Genetic guidance, development and plasticity of the brain

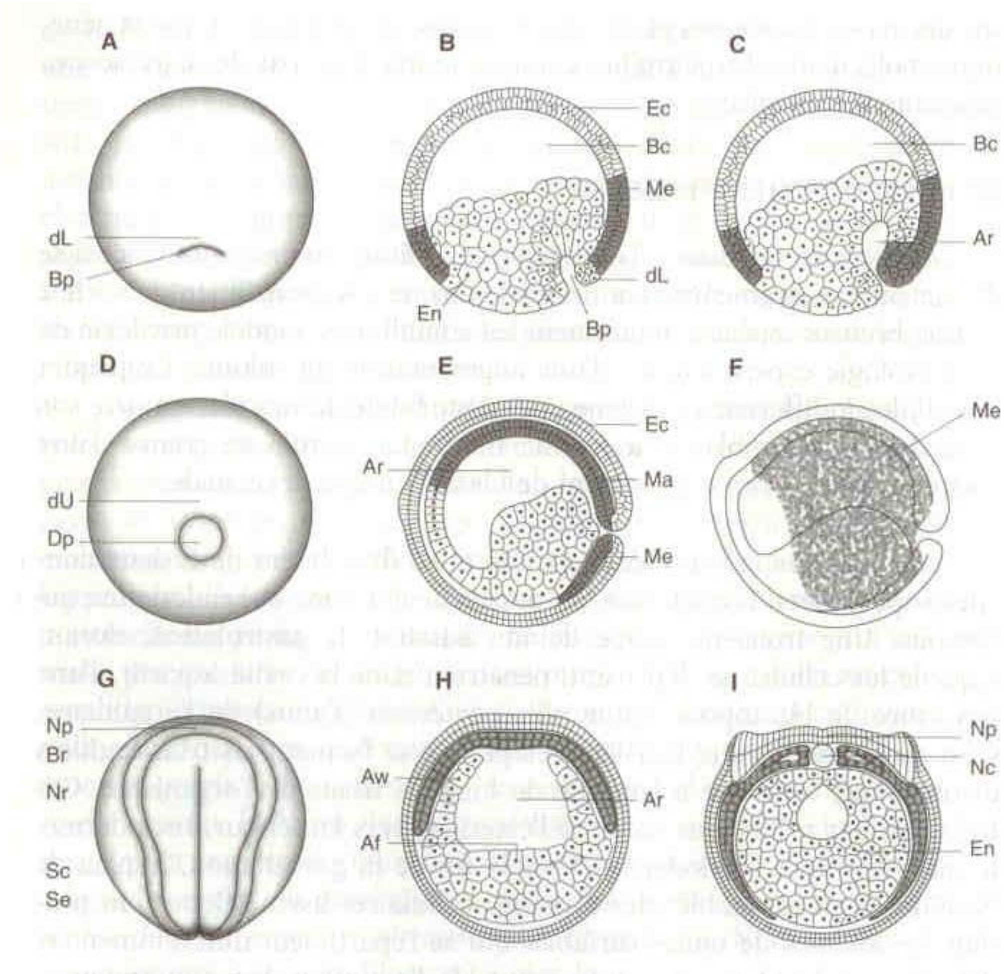
GDP1, 2012-11-26, Florent Meyniel

Morphogenesis: from a single cell to a complex brain

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

Morphogenesis: from a single cell to a complex brain

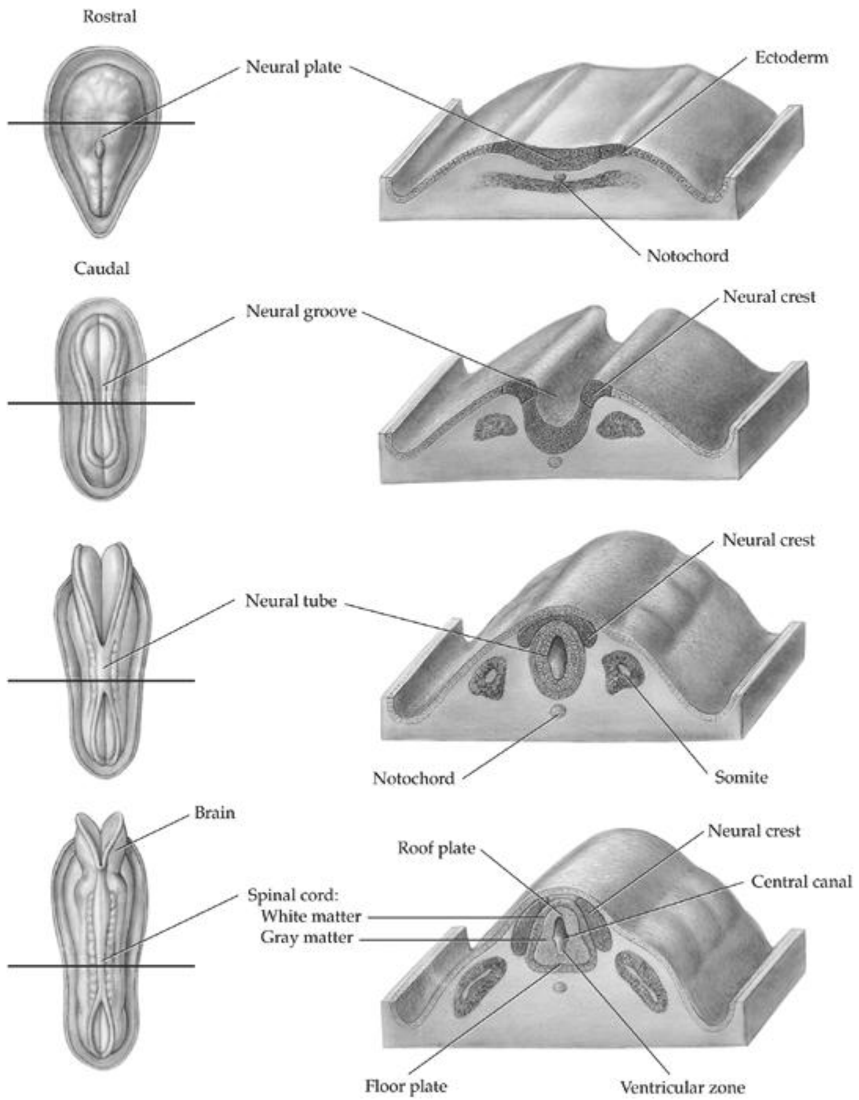
Formation of the neural tube



M. Imbert

Morphogenesis: from a single cell to a complex brain

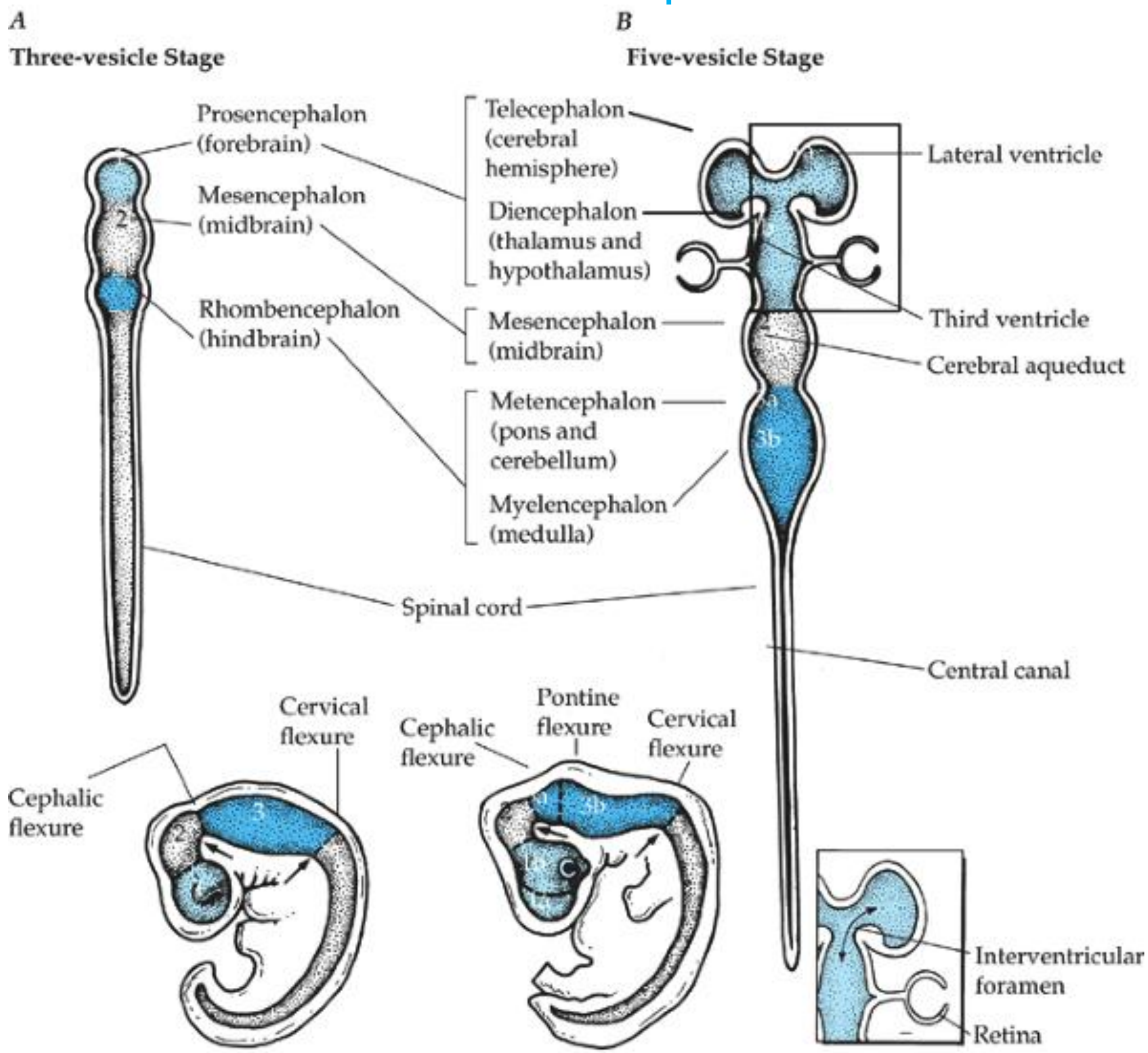
Formation of the neural tube



J.H. Martin

Morphogenesis: from a single cell to a complex brain

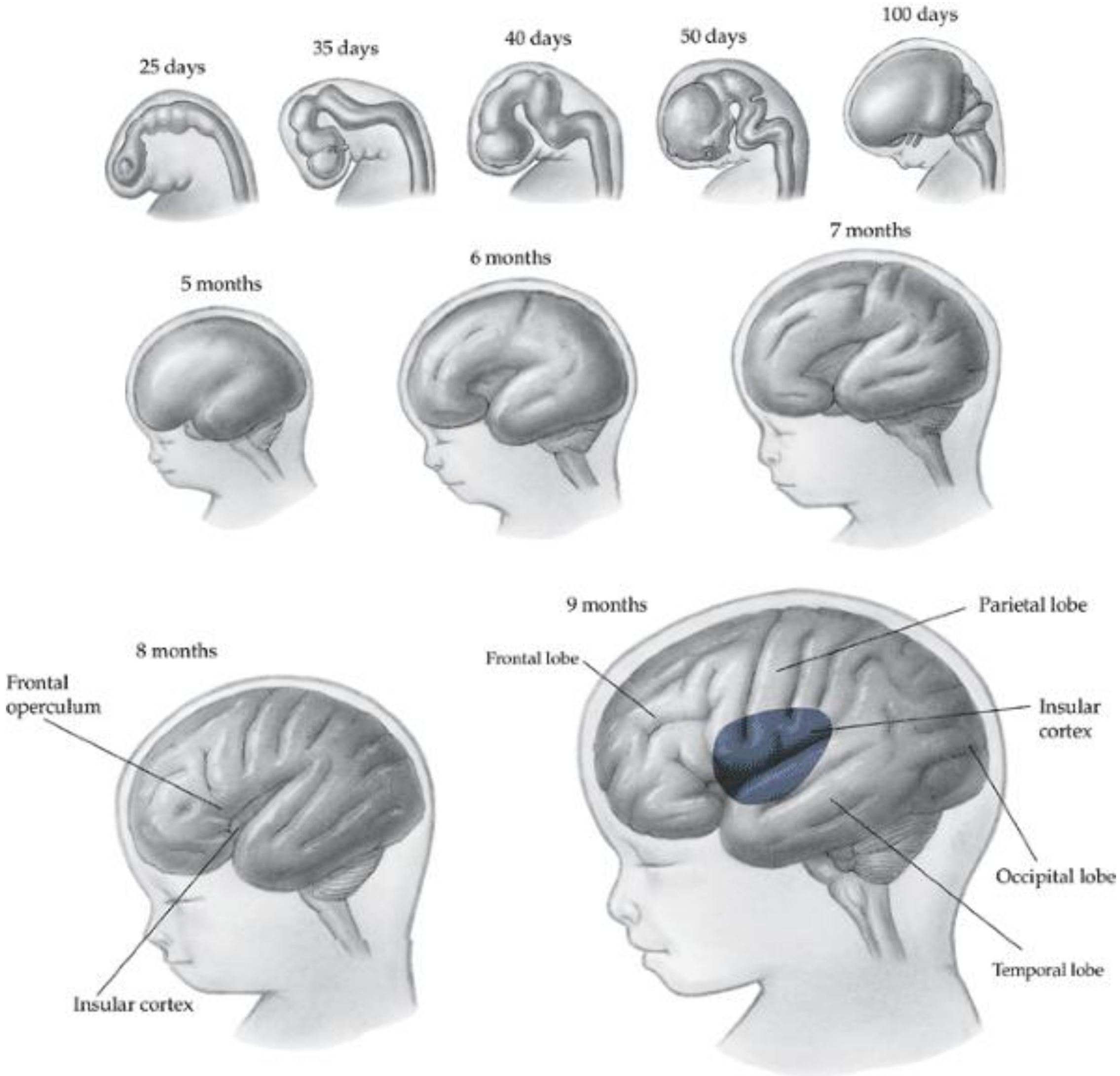
Differentiation of cephalic vesicles



J.H. Martin

Morphogenesis: from a single cell to a complex brain

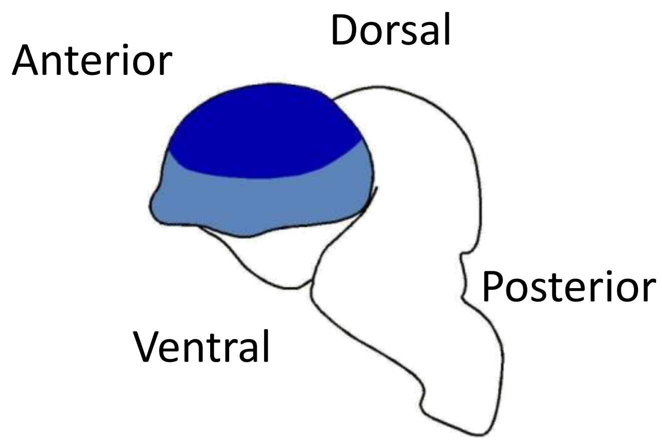
Differentiation of cephalic vesicles

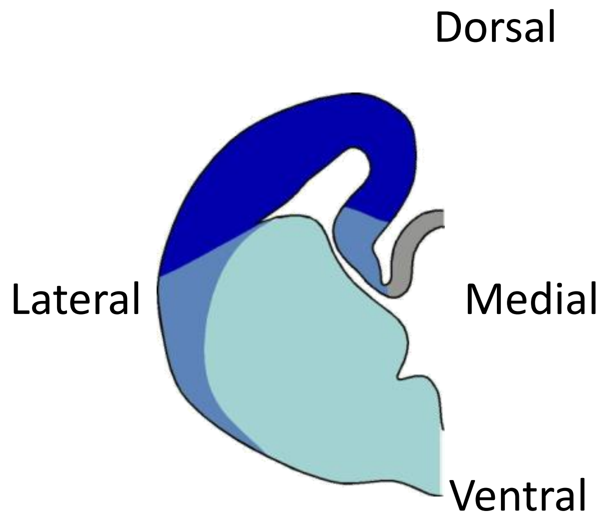


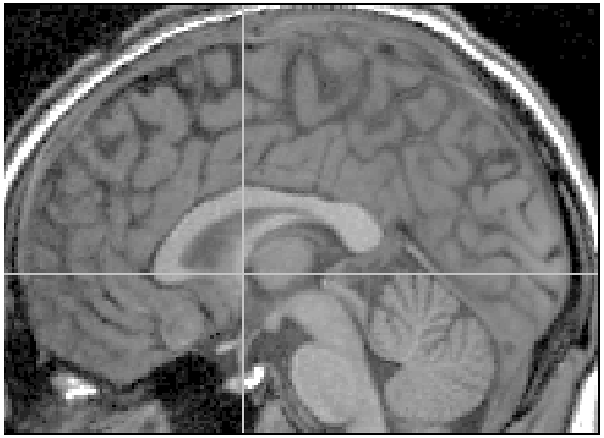
J.H. Martin

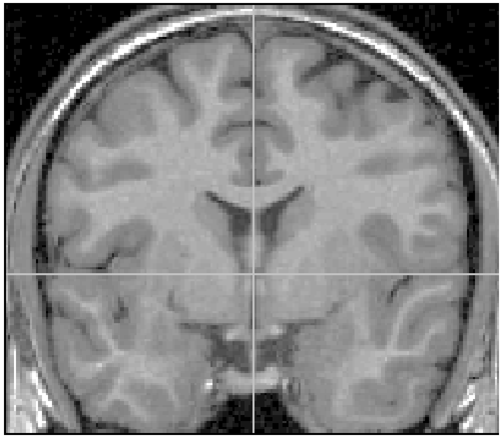
Morphogenesis: from a single cell to a complex brain

Expansion of the telencephalon / diencephalon



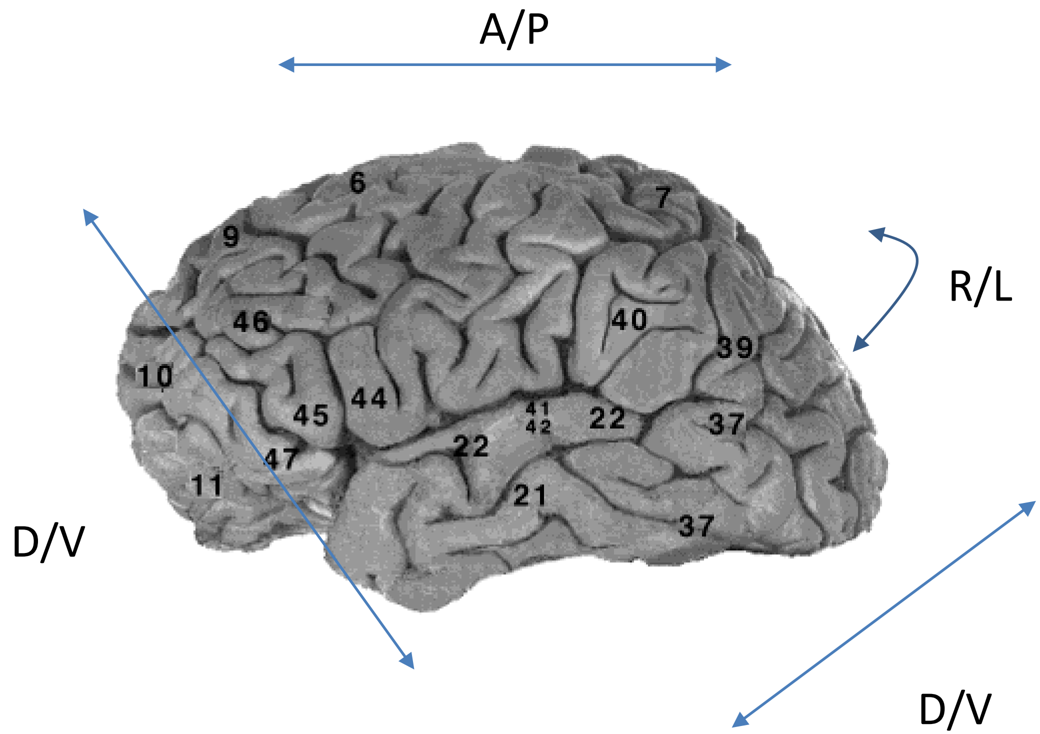






Morphogenesis: from a single cell to a complex brain
Characteristics of the adult brain

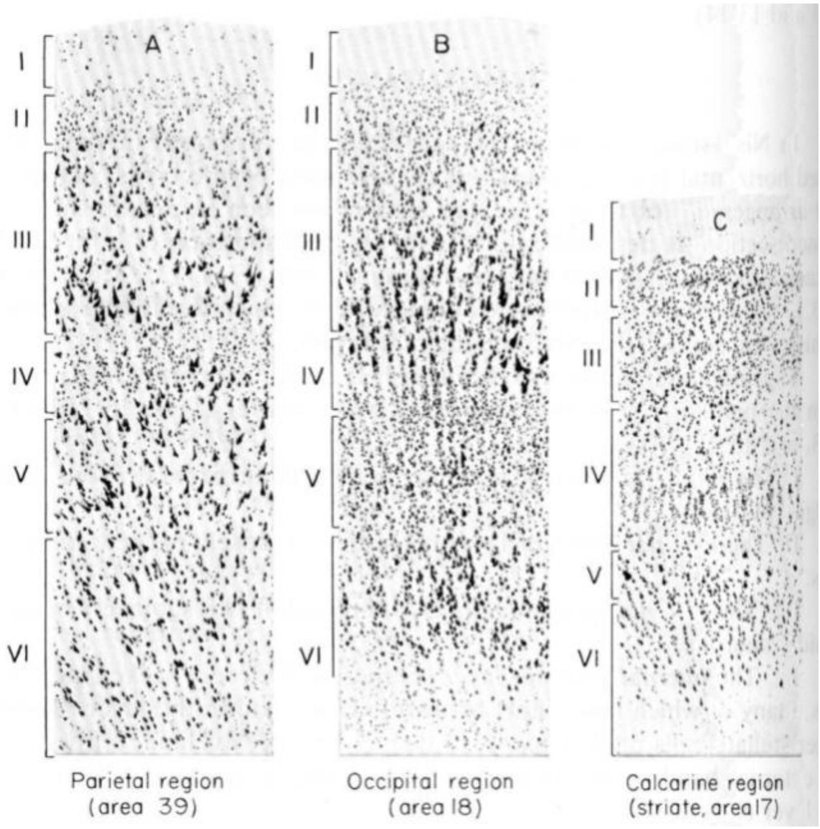
- Polarization



Morphogenesis: from a single cell to a complex brain

Characteristics of the adult brain

- Laminar organization of the cerebral cortex



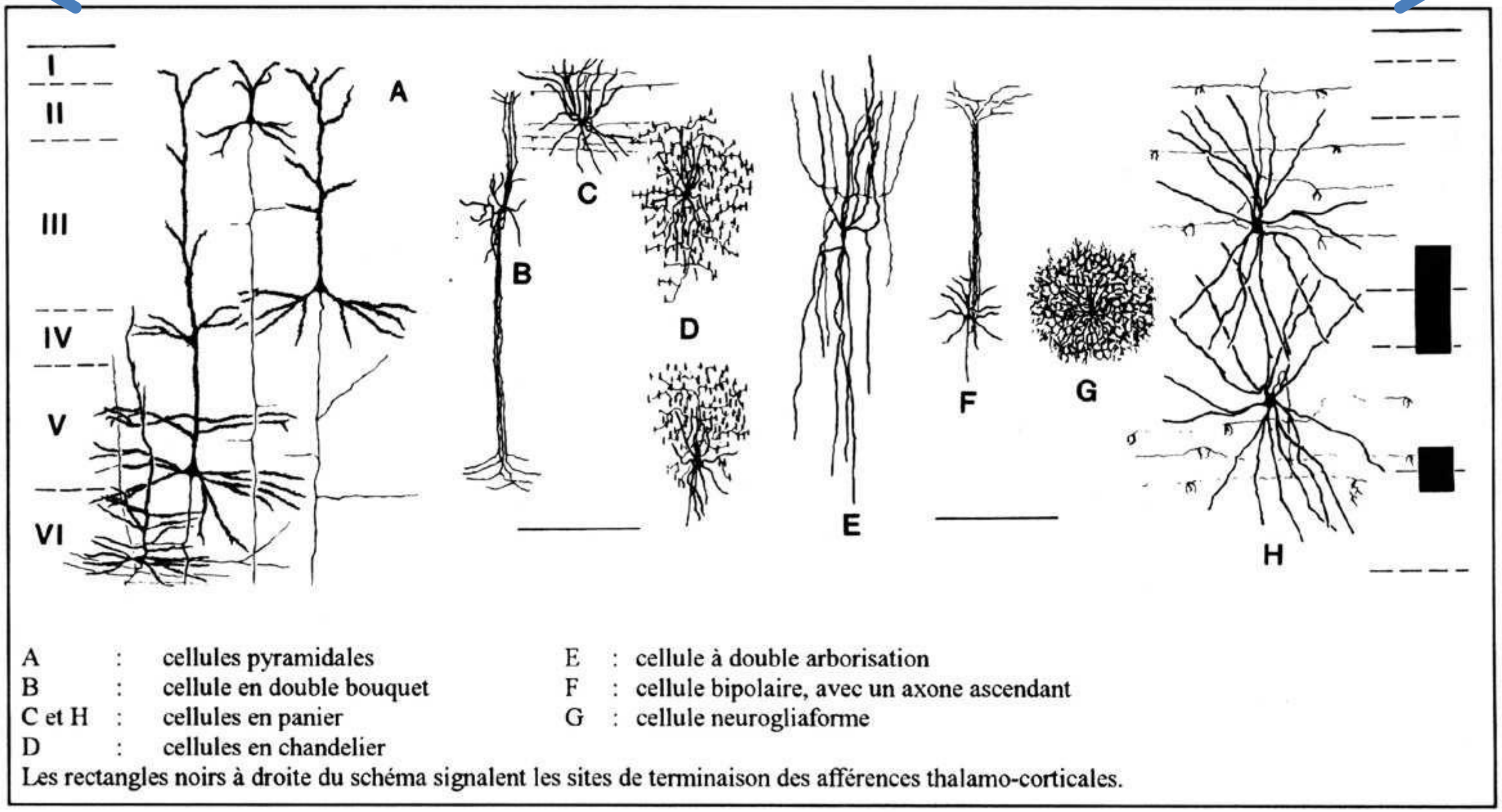
Morphogenesis: from a single cell to a complex brain

Characteristics of the adult brain

- Cell diversity

Excitatory (80% of neurons)

Inhibitory (20% of neurons)

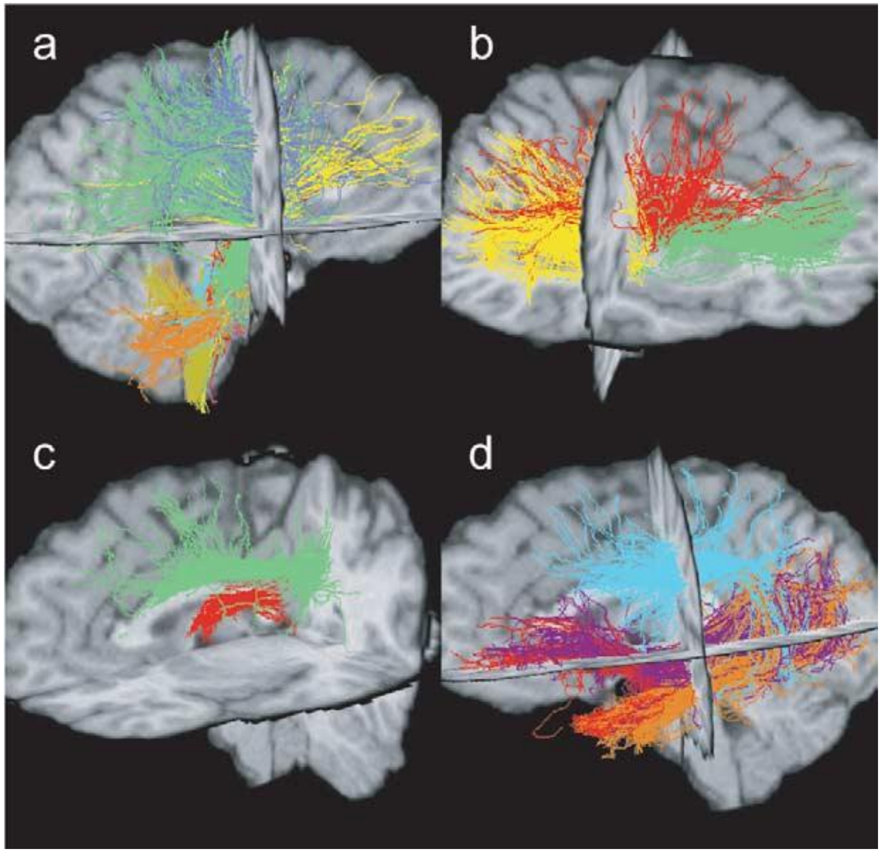


Les principaux types de neurones corticaux (d'après Hendry et Jones, 1981).

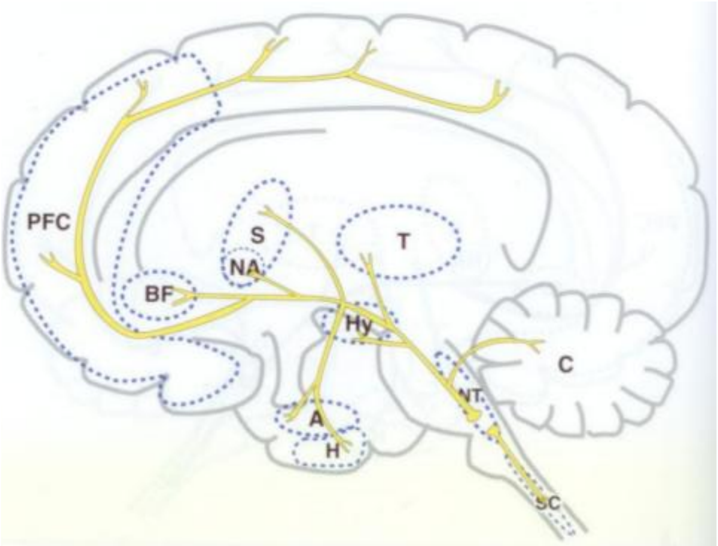
NB: more inhibitory interneurons in primates than in other animals

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

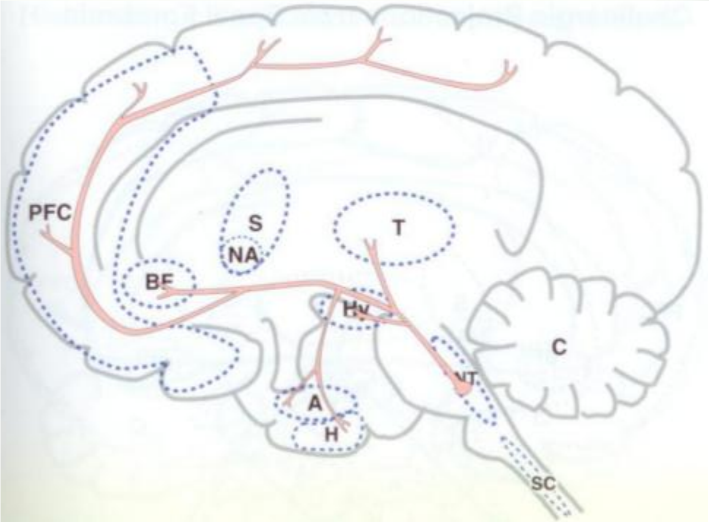
- Hodology



Hagmann, 2003, NeuroImage



Serotine projection



Acetycholine projection

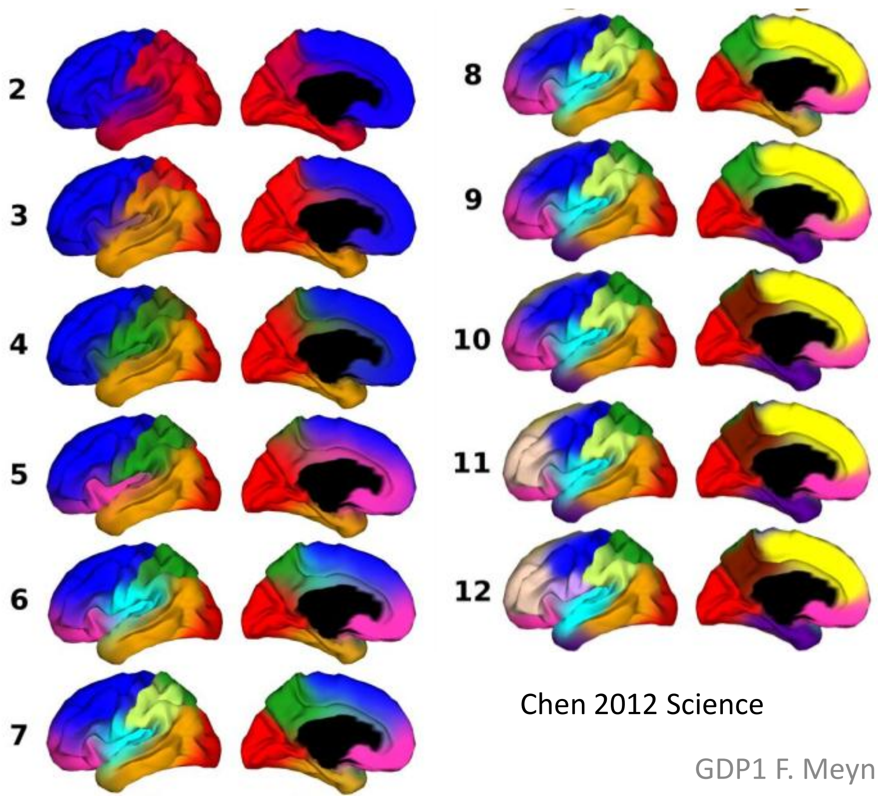
Stahl's Essential Psychopharmacology, 3rd Ed, 2008

Morphogenesis: from a single cell to a complex brain

Characteristics of the adult brain

Rivière 2002 Medical Image analysis

Surface morphology and genetic relatedness



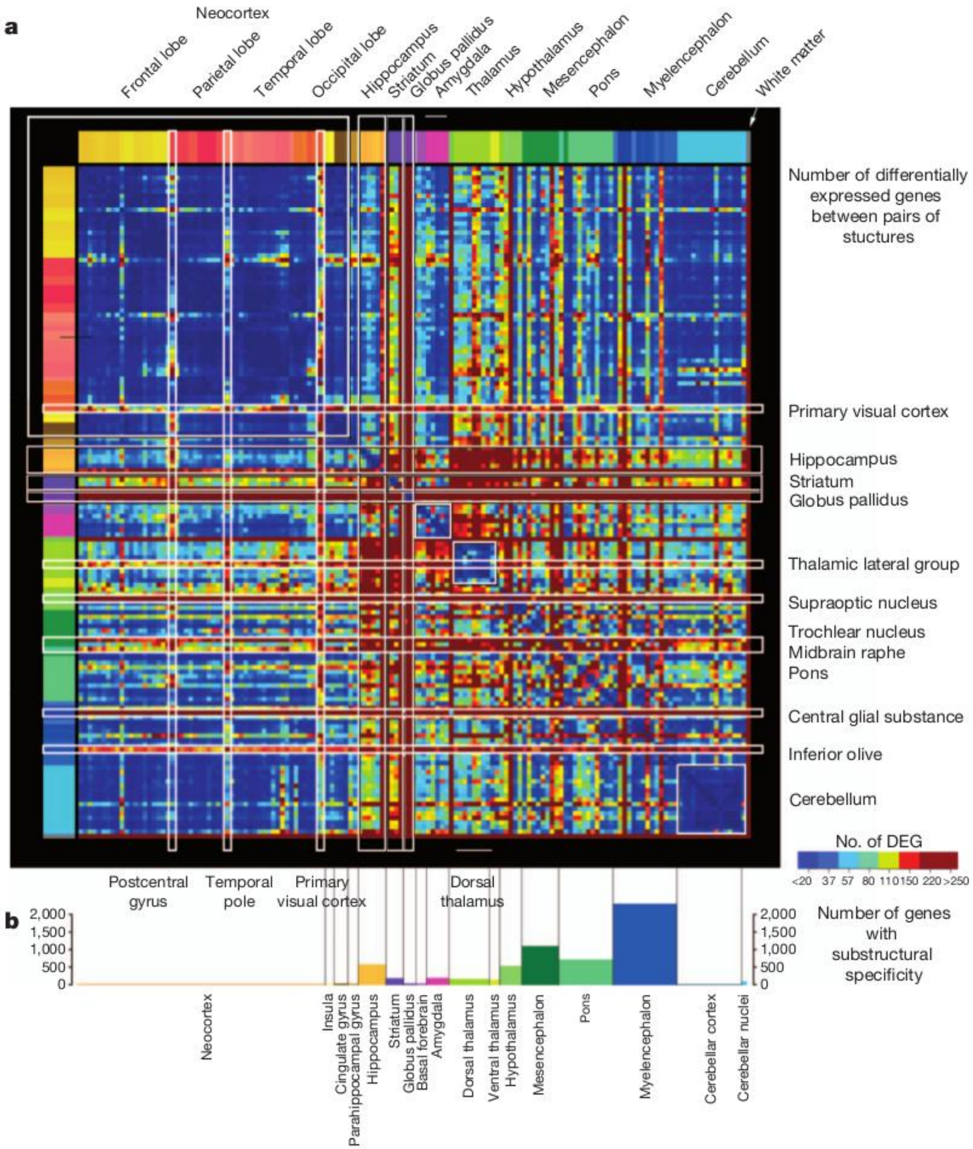
Chen 2012 Science

MZ-DZ twin design:

- The local cortical surface size is regressed onto A (additive genetic + non additive influence) and E (non-shared environmental influence (common influence assumed null).
- Correlation Ai Aj between all pair of local cortical area
- Unconstrained for space hierarchical clustering
- => hierarchical genetic organization, revealed with a functional mapping.

Morphogenesis: from a single cell to a complex brain

Characteristics of the adult brain



The human brain transcriptmone: the Allen Brain Atlas (www.brain-map.org) Hawrylycz et al Nature 2012 (2 'and a half' male brain)

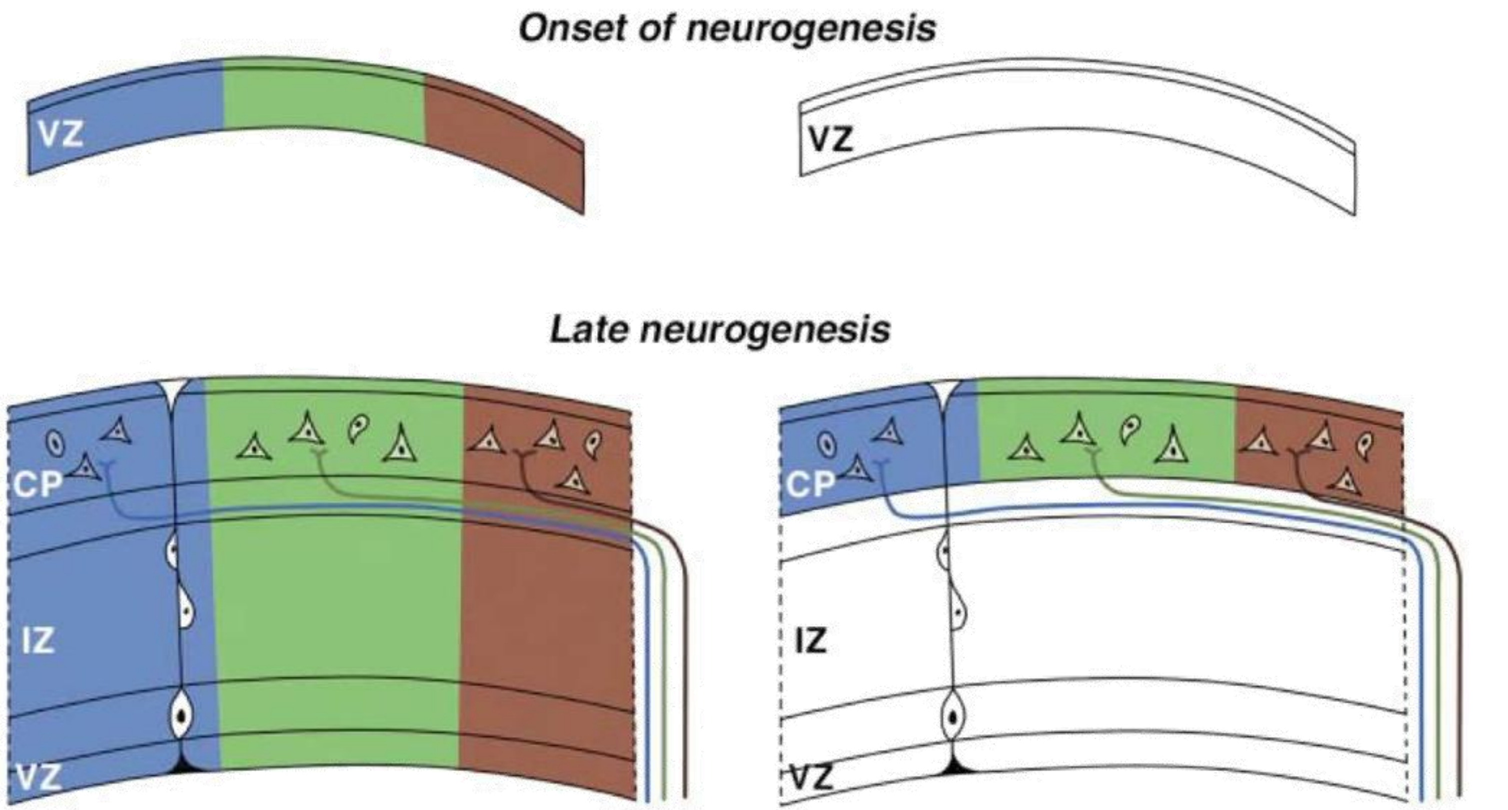
Low internal variation in gene expression in the neocortex
=> Something else than gene involved?

The developmental processes

- Introduction
- Setting components: The radial unit hypothesis
- Genetic patterning
- Activity dependent patterning

The developmental processes
Introduction

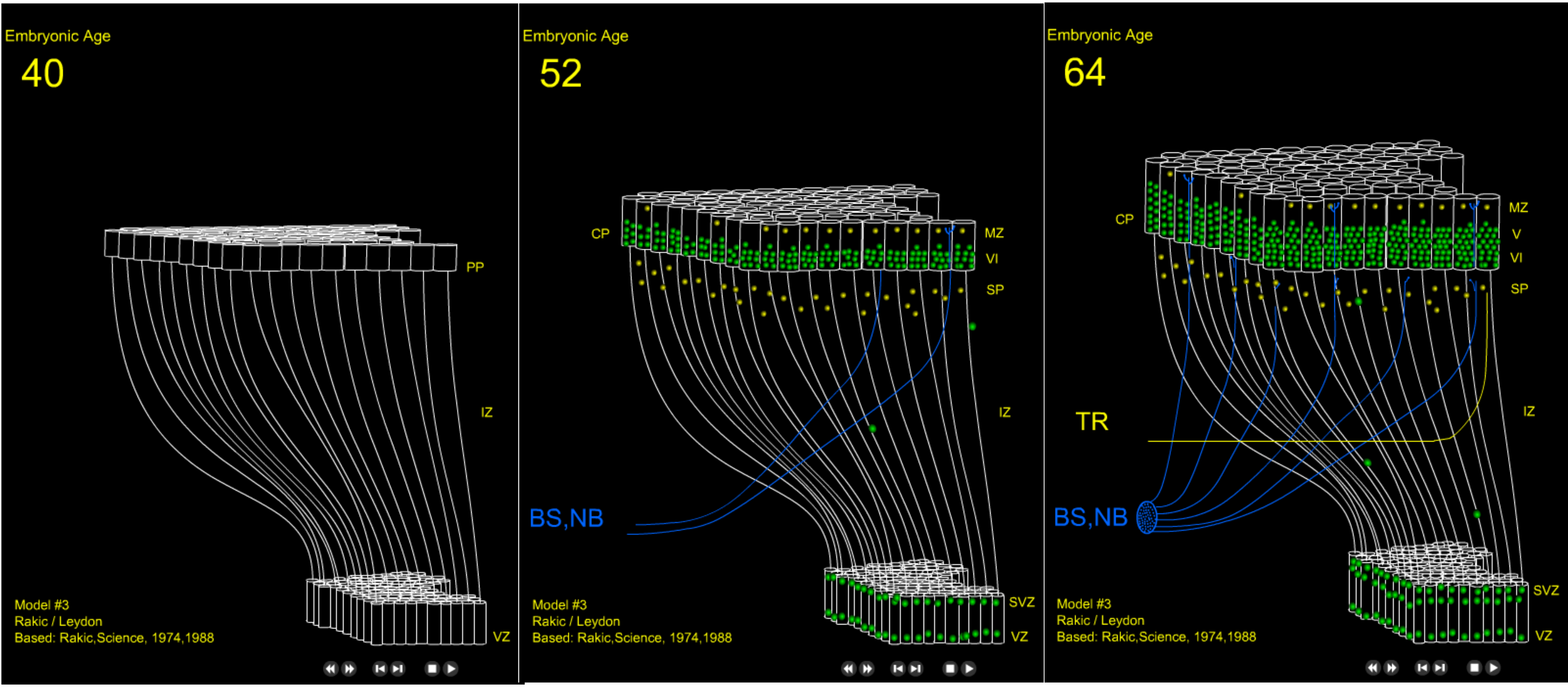
- Intrinsic vs. extrinsic determinants: Protomap vs. protocortex



Grove & Fukuchi-Shimogori 2003 Annu. Rev. Neurosci

The developmental processes
Setting components: the radial unit hypothesis

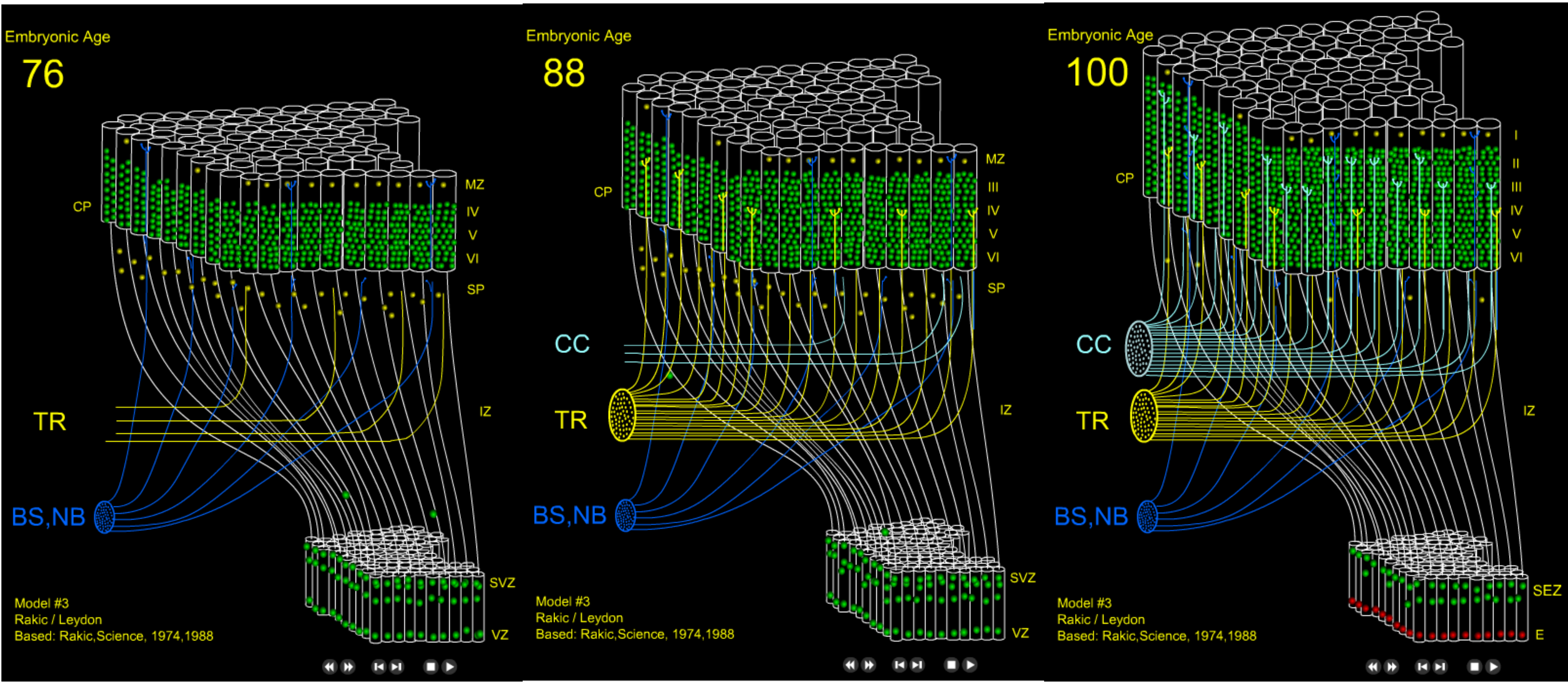
Mechanism and storytelling



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

The developmental processes

Setting components: the radial unit hypothesis



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

The developmental processes

Setting components: the radial unit hypothesis

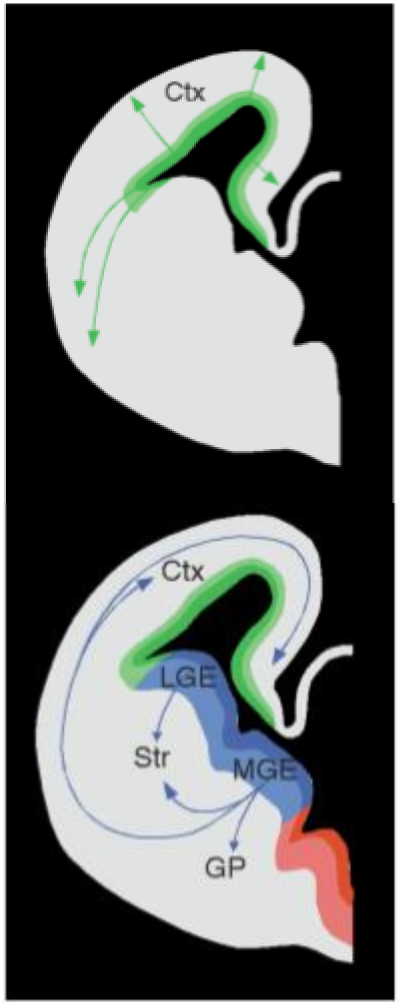
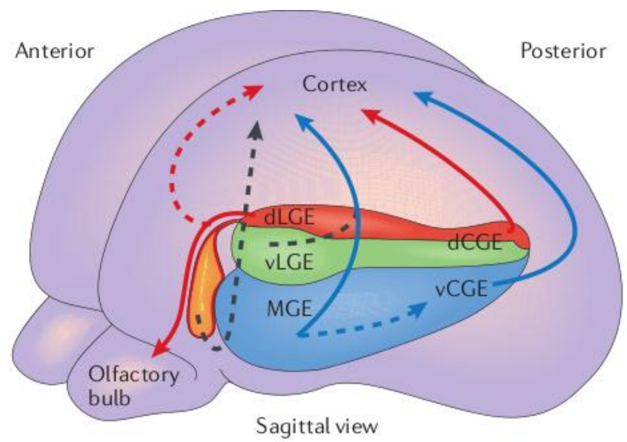


Table 1 | **Summary of interneuron neurochemical subgroup characteristics in mice**

Neurochemical marker	Relative % of GABA+ cells	Characteristic morphology	Axonal targeting on projection neurons*	Intrinsic physiology‡
Somatostatin	~30%	Small basket	Proximal dendrites/soma	RSNP
		Martinotti	Distal dendrites	BSNP
Parvalbumin	~50%	Large basket	Proximal dendrites/soma	FS
		Nest basket	Soma	FS/RSNP
		Chandelier	Axon initial segment	FS
Calretinin	~15%	Small bipolar	Proximal dendrites; also, other GABA+ cells	RSNP/BSNP

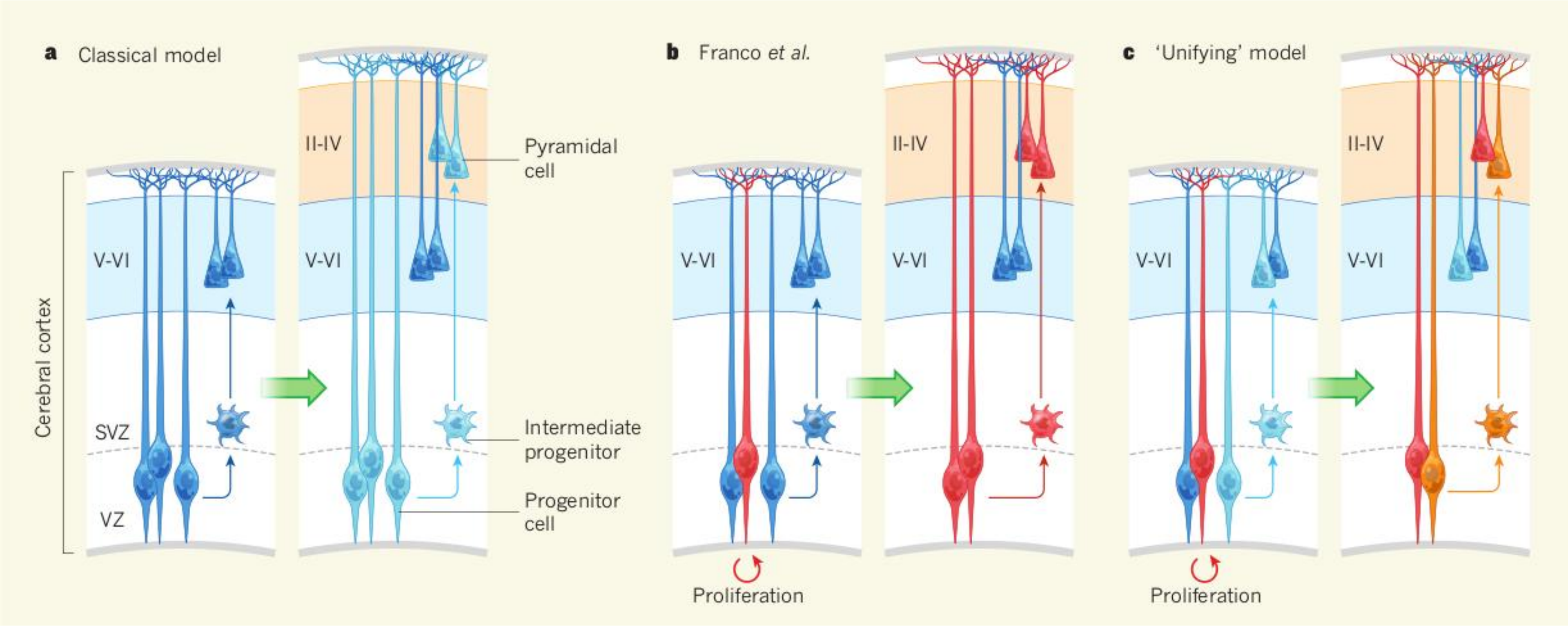


Wonders NNR 2006

- MGE (medial ganglionic eminence) -> somatostatin & parvalumin interneurons (Nkx2.1)
- dLGE (dorso-lateral GE) -> calretinin (ER81)
- vLGE (ventral) -> undetermined subgroup

The developmental processes
Setting components: the radial unit hypothesis

Breaking news! Model still debated…

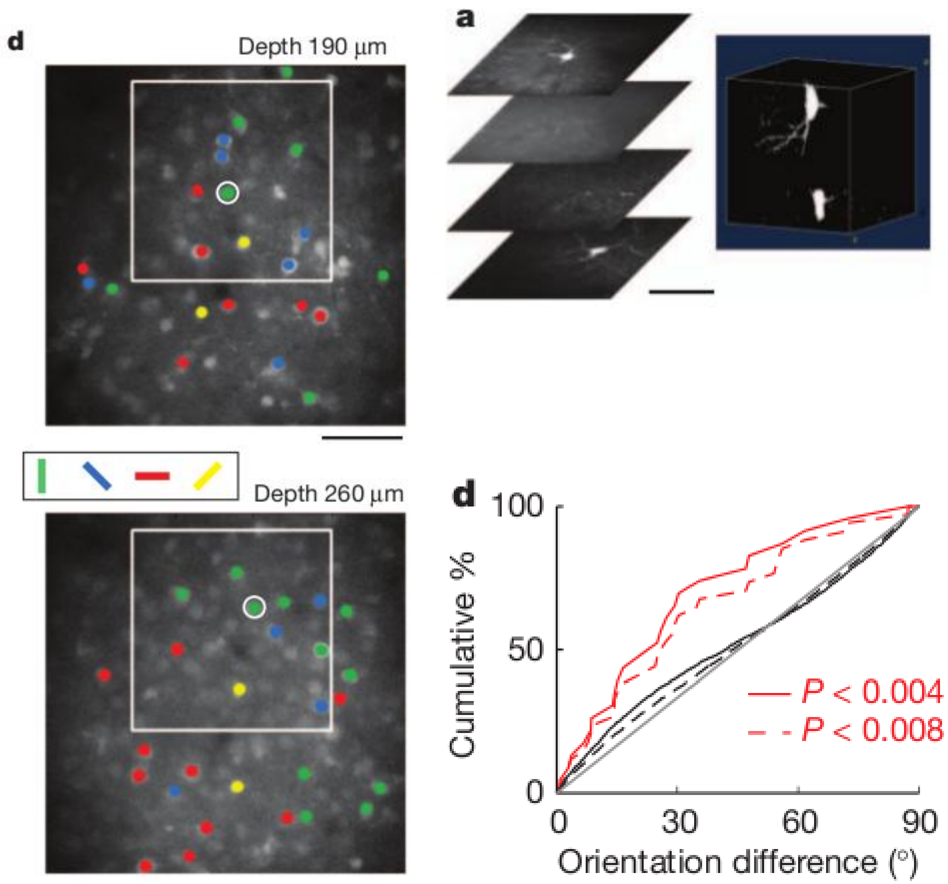


Study by Franco Science 2012, reported by Marin Nature 2012

The developmental processes

Setting components: the radial unit hypothesis

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

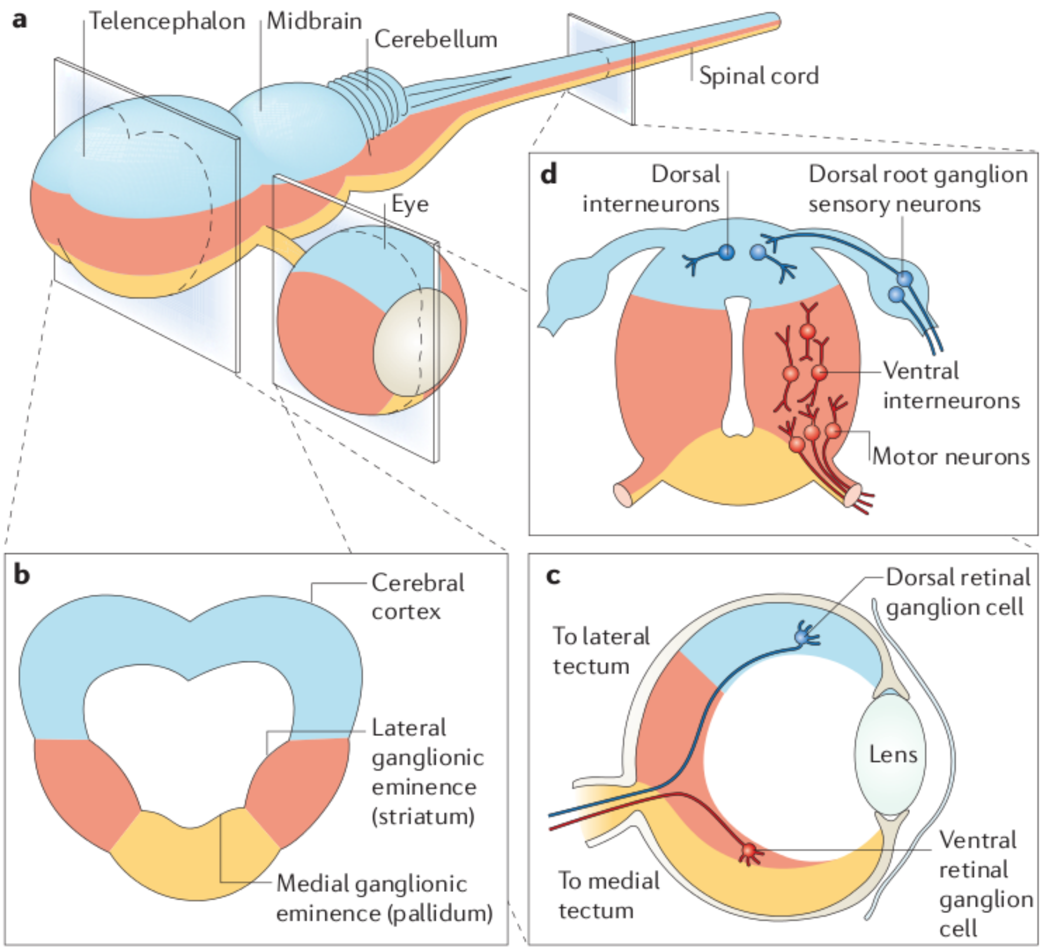
The developmental processes

Genetic patterning

- Constraints on genetic expression to determine the cellular fate:
  - Transcription factors
  - RNA splicing
  - Post-transcriptional gene silencing
  - … see introduction to genetics
- Result: differentiation of cells (corollary of specification) restricts progressively the range of fates.

The developmental processes
Genetic patterning

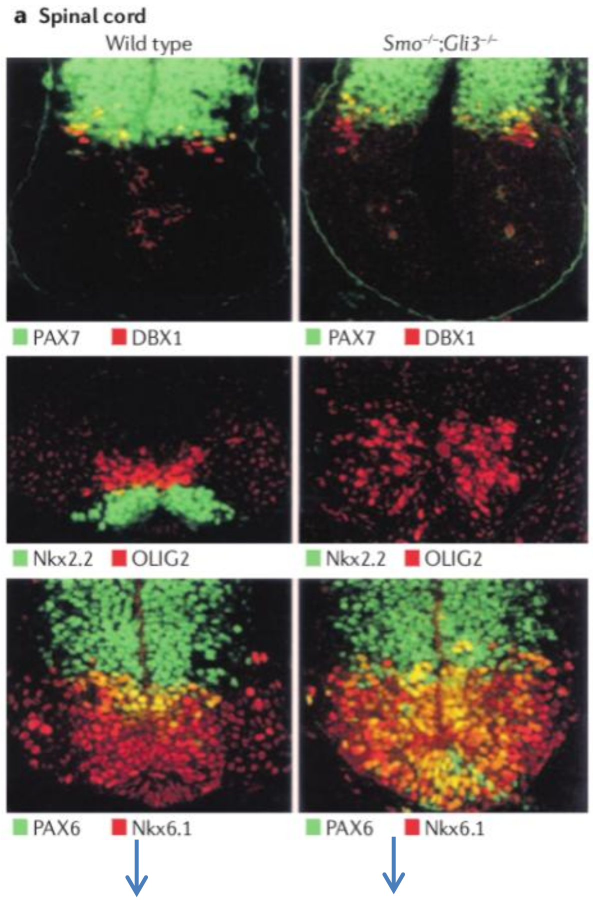
- The example of dorso-ventral regionalization

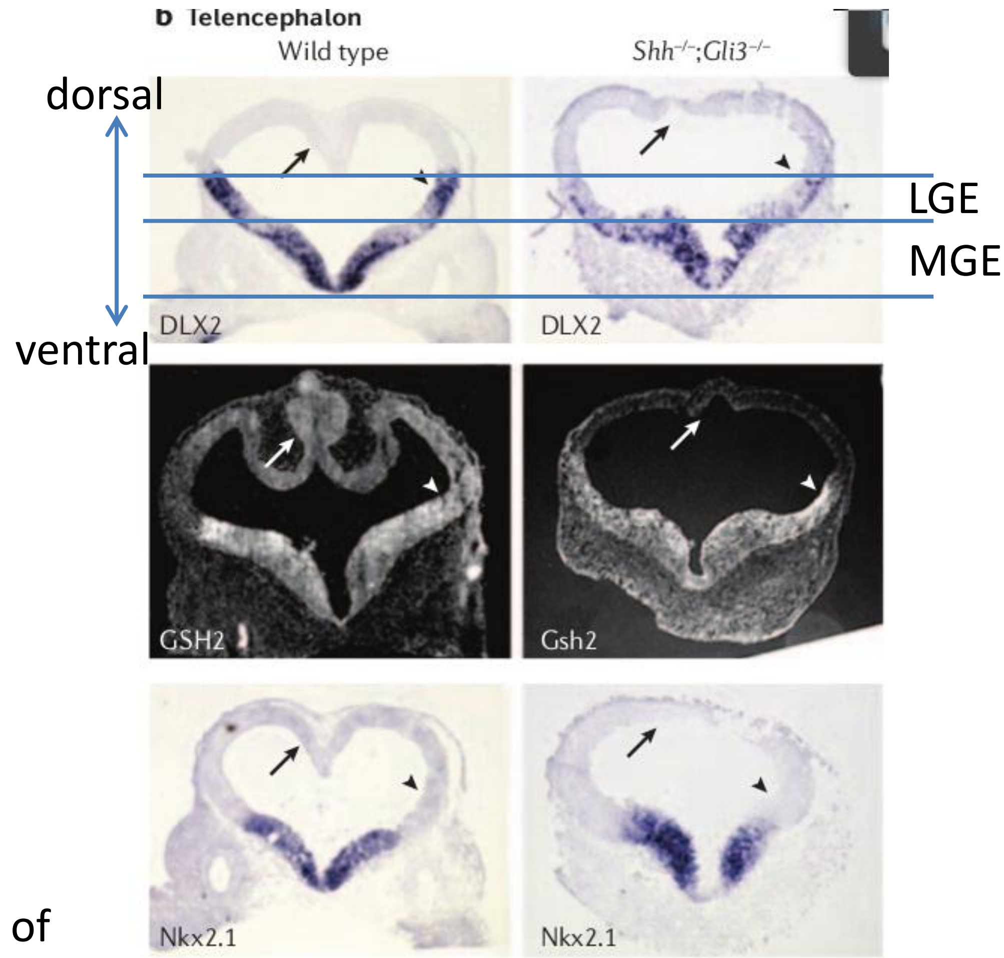


Lupo 2006 NNR

The developmental processes
Genetic patterning

- Regionalization & function of morphogens





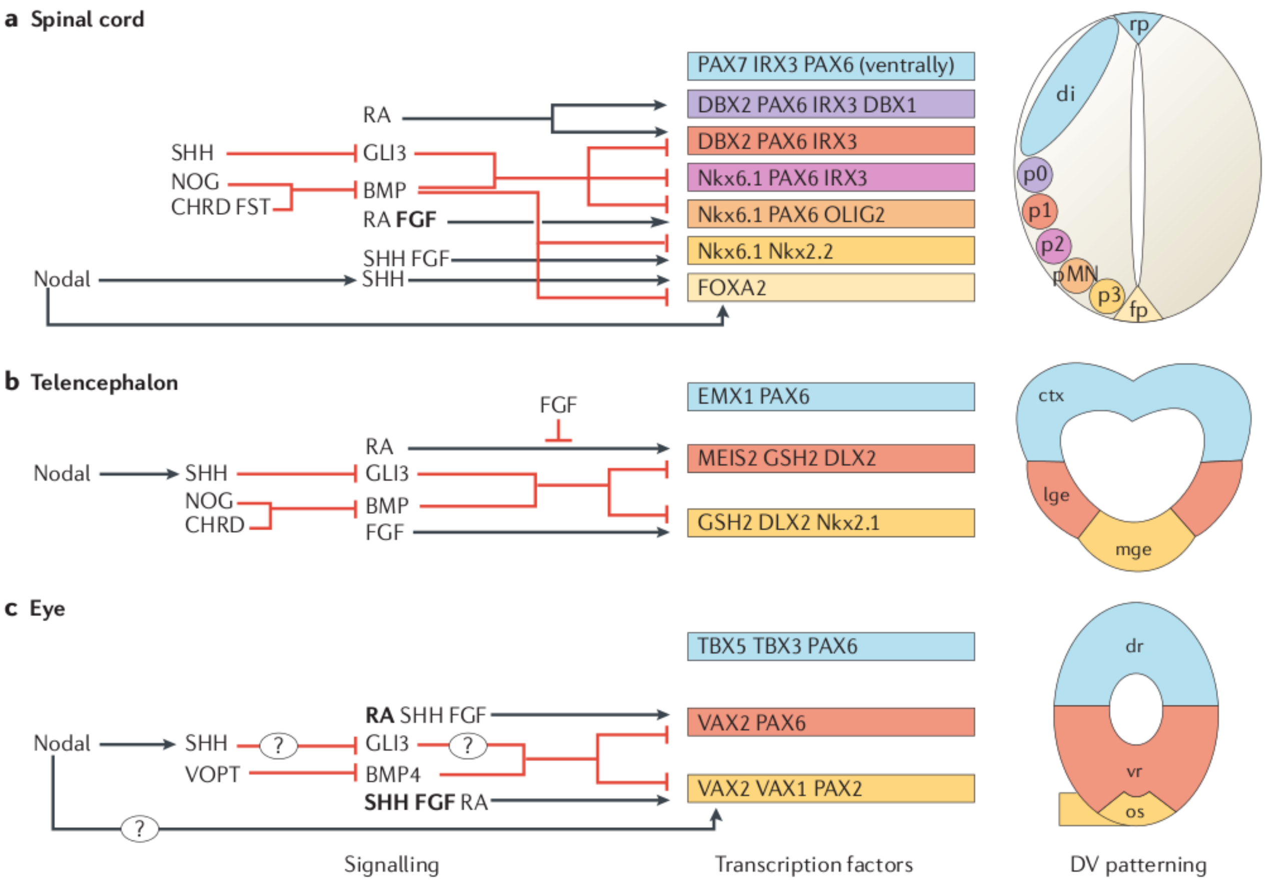
Regionalization of morphogens

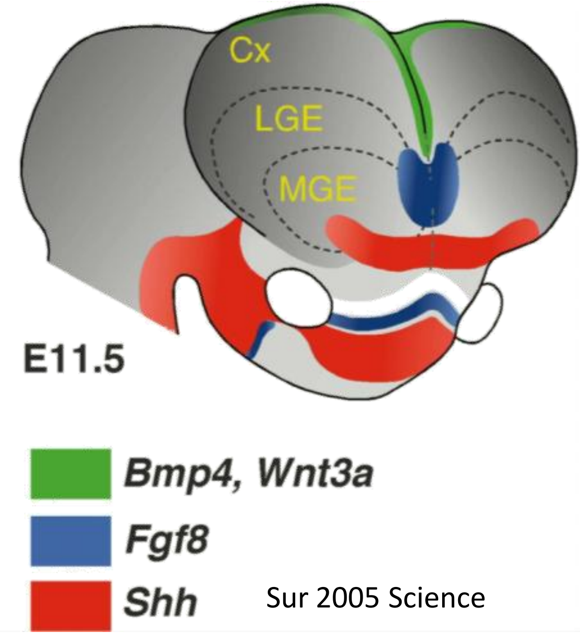
Under the control of other (upstream) morphogens

The developmental processes

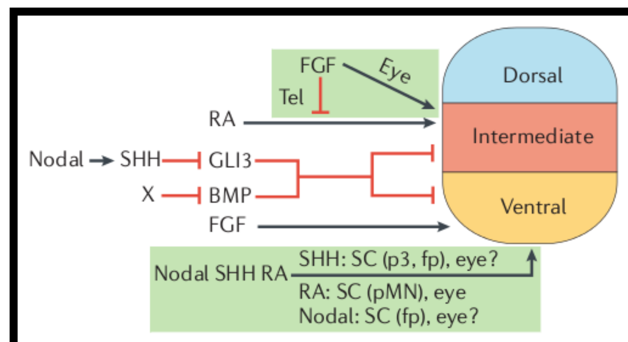
Genetic patterning

- Common regulation of dorso-ventral regionalization





Sur 2005 Science



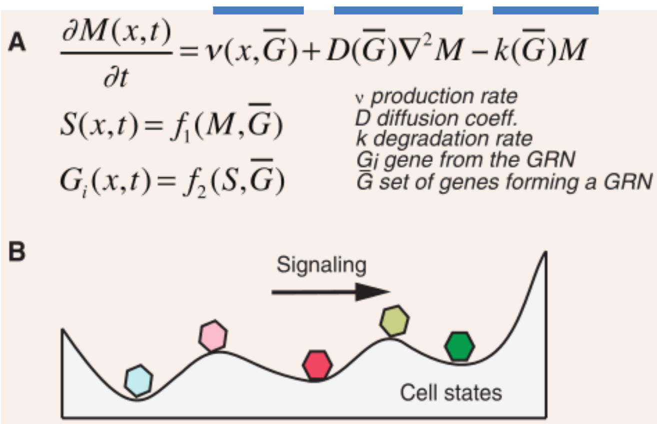
Lupo 2006 NNR

The developmental processes

Genetic patterning

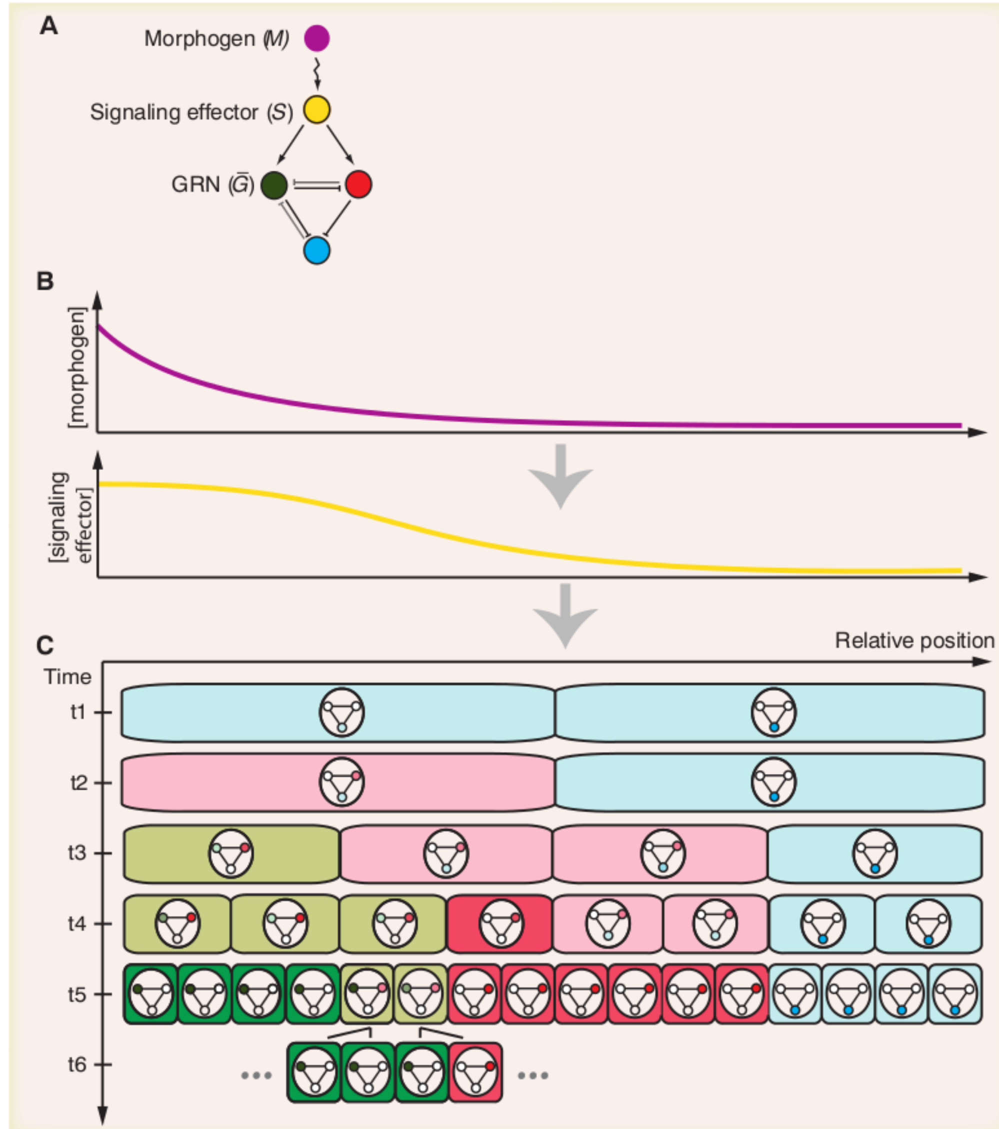
- Morphogen: mechanism

Production diffusion clearance



Kicheva Nature Rev 2012

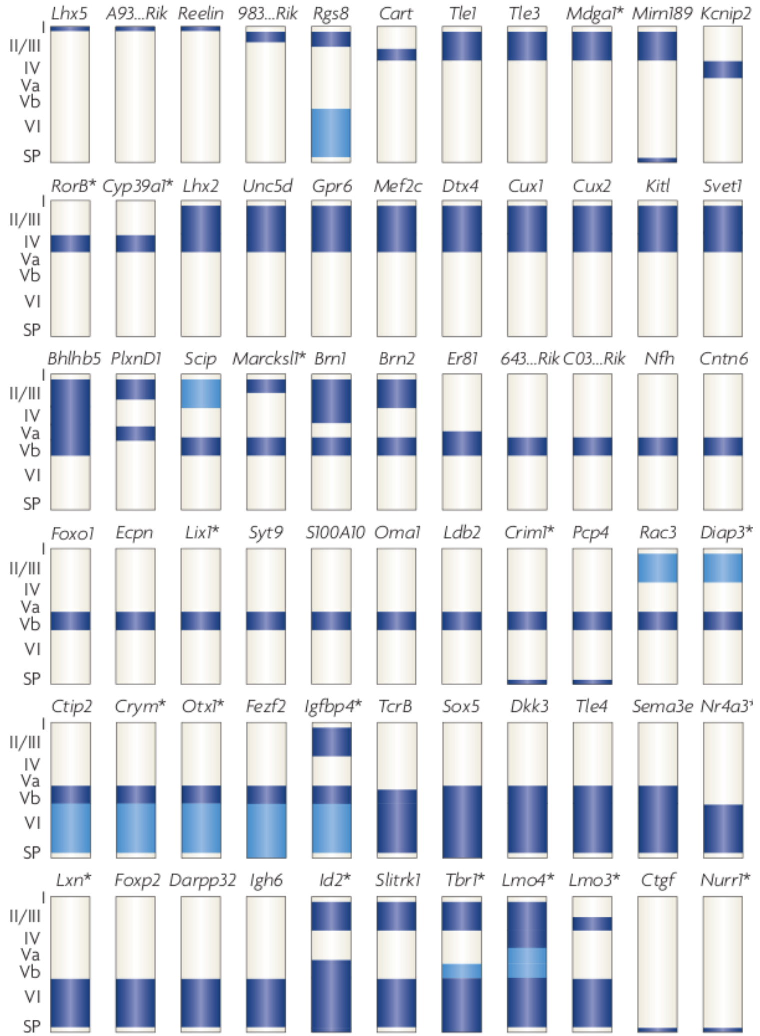
Genetic patterning: an emergent behavior of coordinated event at the molecular, cellular & tissue-level scales.



The developmental processes

Genetic patterning

- Neuronal subtype specification in the cerebral cortex

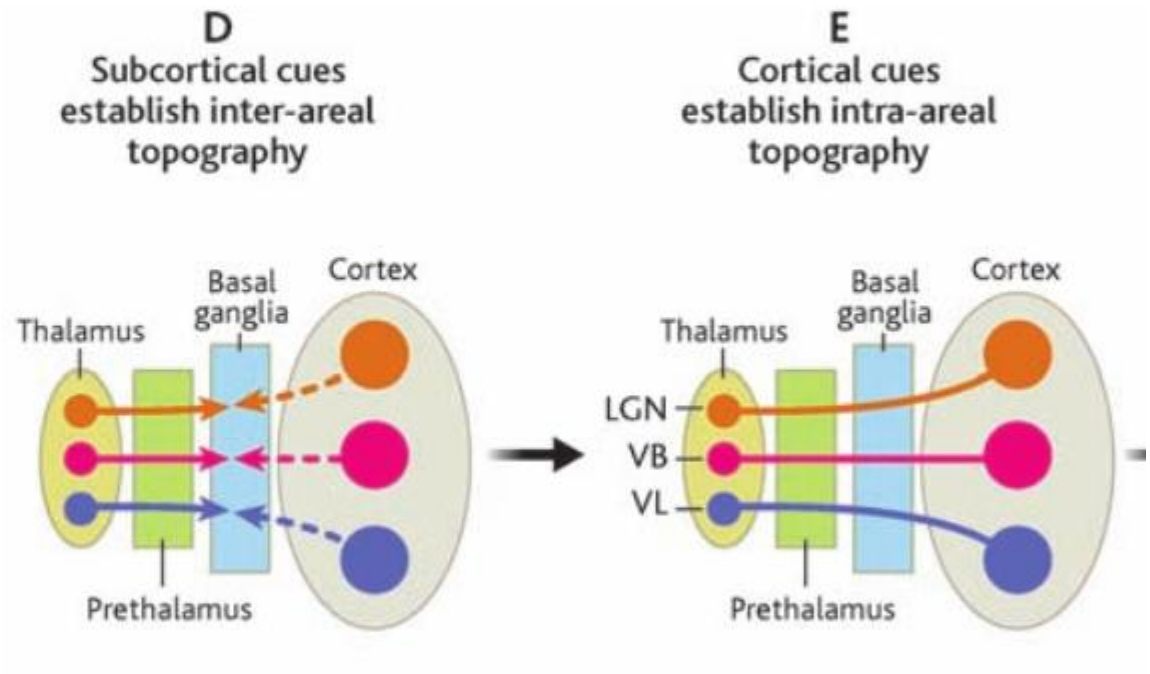


Molyneaux NNR 2007

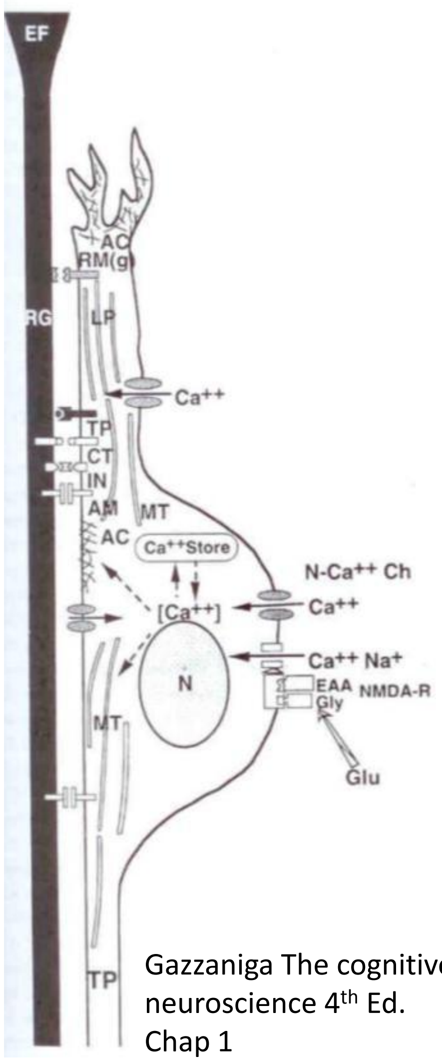
The developmental processes

Genetic patterning

Projection patterns & axon guidance



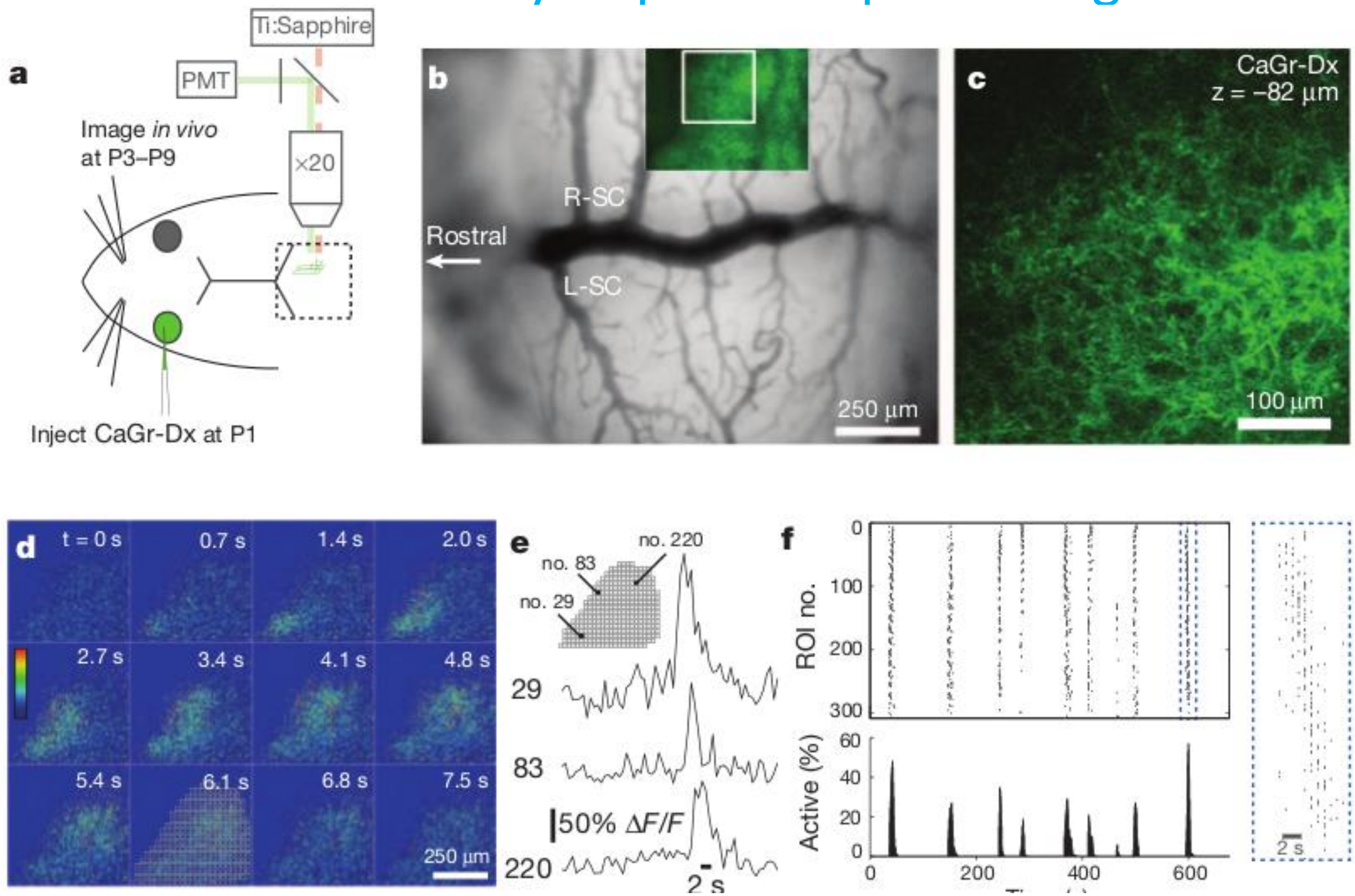
Sur 2005 Science



Gazzaniga The cognitive neuroscience 4th Ed. Chap 1

The developmental process

Activity-dependent patterning



Ackman 2012 Nature

Retinal waves propagate to colliculi (and V1, not shown) in P5 mouse (eye openning > P10).
Pharmacological blocking of waves => impaired visual maps.

The developmental processes

Activity-dependent patterning

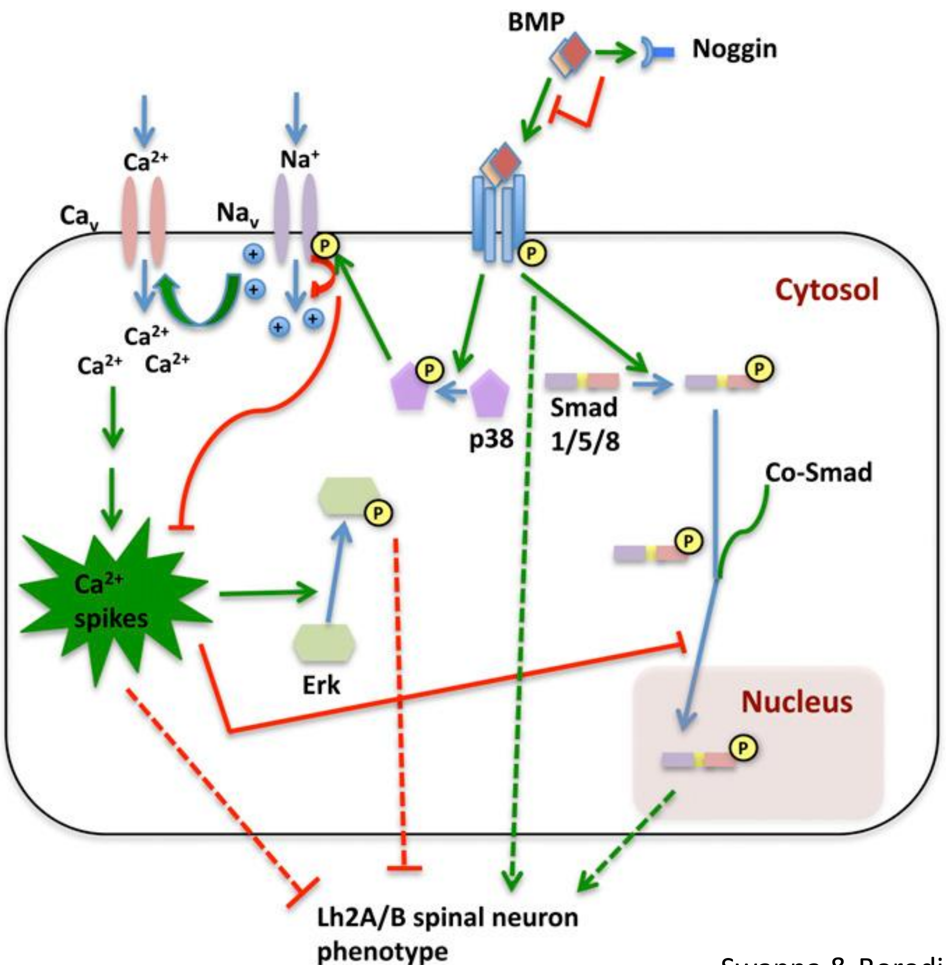
Table 1 | **Summary of important features of spontaneous network activity recorded in rodents**

	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
Activity-dependent patterning

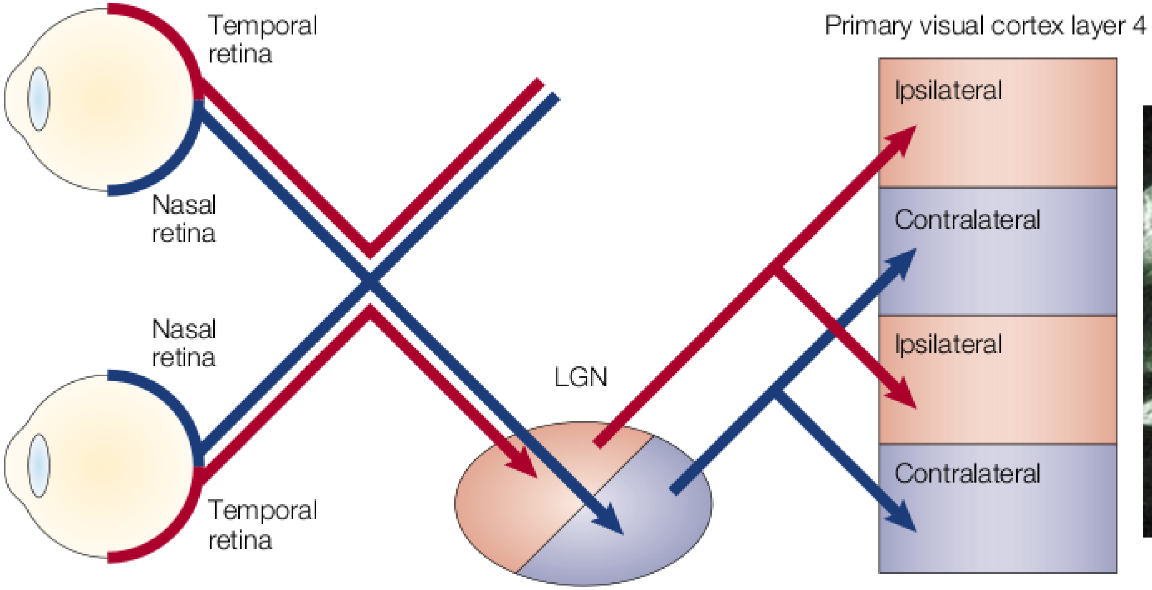
Activity-dependent patterning Genetic patterning

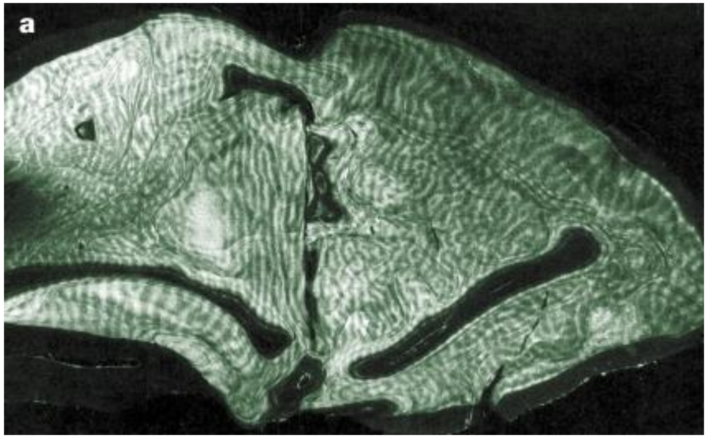


Swapna & Borodinsky PNAS 2012

The developmental process
Activity-dependent patterning

The canonical example of ocular dominance columns

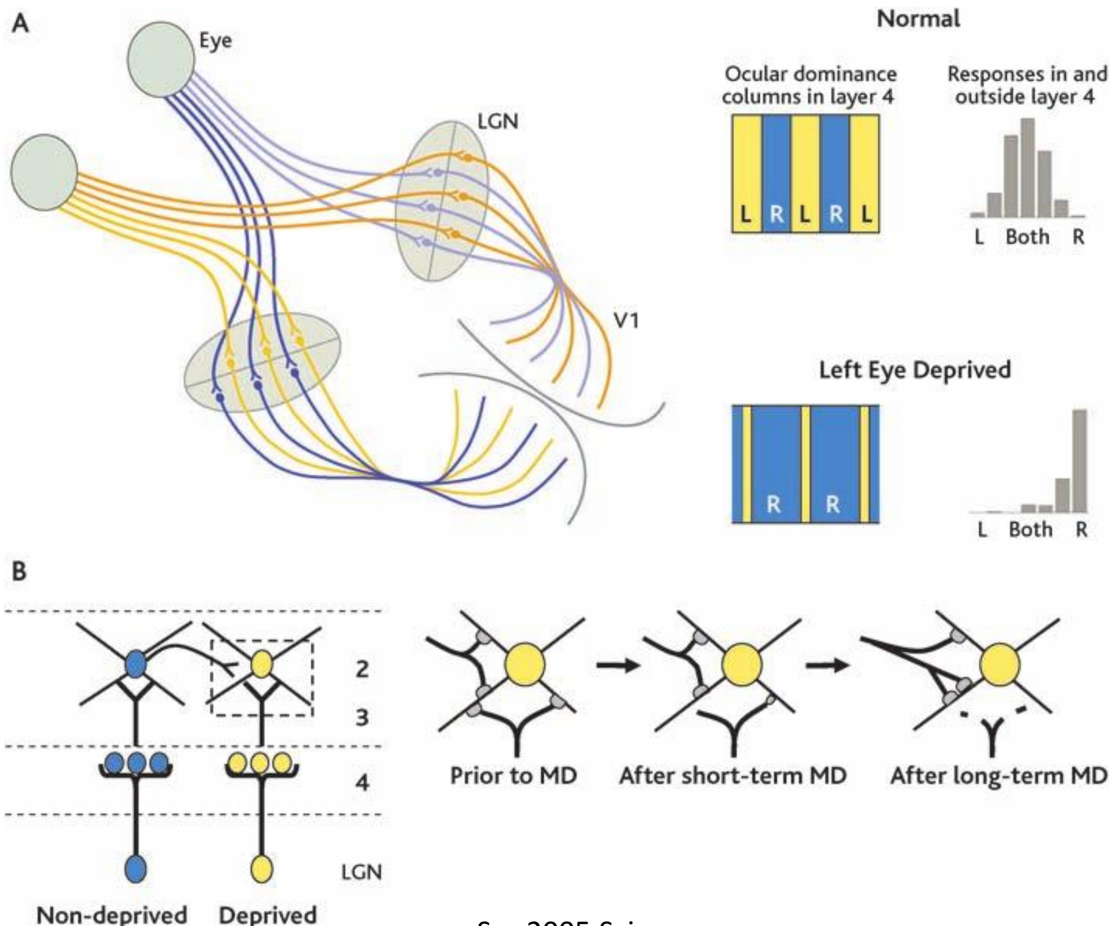




Katz 2002 NNR

The developmental processes
Activity-dependent patterning

The canonical example of ocular dominance columns



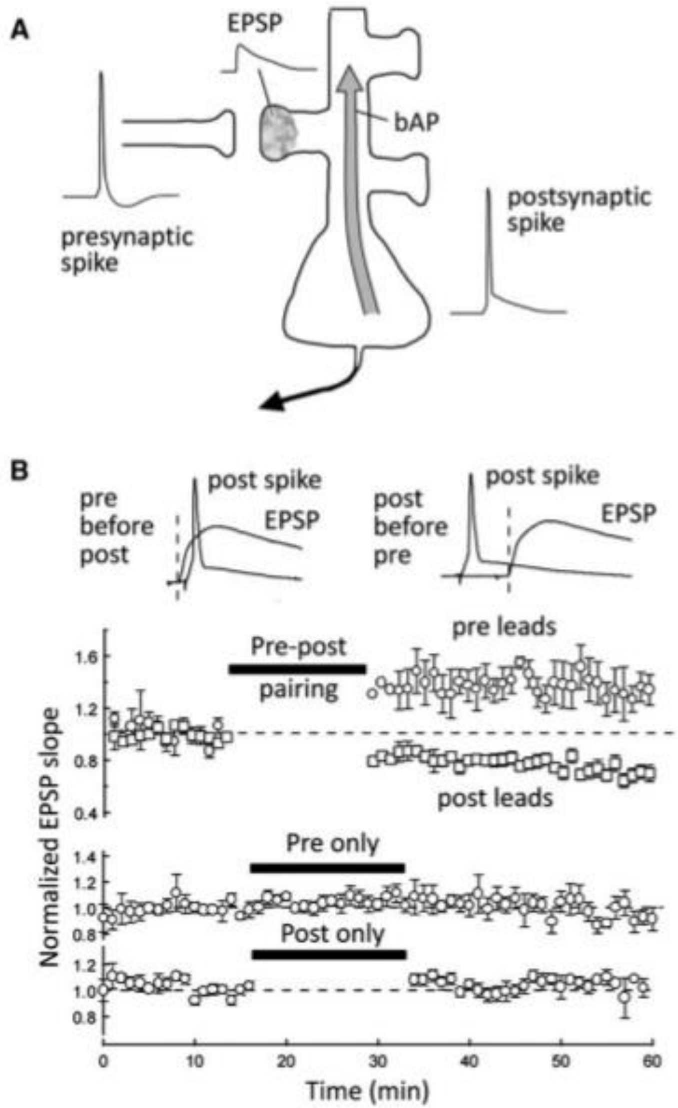
Sur 2005 Science

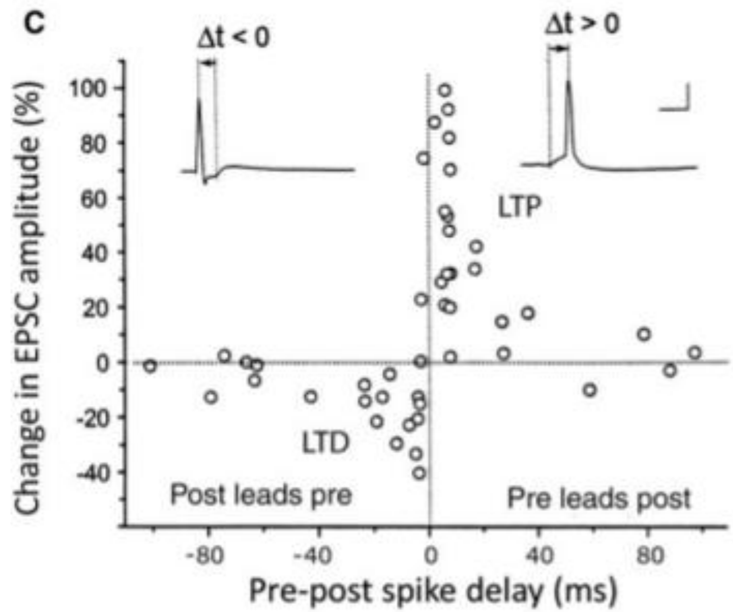
Plasticity of the brain

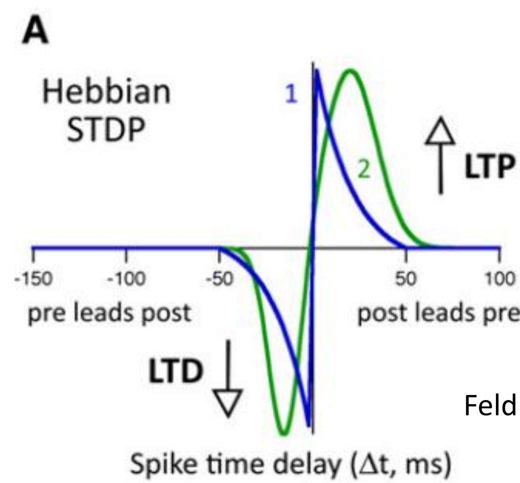
- Plasticity is crucial for shaping the brain
- Critical period and interactions with the environment: the case of the prefrontal cortex
- Plasticity in the adult brain
- Adult neo-neurogenesis?

Plasticity of the brain

Plasticity is crucial for shaping the brain



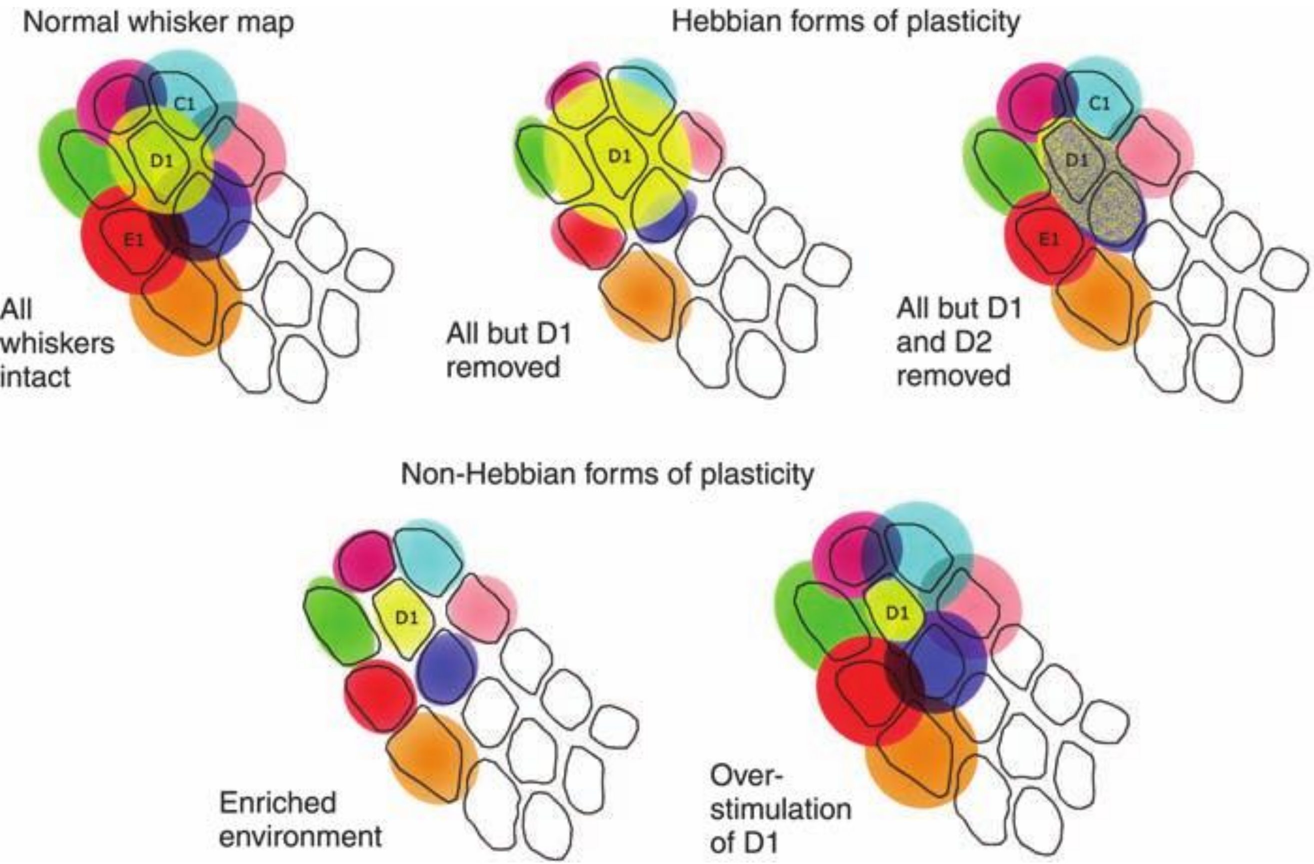




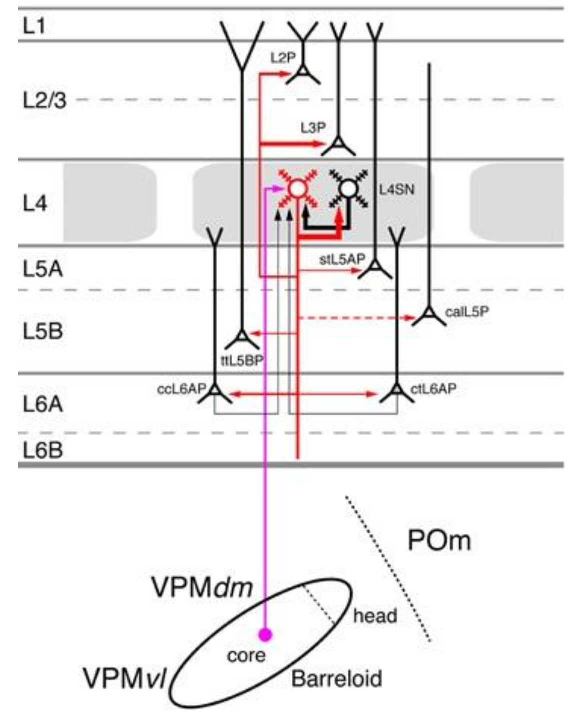
Feldman Neuron 2012

Plasticity of the brain

Plasticity is crucial for shaping the brain



Feldman 2005 Science

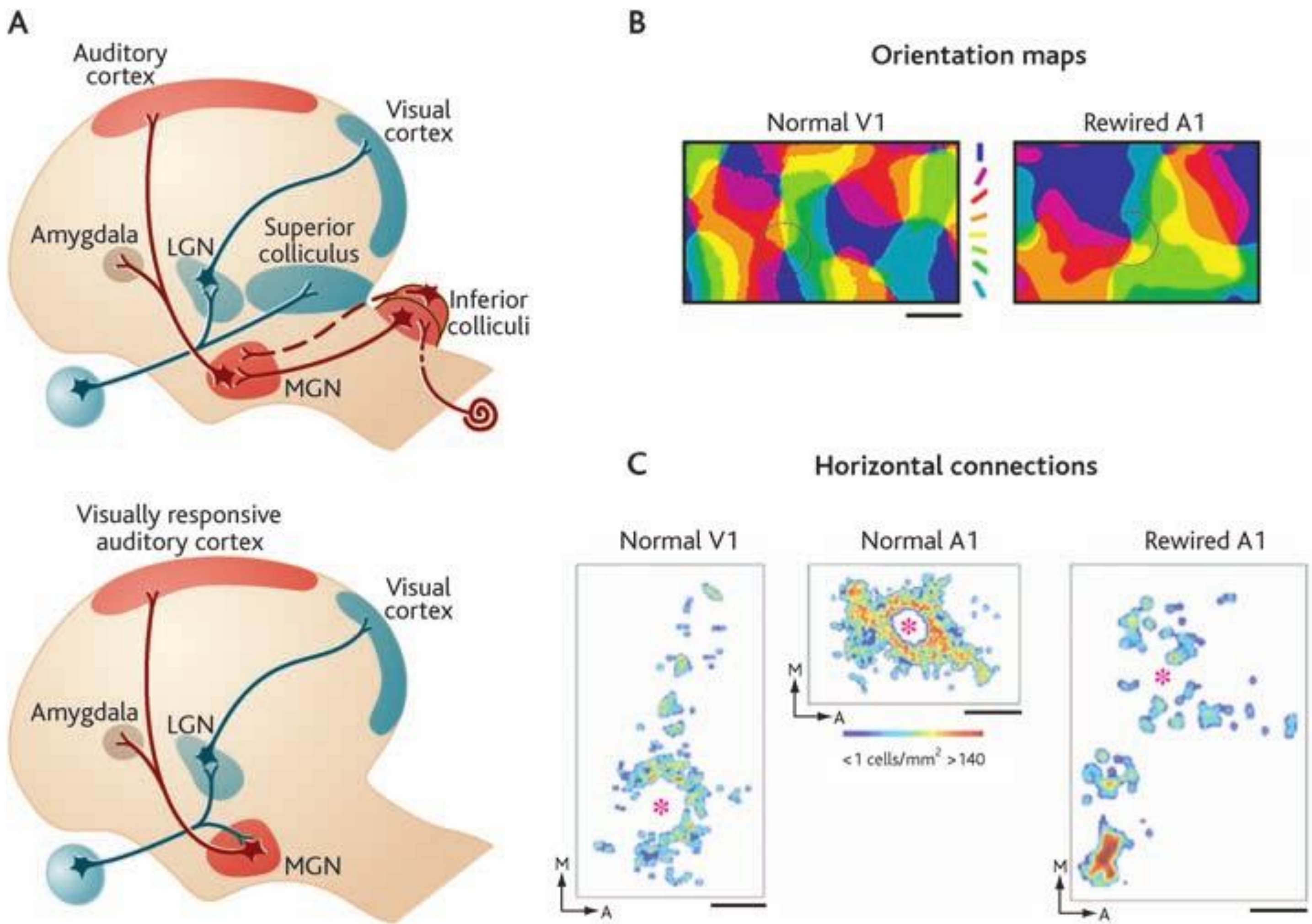


Feldmeyer 2012 Front in Neuroanat

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

Plasticity of the brain

Plasticity is crucial for shaping the brain

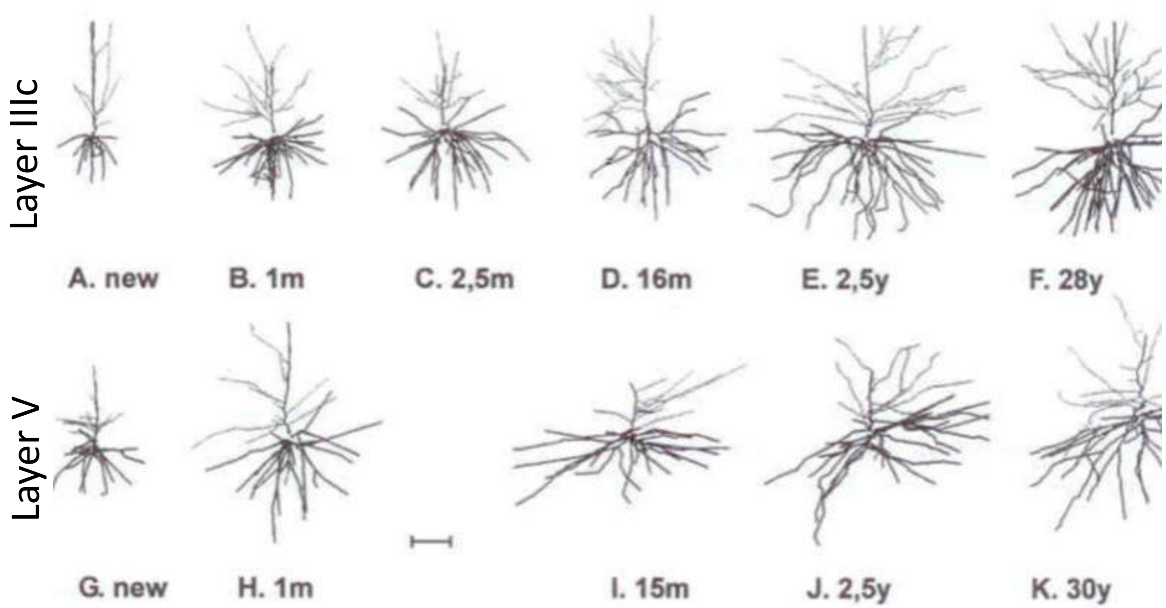


Sur 2005 Science

Plasticity of the brain

Critical periods and interaction with the environment: the case of the prefrontal cortex

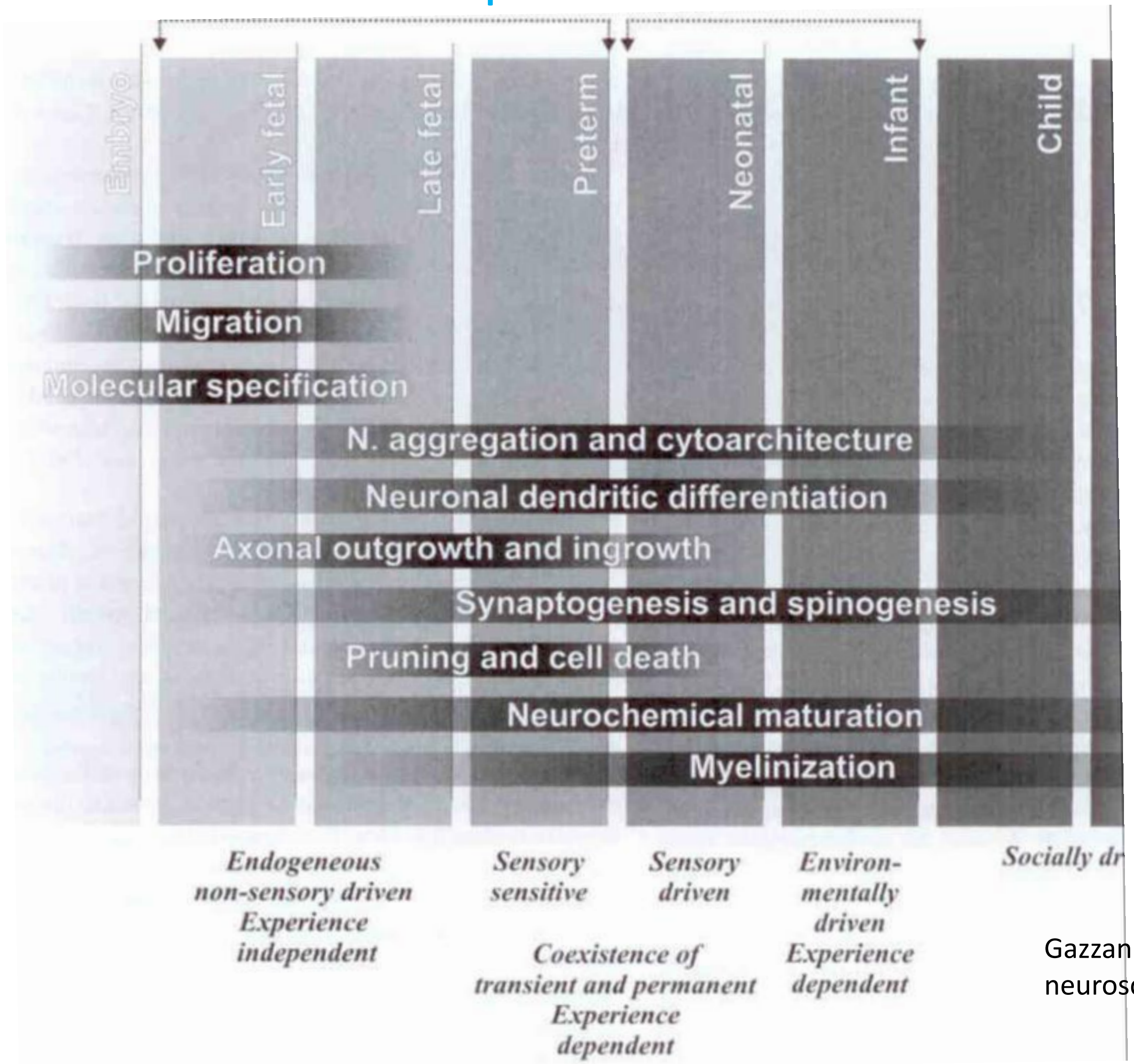
Period	Kind of circuit	Type of activity
Neonate	Permanent, with transient elements	Sensory-driven, centered on layer V
2-6 month	Permanent with transient elements	Sensory-driven, columnar processing
7-12 month	Initial cognitive circuit	Environmental driven, local circuit
12-24 month	Cognitive	Socially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



Gazzaniga The cognitive neuroscience 4th Ed. Chap 2

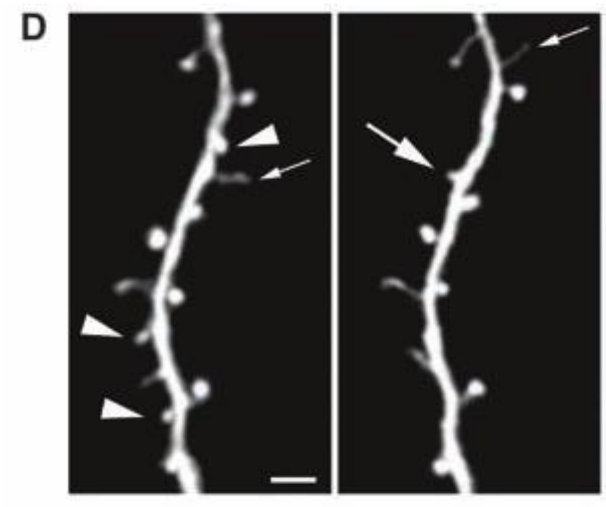
Plasticity of the brain

Critical periods and interaction with the environment: the case of the prefrontal cortex



Gazzaniga The cognitive neuroscience 4th Ed. Chap 2

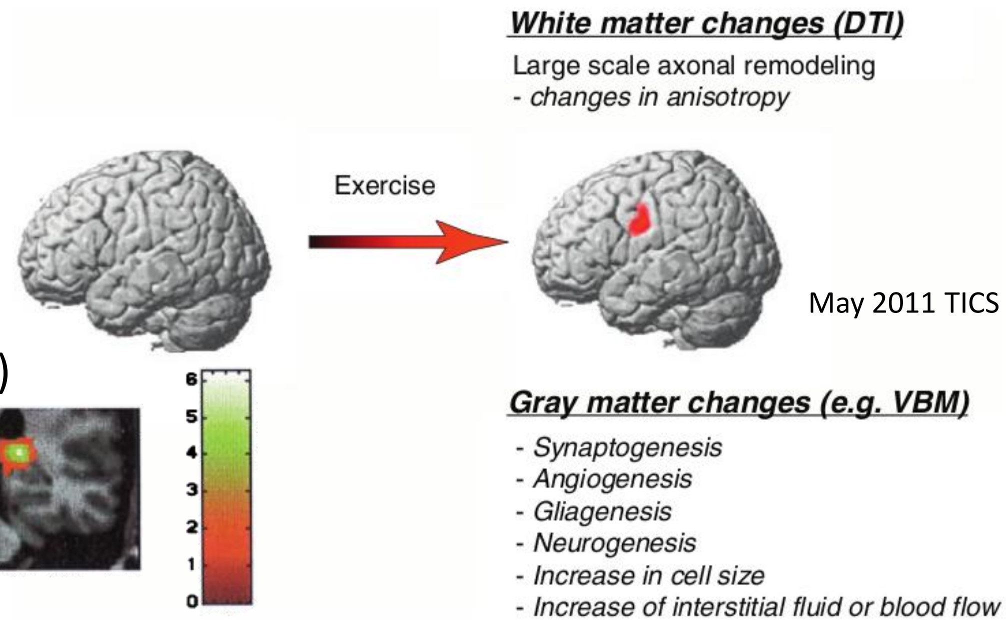
Plasticity of the brain
Plasticity in the adult brain



Feldman 2005 Science

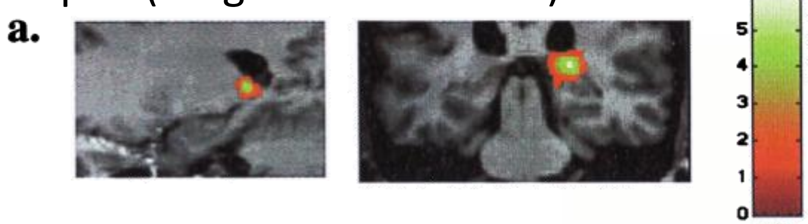
Plasticity of the brain

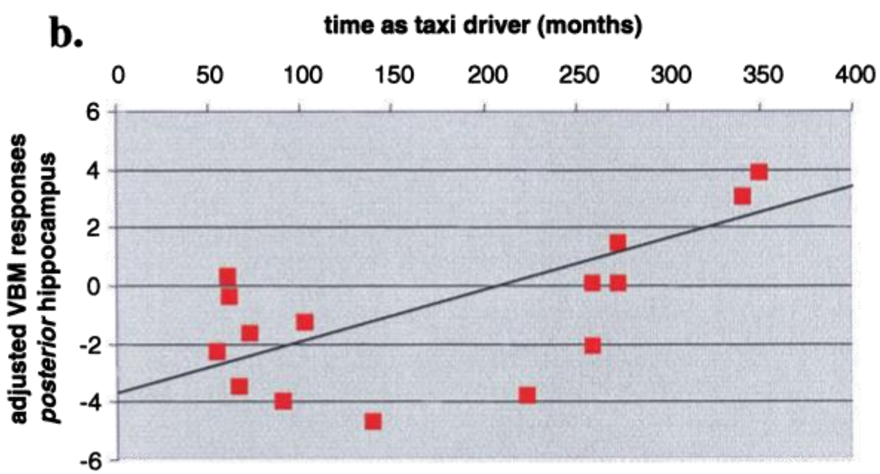
Plasticity in the adult brain



May 2011 TICS

Example: (Maguire PNAS 2000)





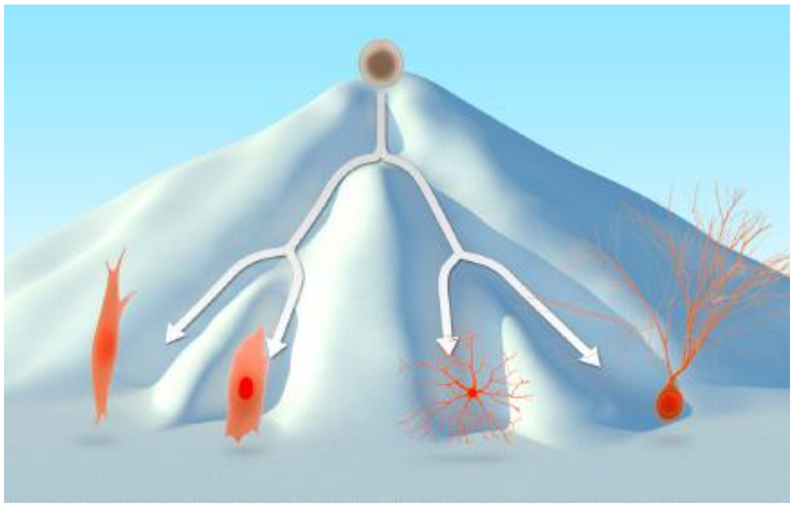
Plasticity of the brain
Adult neo-neurogenesis?

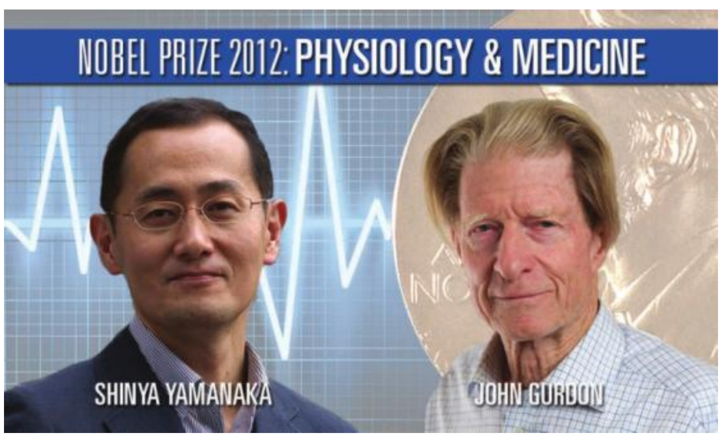
- In humans: new neurons generated throughout life in the hyppocampal region
- In rodent: new neurons in the olfactory bulb
- However, the ‘big picture’: manage a given pool of neurons throughout life.

Take-home messages

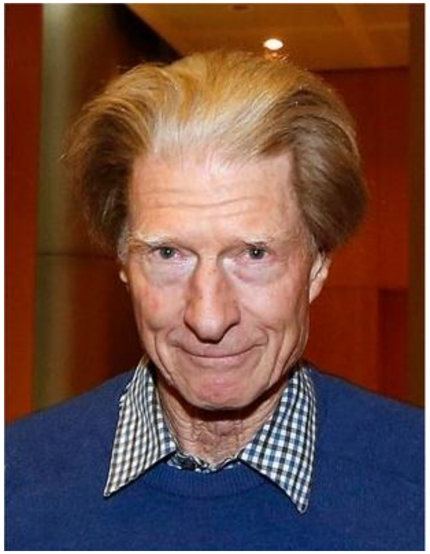
- Morphogenesis and regionalization:
  - Is under dynamic genetic control (intrinsic factors)
  - Depends on spontaneous electrical activity (extrinsic factors)
  - Extrinsic and intrinsic factors are complementary & interact
  - Involves limited but crucial pruning
- The critical period is characterized by massive plasticity
  - Required to consolidate the architecture
  - Shaped by interaction with the environment (evoked activity)
  - Is limited in time (followed by a freezing of the system)
- Plasticity is much important
  - 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: crucial for the adaptation to the environment

2012 Nobel Prize: induced pluripotent cells



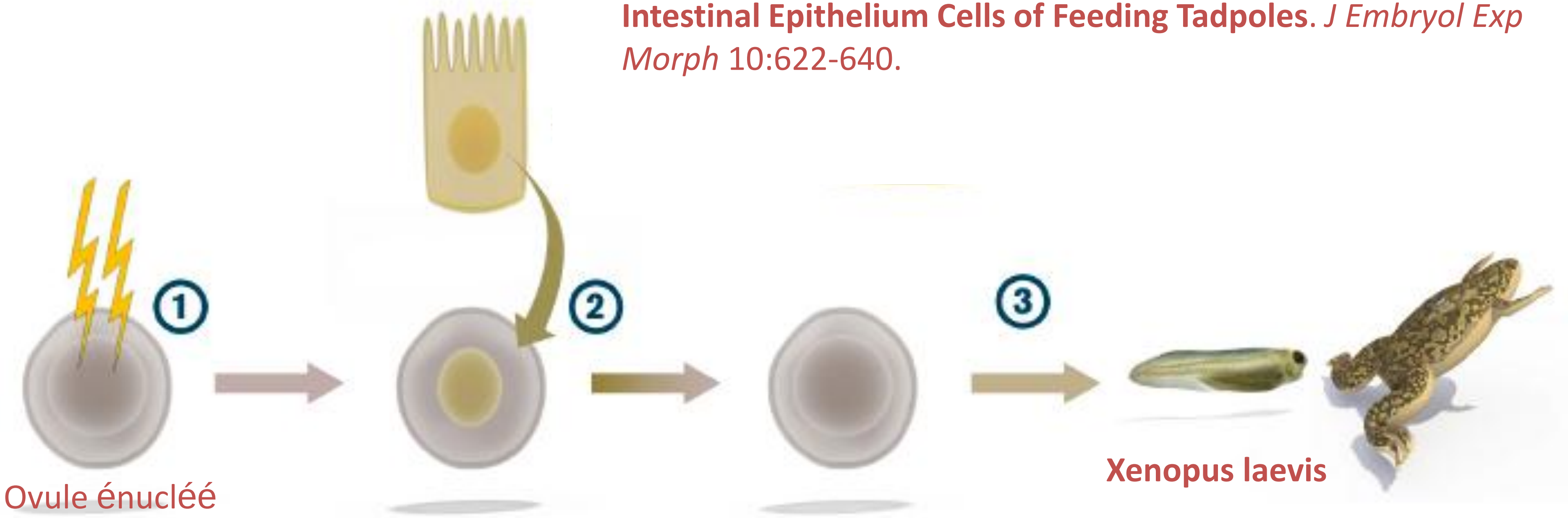


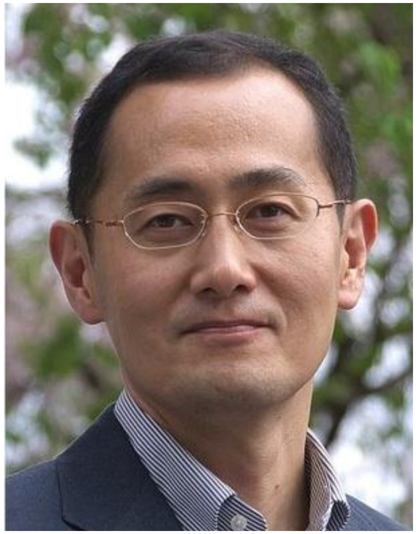
- Development progressively restricts cellular fates
- Can the clock be reversed?
- Induced pluripotent cell (iPS): specialized cell that are induced pluripotent (i.e. able to undergo development once again!).
- Gurdon: put mature cell nucleus in an egg to (little chance though…) make it pluripotent
  - mature cells keep their whole genetic package.
  - But: does not work in humans…
- 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



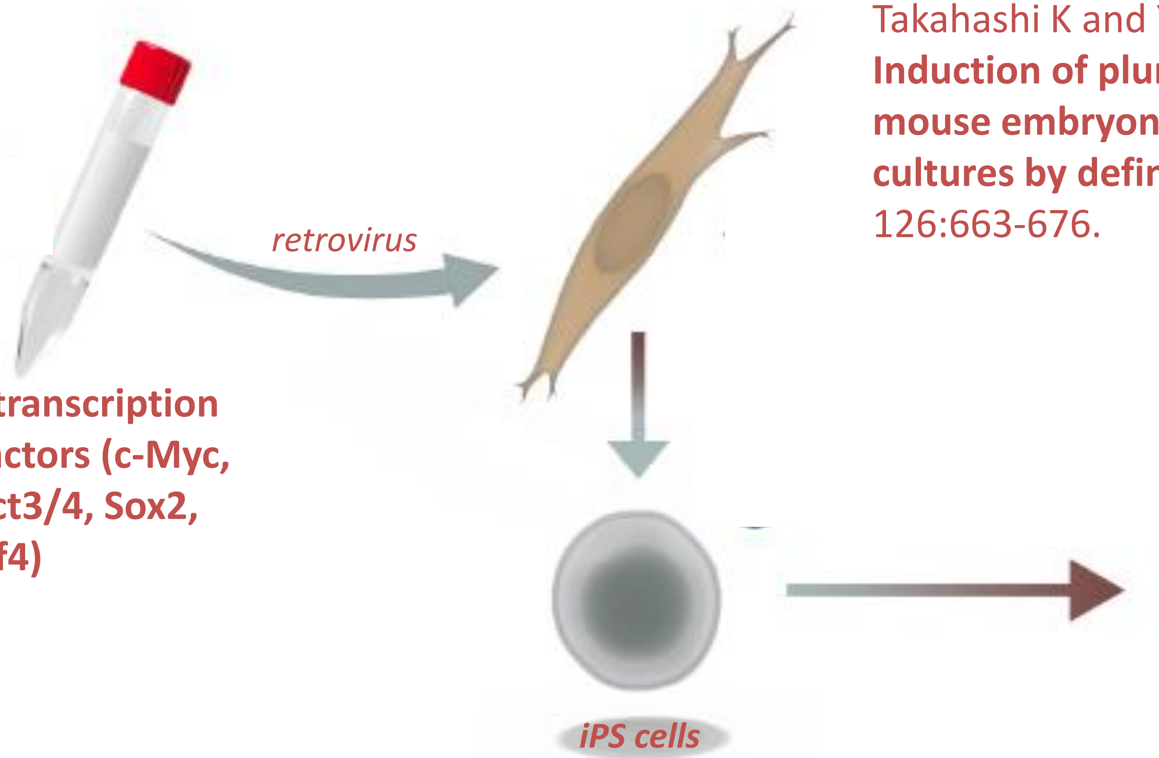
- Gurdon: put mature cell nucleus in an egg to make it pluripotent (little chance though…)
  - Evidence that mature cells keep their whole genetic package.
  - But: it does not work in humans…

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

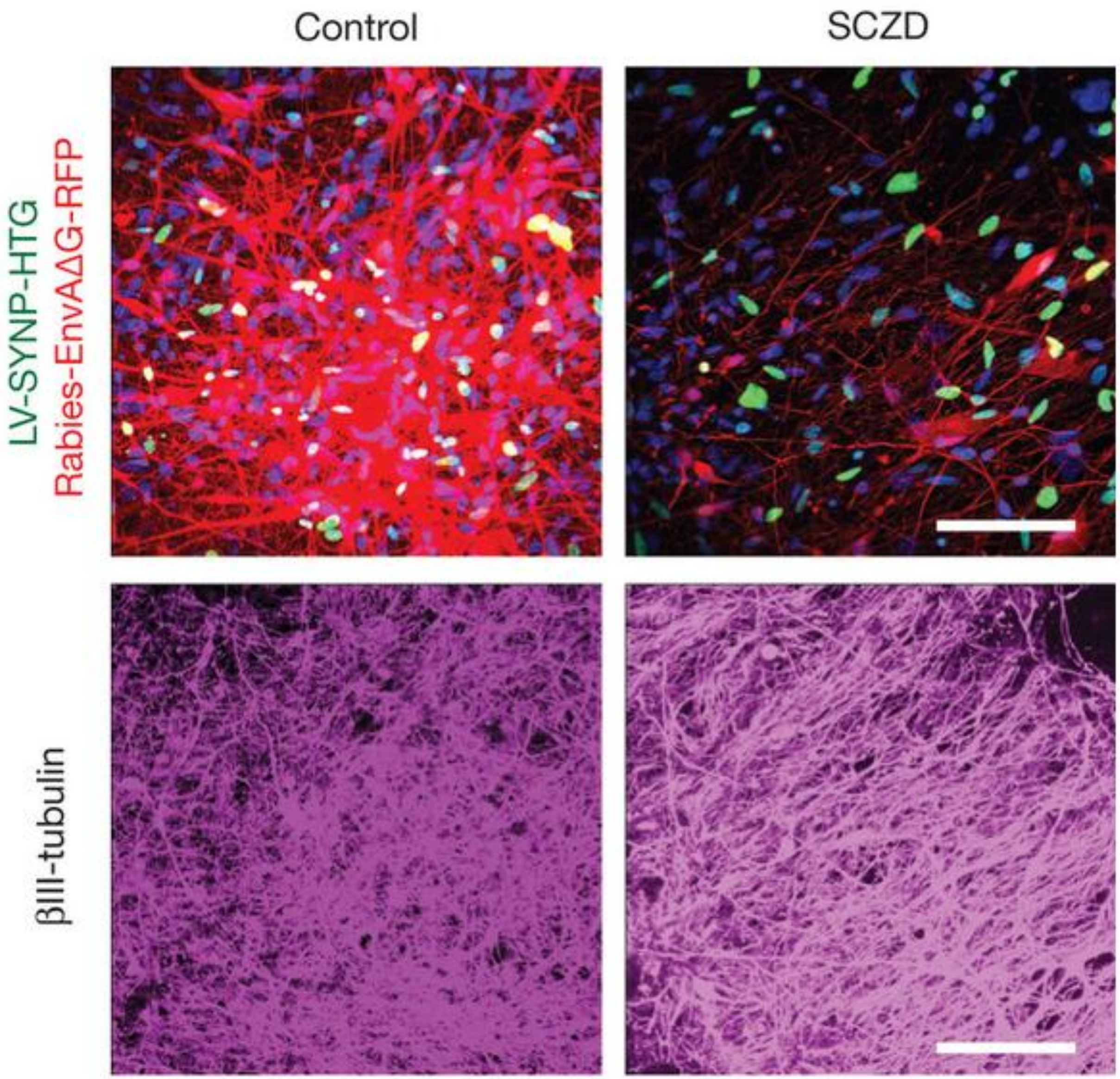


Takahashi K and Yamanaka S (2006). **Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.** *Cell* 126:663-676.

4 transcription factors (c-Myc, Oct3/4, Sox2, Klf4)

Mice - 2006
Humans - 2007

Decreased neuronal connectivity in SCZD hiPSC neurons.

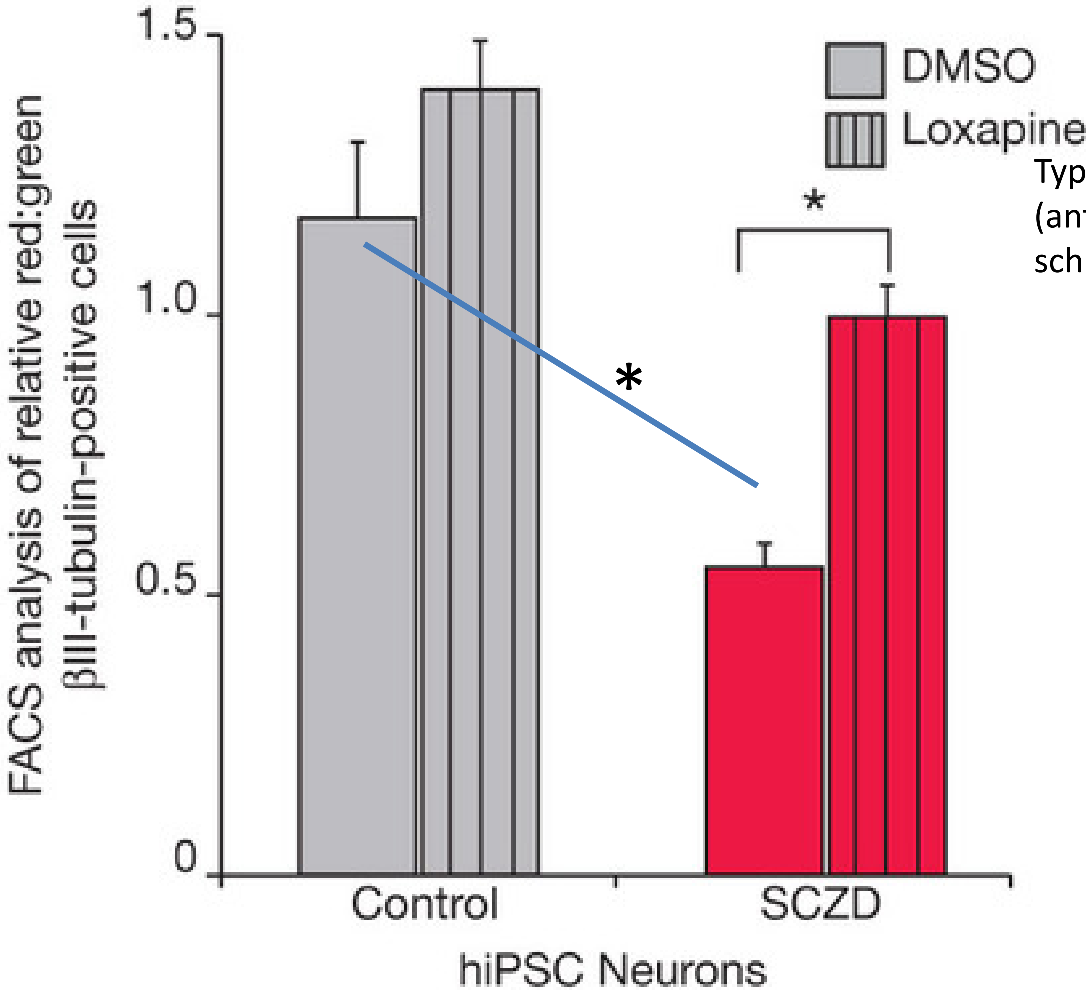


Spread of rabies via synaptic contacts => estimate of connectivity

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.

Decreased neuronal connectivity in SCZD hiPSC neurons.



Typical benzodiazepin (antipsychotic drug, used in schizophrenia)

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.

References

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

- Major references:
  - In M. Gazzaniga, The cognitive neurosciences, 4th edition
    - 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)