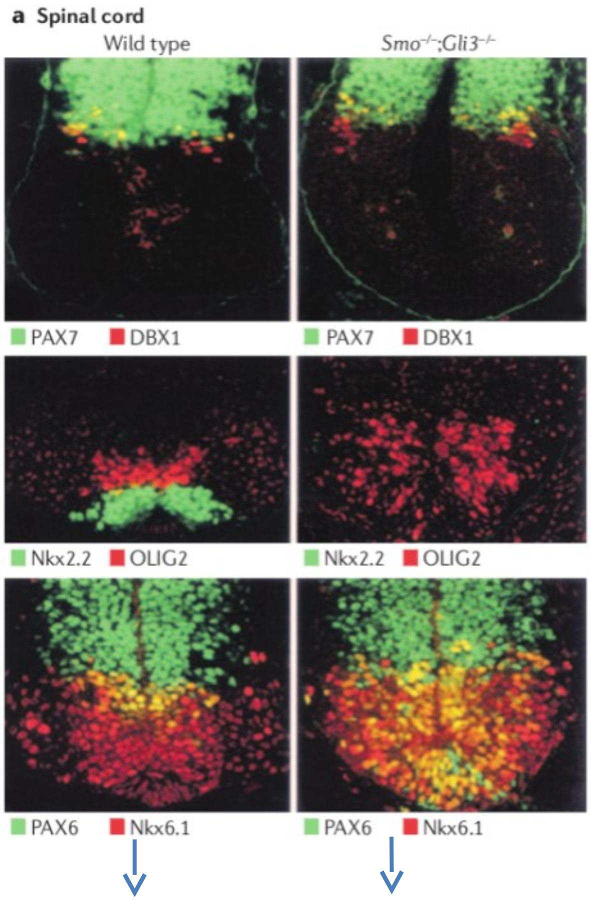
Key morphogens and signaling centrers for the dorso-ventral regionalization

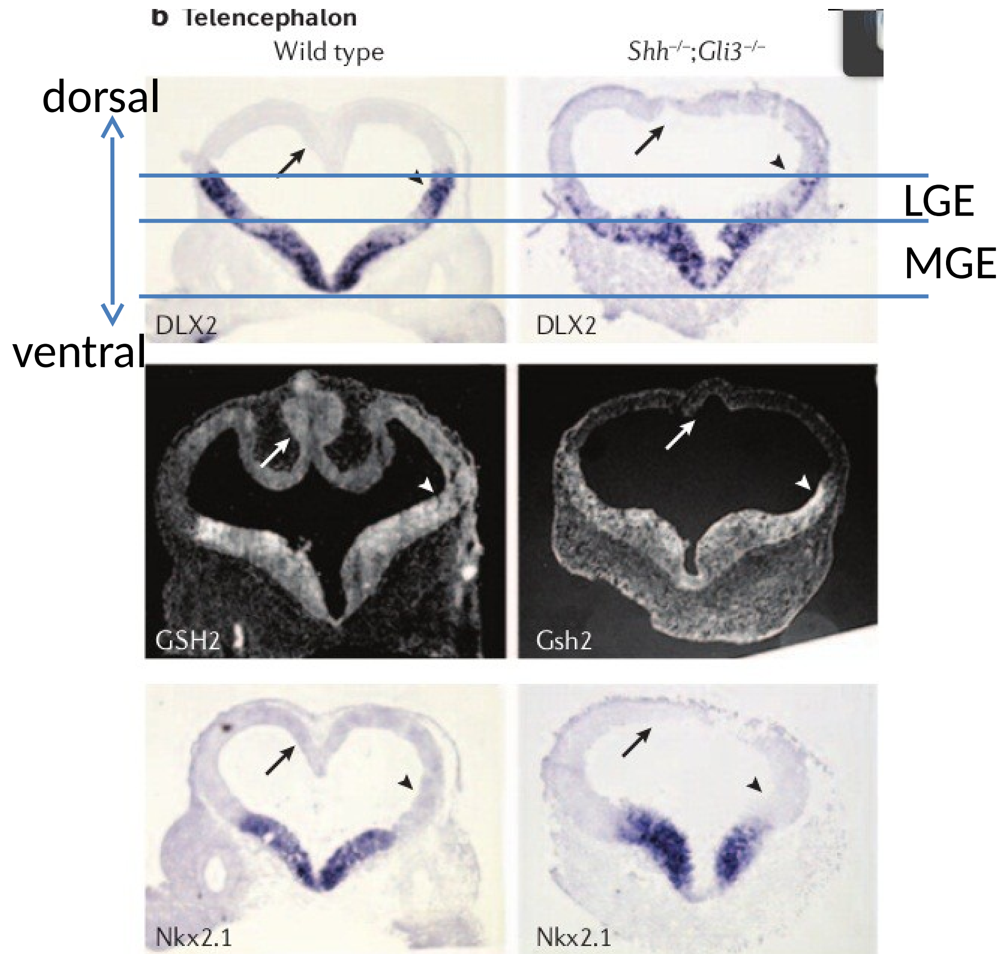


Sur 2005 Science

The developmental processes

In situ localization of morphogens and their interactions



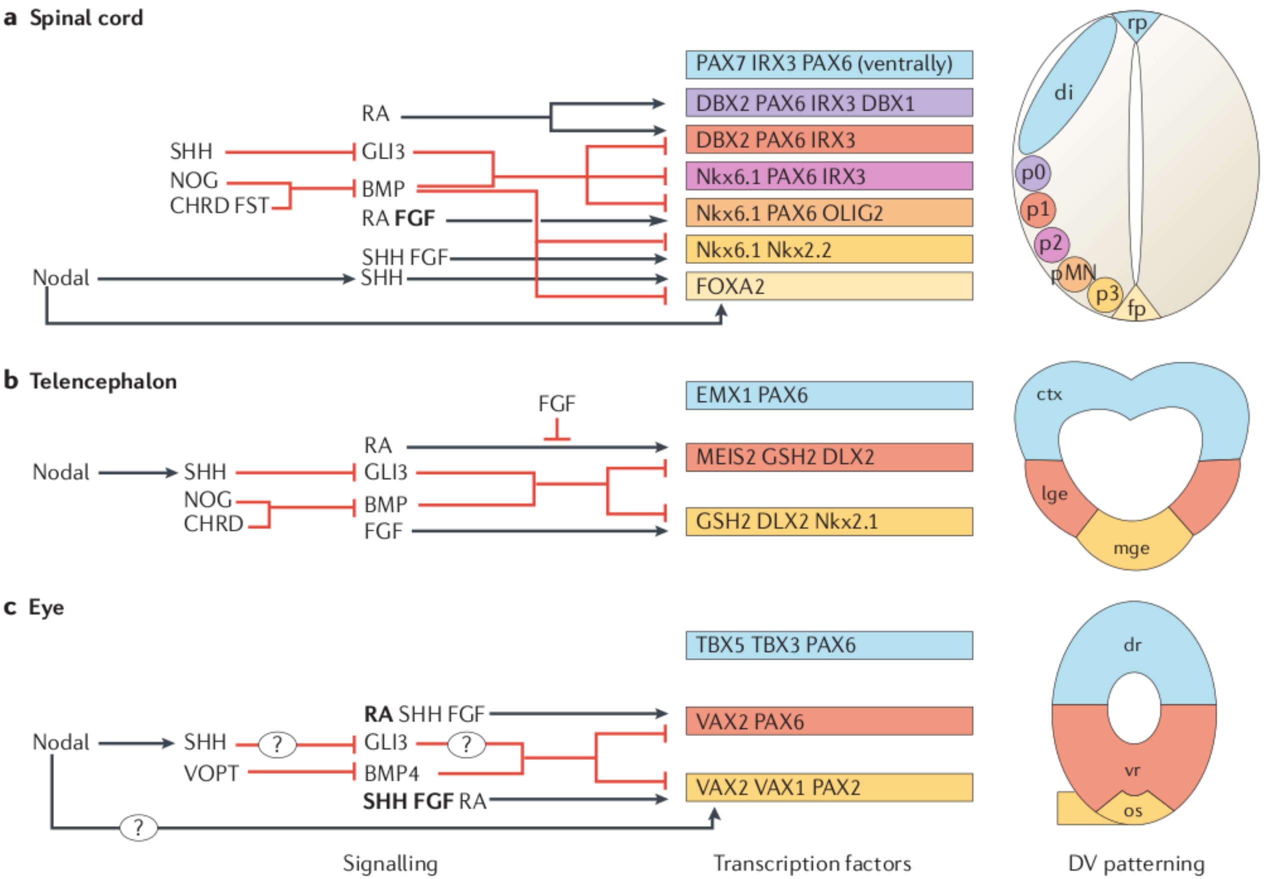


Regionalization of morphogens

Under the control of other (upstream) morphogens

The developmental processes

A glimpse into the complexity of genetic patterning



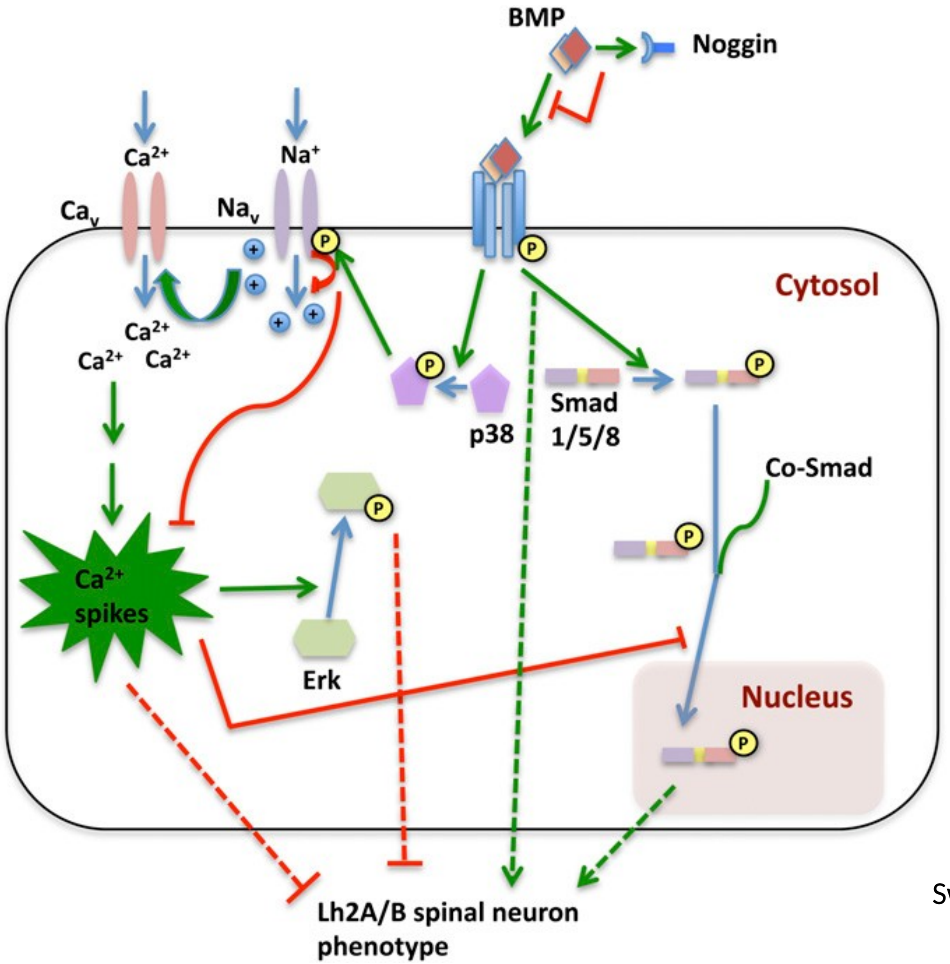
- There are “networks of interactions” between morphogens
- These networks show variations between different structures of the nervous system
- These networks also have a temporal dynamic

Lupo 2006 NNR

The developmental processes

Interaction between genetic patterning and activity-dependent patterning: “intrinsic” and “extrinsic” factors

Activity-dependent patterning | Genetic patterning



Smad is an essential relay for BMP signaling

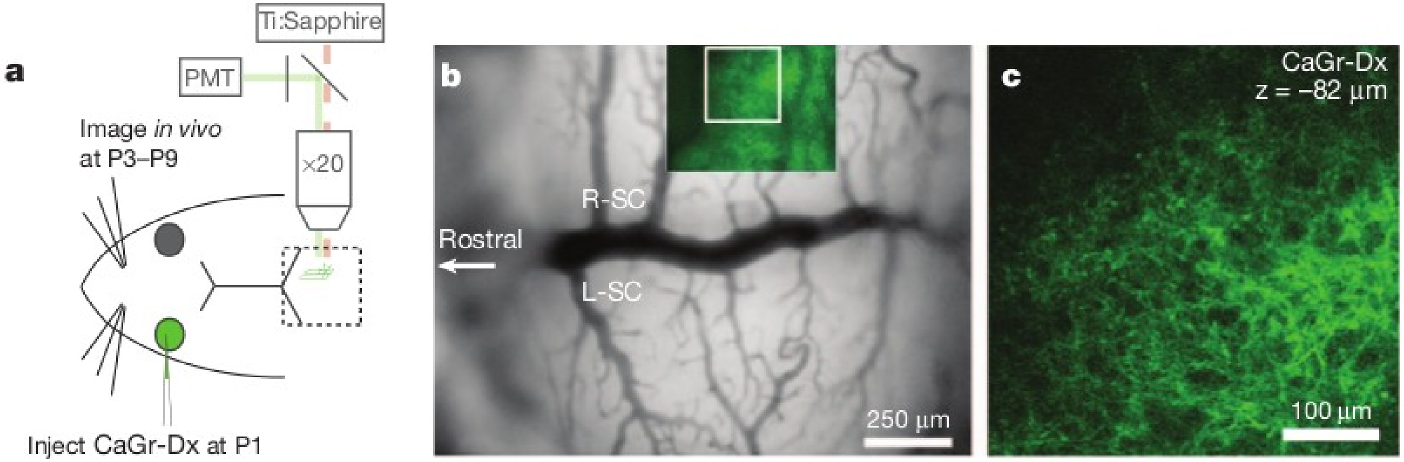
Ca+2 electric activity block Smad, and hence BMP signaling.

Swapna & Borodinsky PNAS 2012

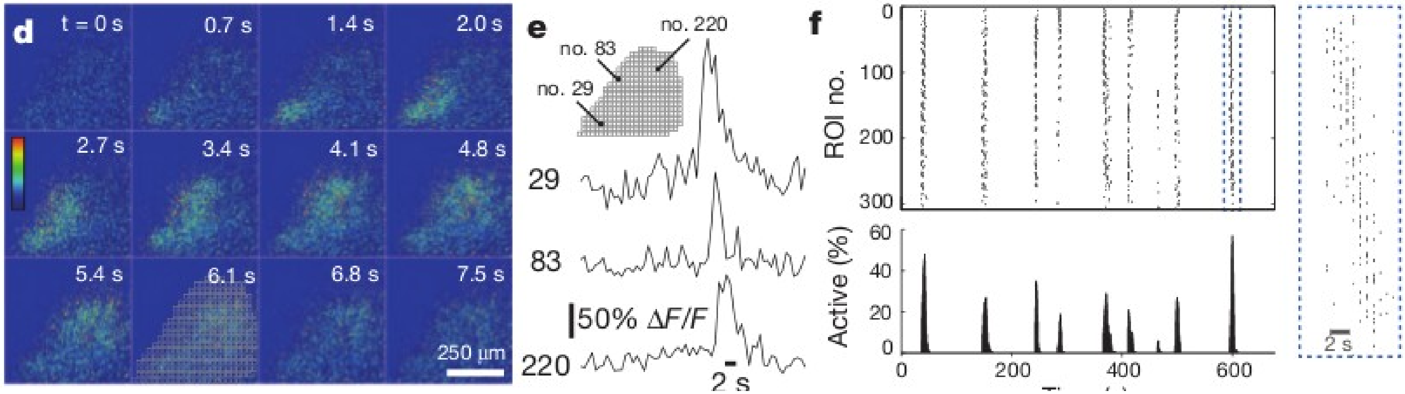
An interplay of Ca+2 and BMP signals regulates the dorsao-ventral specification in the spinal chord.

The developmental process

Spontaneous (without input) Ca2+ in the developing brain



Labelling of retinal ganglion cells and projections to the colliculi



Calcium transient from retina ganglion cell axons show waves of activity

Ackman 2012 Nature

Retinal waves propagate to colliculi (and V1, not shown) in P5 mouse long before eye opening at P10.
These waves provides a patterned activity that encompass the visual field.
Pharmacological blocking of such waves impairs the formation of visual maps.

The developmental processes

Pervasive spontaneous, transient activity in the developing brain

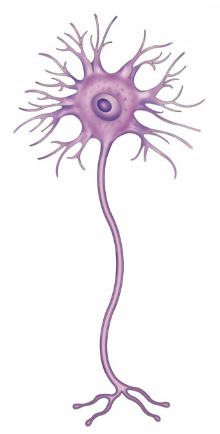
Table 1 | **Summary of important features of spontaneous network activity recorded in rodents**

	Retina			Spinal cord		Hippocampus		Cochlea	Cerebellum
Stage	**E17–P1**	**P1–P10**	**P10–P14**	**E12–E15**	**E15– E18**	**E18–P5 (SPAs)**	**P3–P10 (GDPs)**	**P7–P10**	**P4–P6**
Description of projection neuron firing patterns	Bursts that propagate over a limited region of the GCL	Bursts that propagate over a large region of the GCL	Clusters of bursts that propagate over a large region of the GCL	Bursts of oscillatory activity that propagate within and between segments	Bursts of oscillatory activity that propagate within and between segments	Ca^{2+} spikes correlated over few pyramidal cells	Bursts correlated across CA3 and CA1 subfields	Bursts of action potentials; correlation pattern unknown	Travelling waves of action potentials that propagate from the apex to the base of cerebellar lobules
Inter-event interval	30 s	1–2 min	1 min	2–3 min	1 min	8 s	3–10 s	5–60 s	100 ms
Mechanisms of initiation	Unknown	Spontaneous Ca^{2+} spikes in starburst amacrine cells	Unknown	Network interactions	Network interactions	Spontaneous Ca^{2+} spikes in pyramidal cells	Intrinsic bursts in CA3 interneurons	Unknown	Spontaneous firing in Purkinje neurons
Primary source of depolarization	Gap junctions	nAChRs	iGluRs	nAChRs, $GABA_A$Rs and Gly receptors	iGluRs, nAChRs, Gly receptors and $GABA_A$Rs	L-type Ca^{2+} channels and gap junctions	$GABA_A$Rs and NMDARs	ATP release from supporting cells in Kölliker's organ	$GABA_A$Rs
State of network at end	Maturation of cholinergic circuit	Maturation of glutamatergic circuits	Onset of vision	Loss of requisite role for nAChR signalling	GABA signalling becomes inhibitory	Maturation of GDP circuits	GABA signalling becomes inhibitory	Kölliker's organ disappears	GABA signalling becomes inhibitory
Recorded *in vivo*	No	Yes[3]	Yes[26,27]	Yes (chick[29])	Yes (chick[29])	No	Yes[125]	Yes[41]	No

Blankenship NNR 2010

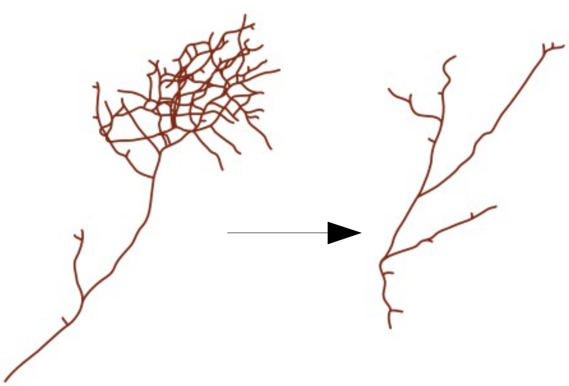
The developmental processes

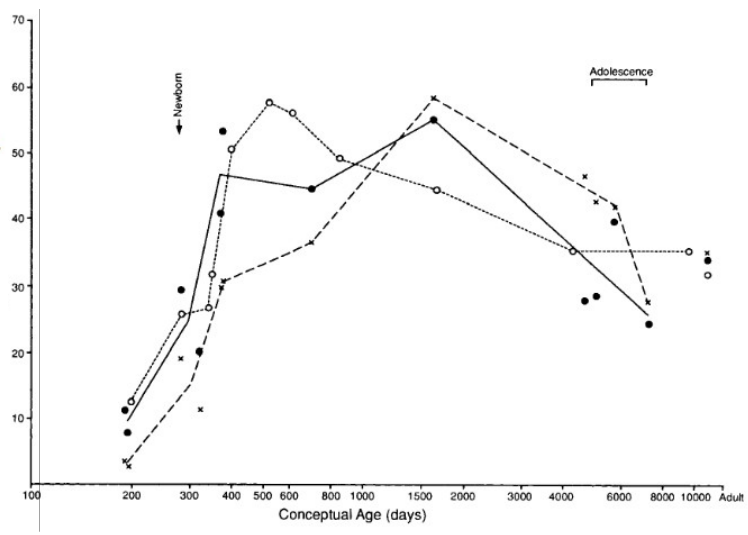
Genetic signals result in an exuberant development that is later refined by intrinsic and extrinsic factors



NEURONS

Massive elimination of neurons: 30 to 80% of neurons undergo cell death across regions during prenatal development.
This elimination follows a genetic "suicide" program: the ***apoptosis***.
Apoptosis is regulated by ***neurotrophic factors*** produced by target cells in an activity dependent manner: this mechanism implements an activity-dependent elimination.





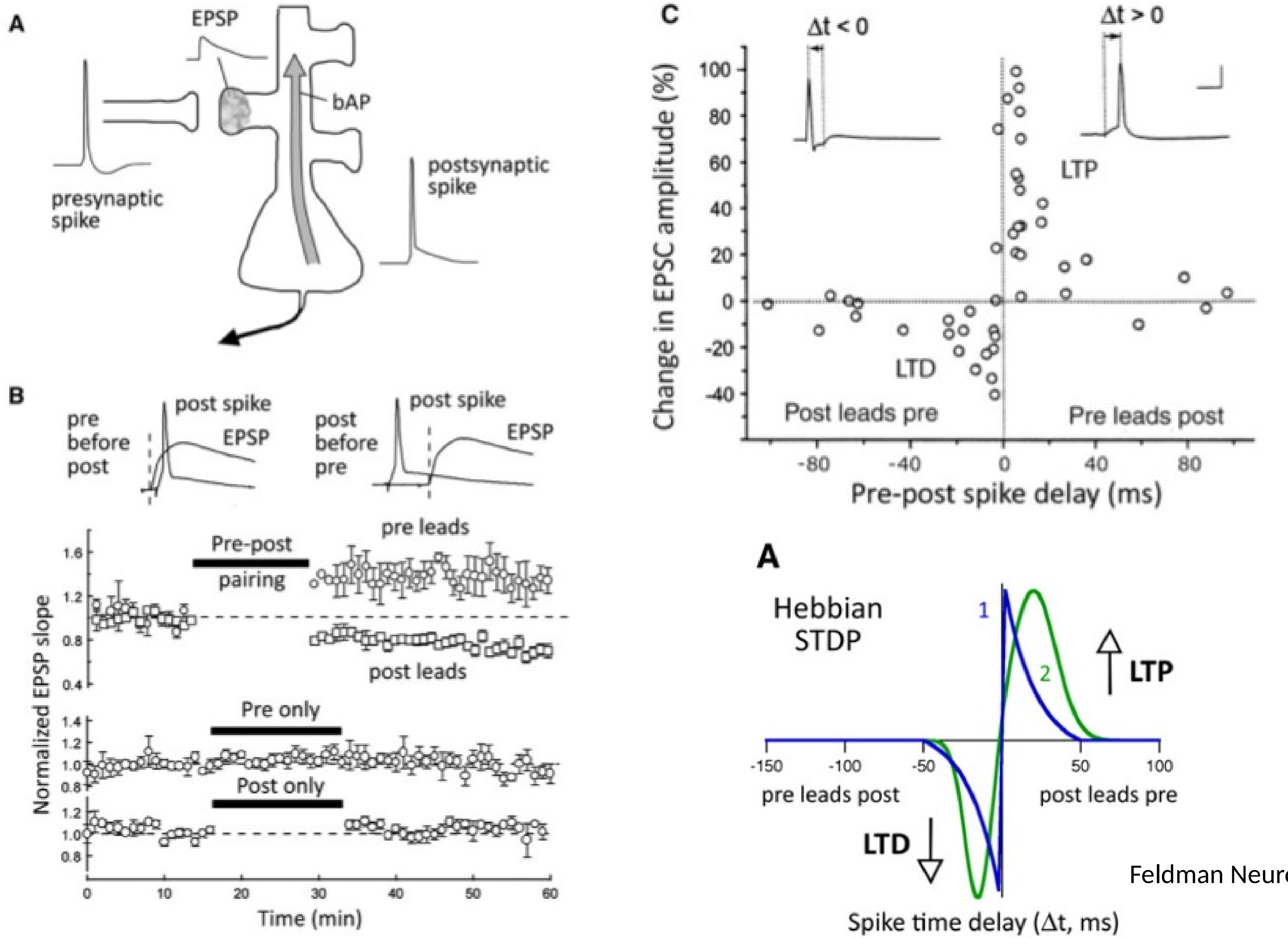
Huttenlocher and Dabholkar, 1997

SYNAPSES

During pre-natal development, there is concurrent formation and elimination of synapses.
The elimination is a protracted process that continues during post-natal development until adolescence.
This elimination is activity-dependent, associated with Hebbian learning.

The developmental processes

Activity-dependent changes (potentiation, depotentiation) and "hebbian" plasticity: cells that fire together work together

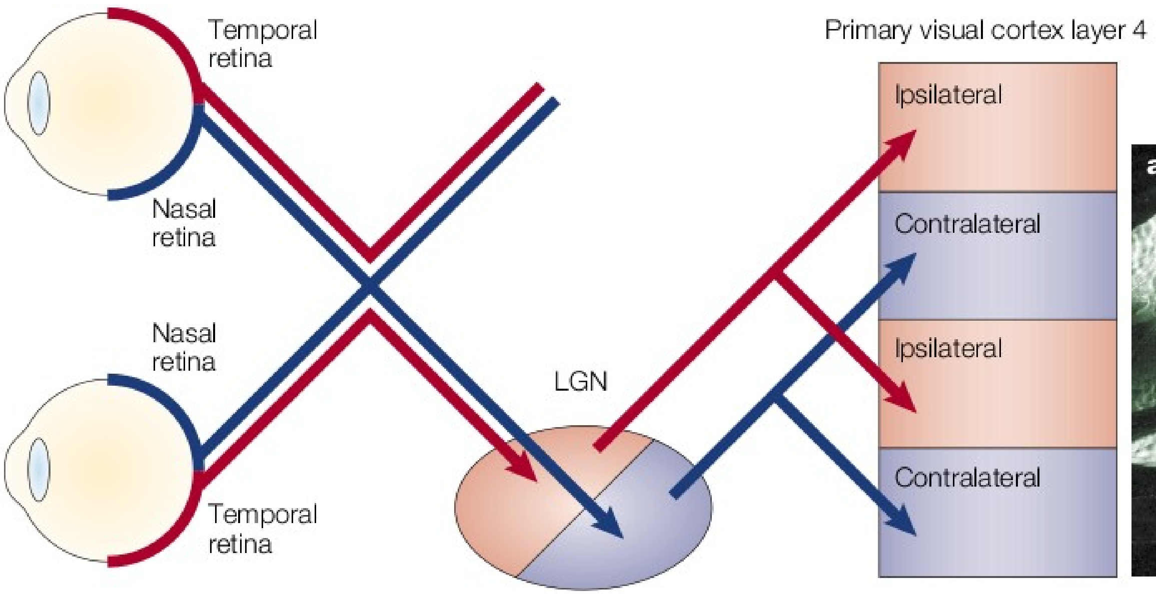


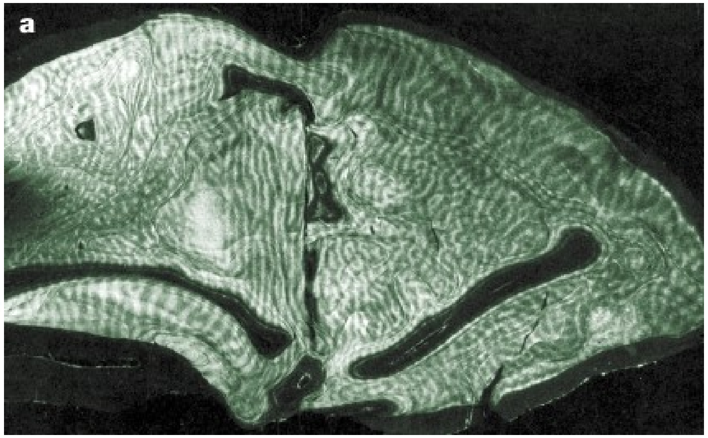
Feldman Neuron 2012

The developmental processes

There is functional segregation in the brain cortex

The canonical example of ocular dominance columns



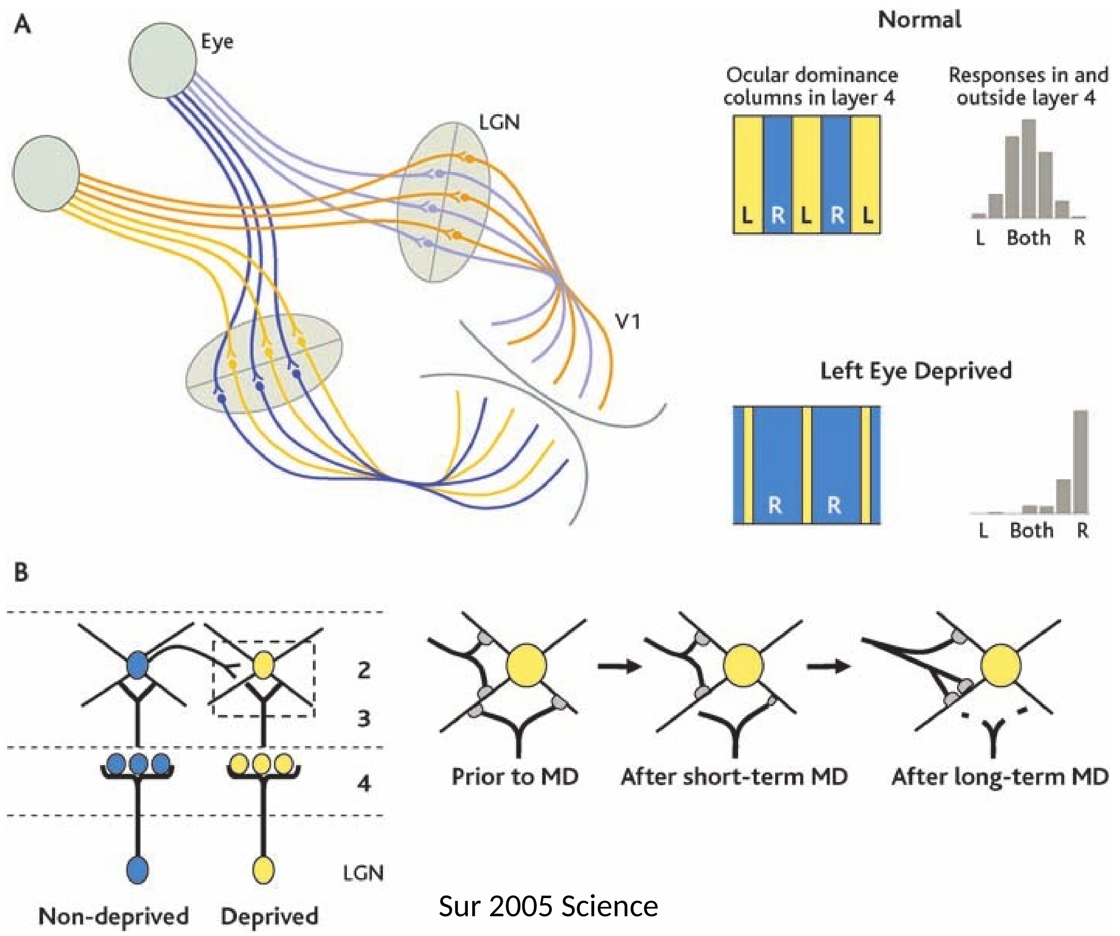


Katz 2002 NNR

The developmental processes

Functional segregation requires the activity-dependent pruning of neuronal connections

The canonical example of ocular dominance columns

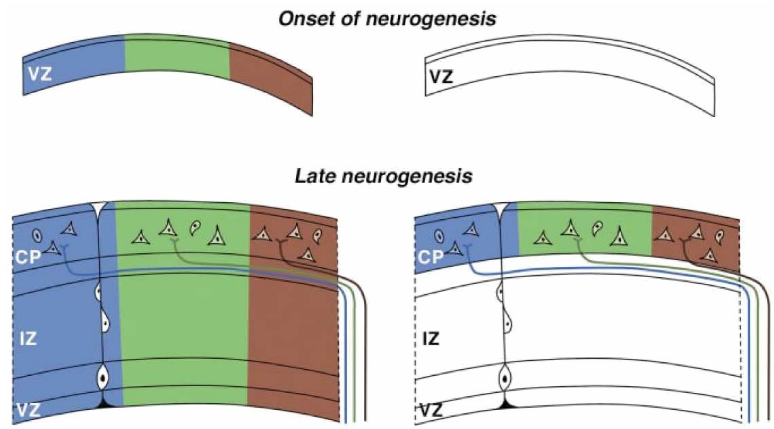


Sur 2005 Science

The initial formation of ocular dominance columns relies on activity-dependent and activity-independent factors, and is still not clearly understood. By contrast, the role of activity-dependent, competitive interactions during later stages is well established.

The developmental processes

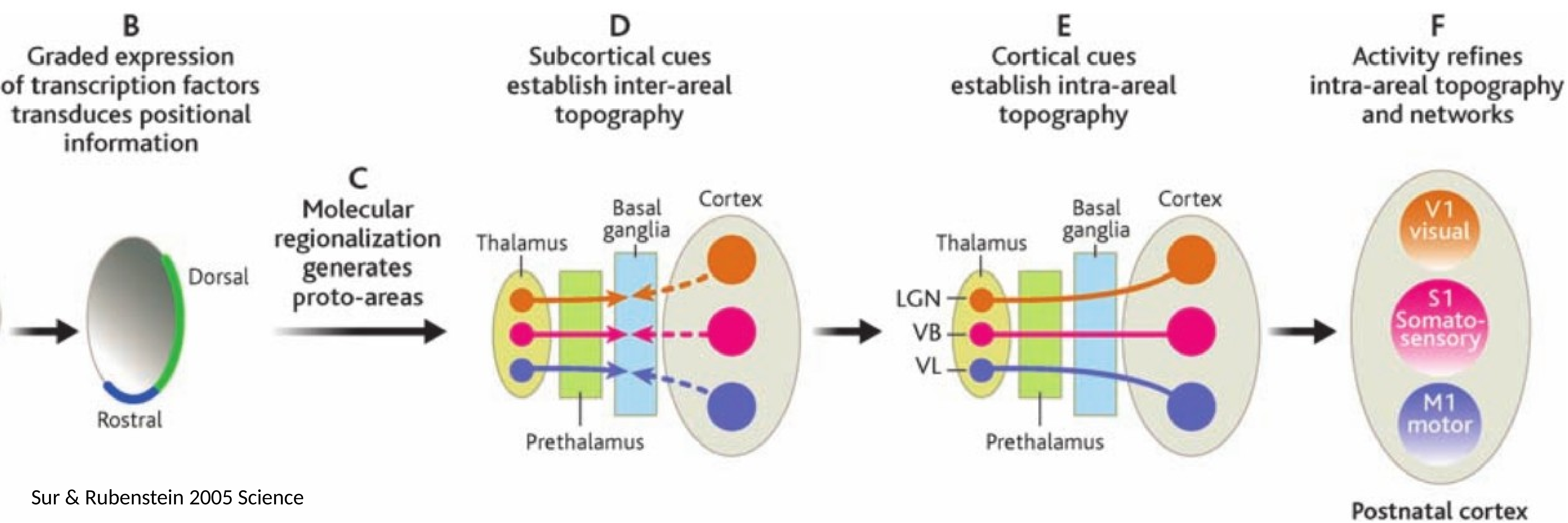
Summary: an interplay between extrinsic and intrinsic factors



Grove & Fukuchi-Shimogori 2003 Annu. Rev. Neurosci

Two views on arealization in the developing cortex:
"protomap": emphasizes the role of molecular signaling of neural progenitors (intrinsic factors)
"protocortex": emphasizes the homogeneity of the neocortex, and its functional segregation based on differential input activity (extrinsic factors).

The recent view: there is a sequence of intrinsic and extrinsic factors.



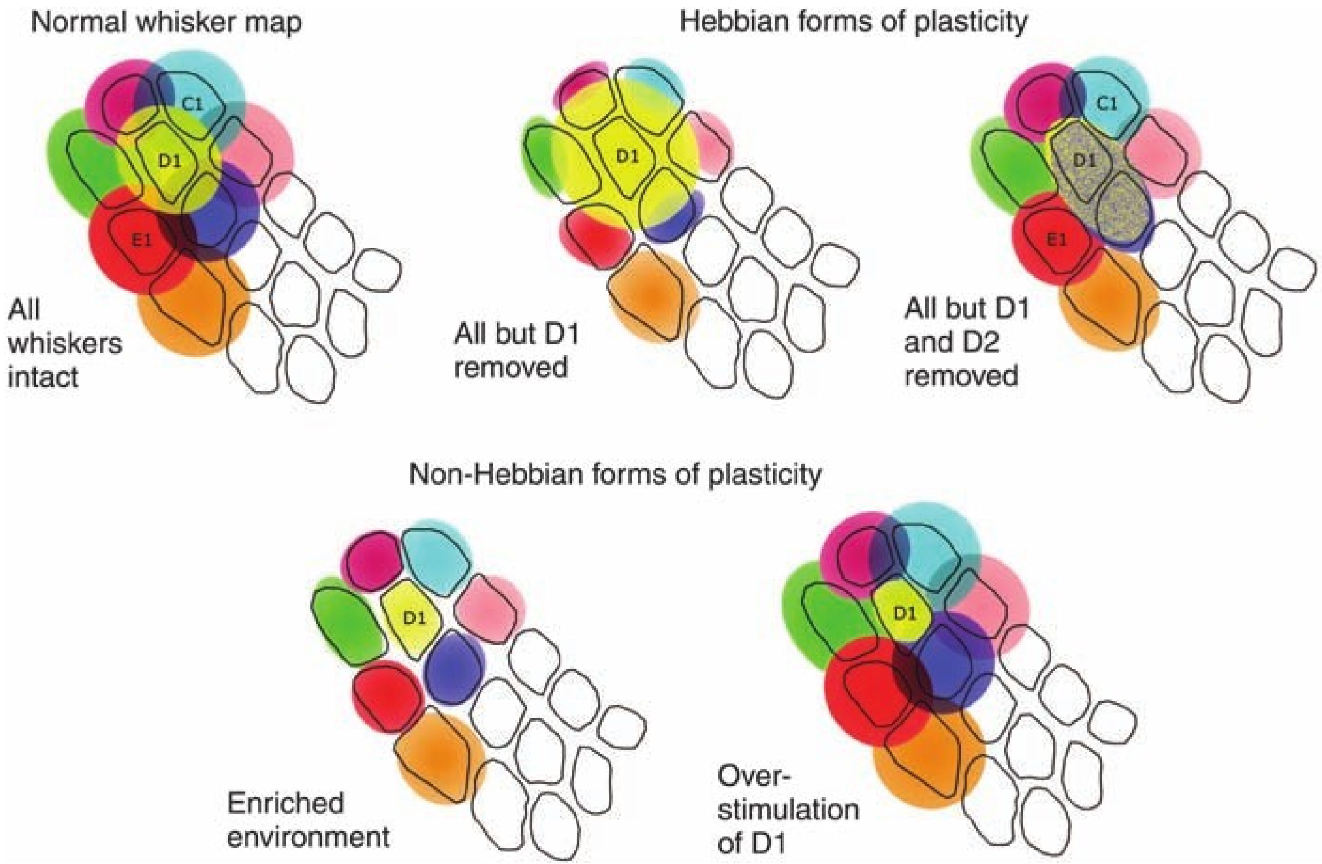
Sur & Rubenstein 2005 Science

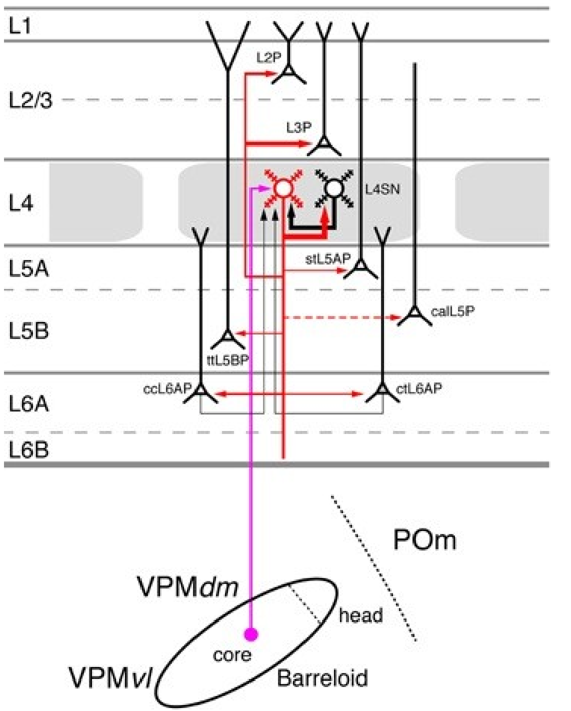
Plasticity of the brain

- Further activity-dependent shaping of cortical networks during a protracted post-natal development
- The notion of critical period
- Plasticity in the adult brain
- Adult neo-neurogenesis?

Plasticity of the brain

Interactions with the environment prune synapses and refine sensory maps





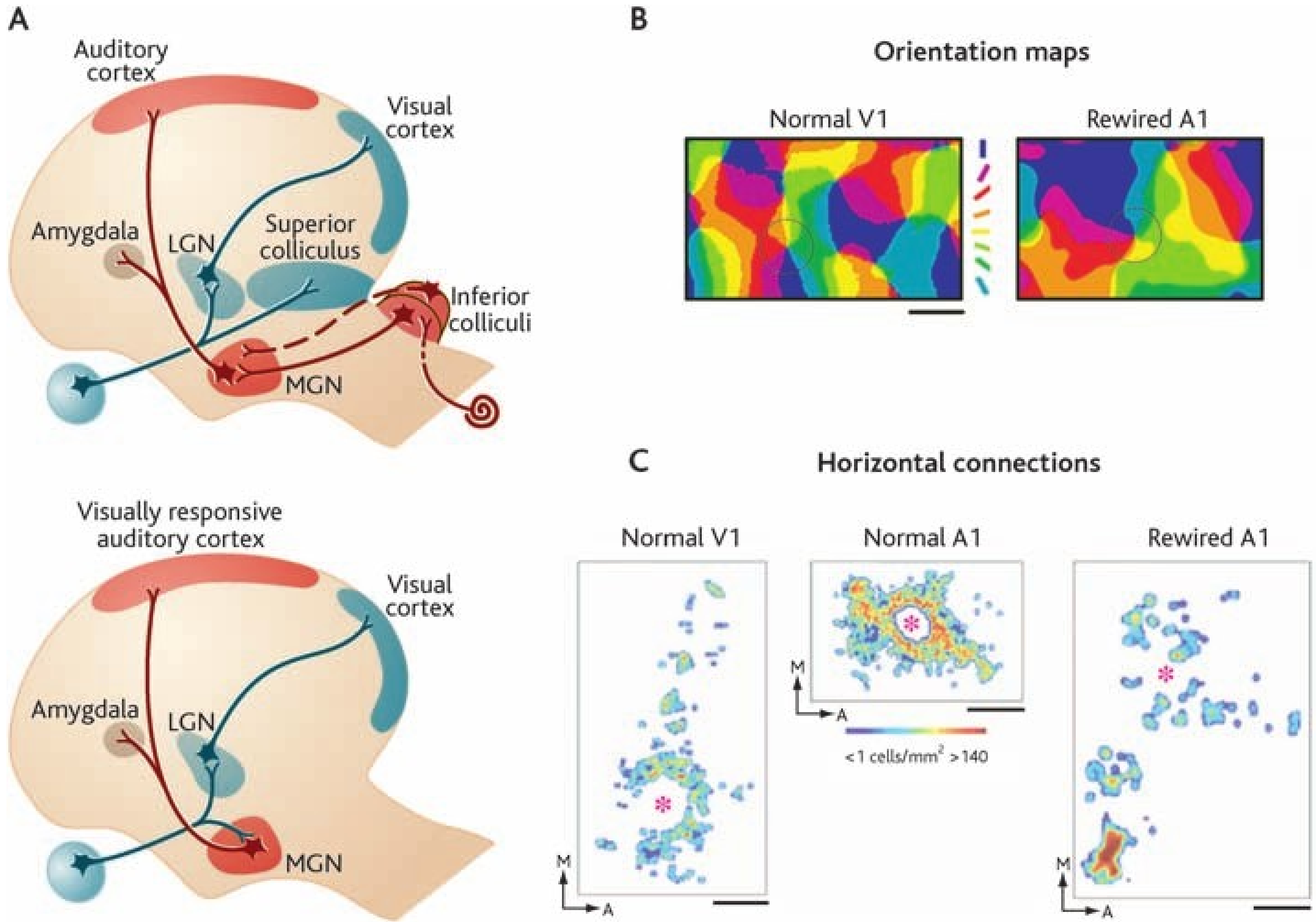
Feldmeyer 2012 Front in Neuroanat

Field in superficial layer (L2/3). Barrel limit (L4) in black

Feldman 2005 Science

Plasticity of the brain

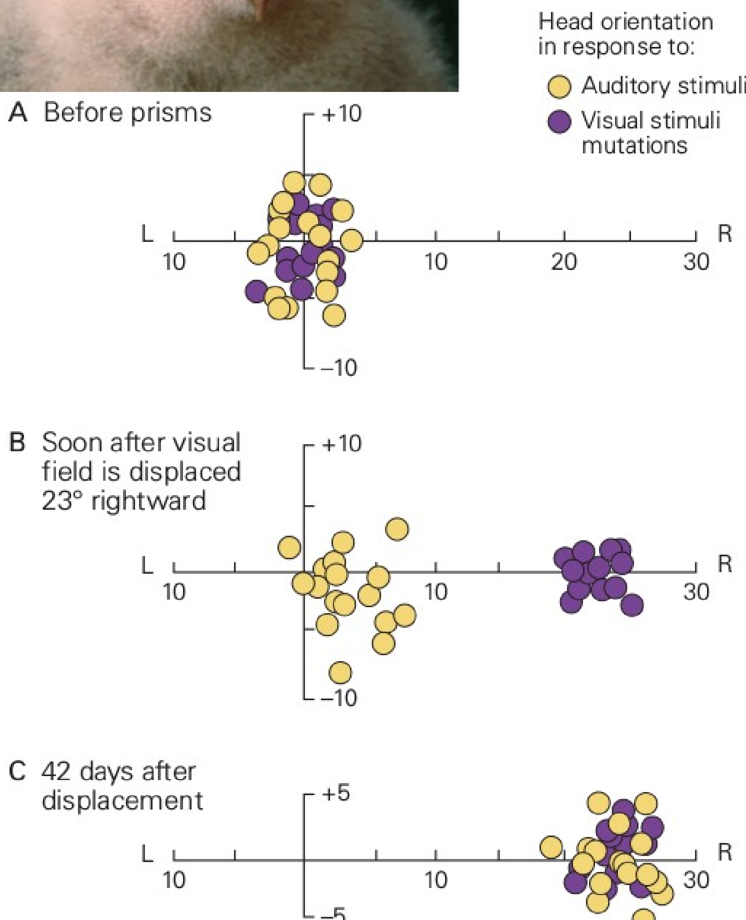
An extreme example of plasticity: reorganization of sensory maps



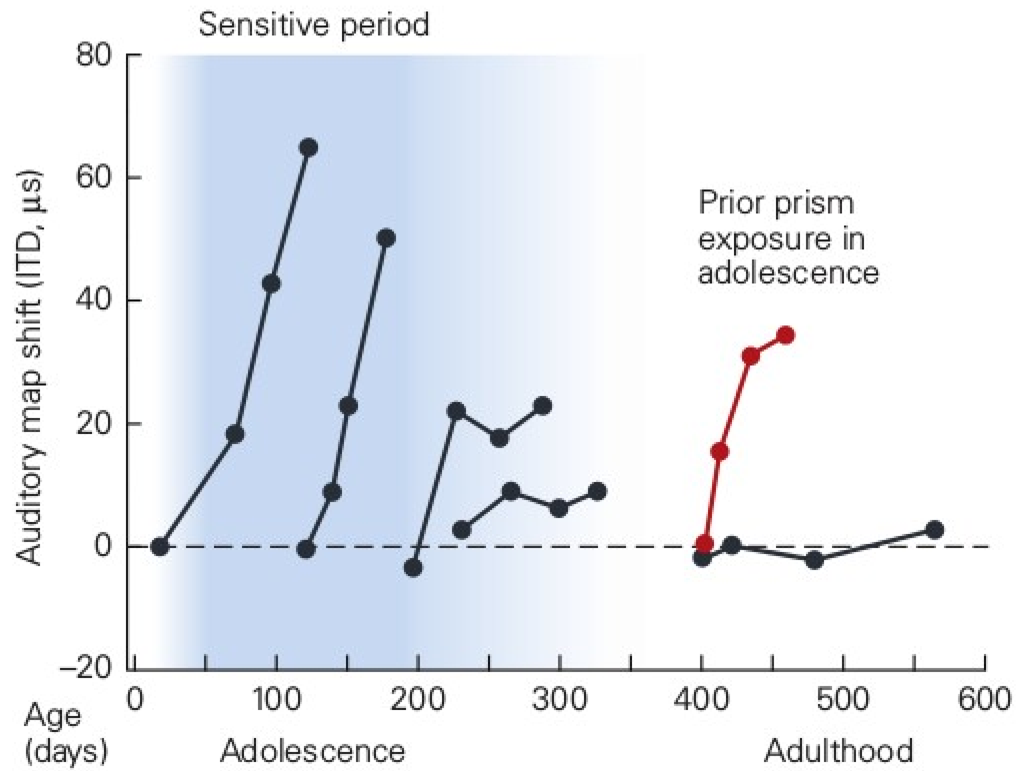
Sur 2005 Science

Plasticity of the brain

Specific time-windows for plasticity: the notion of critical period



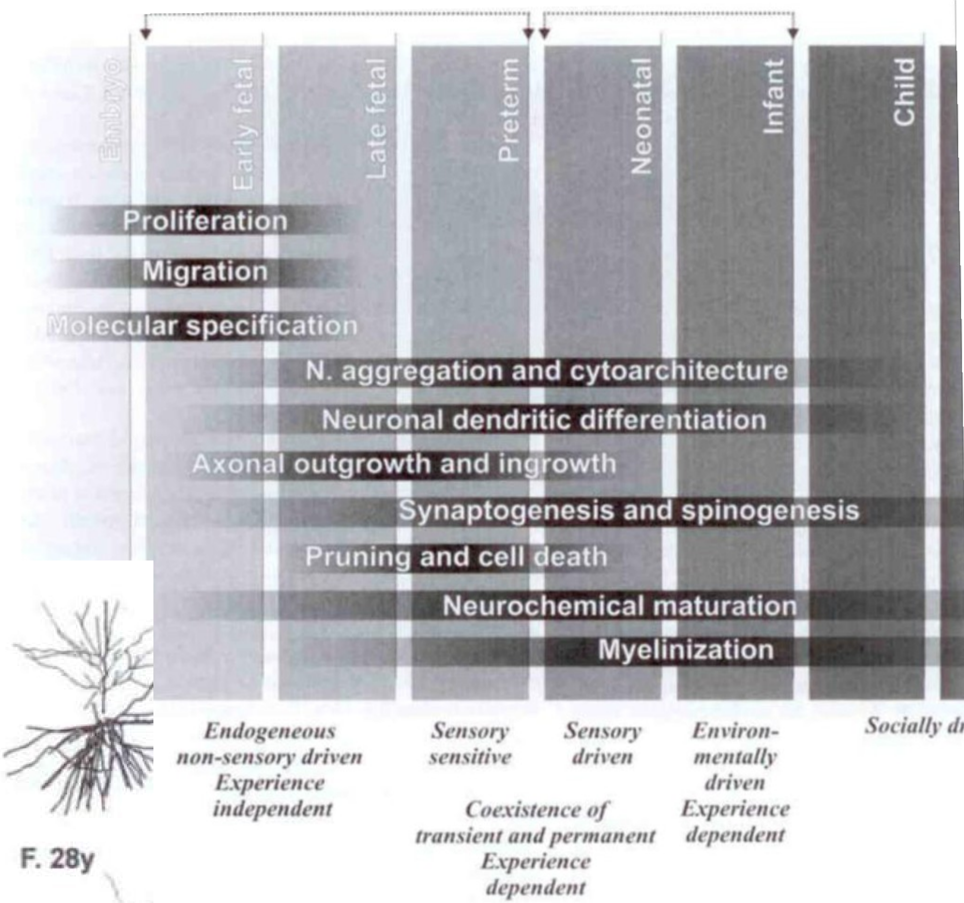
The displacement of optic signals by prism goggles induce an alignment of auditory maps only during a specific period of time during development.

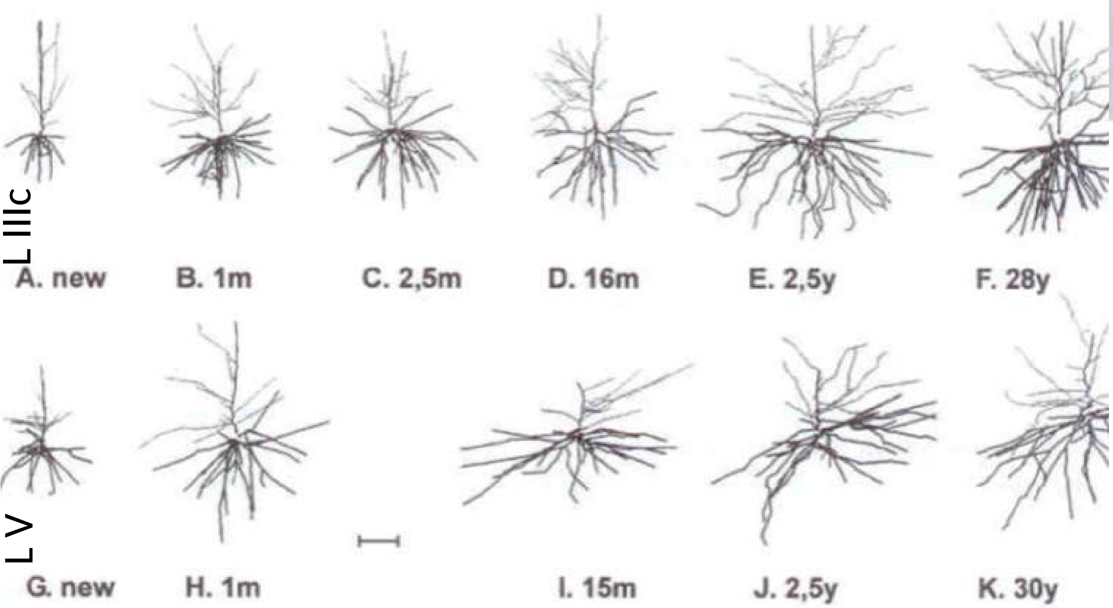


Plasticity of the brain

Notion of critical period and interaction with the environment: the case of the prefrontal cortex

Period	Circuit	Type of activity
Neonate	Permanent, with transient elements	Sensory-driven, centered on layer V
2-6 mo	Permanent with transient elements	Sensory-driven, columnar processing
7-12 mo	Initial cognitive circuit	Environmental driven, local circuit
12-24 mo	Cognitive	Socially driven, centered on layer III



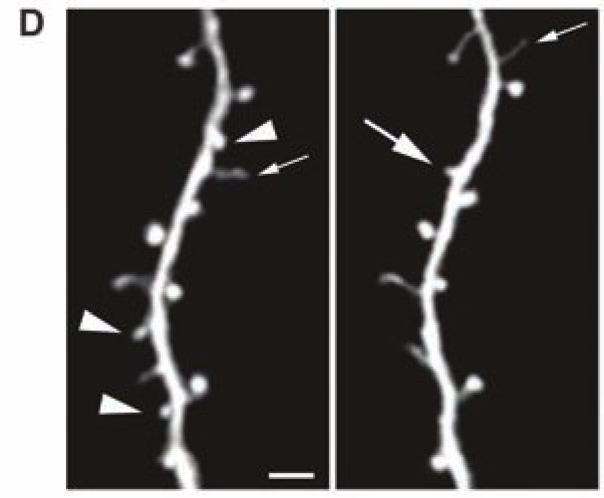


Gazzaniga The cognitive neuroscience 4th Ed. Chap 2

Plasticity of the brain

In vivo observation of plasticity: dynamic dendritic spines

2 weeks after

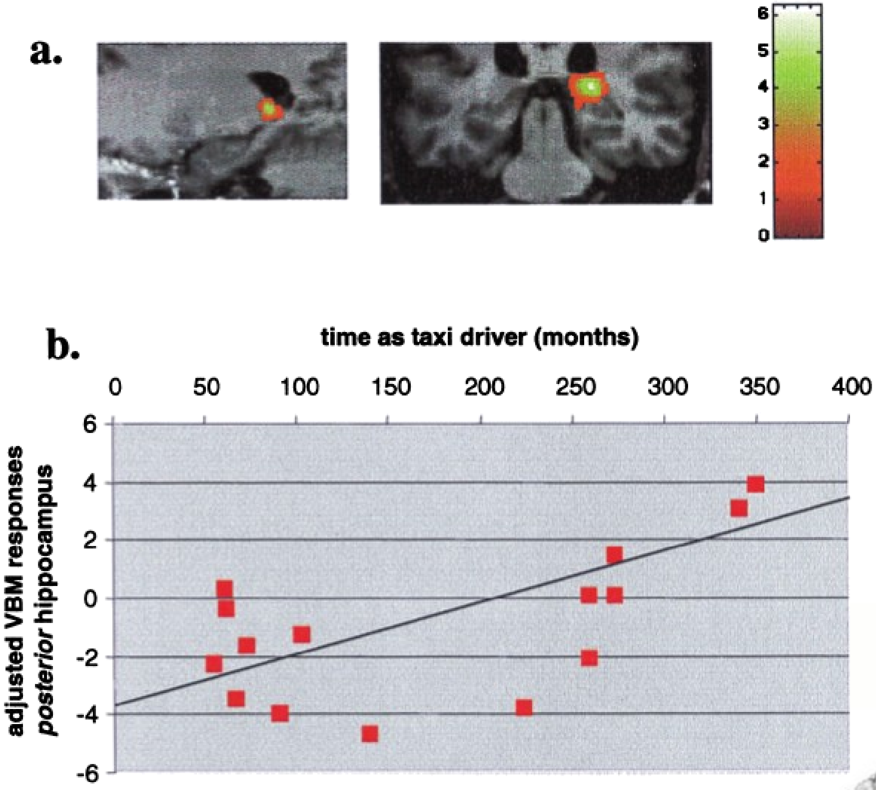


Feldman 2005 Science

Two-photon imaging of the primary somato-sensory cortex of an adolescent rat.

Plasticity of the brain

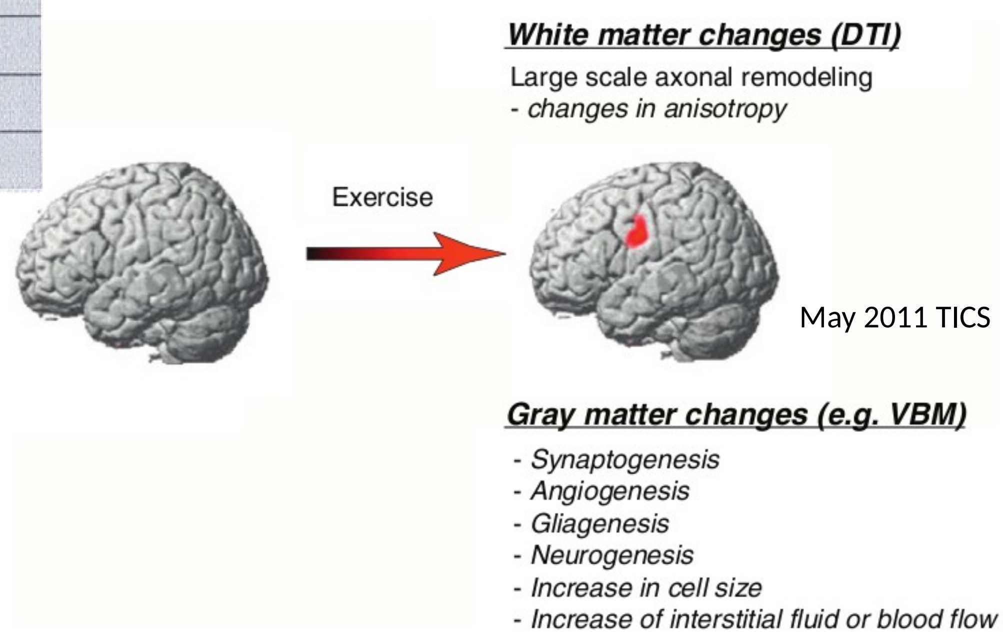
Experience-dependent morphological changes in the adult brain



Maguire PNAS 2000

Larger hippocampus in experienced taxi driver

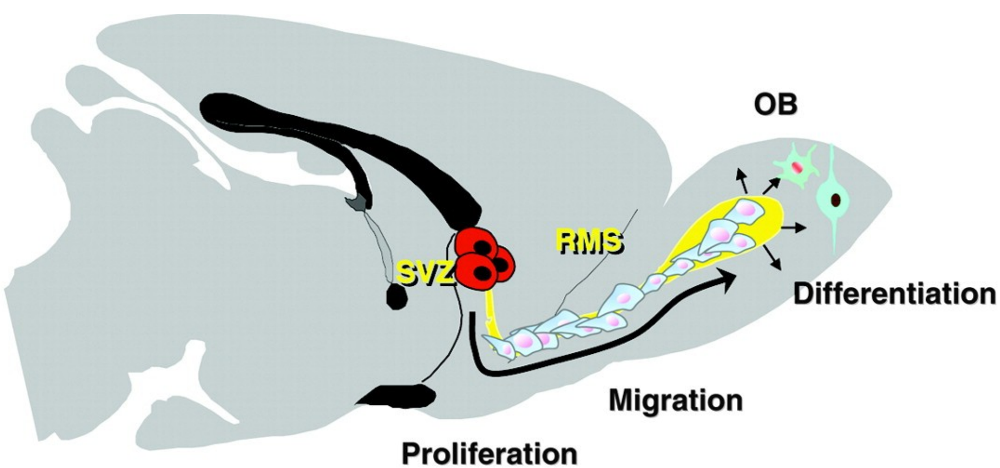
Potential anatomical changes detected with MRI scanners:



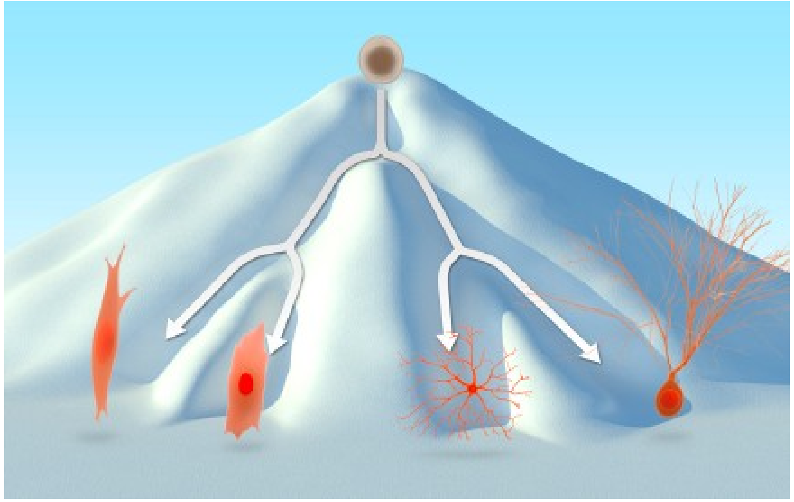
May 2011 TICS

Plasticity of the brain
Adult neo-neurogenesis?

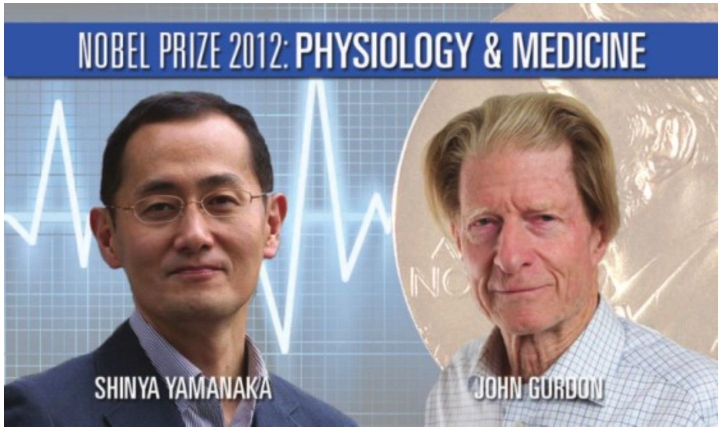
- In humans: new neurons are generated throughout life in the hippocampal region
- In rodent: also new neurons in the olfactory bulb
- However, the ‘big picture’: there is a given pool of neurons throughout life.

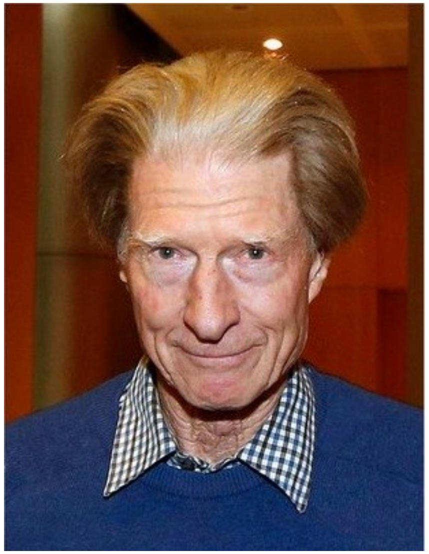


2012 Nobel Prize: induced pluripotent cells



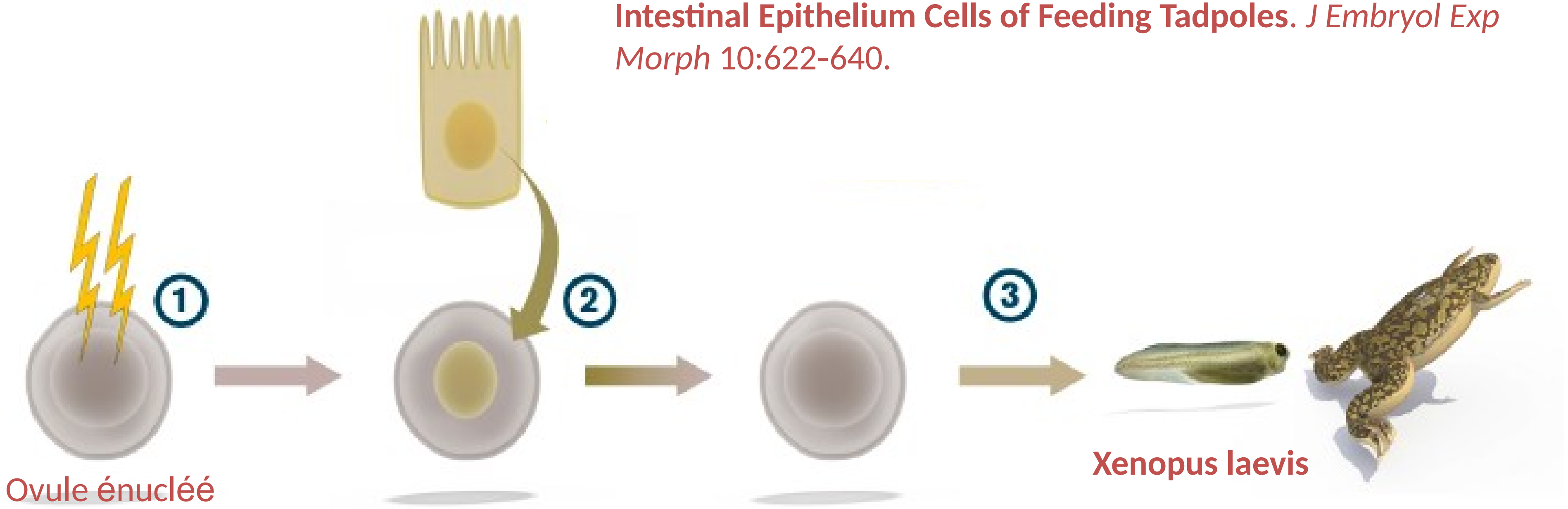
- Development progressively restricts cellular fates
- Can the clock be reversed?
- Induced pluripotent cell (iPS): specialized cell that are induced pluripotent (i.e. able to undergo development once again!).
- Gurdon & Yamanaka were rewarded the 2012 Nobel Prize for achieving this feat.

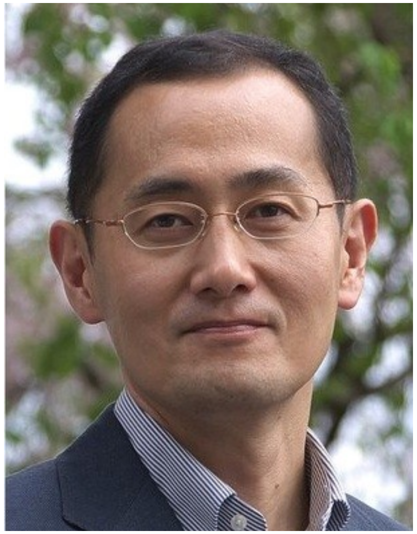




- Gurdon: put mature cell nucleus in an egg to make it pluripotent (little chance though…)
  - Evidence that mature cells keep their whole genetic package.
  - But: it does not work in humans…

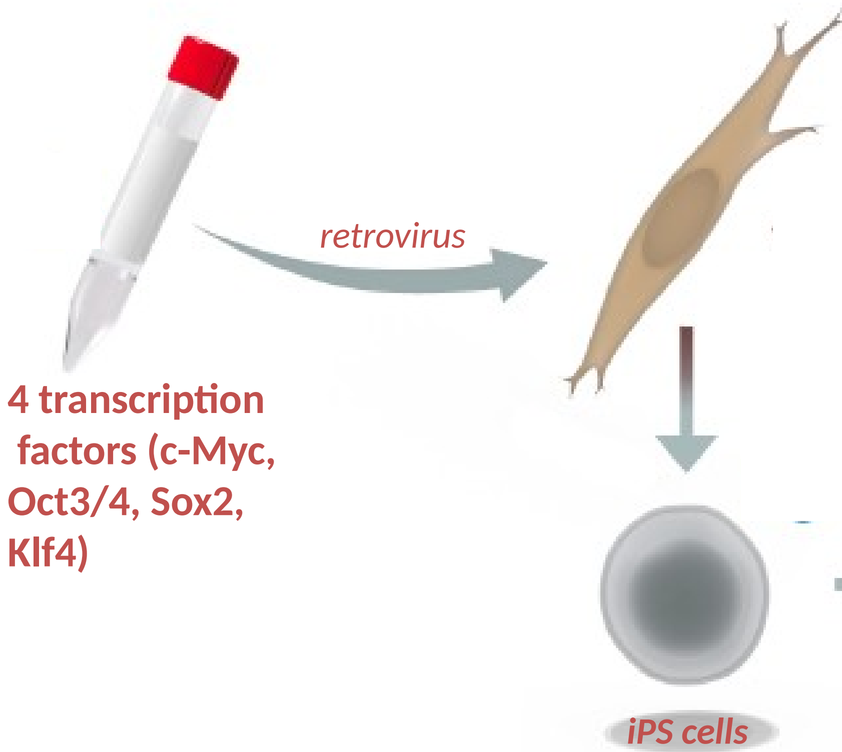
Gurdon JB (1962). **Developmental Capacity of Nuclei Taken from Intestinal Epithelium Cells of Feeding Tadpoles**. *J Embryol Exp Morph* 10:622-640.

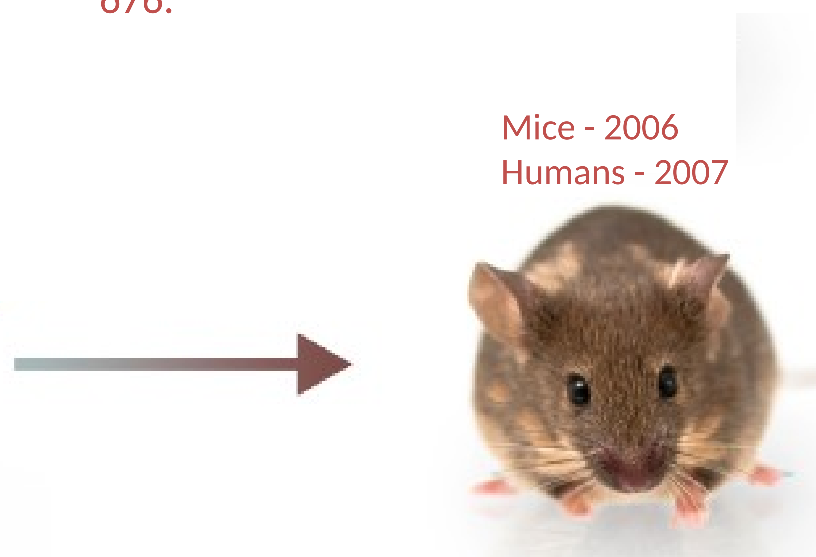




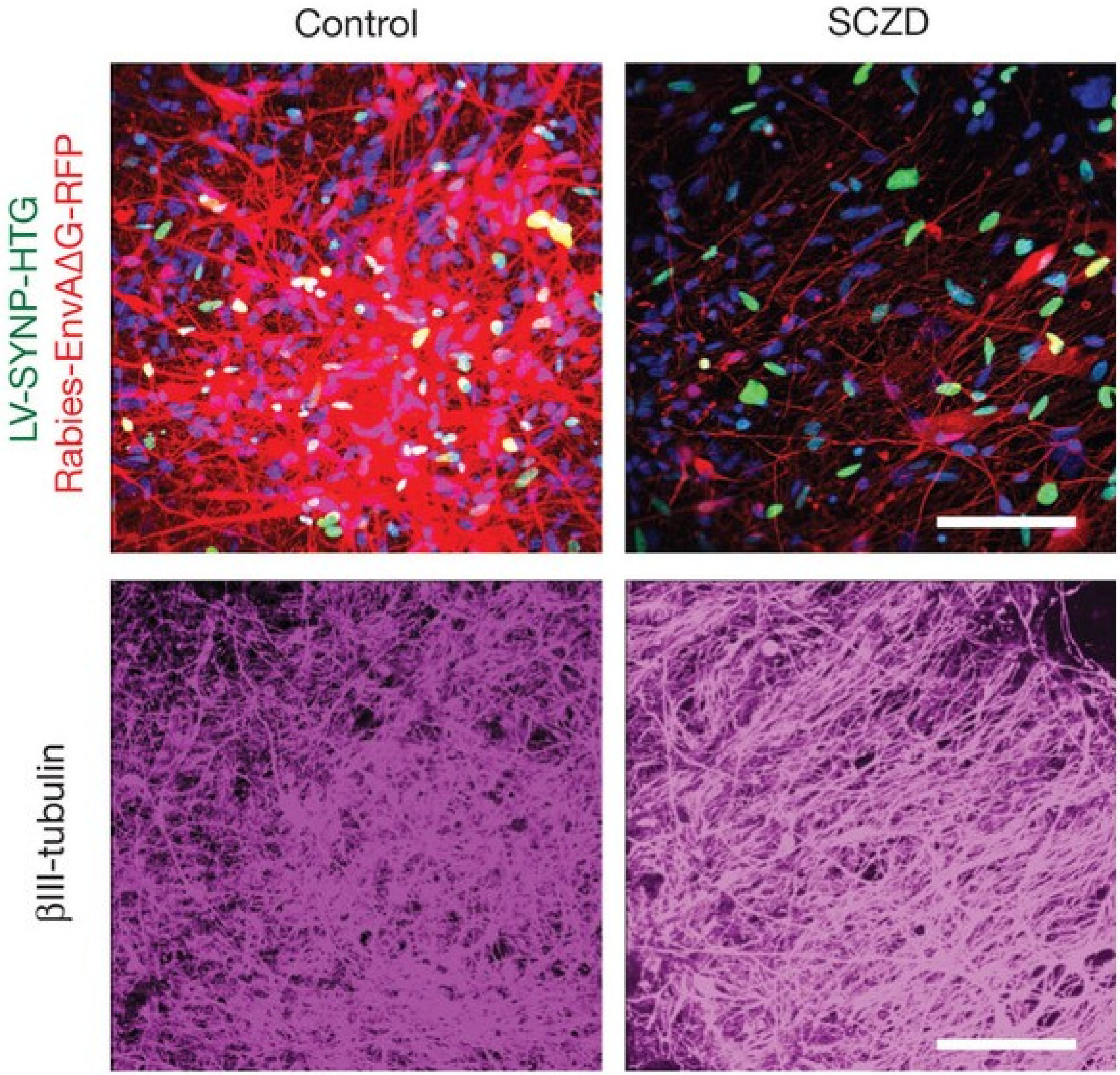
- Yamanaka: had some genes expressed during development added in mature cells (4 are enough) to induce cells to become embryonic stem cells
  – Developed in rodent
  – Now works in humans

Takahashi K and Yamanaka S (2006). **Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.** *Cell* 126:663-676.





Decreased neuronal connectivity in SCZD hiPSC neurons.



Spread of rabies via synaptic contacts => estimate of connectivity

Tubulin to localize neurites

Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, Li Y, Mu Y, Chen G, Yu D, McCarthy S, Sebat J, Gage FH. **Modelling schizophrenia using human induced pluripotent stem cells.** *Nature.* 2011 May 12;473(7346):221-5.

Take-home messages

- Morphogenesis and regionalization:
  - Are under dynamic genetic control (intrinsic factors)
  - Depend on spontaneous electrical activity (extrinsic factors)
  - Depend on complementary interactions of extrinsic and intrinsic factors
  - Involve pruning
- The critical period is characterized by massive plasticity
  - It is required to consolidate the architecture
  - It is haped by interactions with the environment (evoked activity)
  - It is limited in time (followed by a freezing of the system)
- Plasticity is crucial
  - During the development, in particular for the transient vs. remnant structures
  - During the adulthood (but the brain plasticity of adult << during development)
  - In both cases: critical for the adaptation to the environment

References

- Acknowledgements: Previous GPD1 courses by Elodie Cauvet, Sonia Garel, Franck Ramus, Héloïse Théro

- Major references:
  - Stiles, The fundamentals of brain development (2008)
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    - Rakic, Arellano & Breunig, Development of the primate cerebral cortex (chap. 1)
    - Kostovic & Judas, Early development of neuronal circuitry of the human prefrontal cortex (chap. 2)
  - Imbert, Traité du cerveau, chap. 2 (Mise en place du cerveau)
  - Martin, Neuroanatomy, text and atlas, 3rd edition, chap. 3 (development of the central nervous system)
  - *Science* special issue 'systems-level brain development' (november 2005, vol 310, p805)
- Other references
  - Katz & Crowley, Development of cortical circuits: lessons from ocular dominance columns (*Nat. Neurosci. Rev.* 2002 vol 3, p34)
  - Lupo, Harris & Lewis, Mechanisms of ventral patterning in the vertebrate nervous system (*Nat. Neurosci. Rev.* 2006 vol 7, p103)
  - Molyneaux et al, Neuronal subtype specification in the cerebral cortex (*Nat. Neurosci. Rev.* 2007 vol 8 p 427)
  - Blankenship & Feller, Mechanisms underlying spontaneous patterned activity in developing neural circuits (*Nat. Neurosci. Rev.* vol 11 p 18)