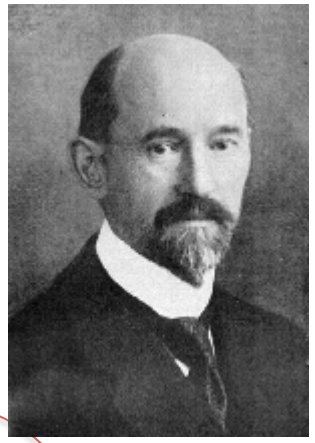
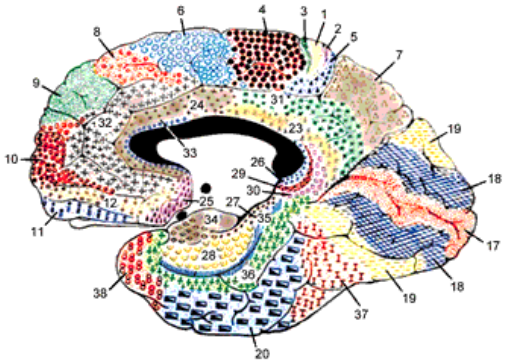
The neocortical bauplan

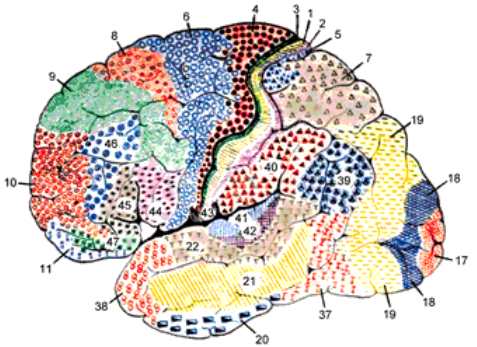
The **neocortex** is not a homogeneous structure: it is tangentially subdivided into multiple **functional areas** → defined by their connectivity and cytoarchitectonic peculiarities



- elaboration of sensory information
- association between different stimuli
- selection and triggering of voluntary movements

"the organs of the brain" (Brodmann, 1909).

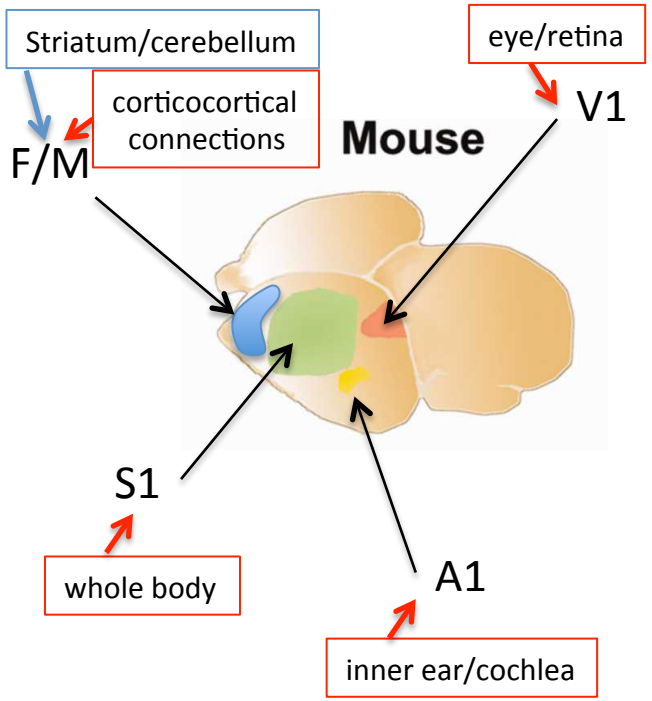




Arealization

The process subdividing the neocortical field into several functional areas

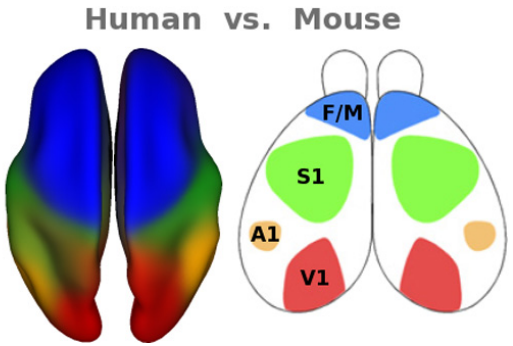
The **basic plan** of the eutherian mammalian neocortex comprises 4 primary areas



Each area is defined by both its structure and connectivity

The relative cell number and the size of the cells in each layer are quite variable and specialized for the specific function of that area

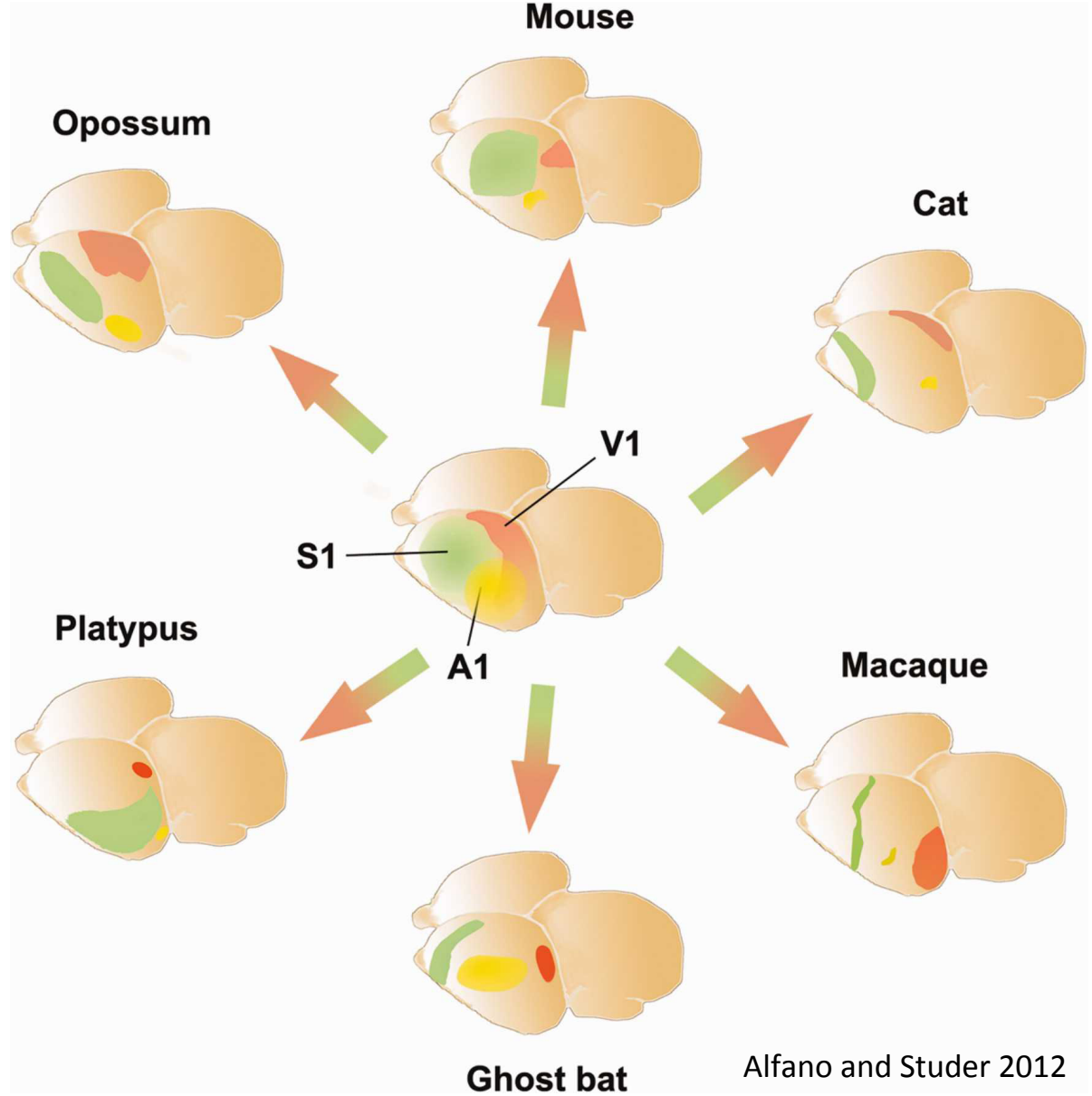
Neocortical areal patterning is highly conservative in its basic constituents among different clades of the mammalian class.



F/M= frontal motor area
S1= primary somatosensory area
V1= visual area
A1= auditory area

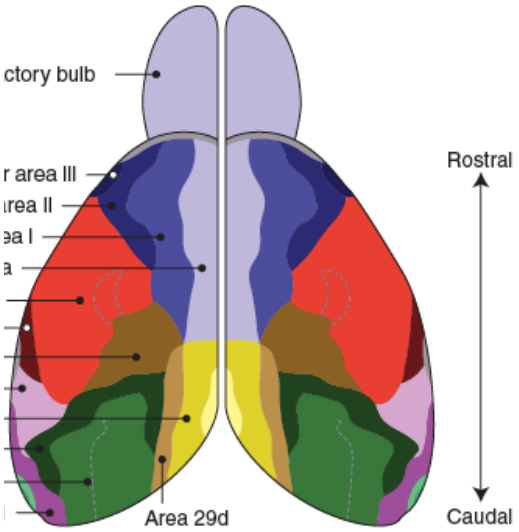
Model showing the positioning of **primary sensory areas** in different mammals

The reciprocal position of primary areas with respect to a common ancestor (on which prospective areas are represented) is maintained

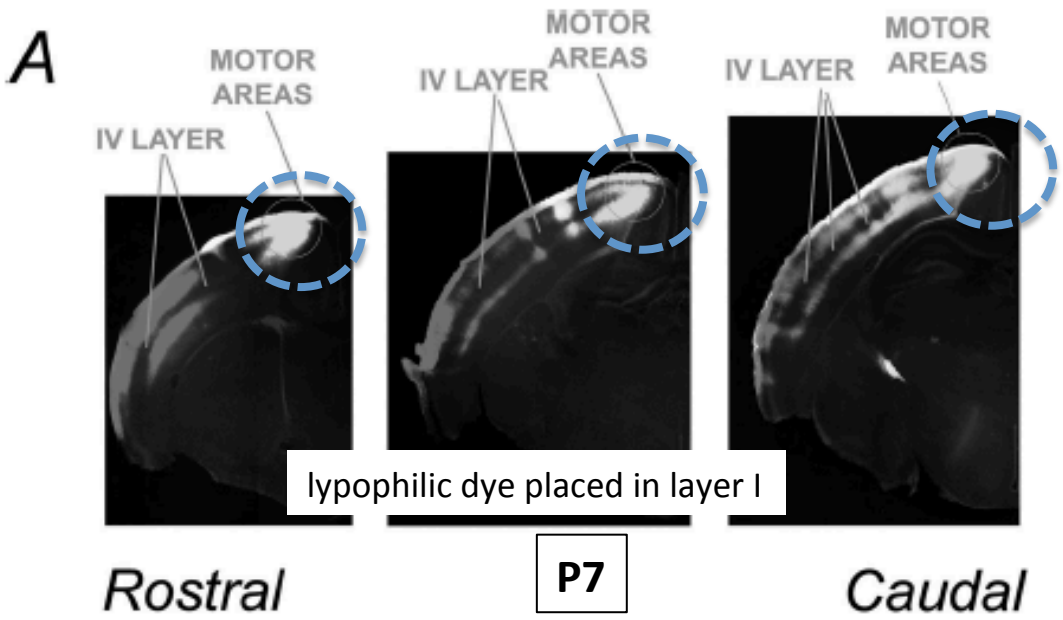


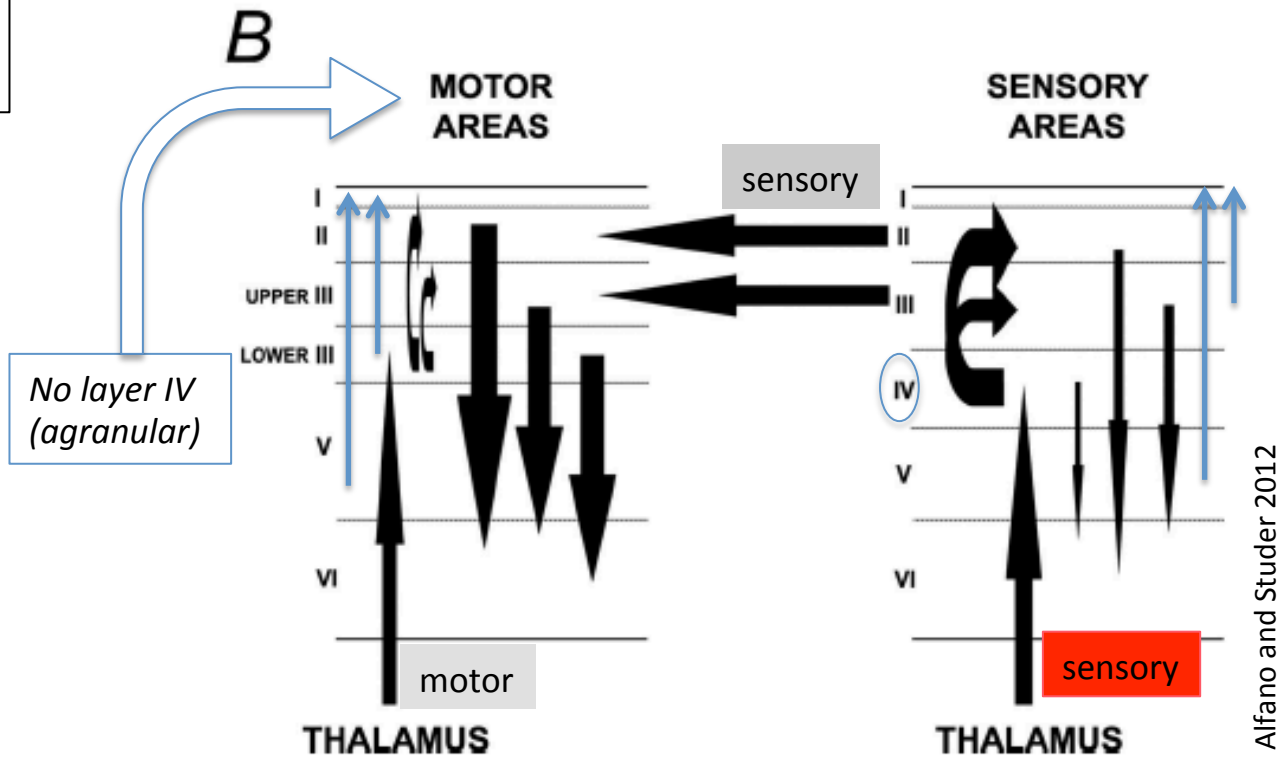
Alfano and Studer 2012

All proposed model systems are represented with a common shape to simplify the comparison between them



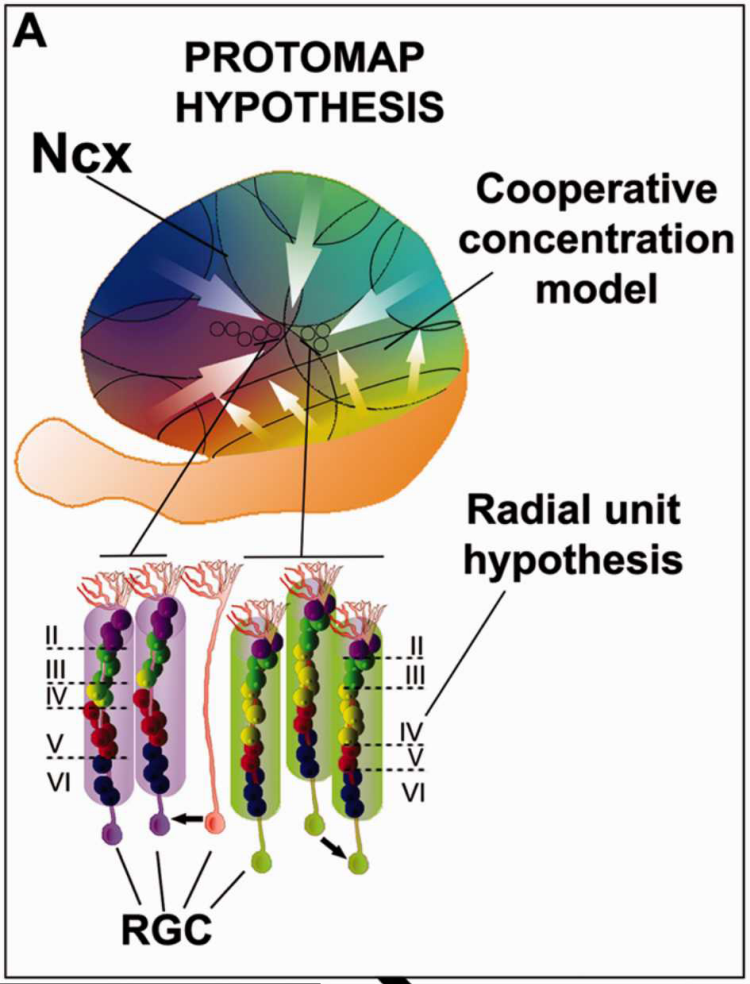
Laminar organization and connectivity
of **motor** and **sensory** areas

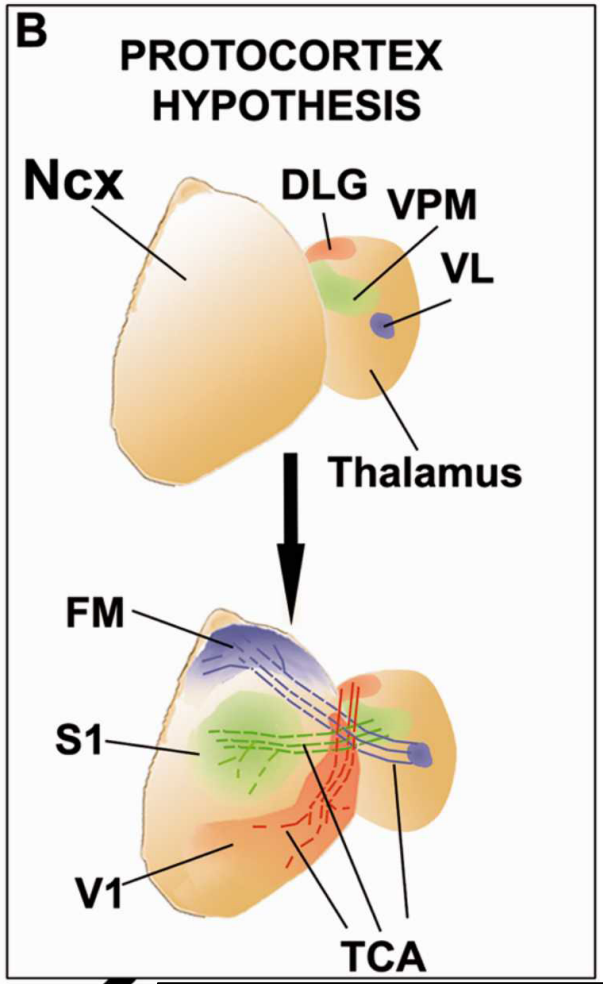




Alfano and Studer 2012

P. Rakic





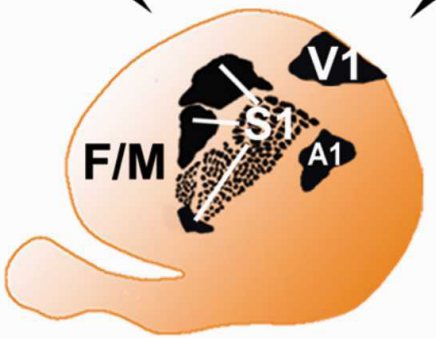
D. O'Leary

Thalamic nuclei

(dLG), dorsolateral geniculate; (VPM), ventropostero medial, (VL) Ventrolateral

cortical arealization is under the genetic control of factors with discrete expression in the cortical field

Intrinsic mechanisms



Cortical arealization is decided upon arrival of TCA (thalamo cortical afferents - E14.5)

Extrinsic mechanisms

Alfano and Studer 2012

The Radial Unit Hypothesis of cortical development

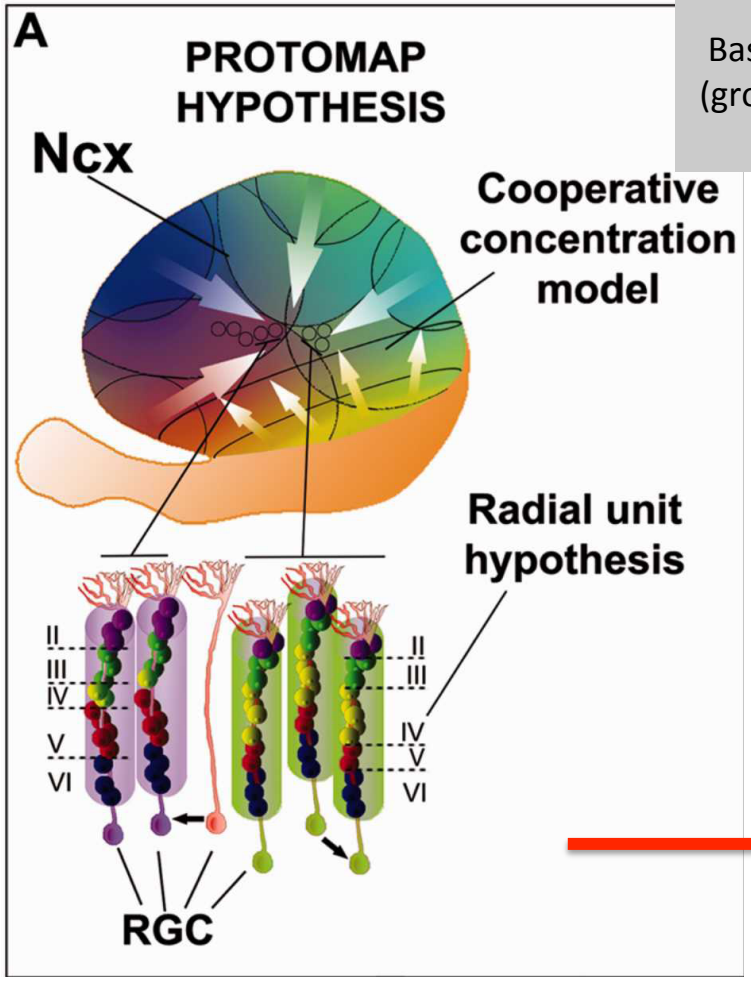
Articles

Science 1988

Specification of Cerebral Cortical Areas

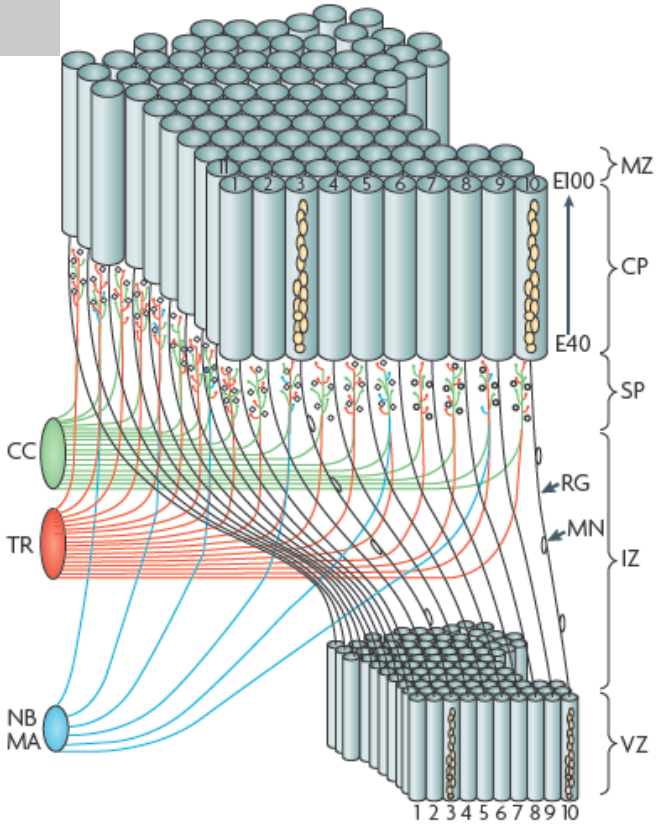
Pasko Rakic

Radial functional columns
=
Basic modules of neocortical areas
(groups of vertically interconnected neurons)



Areal identity: from neural progenitors to their progeny

A spatial pattern in neocortical stem cells is transferred to the neurons of the cortical plate

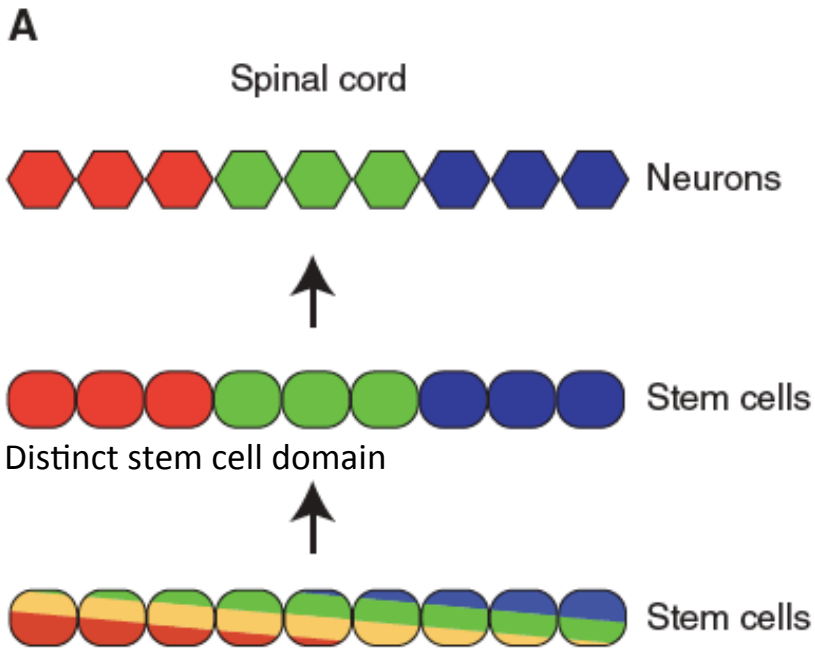


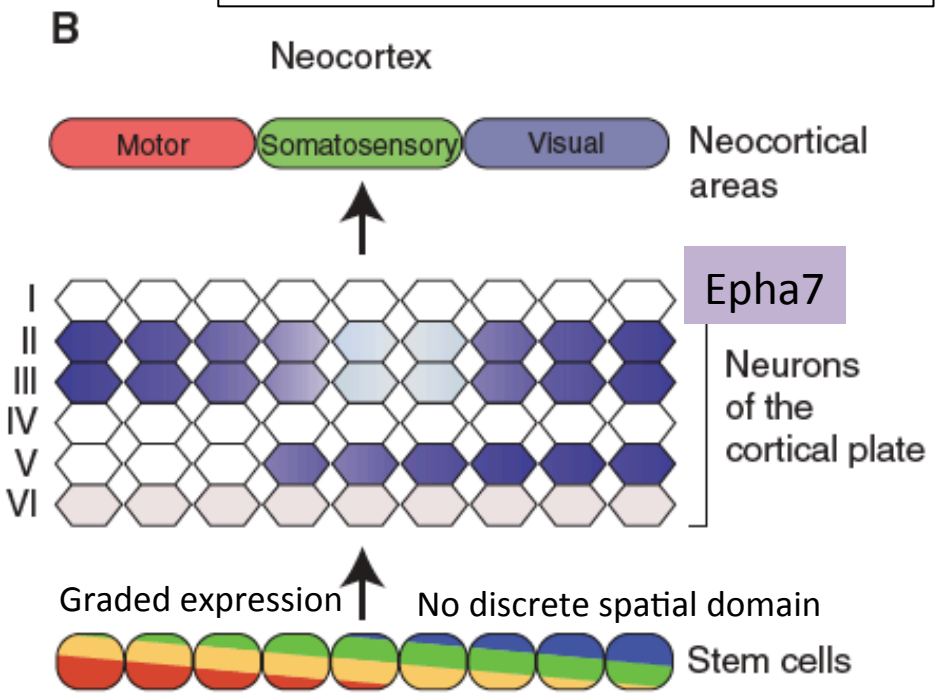
Macaque monkey

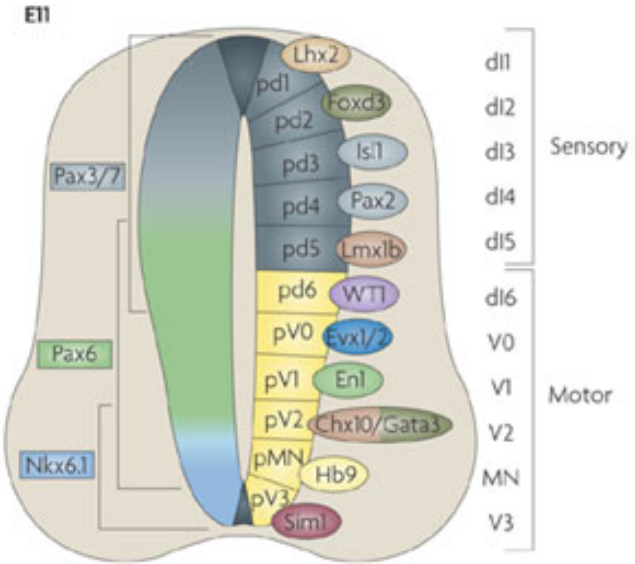
http://rakiclab.med.yale.edu

Rakic, Science 1988

Cooperative concentration model





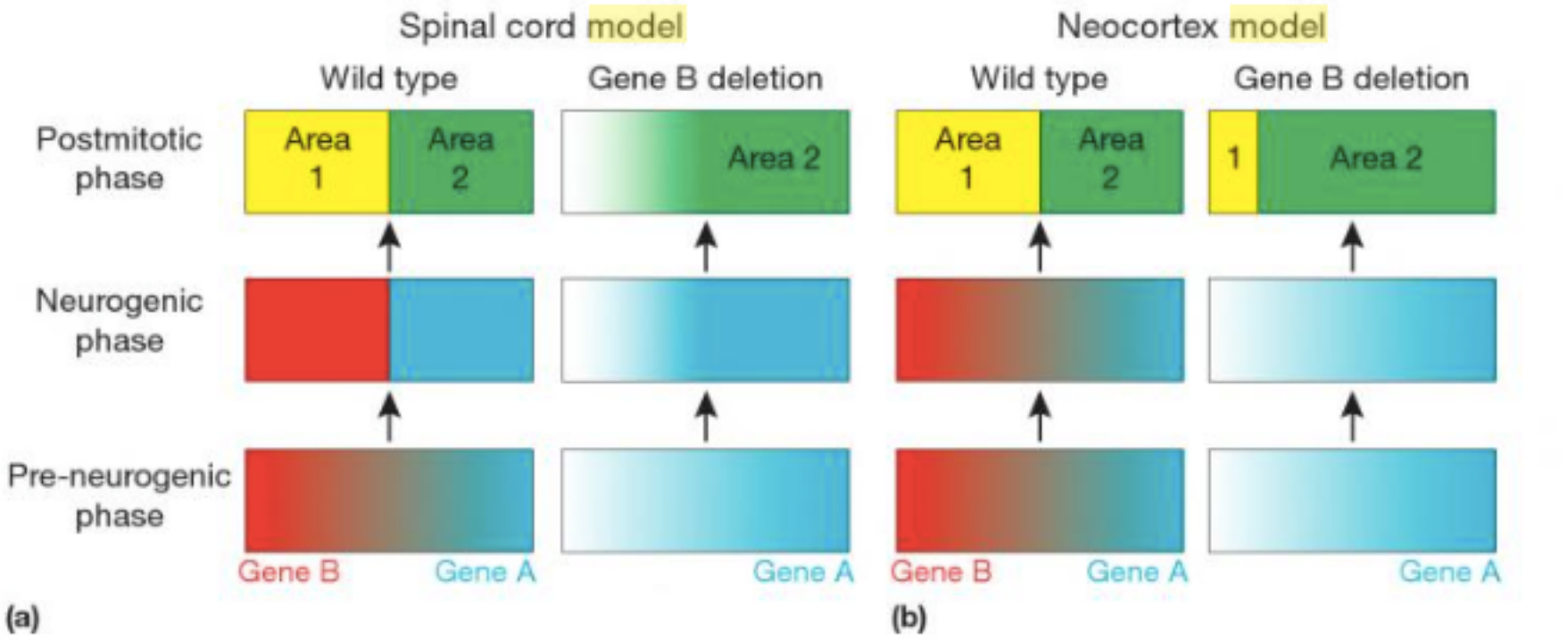


Shh (dorso-ventral axis)

Neocortical stem cells give rise to differently spatially patterned neuronal progeny at different time

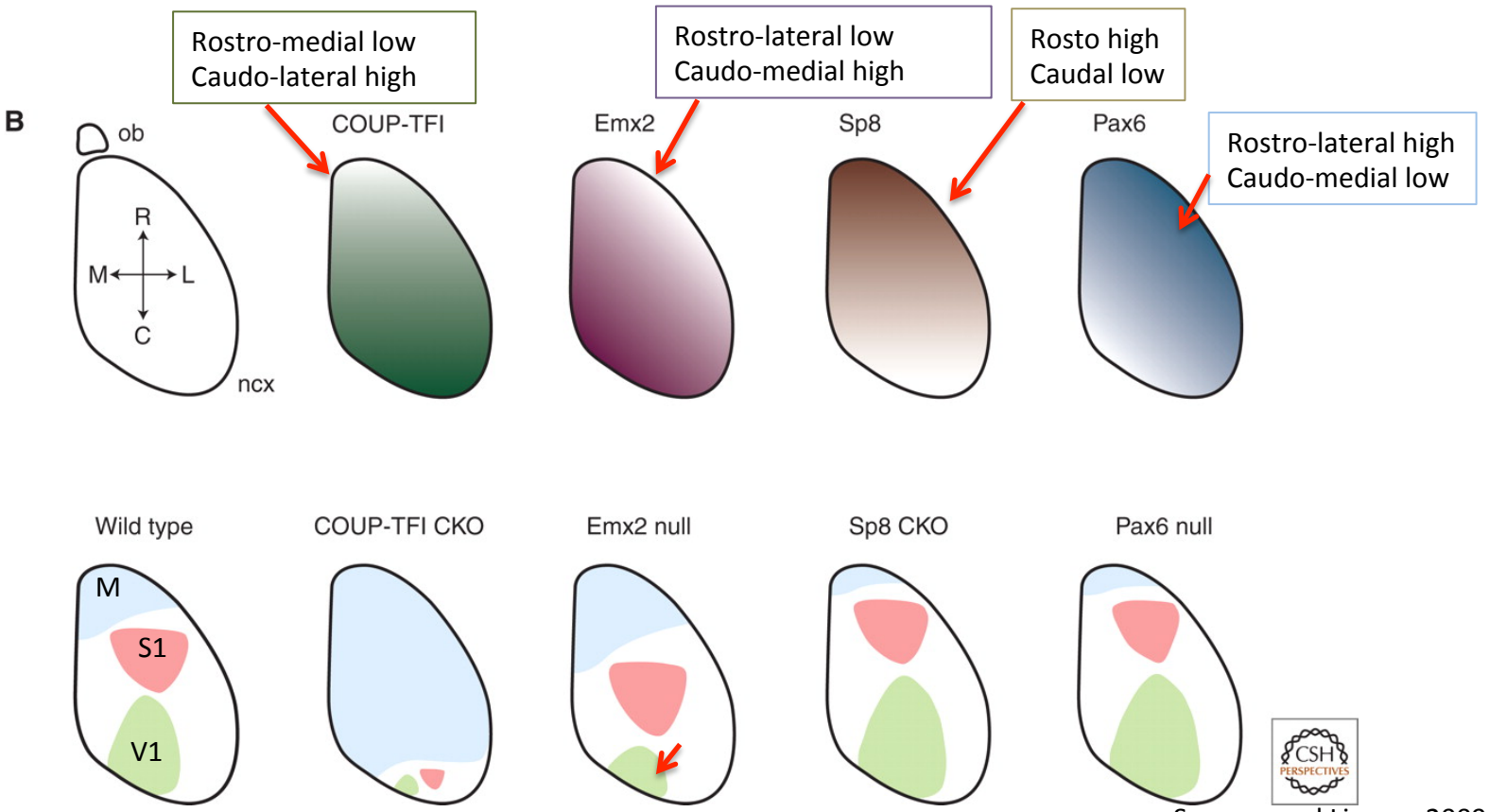
Neocortical stem cells **interpret spatial information** encoded by gradients of gene expression together with **temporal information** to generate the appropriate spatial pattern in each neocortical layer.

Distinc modes of cell-types specification in spinal cord and neocortex



Cooperative concentration model

Neocortical patterning genes



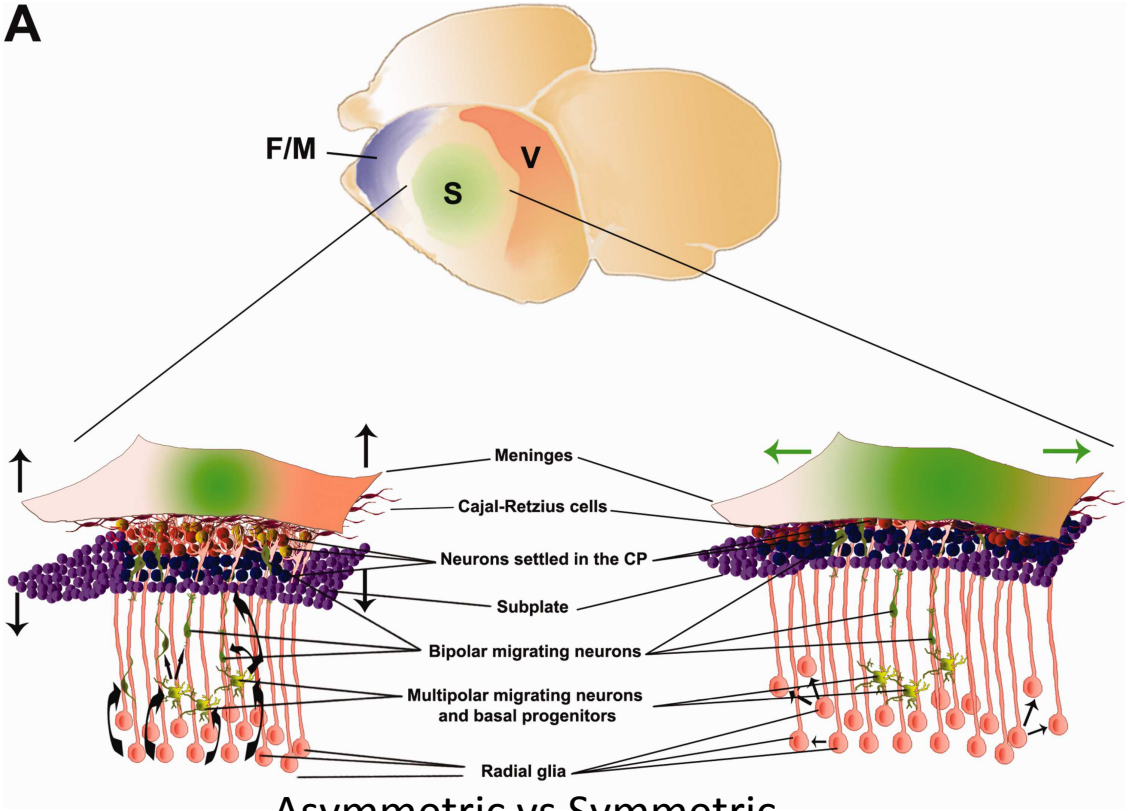
Sansom and Livesey 2009

CKO= cortex specific KO

→ These TFs work in a dose-dependent manner: cortical progenitors acquire different neurogenic potentials depending on their position along the AP and DV axes

- Pax6, Emx2 and COUP-TFI are involved in the control of the neurogenic rate

Neurogenesis increases the thickening of a given area

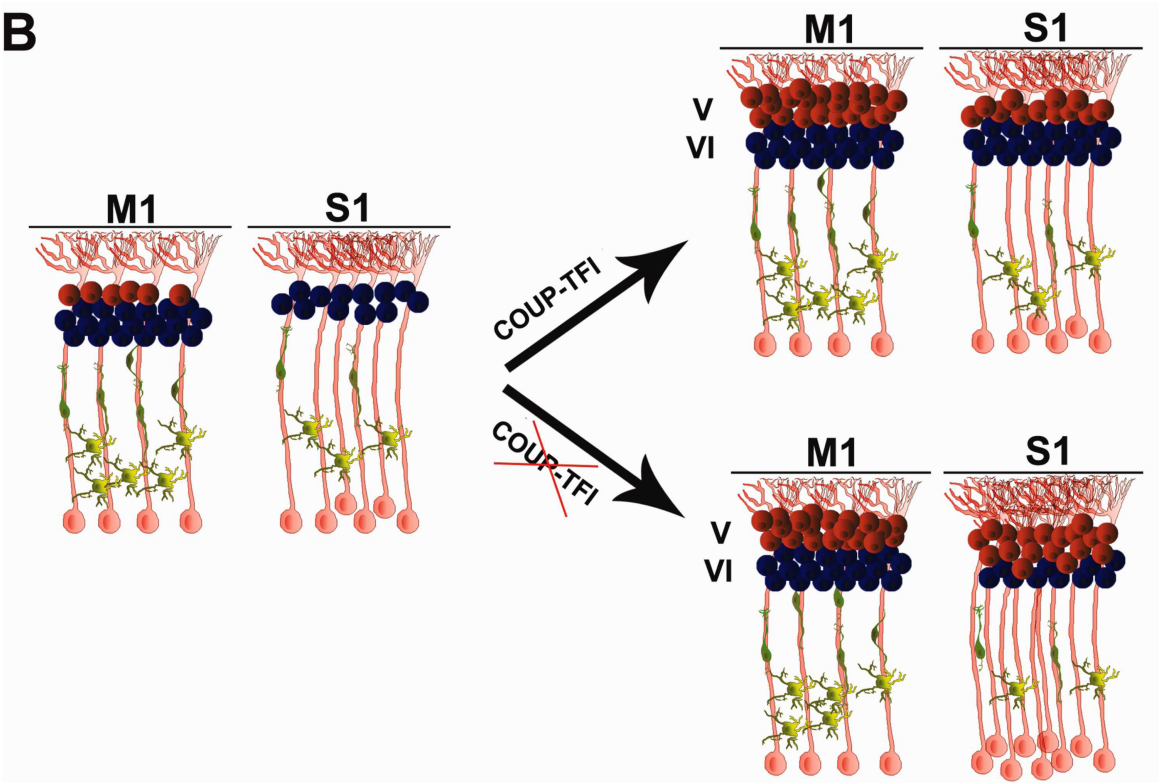


Increase in self-renewing progenitor pool
→ area surface expansion

Asymmetric vs Symmetric

The concept of **radial units** helps in understanding how areal patterning genes may work in controlling the peculiar cytoarchitecture of a given neocortical area

hypothetical function of the areal patterning gene COUP-TFI in the specification of layer VI in primary motor (M1) and somatosensory (S1) areas



COUP-TFI → it delays the onset of the layer V (red) specification program in S1 area, where neurogenesis proceeds slower than in M1 => layer VI (blue) of S1 acquires approximately the same thickness of that of M1, while layer V results thinner in S1 compared to M1.

When COUP-TFI is ablated, it fails to repress layer V program in S1, which in turn expands its layer V neuronal pool at the expense of layer VI neurons.

AREALIZATION

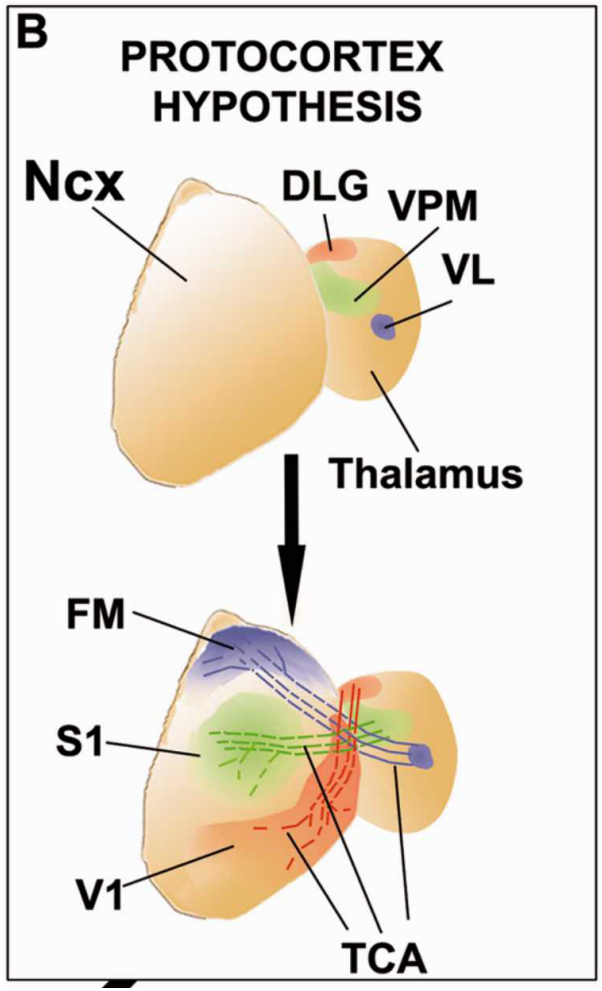
Evidences in favour of the protomap hypothesis

- Heterotopic transplantation studies indicate that neocortical stem cells become regionally specified between E11 and E12 (before arrival of TCA →E14.5)
- Arealization markers begin to be expressed at E8.5 much earlier than the arrival of TCA
- Arealization markers are correctly distributed in mutant brains where TCA were lacking (Mash-1) or disrupted (Gbx-2).

→ Patterning of the cerebral cortex starts during early stages of development through intrinsic mechanisms

What about the **protomap hypothesis**?

Is there a role for TCA in cortical arealization?



What about the protomap hypothesis?

Is there a role for TCA in cortical arealization?

→ TCA final targeting can proceed independently from cortical regionalization:

- Specification of thalamic nuclei (Gbx2; Neurog2; Lhx2)
- Spontaneous calcium activity of thalamic neurons extending the axon
- Regional cues released by subpallium

→The neocortex shows a high degree of plasticity = capacity to direct and/or re-route cortical and subcortical connections when normal connectivity is altered:

*e.g. total loss of **visual inputs** = reduction of V1 size – impairment of its organization and connectivity pattern.*

*e.g. **congenital deaf mice**:*
-lack of auditory inputs to A1
-reduction of A1 dimension
-rerouting of visual and somatosensory afferents to A1
-ectopic innervation of V1 by somatosensory afferents

Protomap and **protocortex** hypotheses of cortical development might be complementary aspects of a single mechanism

Genetic control of cortical arealization
(protomap intrinsic to the neocortical primordium)

+

Role of sensory periphery (TCA) in refining and maintaining arealization

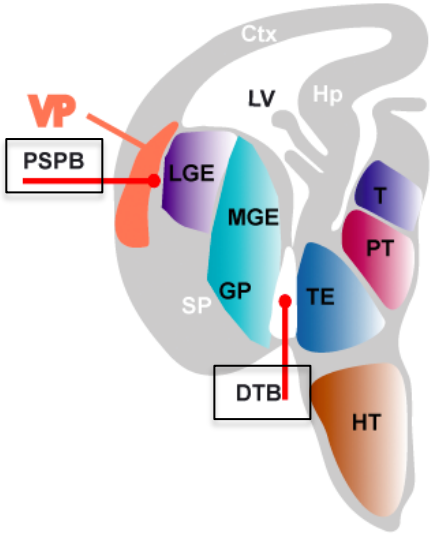
The development of thalamocortical connections relies on multiple mechanisms

Proper development of neural connections requires the guidance of axons to their final destination through the coordinated activity of **growth factors** and **guidance cues** expressed along the pathway they follow.

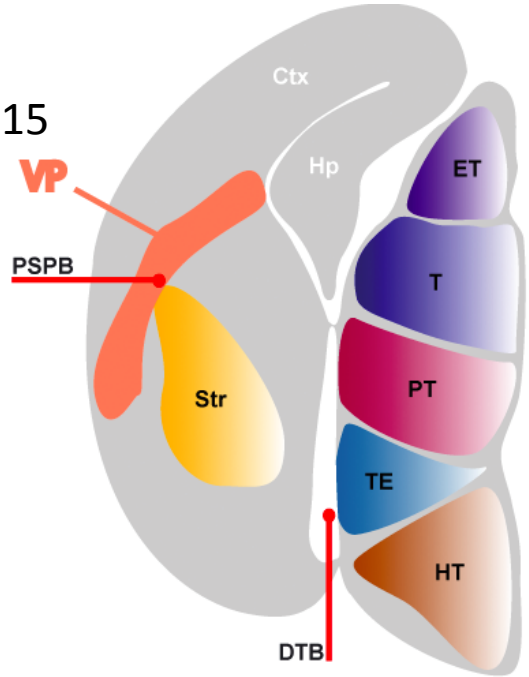
Axon guidance typically involves a complex set of instructions:
→ the generation of specific connectivity requires axons to respond to spatio-temporal guidance cues in a highly regulated manner.

- Trascriptional control of thalamocortical axon guidance
- Repulsive activity from the hypothalamus
- Prethalamic and ventral telencephalic projections
- Corridor cells
- Molecular determinants in the subpallium

E13



E15



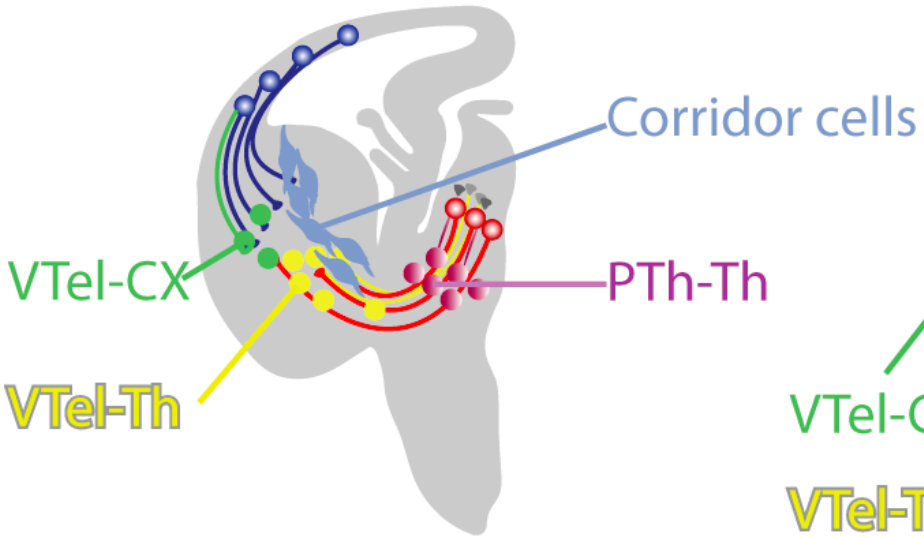
ET, epithalamus;
T, thalamus (dorsal thalamus)
PT, prethalamus (=ventral thalamus)
TE, thalamic eminence
HT,hypothalamus;

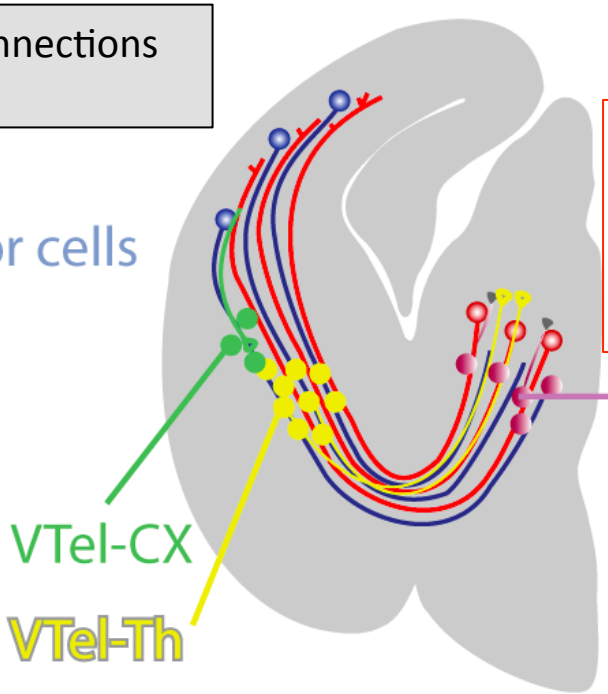
Ctx, cerebral cortex;
SP, subpallium;
Str, striatum;
VP, ventral pallium
GP, globus pallidus

DTB, diencephalic–telencephalic boundary

PSPB, pallial subpallial boundary

The development of thalamocortical connections relies on multiple mechanisms



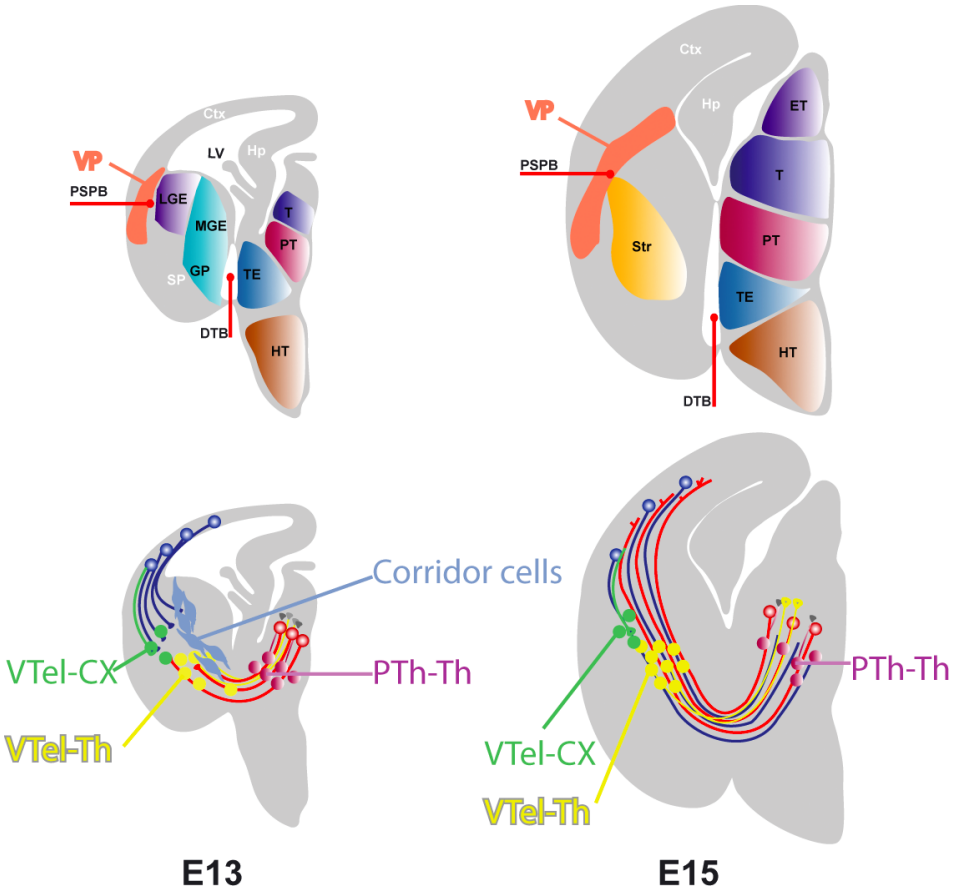


Thalamic projections (red)
Corticofugal projections (blue)

Molnar et al., 2012

E13 E15

1. **Repulsive activity from the hypothalamus**



-TCAs traverse the prethalamus at E11-E13 in mice. They turn sharply away from the hypothalamus into the internal capsule in the direction of the DTB

- the Hyp express high levels of **Slits** (chemorepellent for growing axons) and thalamic axons express Robo receptors

- Hyp explants in culture repel thalamic axons

- in Slit2KO and Slit1,2KO a large number of thalamic axons fail to reach the telencephalon and enter into the Hyp

2. Trascriptional control

Development/Plasticity/Repair

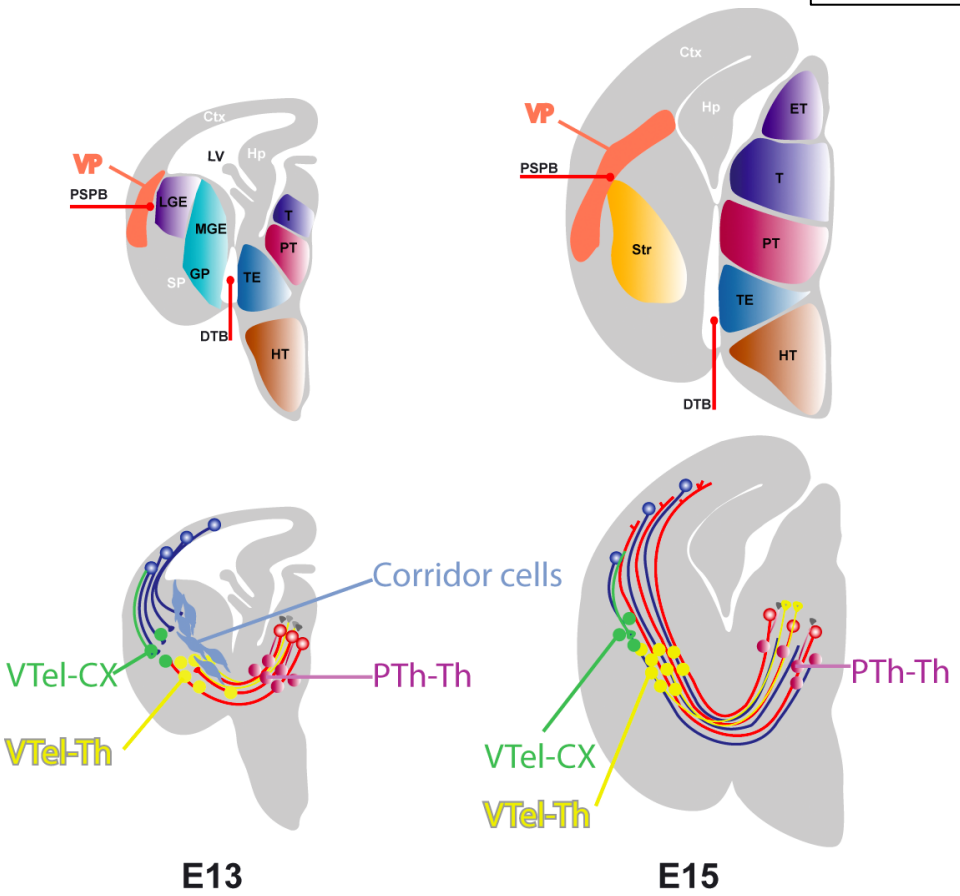
The *Lhx2* Transcription Factor Controls Thalamocortical Axonal Guidance by Specific Regulation of Robo1 and Robo2 Receptors

Paula Marcos-Mondéjar,[1] Sandra Peregrín,[1] James Y. Li,[2] Leif Carlsson,[3] Shubha Tole,[4] and Guillermina López-Bendito[1]

[1]Instituto de Neurociencias de Alicante, Consejo Superior de Investigaciones Científicas and Universidad Miguel Hernández, 03550 Sant Joan d'Alacant, Spain, [2]Department of Genetics and Developmental Biology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, Connecticut 06030-6403, [3]Umeå Center for Molecular Medicine, Umeå University, 901 87 Umeå, Sweden, and [4]Department of Biological Sciences, Tata Institute of Fundamental Research, Colaba, Mumbai 400 005, India

The assembly of neural circuits is dependent upon the generation of specific neuronal subtypes, each subtype displaying unique properties that direct the formation of selective connections with appropriate target cells. Actions of transcription factors in neural progenitors and postmitotic cells are key regulators in this process. LIM-homeodomain transcription factors control crucial aspects of neuronal differentiation, including subtype identity and axon guidance. Nonetheless, their regulation during development is poorly understood and the identity of the downstream molecular effectors of their activity remains largely unknown. Here, we demonstrate that the *Lhx2* transcription factor is dynamically regulated in distinct pools of thalamic neurons during the development of thalamocortical connectivity in mice. Indeed, overexpression of *Lhx2* provokes defective thalamocortical axon guidance *in vivo*, while specific conditional deletion of *Lhx2* in the thalamus produces topographic defects that alter projections from the medial geniculate nucleus and from the caudal ventrobasal nucleus in particular. Moreover, we demonstrate that *Lhx2* influences axon guidance and the topographical sorting of axons by regulating the expression of Robo1 and Robo2 guidance receptors, which are essential for these axons to establish correct connections in the cerebral cortex. Finally, augmenting Robo1 function restores normal axon guidance in Lhx2-overexpressing neurons. By regulating axon guidance receptors, such as Robo1 and Robo2, Lhx2 differentially regulates the axon guidance program of distinct populations of thalamic neurons, thus enabling the establishment of specific neural connections.

3. Prethalamic and ventral telencephalic projections



A scaffold to guida TCAs

PTh-Th and Vtel-Th projections may be involved in early guidance of TCAs:

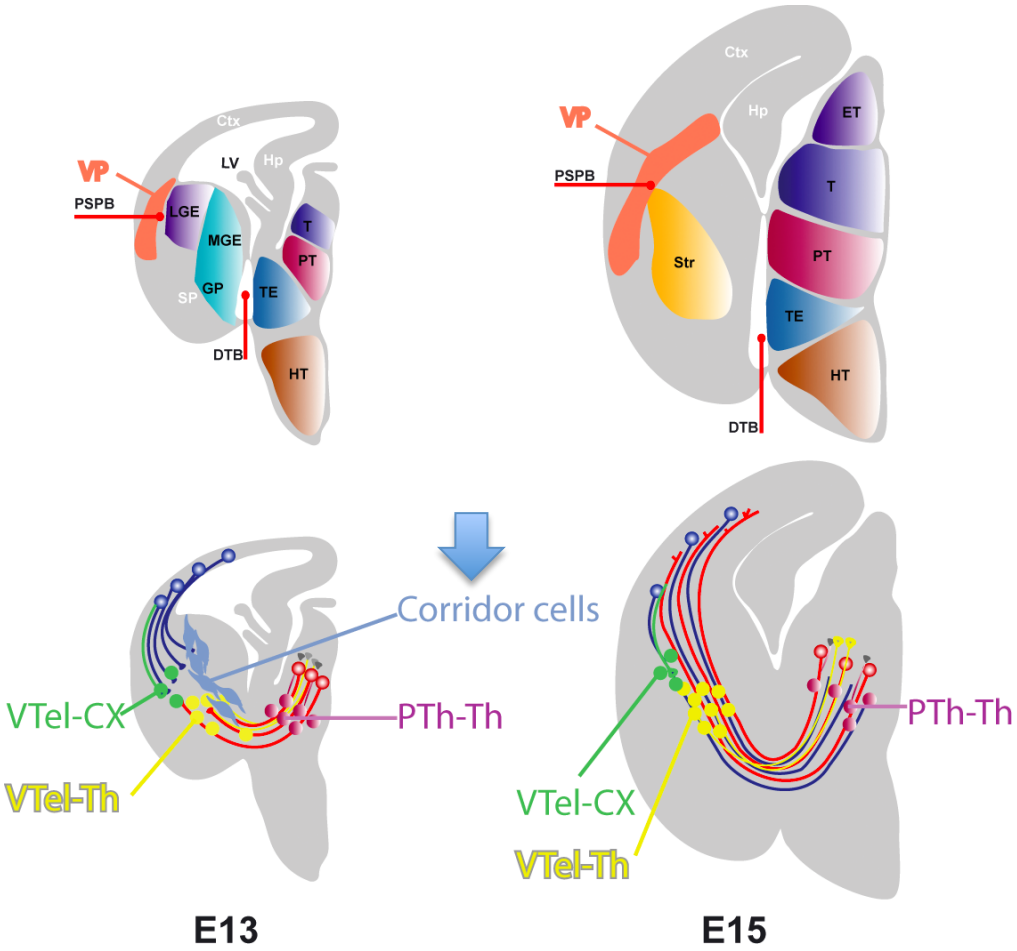
-In Mash1 KO and Pax6 KO Vtel-Th cells are missing and TCAs fail to extend into the Vtel

-In Lhx2KO and Emx2KO Vtel-Th cells are less and displaced…guidance defects in TCAs

-Less functional information available for PTh-Th

However, In the case of both the PTh–Th and VTel–Th groups of axons, an association between the loss of these cells and TCA pathfinding defects in mutants cannot be taken to imply causation

4. The role of the corridor cells



The corridor cells = GABAergic

are located in the MGE

migrate from the LGE into the MGE (from E11 to E14 – superficial mantle of the subpallium)

Express markers typical of the LGE (e.g. Islet 1)

form a cellular corridor between the proliferative zones of the MGE and the GP (globus pallidus) that is permissive for TCAs migration (MGE cells are NOT permissive)

Corridor cells express a membrane bound isoform of **Neuregulin 1** and TCAs express **ErbB4** (→ functional studies show ErbB4-neuregulin pathway regulates TCAs pathfindings through the corridor)

Corridor cells are immature migrating neurons that act via contact or a short-range activity to generate a neuregulin-1-permissive domain that is essential for the internal pathfinding of TCAs within the subpallium

Cell

Tangential Neuronal Migration Controls Axon Guidance: A Role for Neuregulin-1 in Thalamocortical Axon Navigation

Guillermina López-Bendito,[1,5] Aline Cautinat,[2,5] Juan Antonio Sánchez,[1] Franck Bielle,[2] Nuria Flames,[1] Alistair N. Garratt,[3] David A. Talmage,[4] Lorna W. Role,[4] Patrick Charnay,[2] Oscar Marín,[1,6,*] and Sonia Garel[2,6,*]

[1] Instituto de Neurociencias de Alicante, CSIC & Universidad Miguel Hernández, 03550 Sant Joan d'Alacant, Spain

[2] INSERM, U368, École Normale Supérieure, 75230 Paris cedex 05, France

[3] Max-Delbrueck-Centrum, Robert-Roessle-Strasse 10, D-13125 Berlin-Buch, Germany

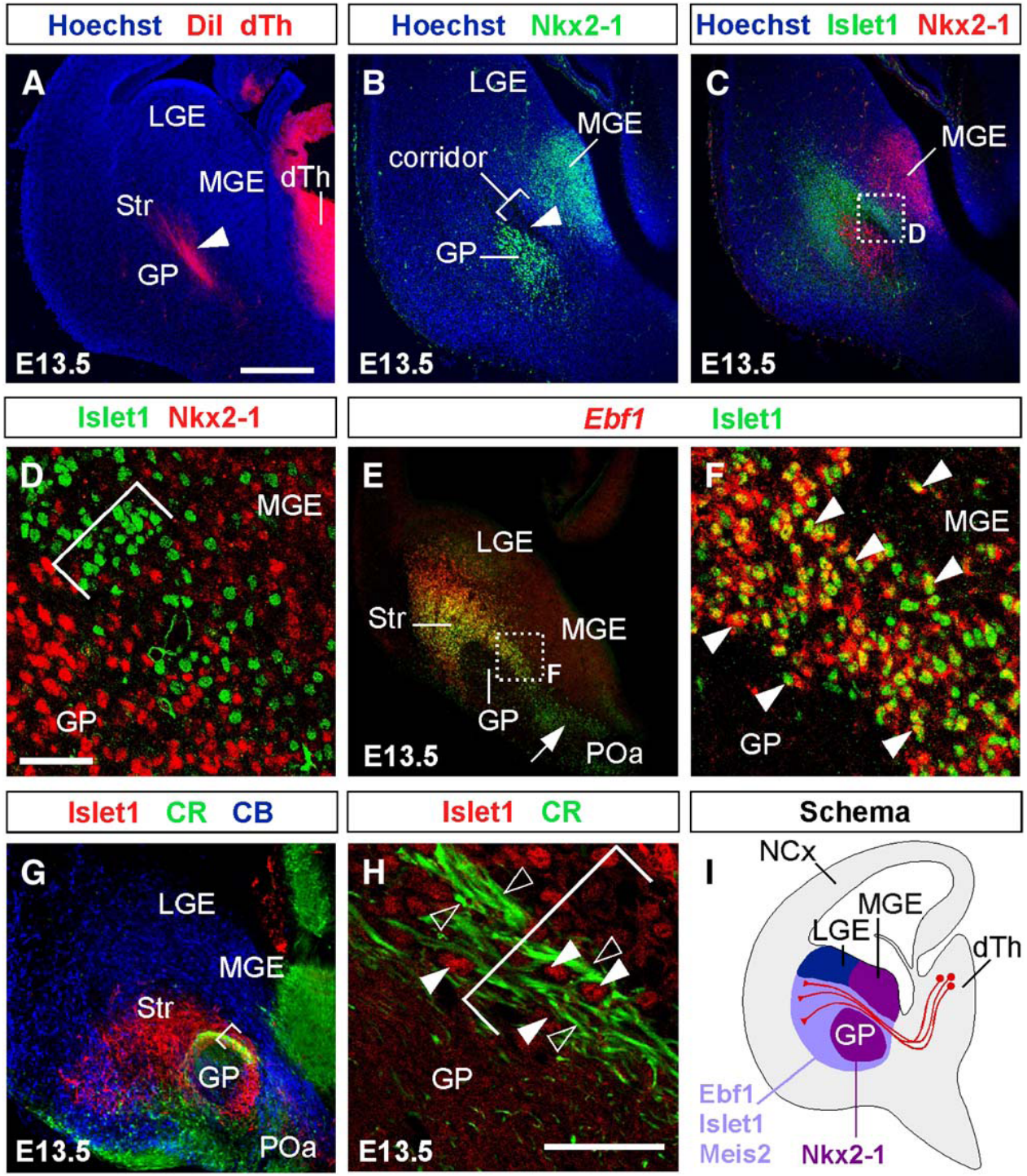
[4] Columbia University Medical Center, New York, NY 10032, USA

[5] These authors contributed equally to this work.

[6] These authors contributed equally to this work.

*Contact: o.marin@umh.es (O.M.); garel@biologie.ens.fr (S.G.)

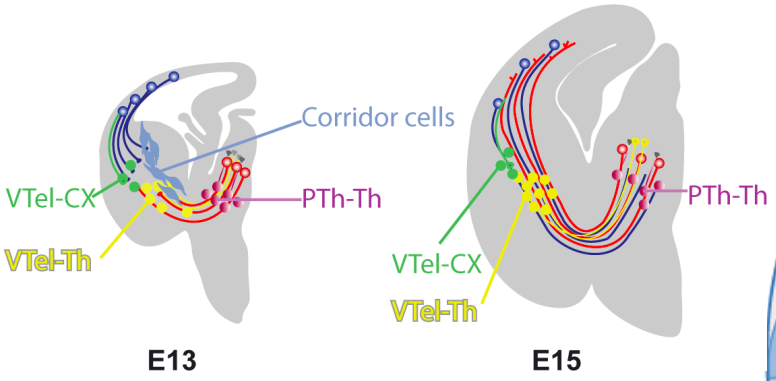
DOI 10.1016/j.cell.2006.01.042



E13.5 coronal mouse telencephalic section showing axonal tracing of dorsal thalamic (dTh) axons (arrowhead) by insertion of a DiI crystal

Thalamocortical axons cross the embryonic forebrain to reach their targets in the neocortex

5. The Subpallium is a main intermediate target for TCA



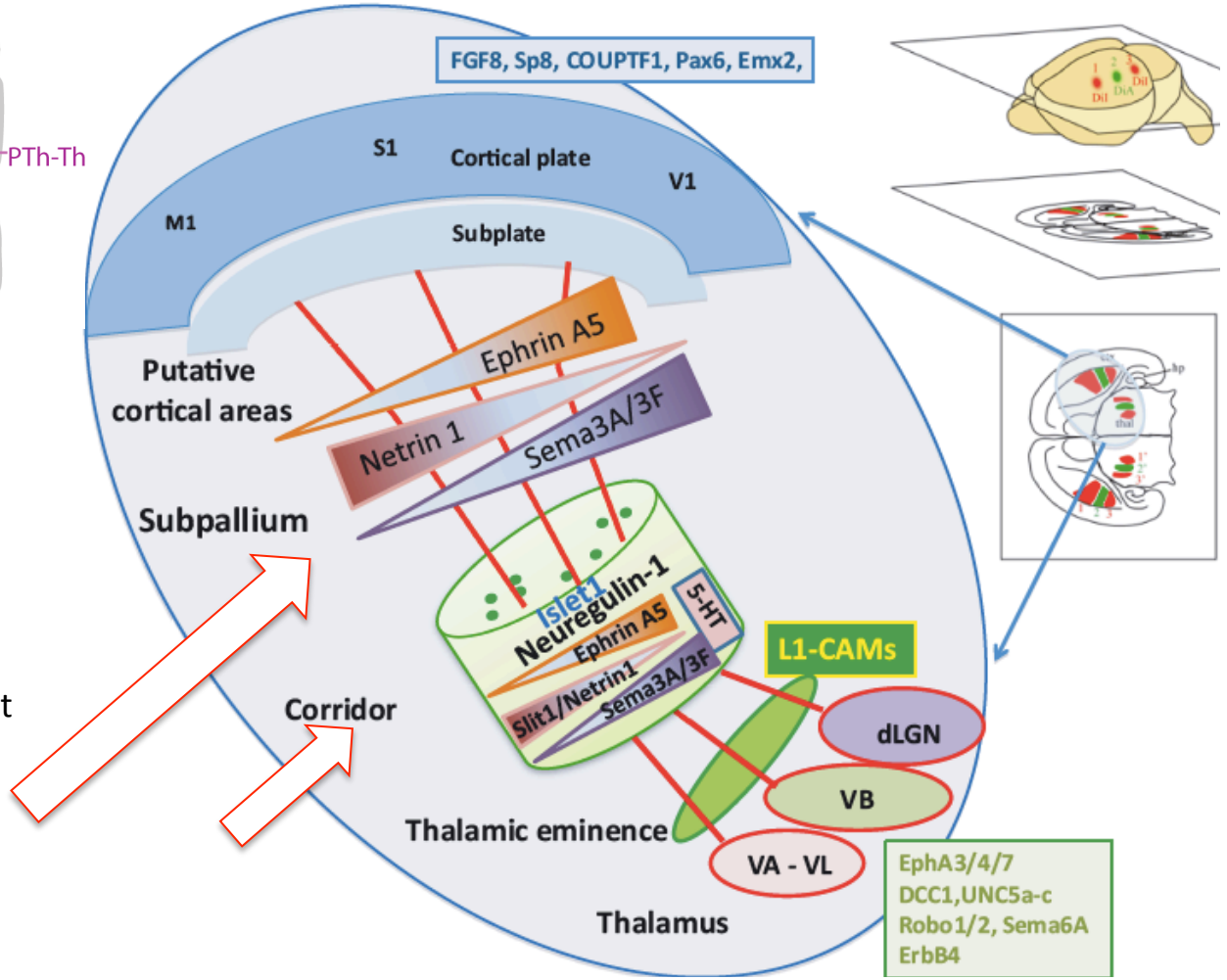
The subpallium attracts the TCAs and Cfu axons

The LGE is particularly involved in their guidance

TCAs travelling in the subpallium diverge rostrocaudally to navigate towards different cortical areas

TCAs express different combinations of guidance cue receptors, are guided by gradients of repellents and attractant cues

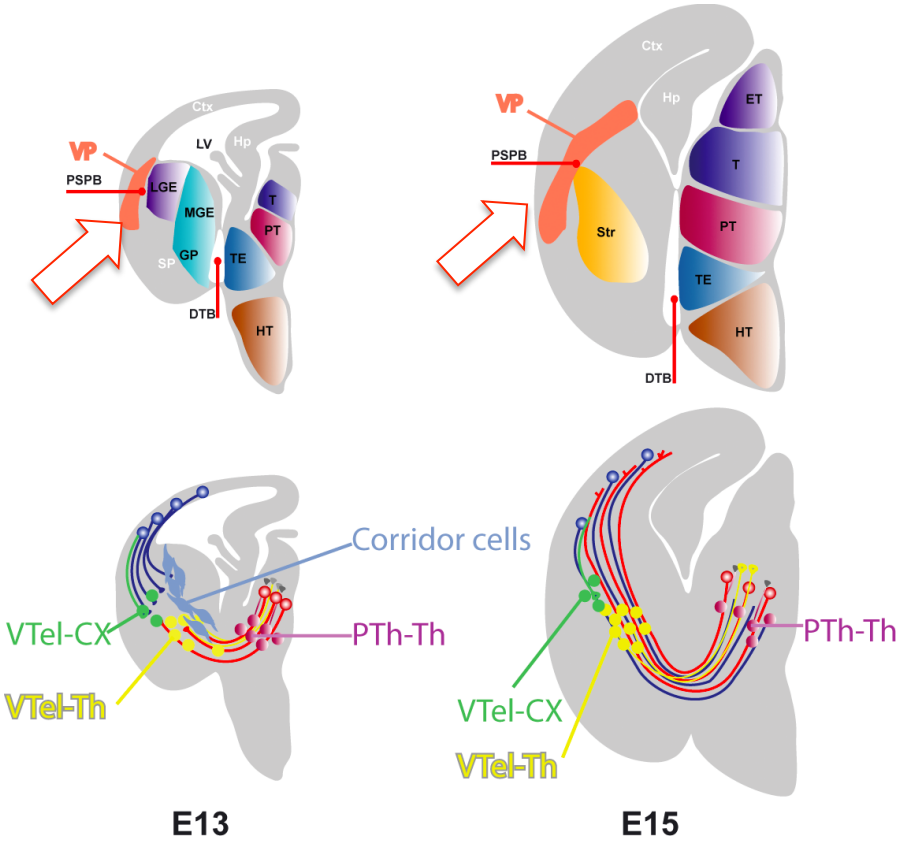
this initial topography is independent of the cortica regionalization and is controlled by informations contained in the subpallium

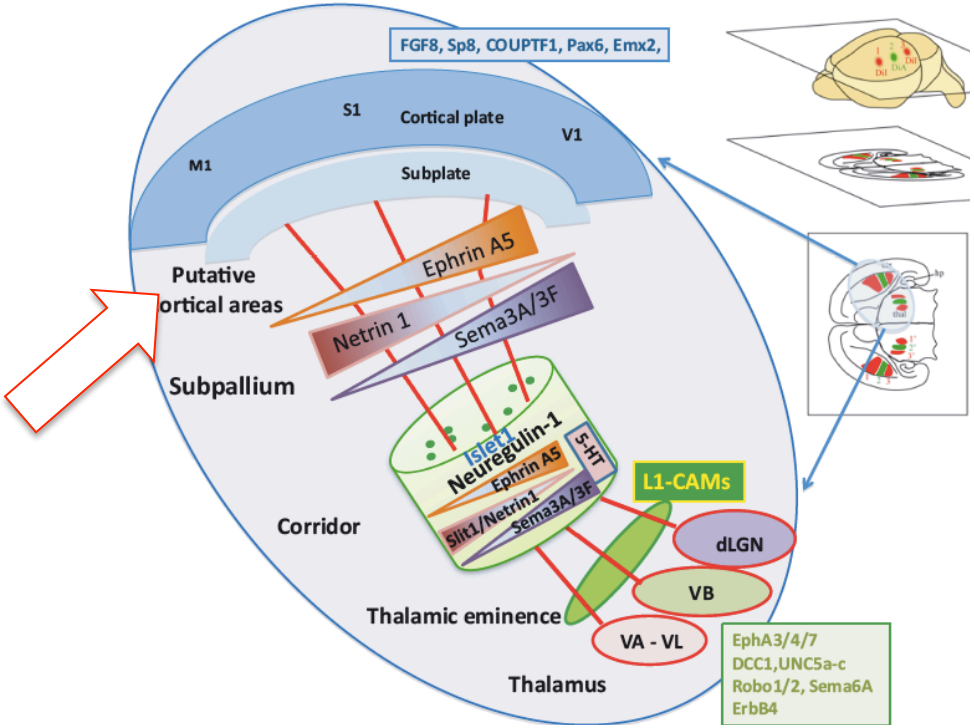


VA - VL= ventroanterior – ventrolateral
dLGN=dorsolateral geniculate nucleus
VB= ventrobasal

Thalamocortical axons cross the embryonic forebrain to reach their targets in the neocortex

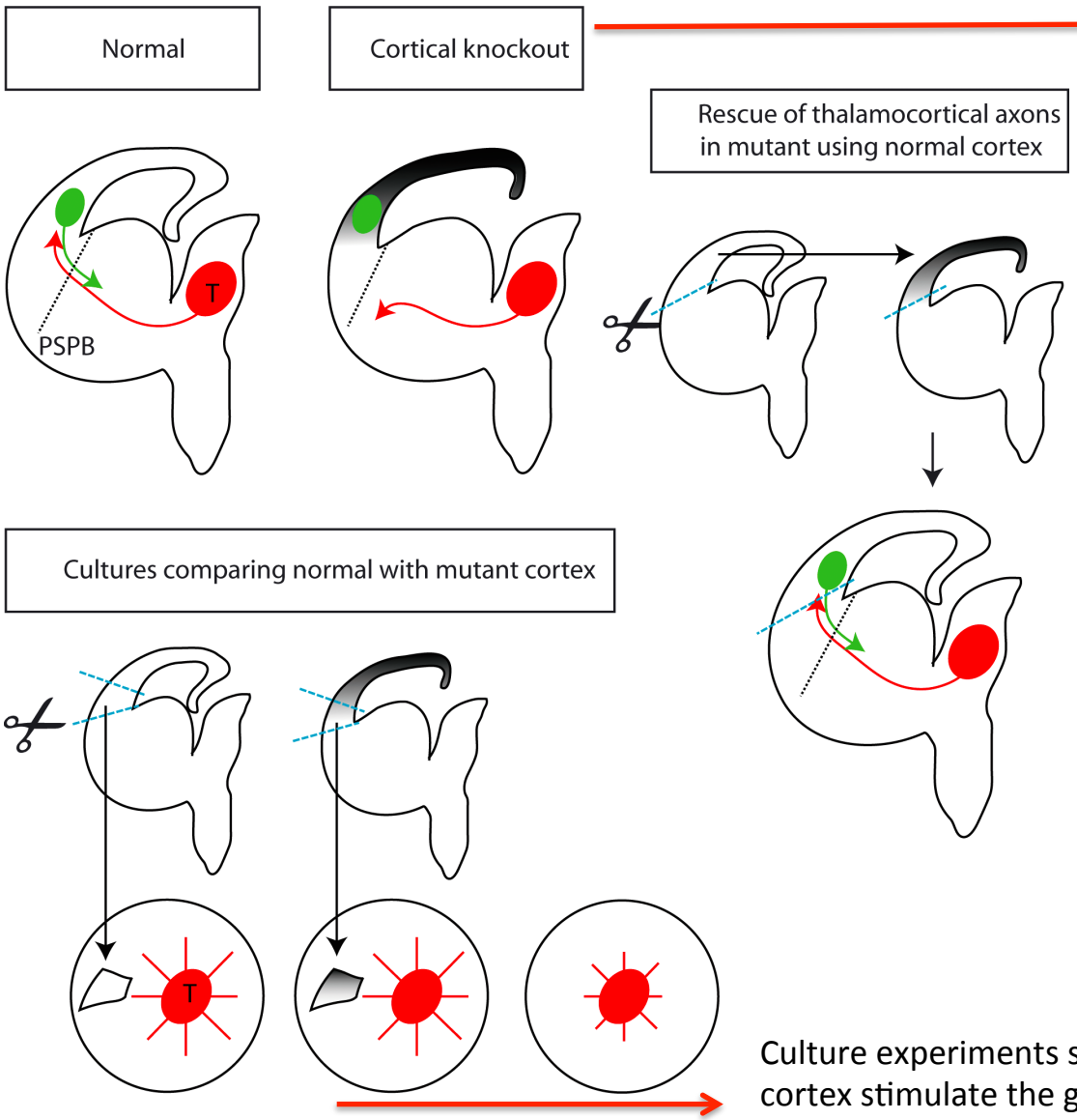
How TCAs enter the cerebral cortex?





TCAs start to approach the PSPB at E13 (mouse)
Pioneer corticofugal axons from the cortex interact with ascending TCAs favoring the crossing of the PSPB

The importance of corticofugal axons for thalamic axon crossing of the PSPB



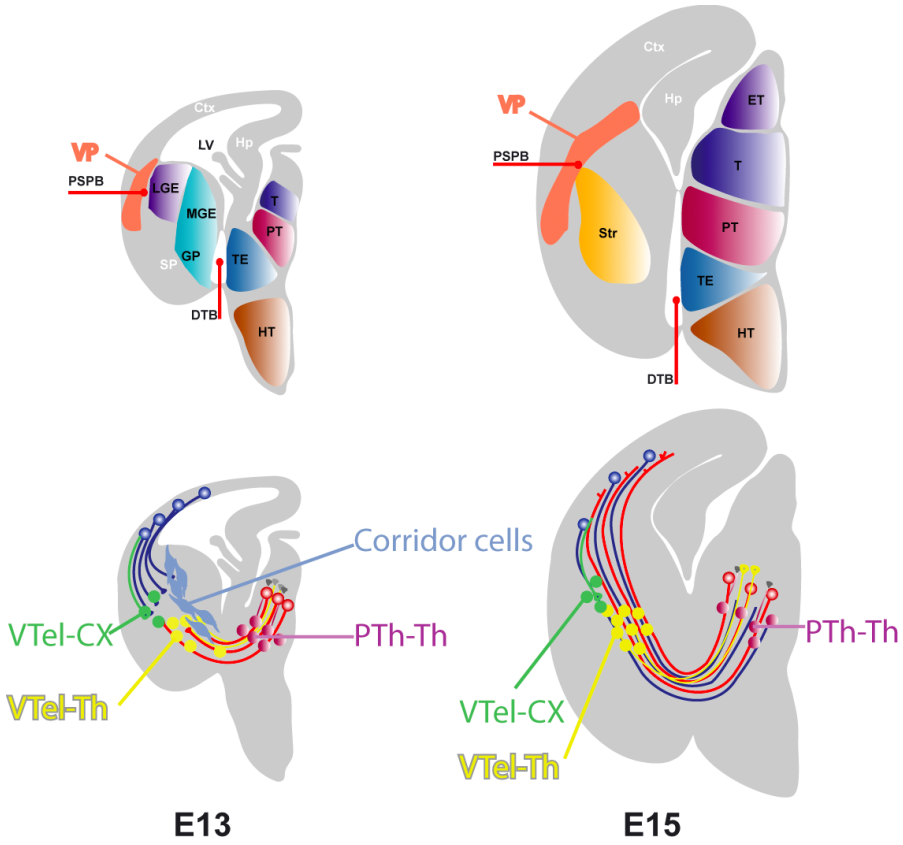
In conditional Emx1Cre;APC loxP / loxP mutants, the development of cortical neurons and hence of corticofugal axons is blocked, but, although the thalamus and VTel are unaffected, thalamic axons do not cross the PSPB

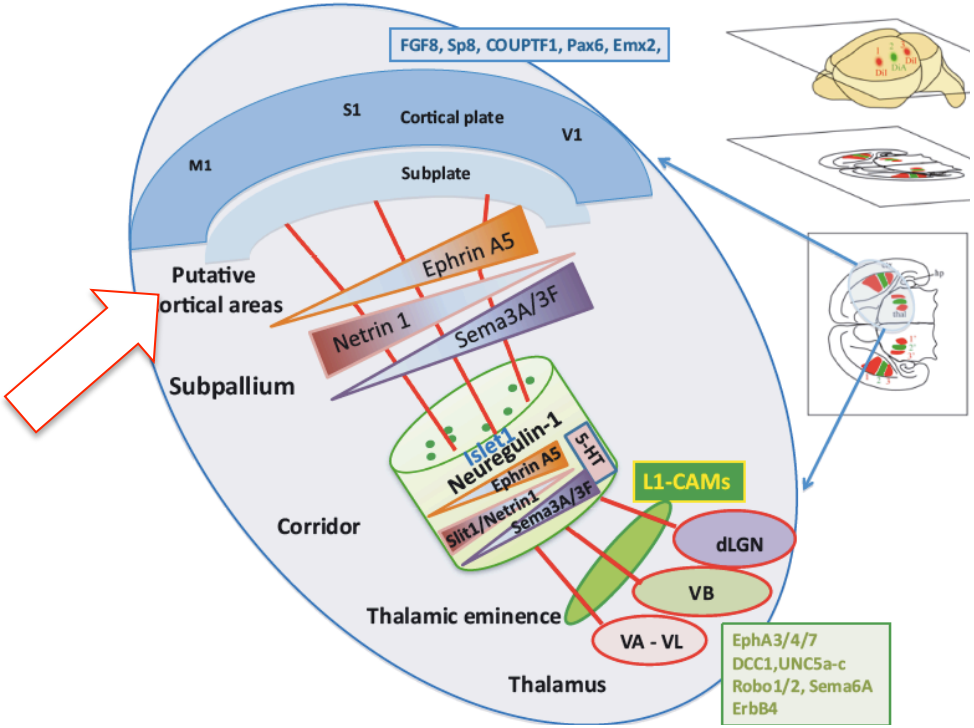
When normal cortex was substituted for mutant cortex in slice cultures from the brains of Emx1Cre;APCloxP / loxP embryos, corticofugal axons were restored, and thalamic axons were able to cross the PSPB.

Culture experiments showed that both normal cortex and mutant cortex stimulate the growth of axons from the thalamus by equal amounts

Thalamocortical axons cross the embryonic forebrain to reach their targets in the neocortex

Guidance of TCAs within the cortex

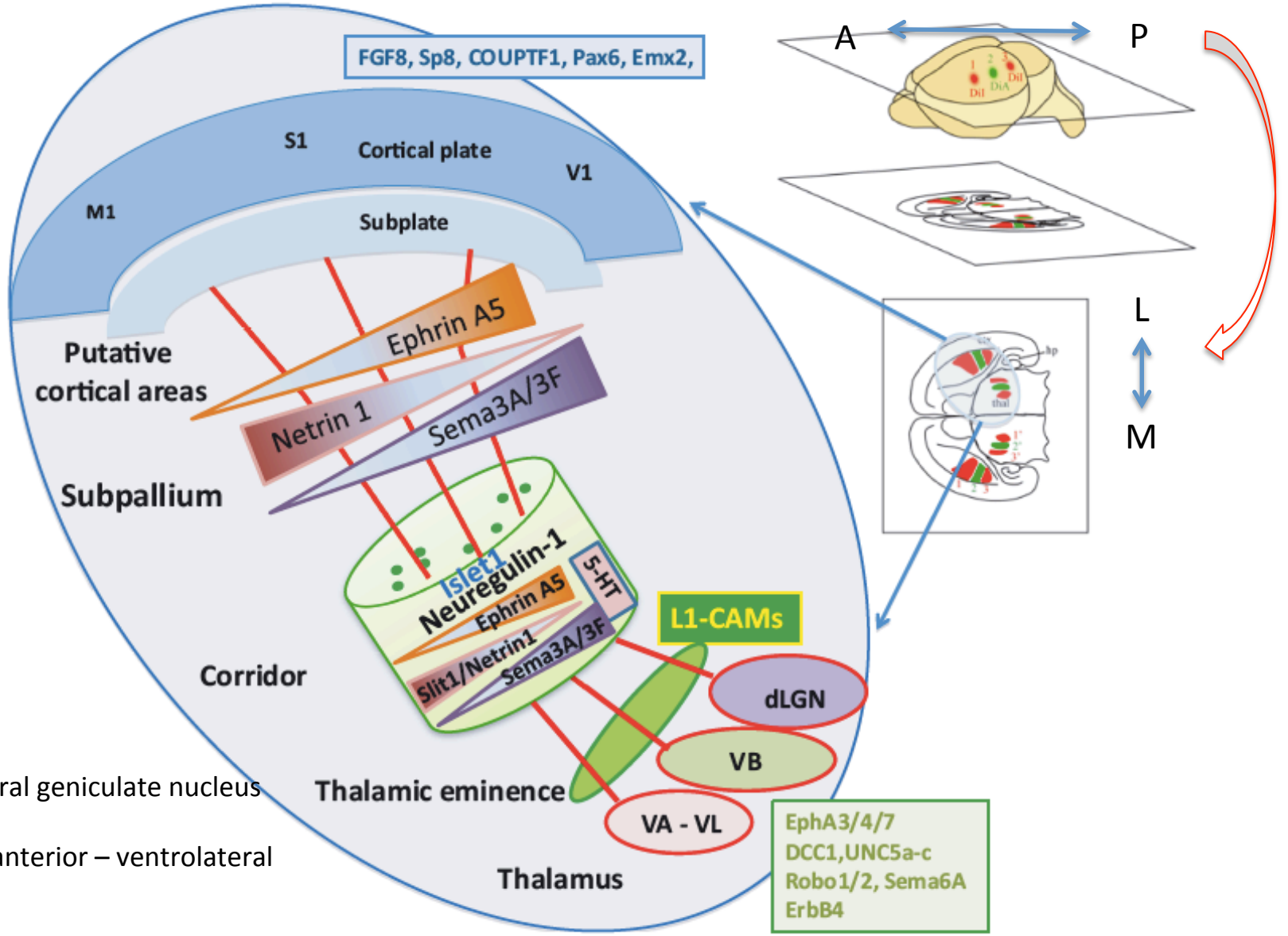




Cortical regionalization reorient thalamocortical map within the neocortex:
Area differences in density, maturity and rearrangement of thalamocortical projections
V1= TCAs undergo significant rearrangement after entry
S1= topography established immediately after entry

Changes in cortical arealization (FGF8 alteration) influence TCAs

The development of thalamocortical connections relies on multiple mechanisms



dLGN=dorsolateral geniculate nucleus
VB= ventrobasal
VA - VL= ventroanterior – ventrolateral