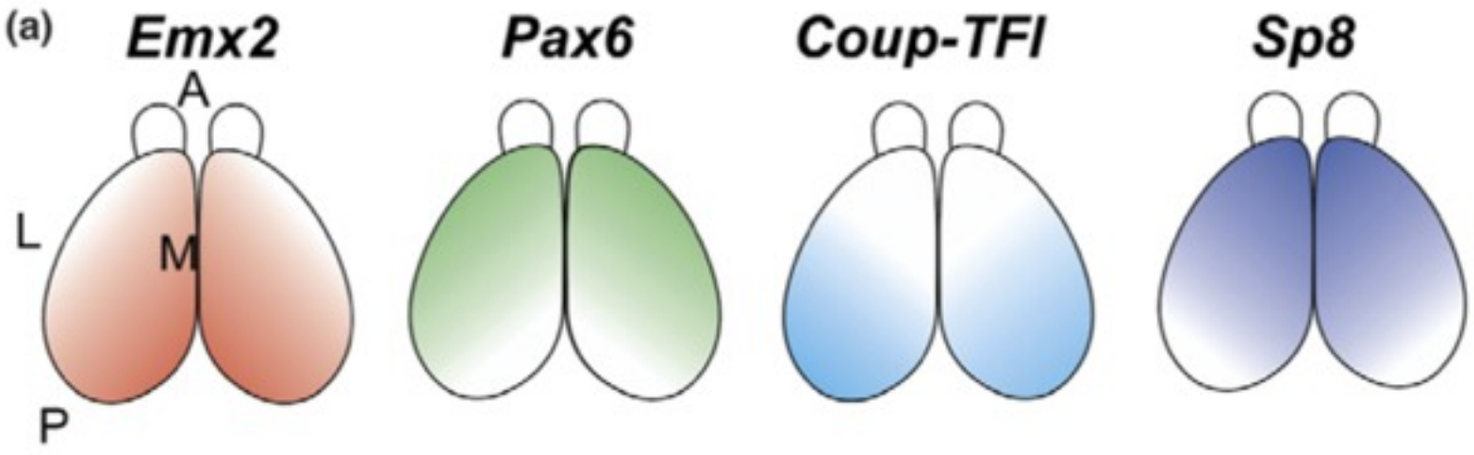
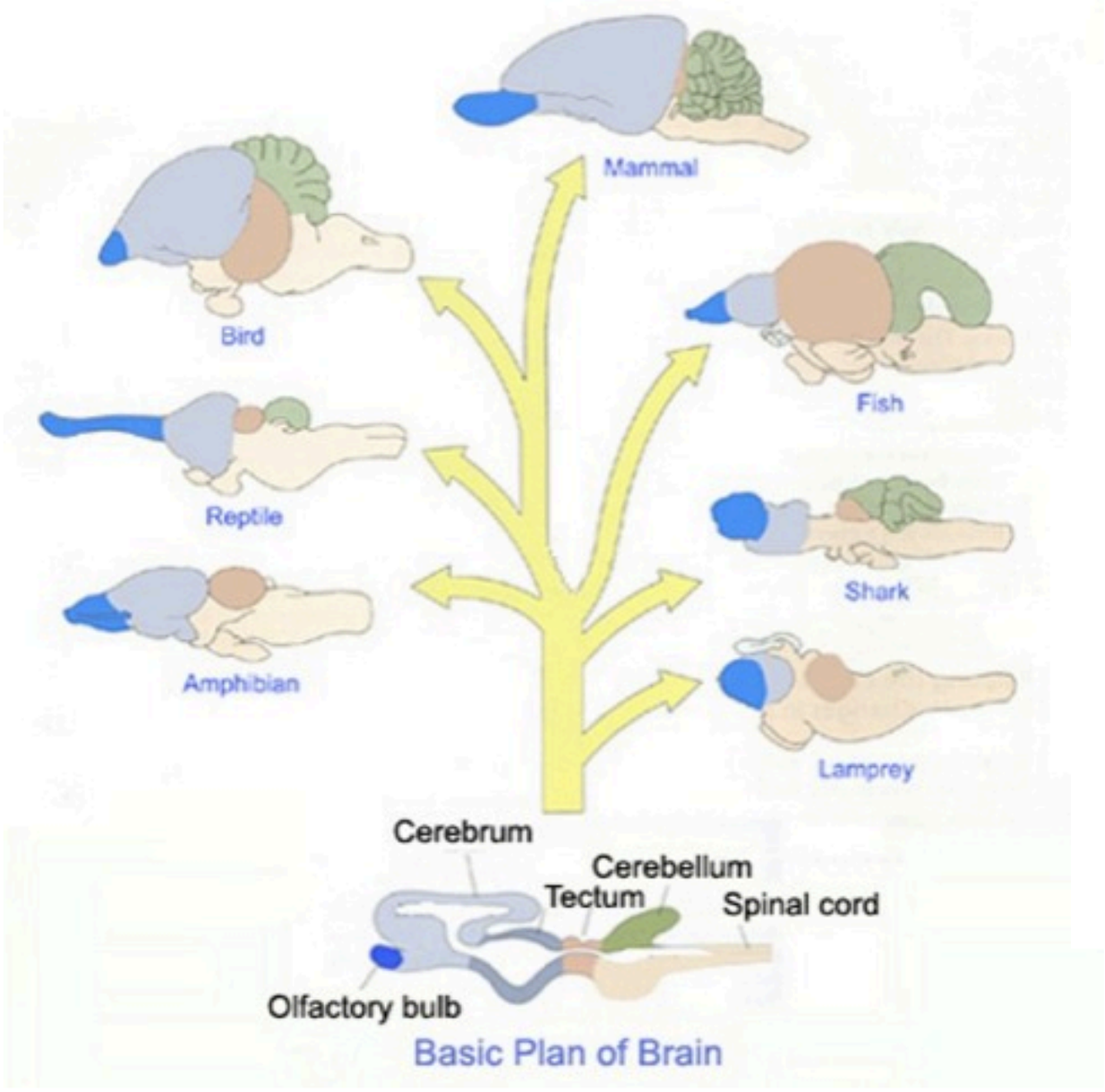
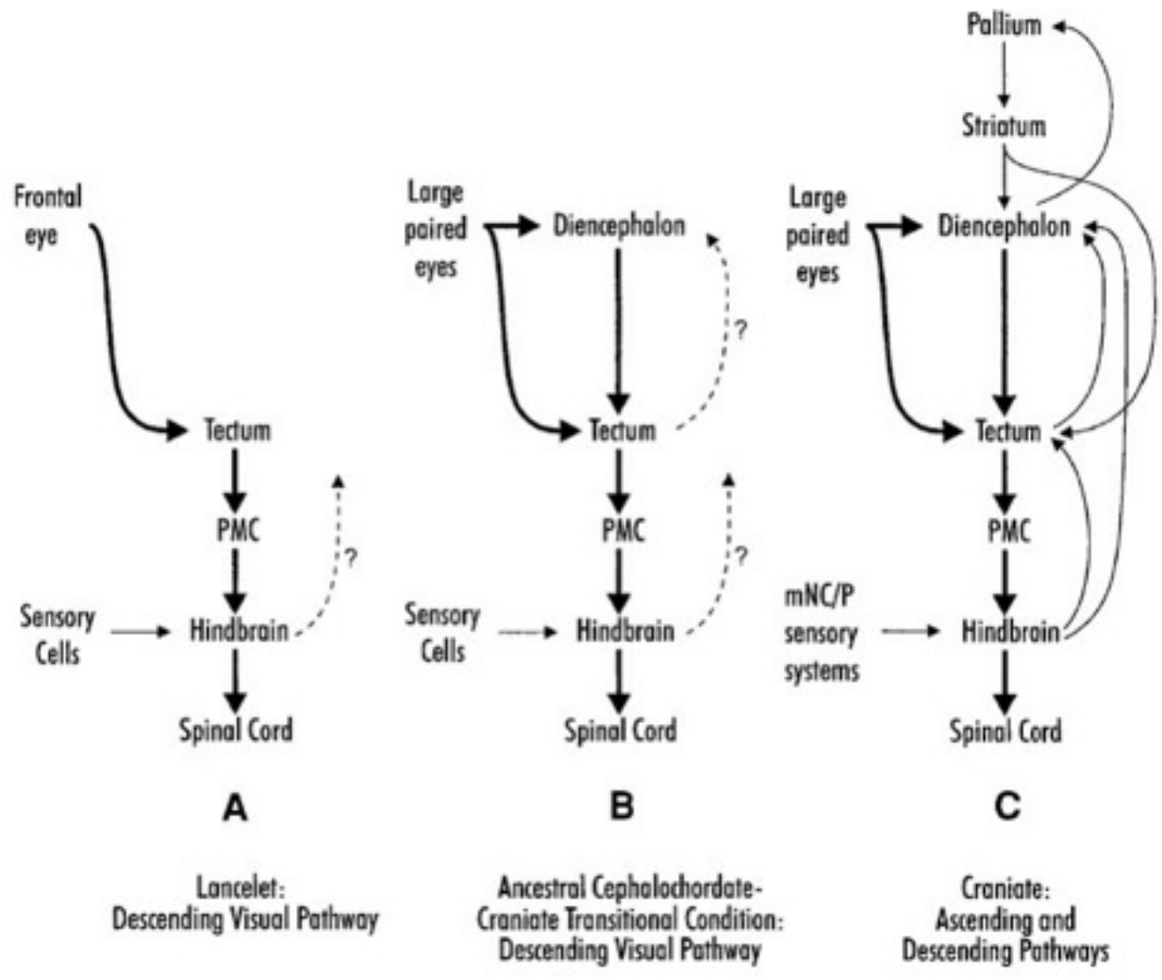
Cortical Patterning



Where we left off...

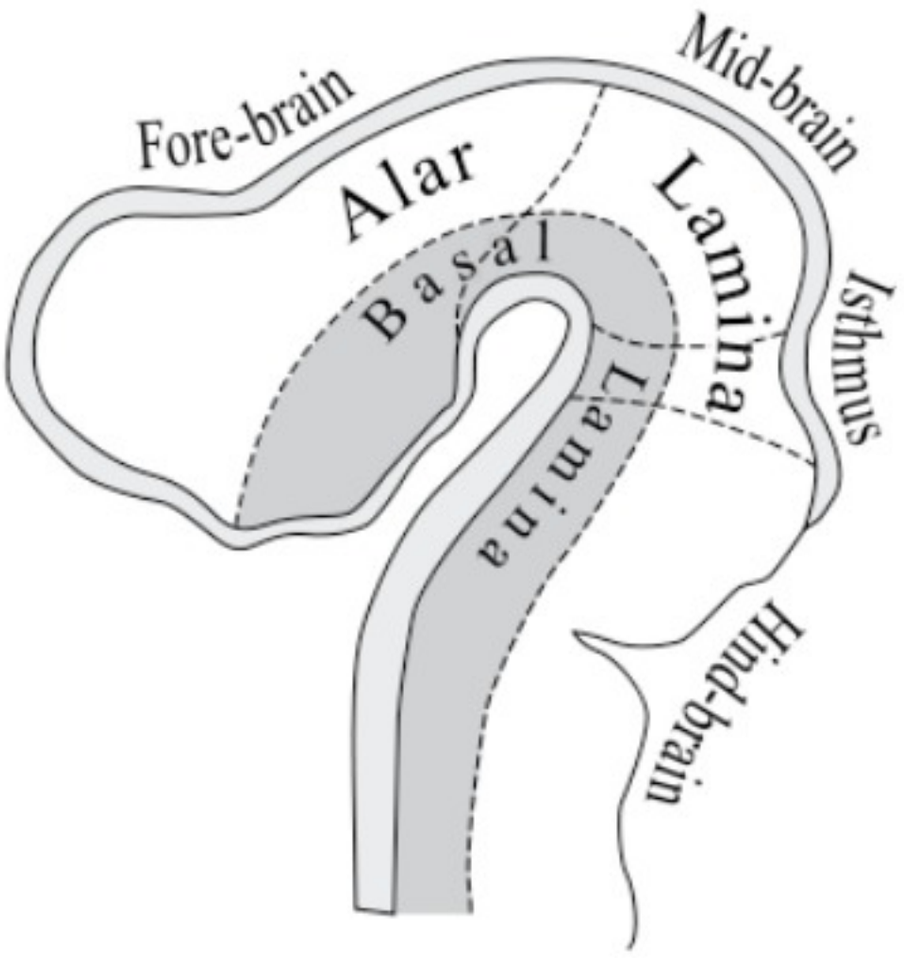
Common Brain Plan

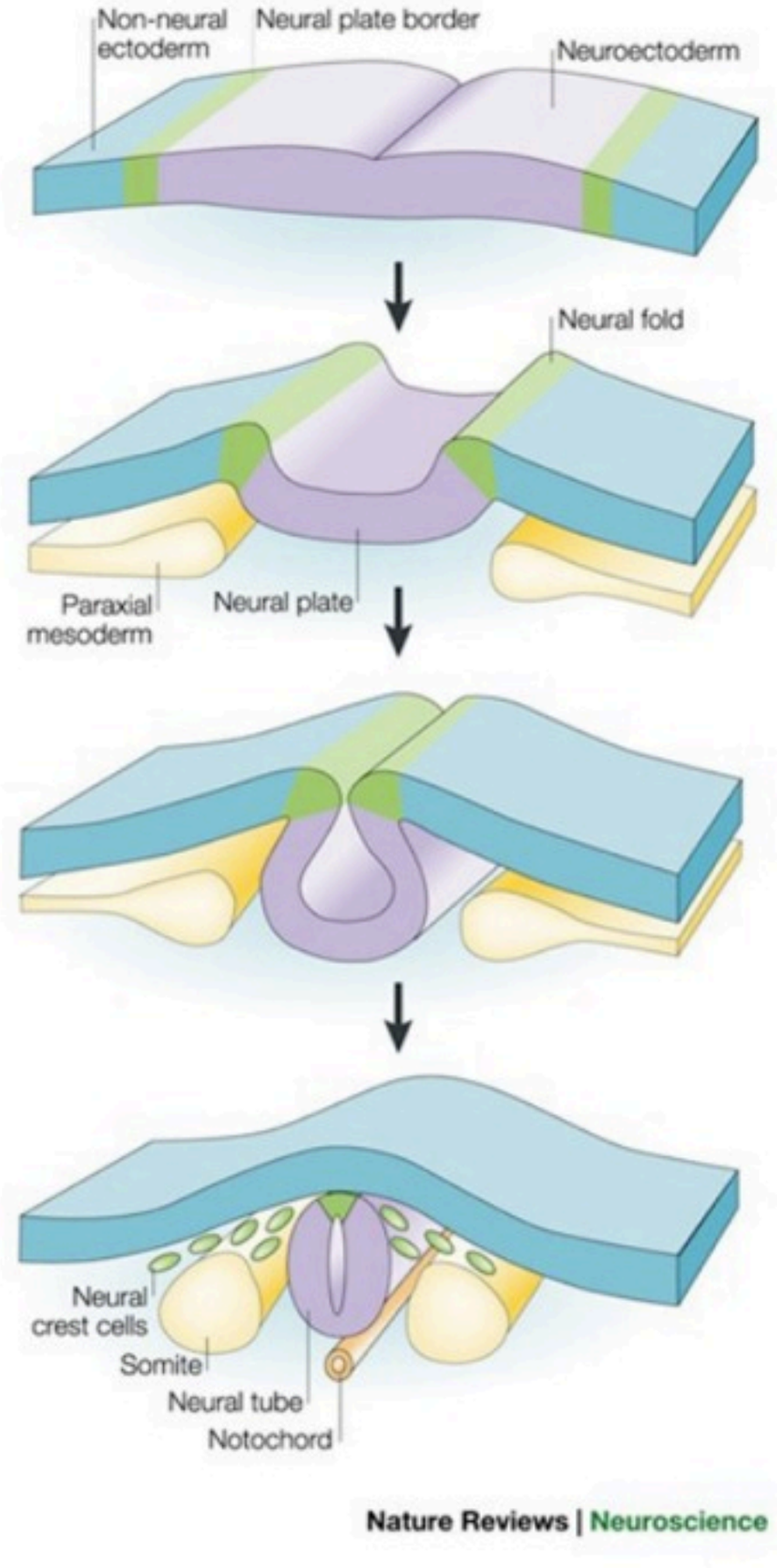




Butler 2000

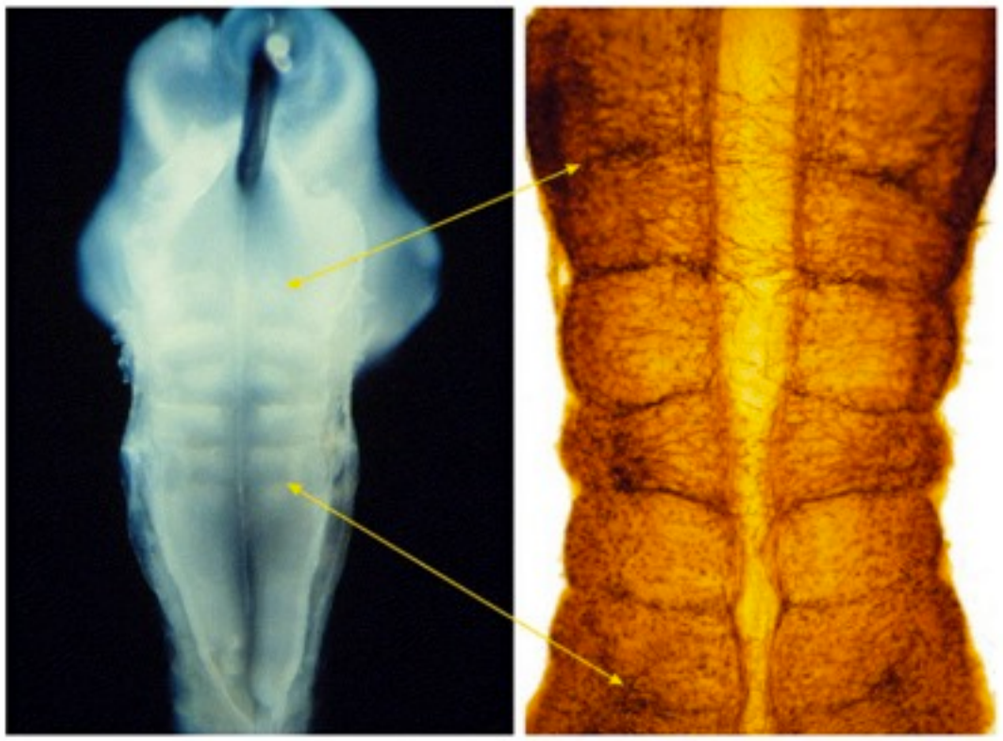
Embryology 101



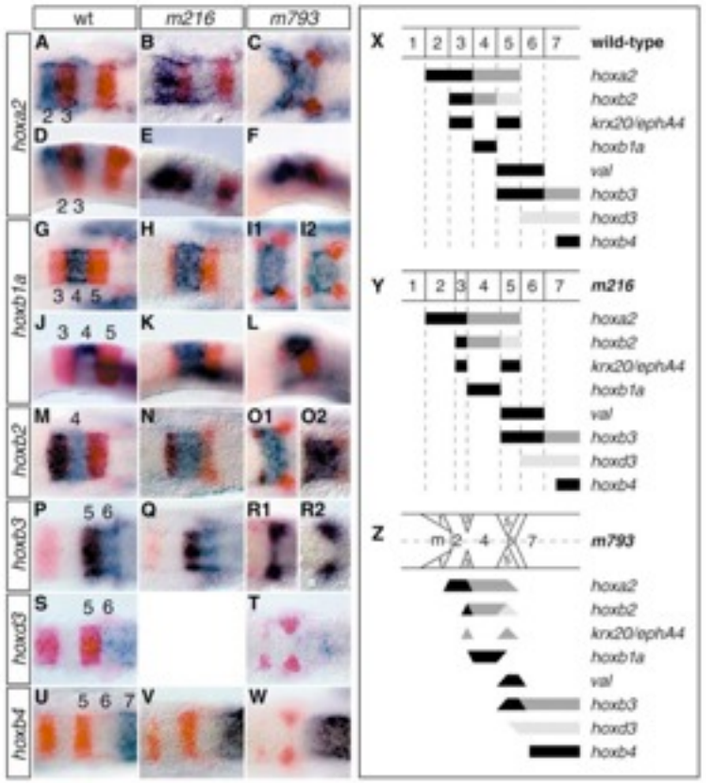


Segmentation & Rhombomeres

Rhombomeres

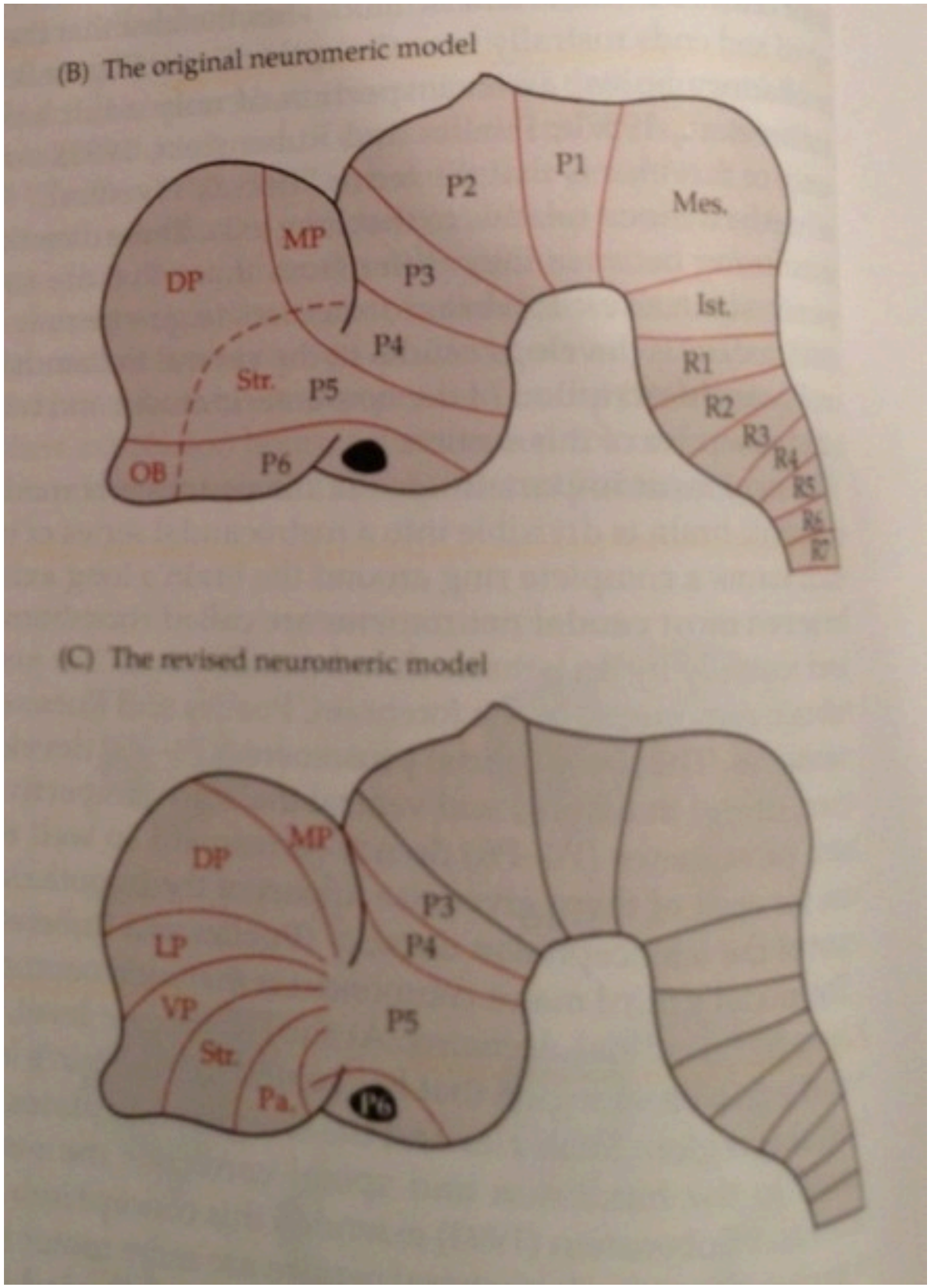


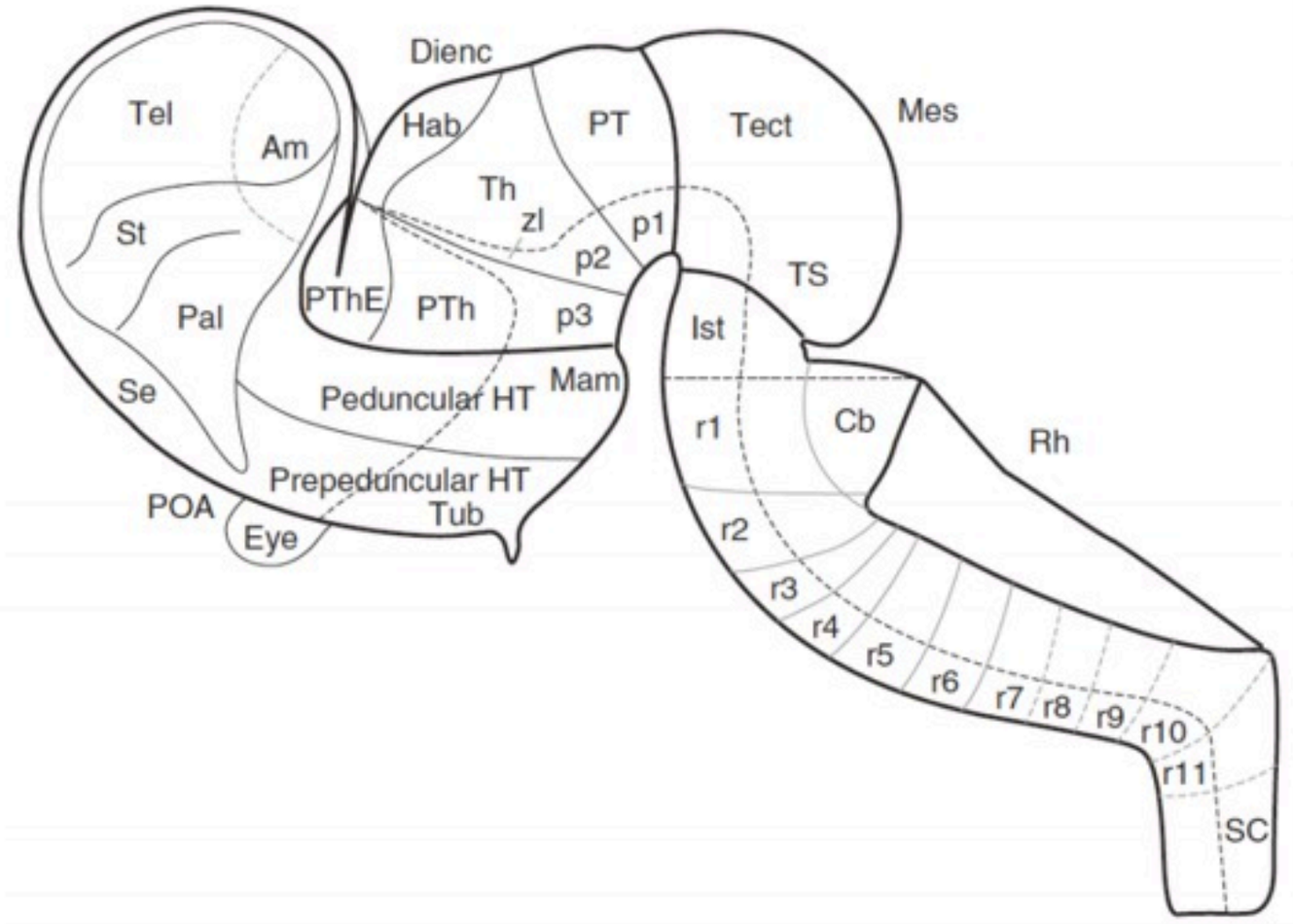
Hox genes provide a unique code for rhombomere identity while other genes set up boundaries



Hauptmann et al. 2002

Neuromeric Model & Prosomeric Model



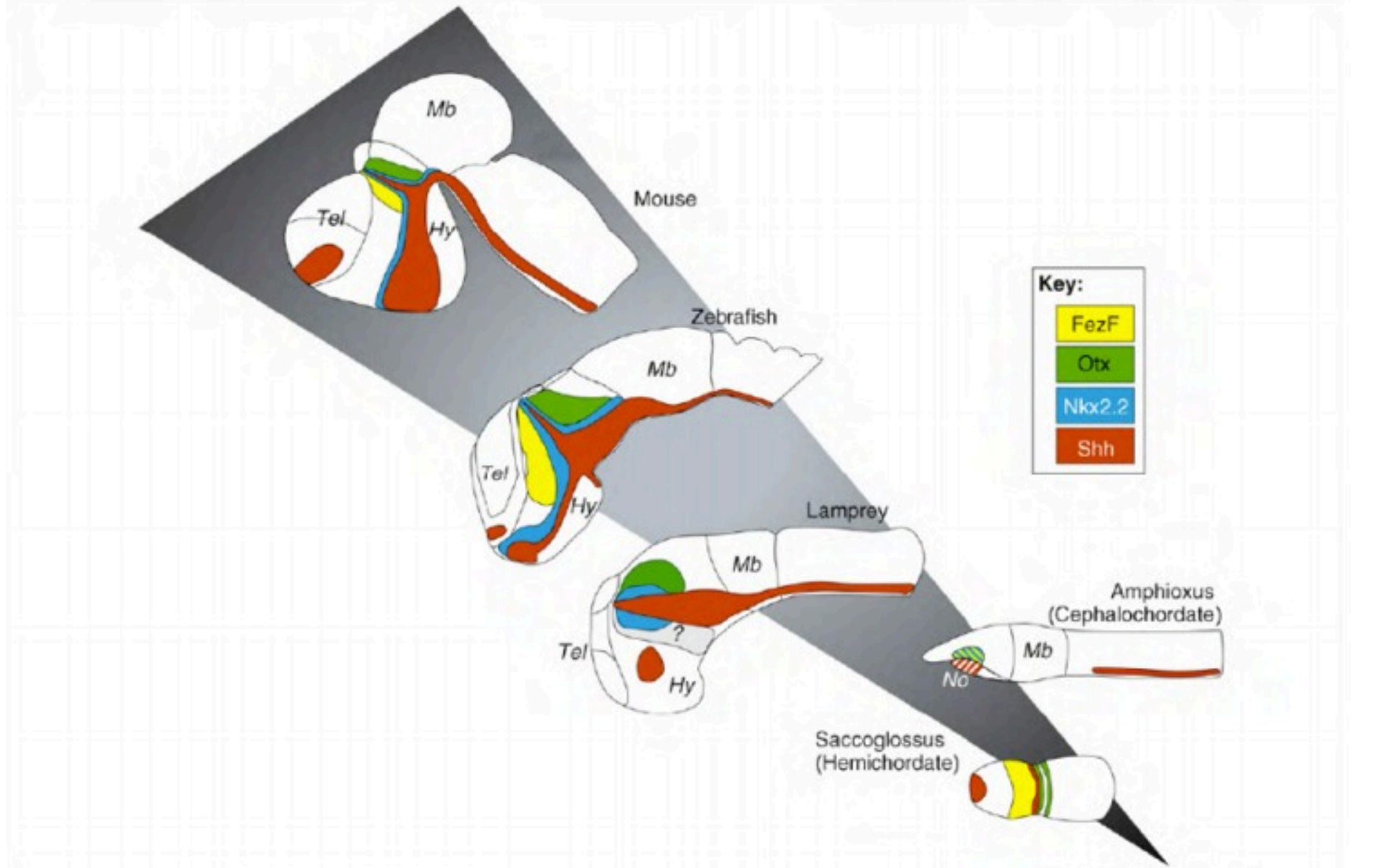


Puelles 2009

not just the hindbrain, but the entire brain of the vertebrate embryo is <u>divisible into a series of neuromeres</u>

each neuromere has an alar & basal domain (sensory/motor)

Neuromeres are not added throughout vertebrate evolution



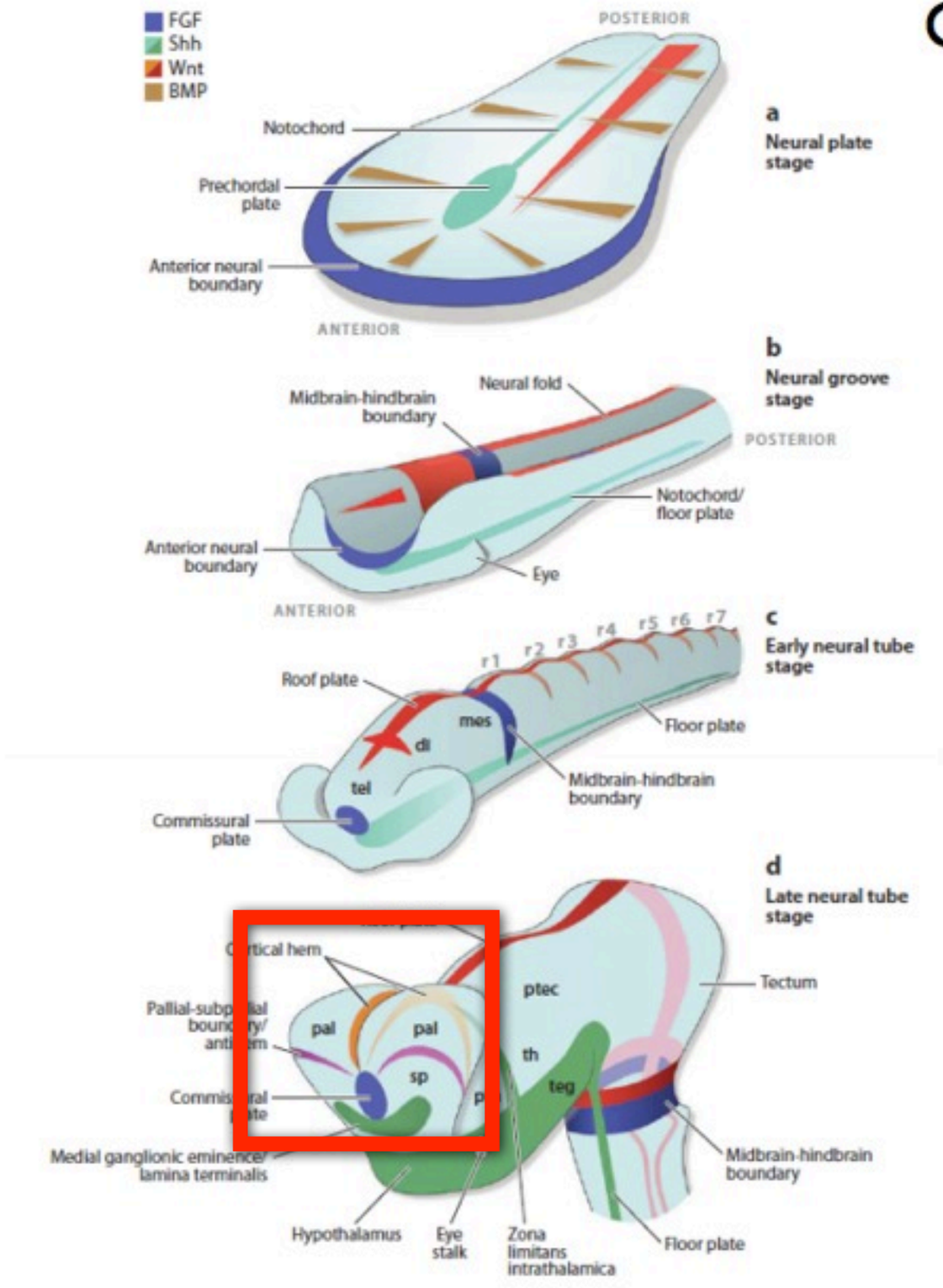
Scholpp and Lumsden 2010

(the brain didn't get bigger/better just by adding on more and more neuromeres)

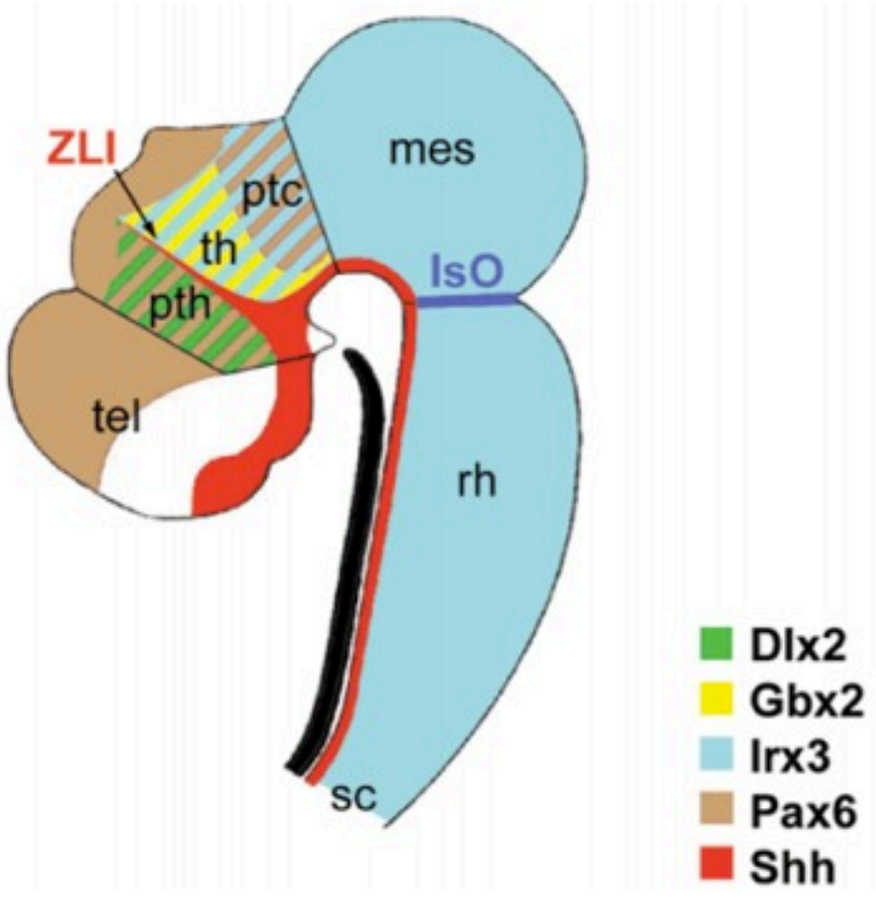
Patterning the Neural Tube

Questions:
what's this cortical hem?

what's special about this SHH gradiant here?

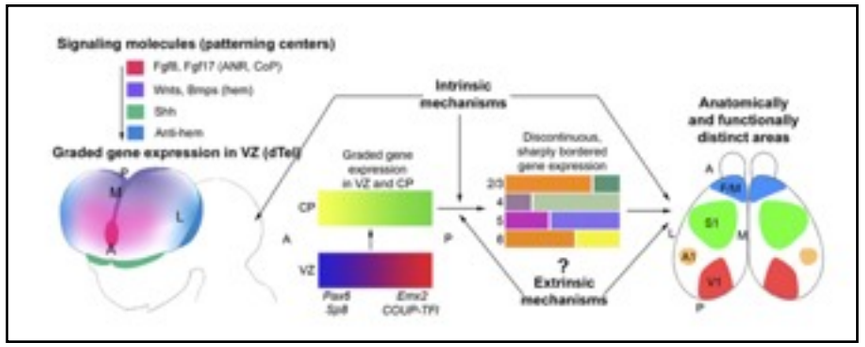


Organizers and chemical signals

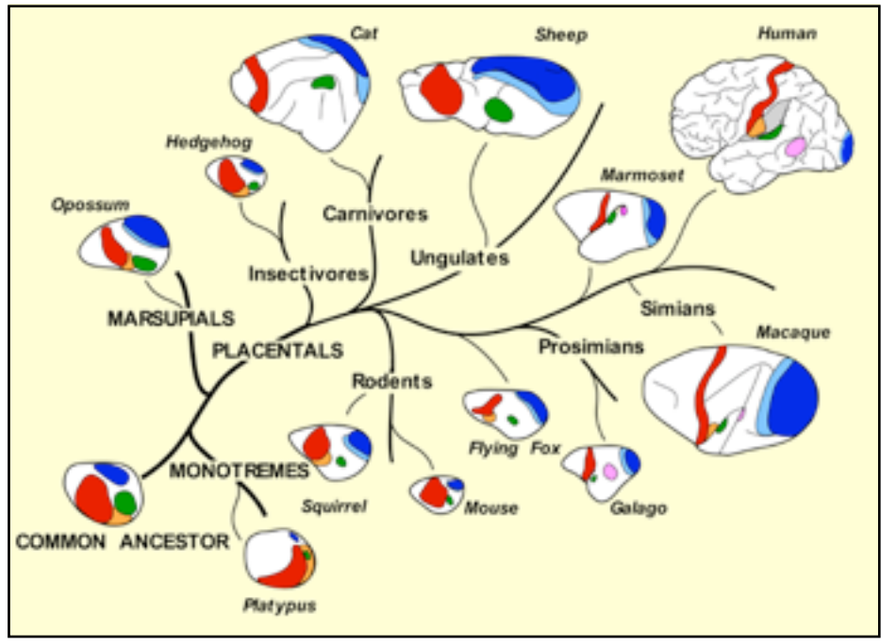


Kiecker and Lumsden 2003, 2012

Patterning the Cortex & Arealization



Dennis O'Leary



Leah Krubitzer

1. Patterning from a developmental perspective

... more embryology 101
... implications for generative models of cortical organization

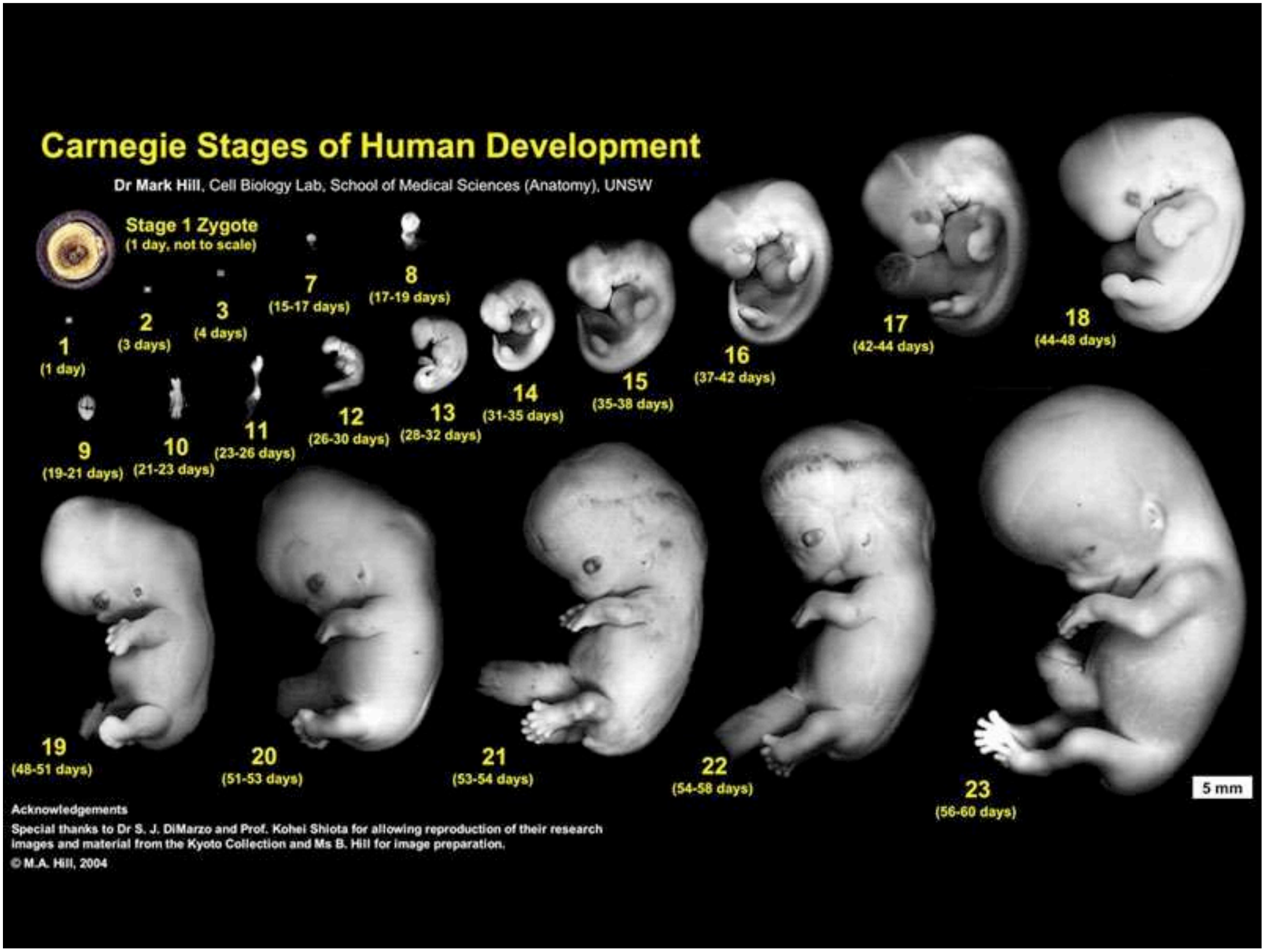
2. Patterning similarities across species and an evolutionary perspective

... leveraging variability within and across species

Broad related question: What's an area?

In understanding the process by which the cortex gets patterned, is there any insight to be drawn about what a good 'unit' or module is? a cortical area? a cortical field/zone? a prosomere? how big is it?

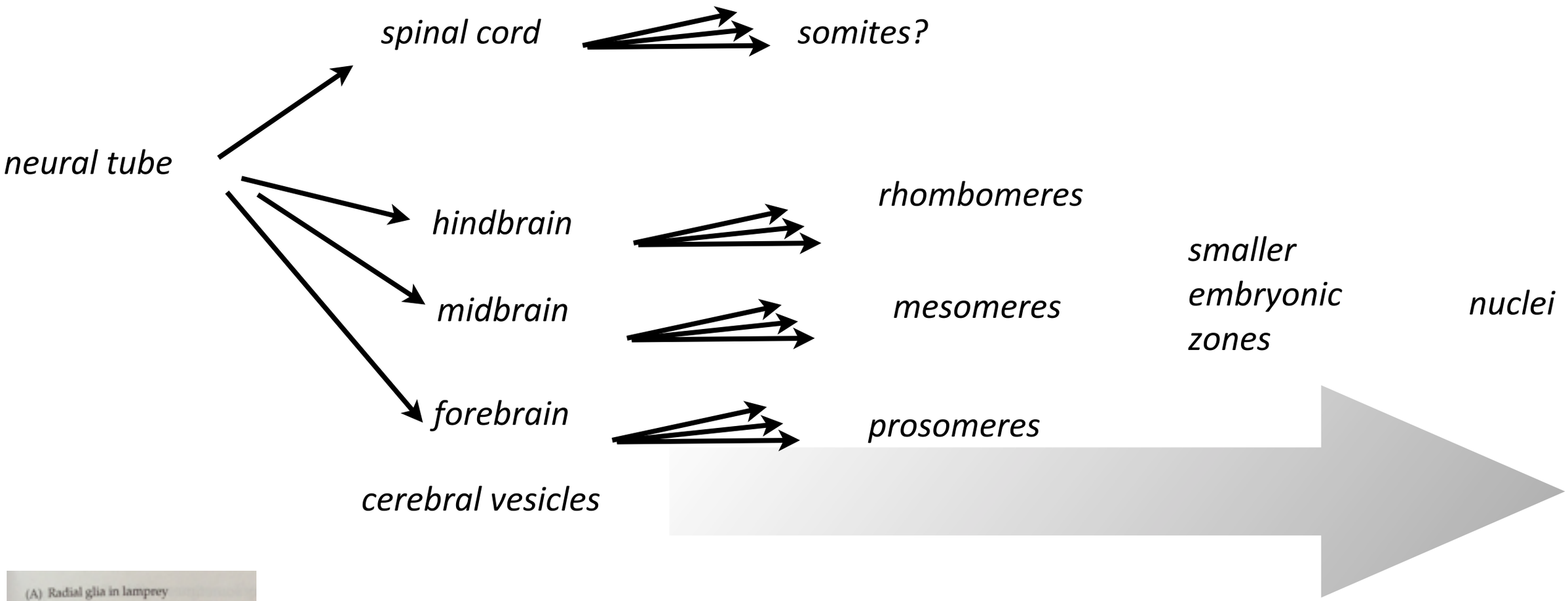
human embryo stages

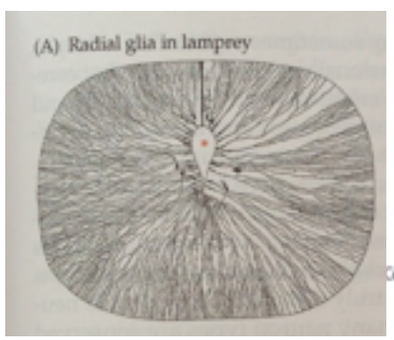


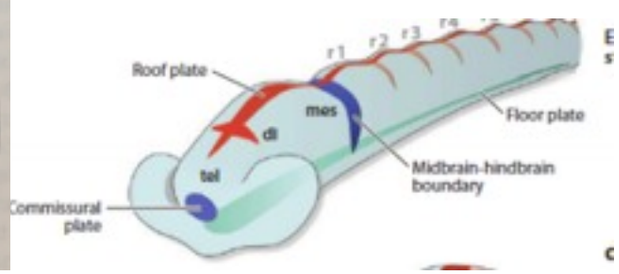
Embryogenesis

- *"proceeds in a tree-like manner"*
- *"branching hierarchy"*
- ***"progressive compartmentalization"***

Question:
how far does this hold for the neocortex/forebrain?



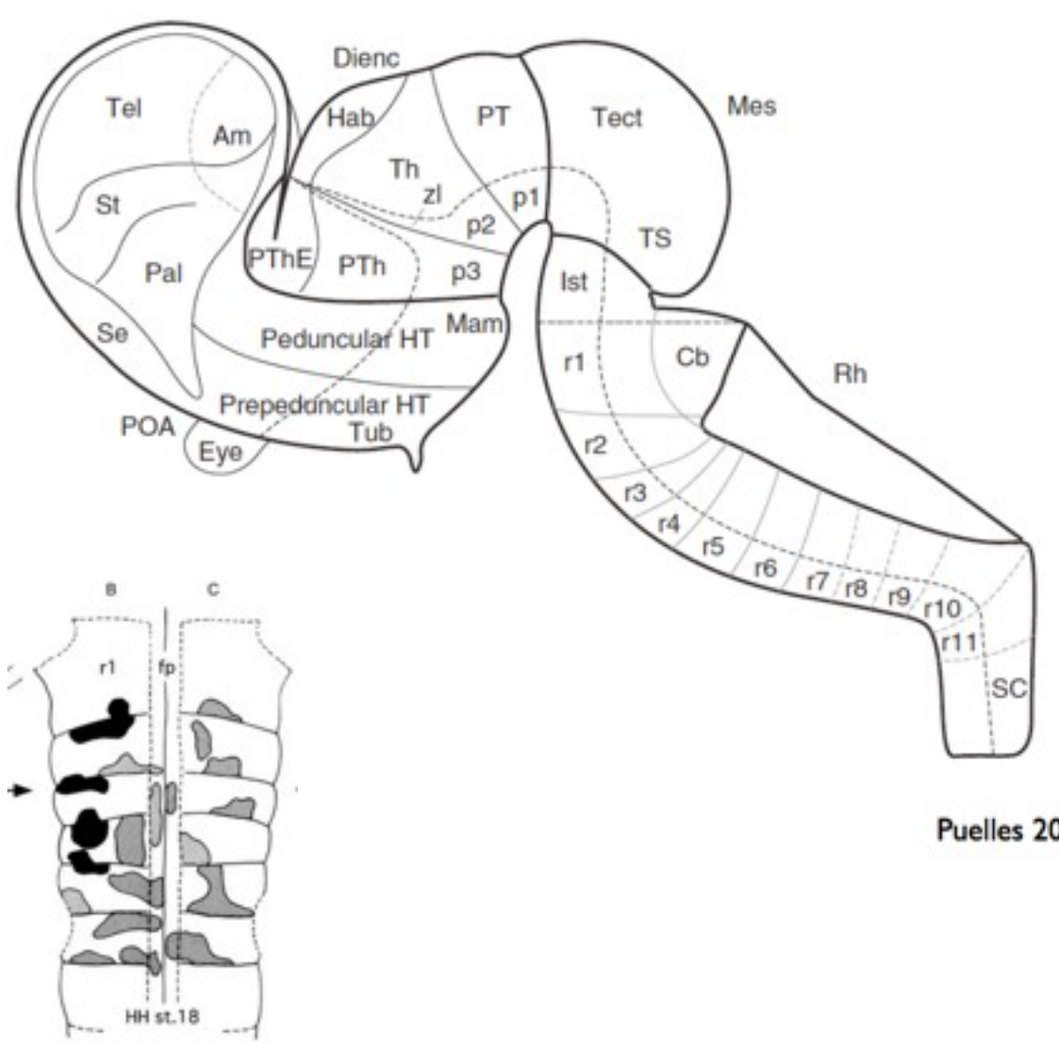




most cells migrate radially (not tangentially), so stay in their zone

related to homologies
"topological position--of both adult structures and their embryonic precursors--is the most useful criterion of character identification for brain regions"

Challenges to Prosomere model



Puelles 2009

Question:
what do we know about regional specification?

Strict compartmentalization breaks down...

*P&R: these are '**embryonic fields**', adopt a phenotype because of regulatory genes. if a cell migrates it should become the type of the field it's in*

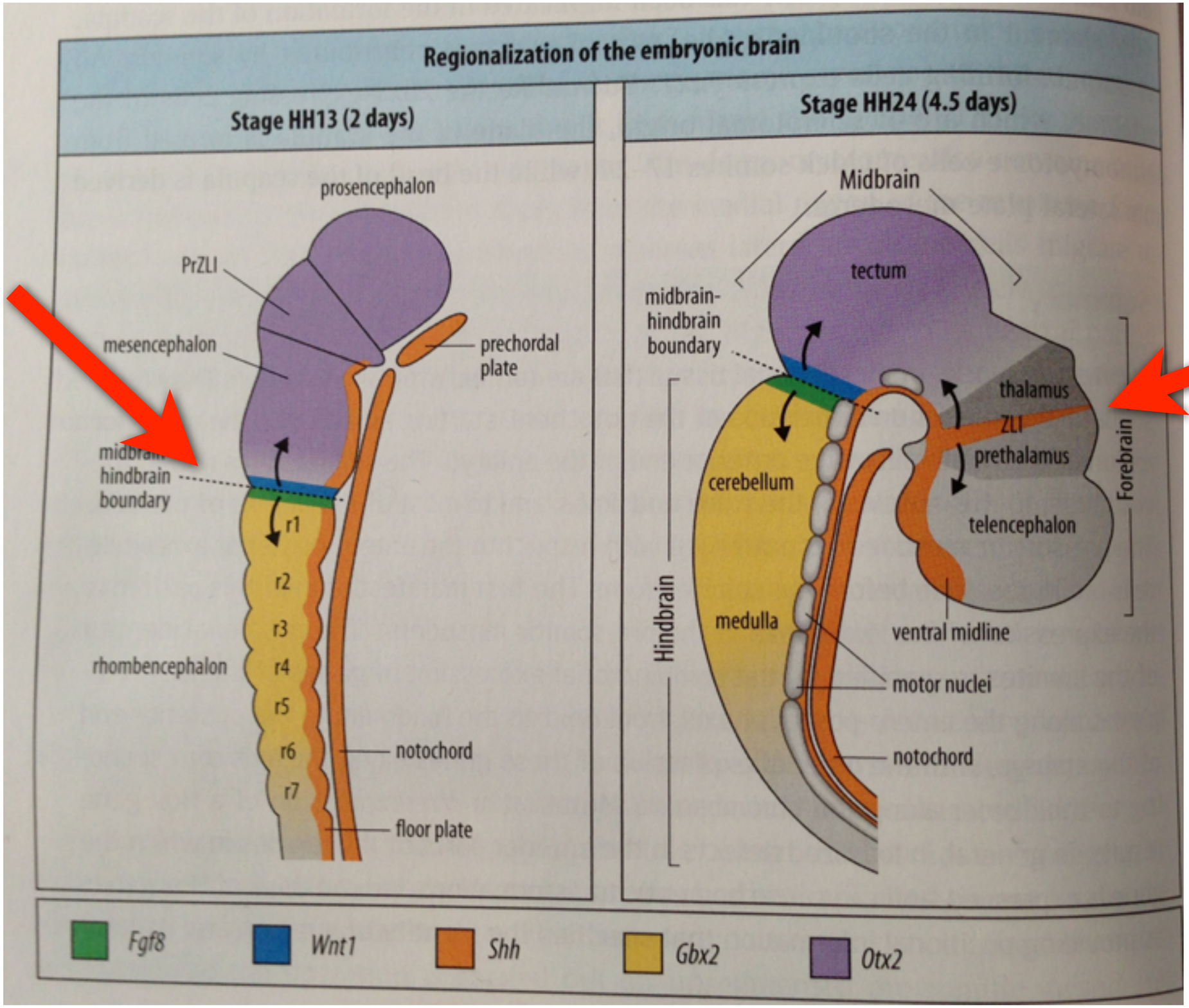
*"The most crucial element of the neuromeric model is not that it's zones are immiscible but that they are **molecularly distinct at the time of regional specification**"*

Two local organizing regions:

tectum = inf/sup colliculi (contra wiring)

Isthmus (MHB)

cerebellum/pons (ipsi wiring)



ZLI

Zona Limitas intrathalamica

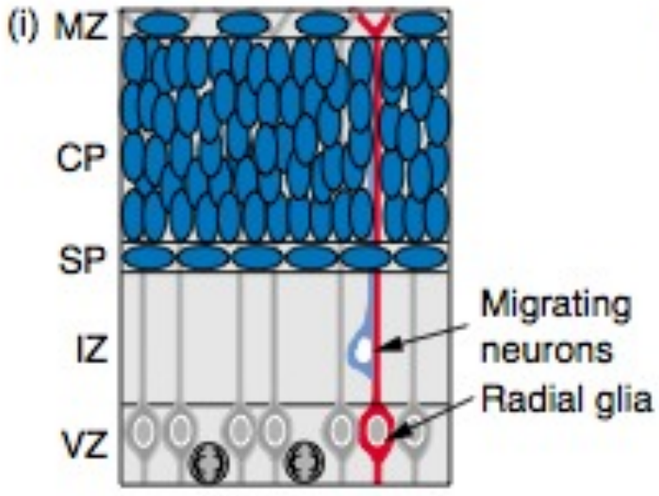
dorsal thalamus

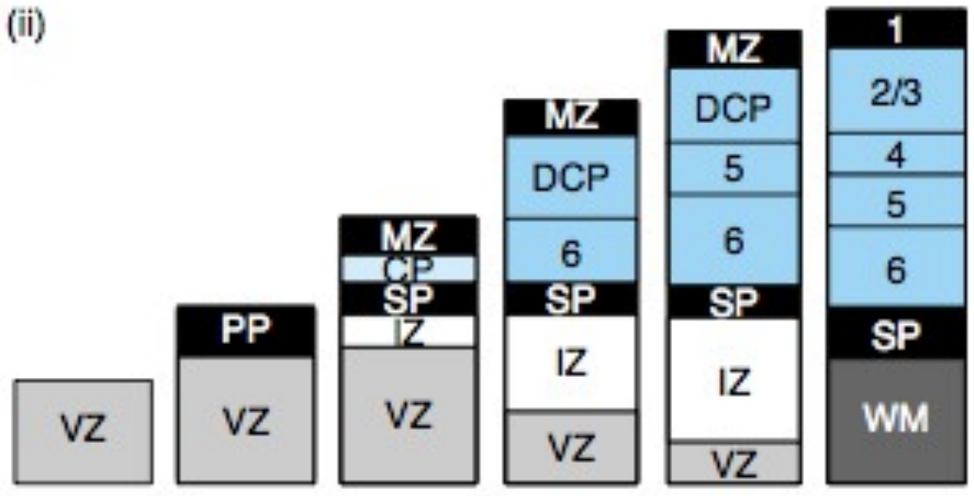
ventral thalamus

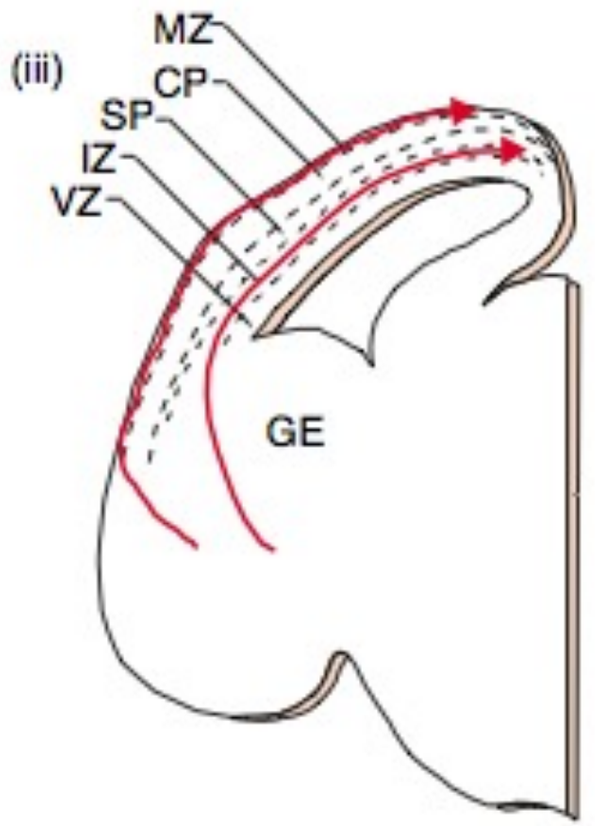
later, the ZLI degrades and these zones merge and cells can cross

Corticogenesis Review

from O'Leary & Nakagawa 2002



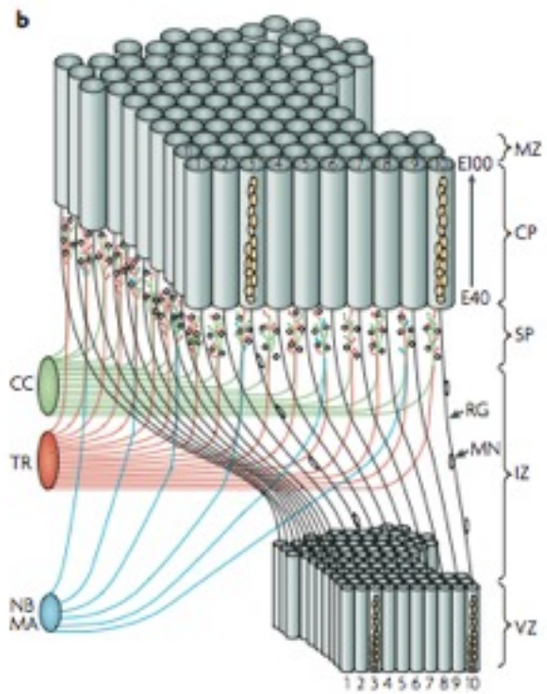




Cortex + wiring Timeline?

Whole Cortical Plate

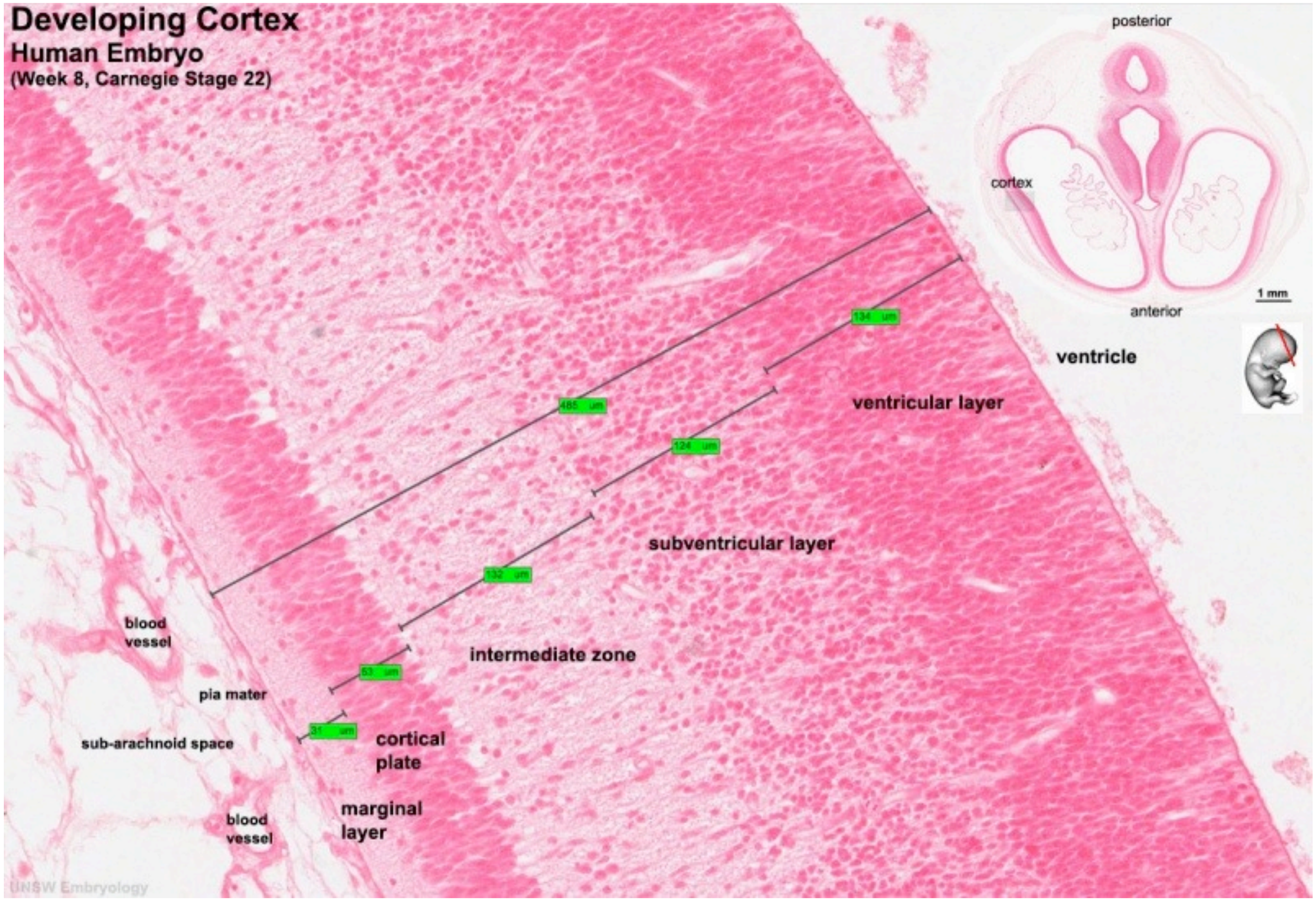
Thalamocortial invasion!



Rakic 2009

Simultaneous: Corticogenesis + Long-range (cortico-cortical and thalamocortical relays)

Developing cortex



layer1/MZ

layer 2/3

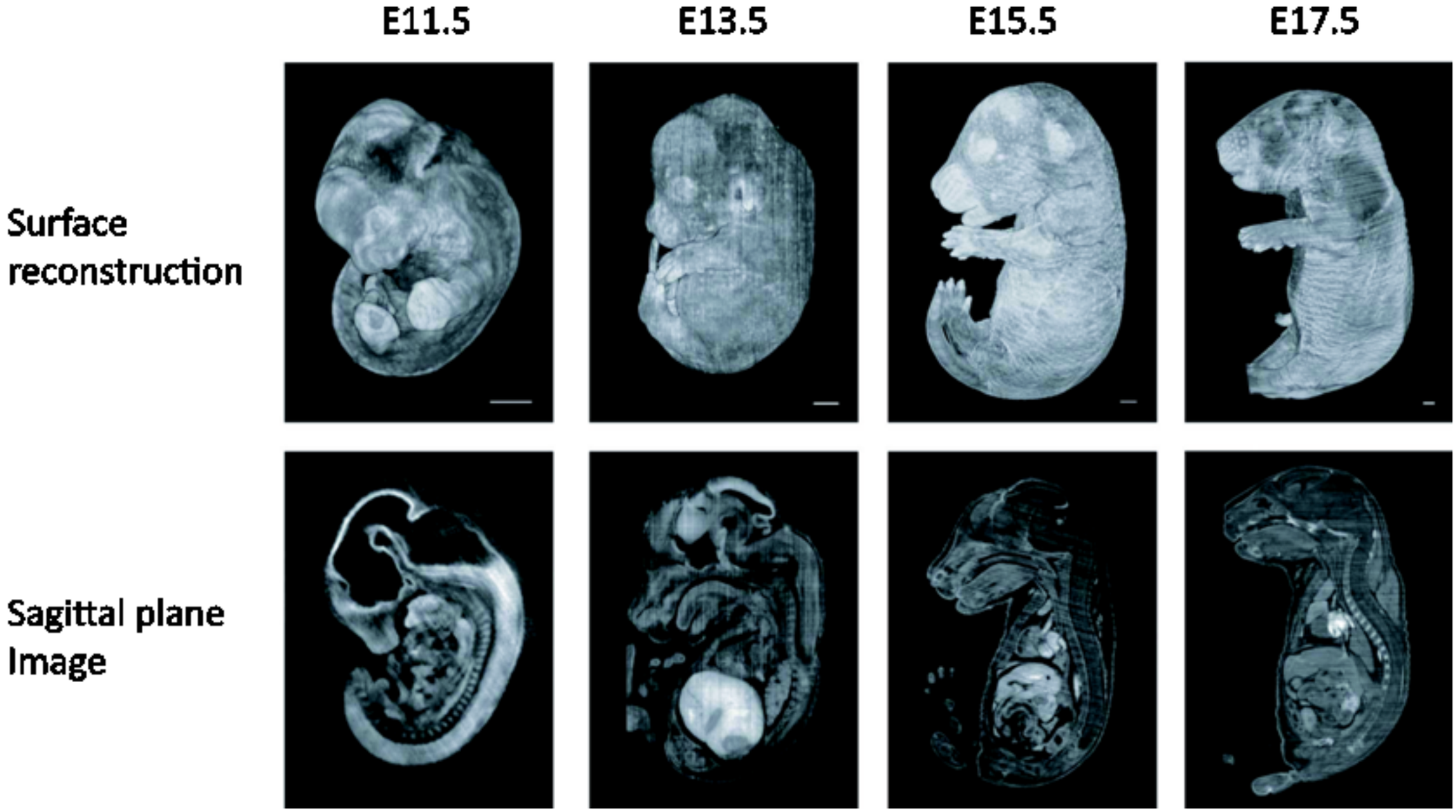
layer 5/6

SVZ

VZ

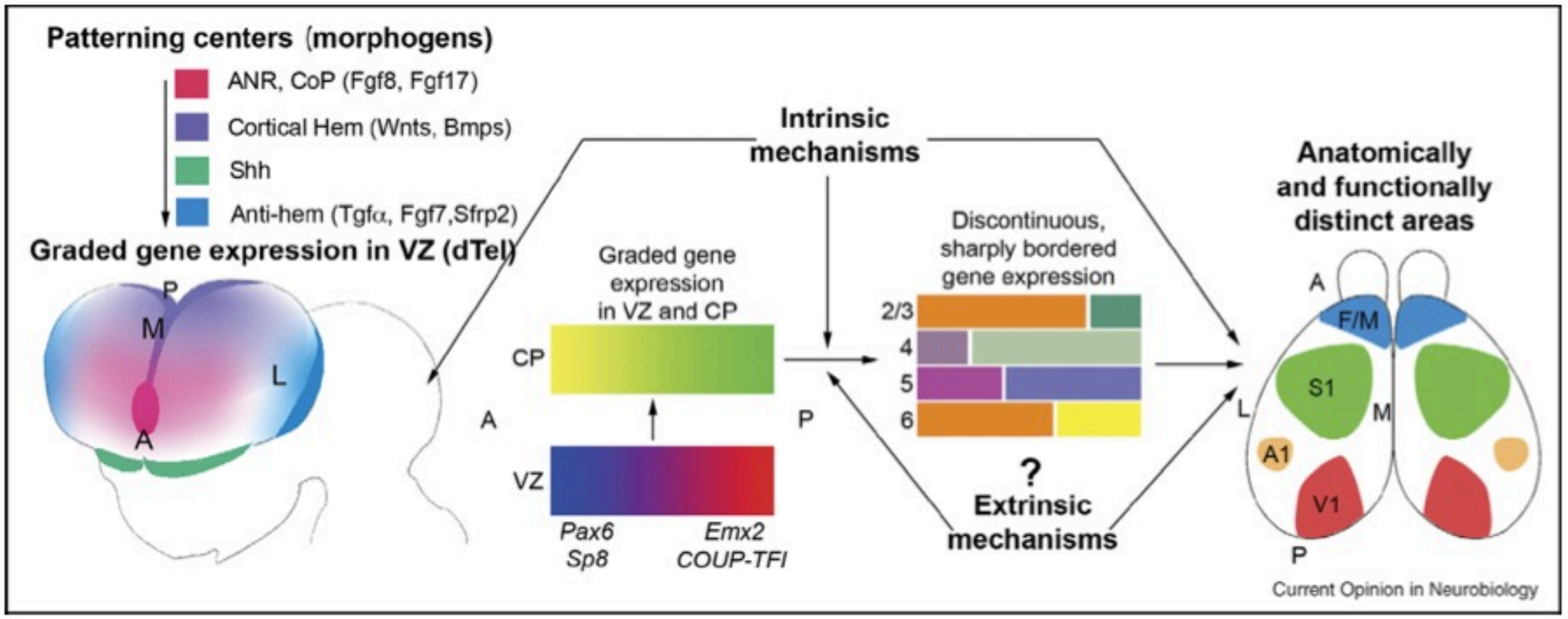
cells from ventricular zone, later subventricular zone

Development and Migration of Neocortical neurons



in mouse, day 10 to day 17 is when the neocortical neurons are formed

Overview of Arealization



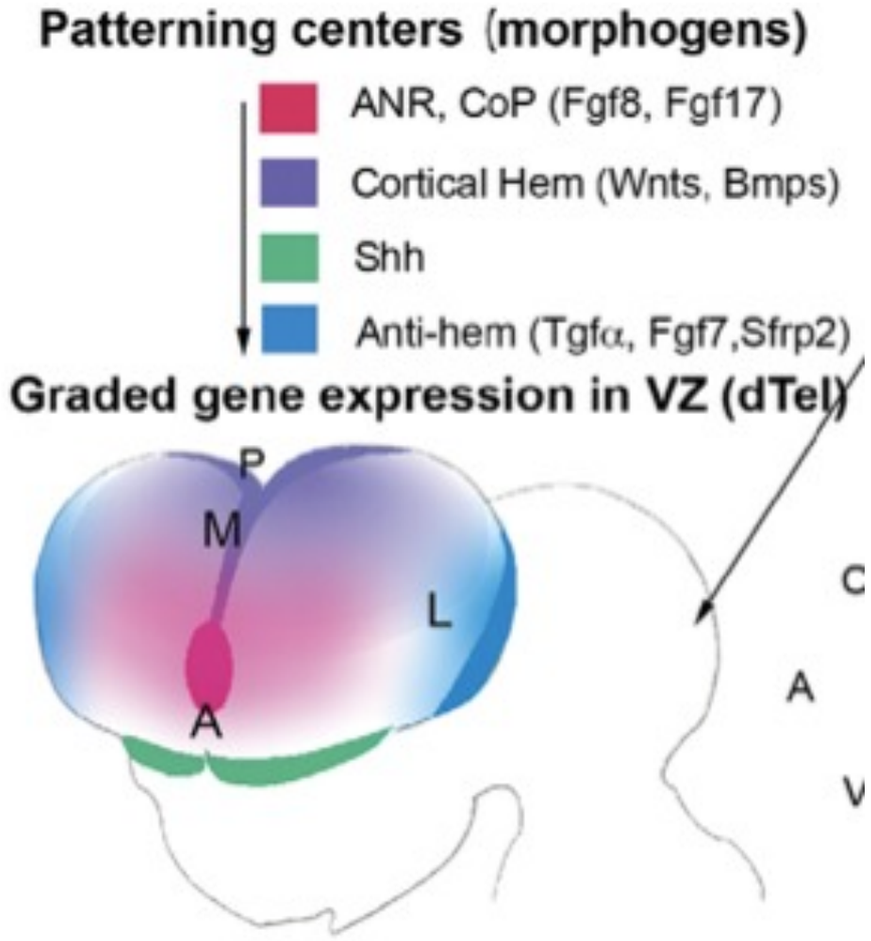
(1) morphogens secreted by patterning centers

... which regulate...

(2) transcription factors expressed in cortical cells

*+ "**extrinsic**"*
thalamocortical axon input

Four Patterning Centers



1. Commisural Plate (CoP)

ANR = anterior neural ridge
patterning dorsal/ventral frontal cortex

2. Cortical Hem

hippocampal organizer
role in Cajal-Retzius neurons

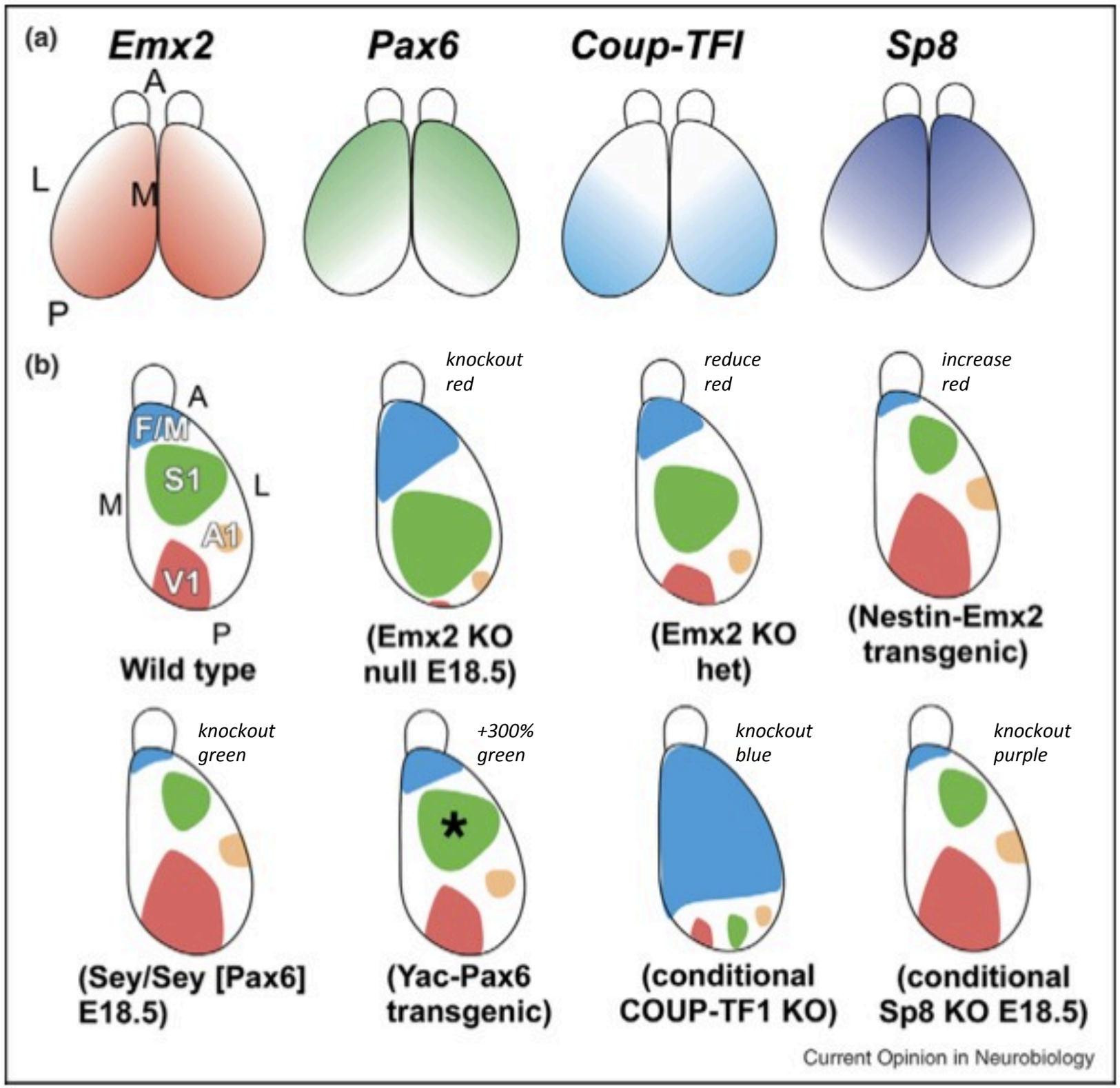
3. Cortical AntiHem

role unclear, maybe Medial-lateral?

4. Sonic Hedgehog (ssh)

role unclear, not necessarily strong role in telencephalon development

Four transcription factors

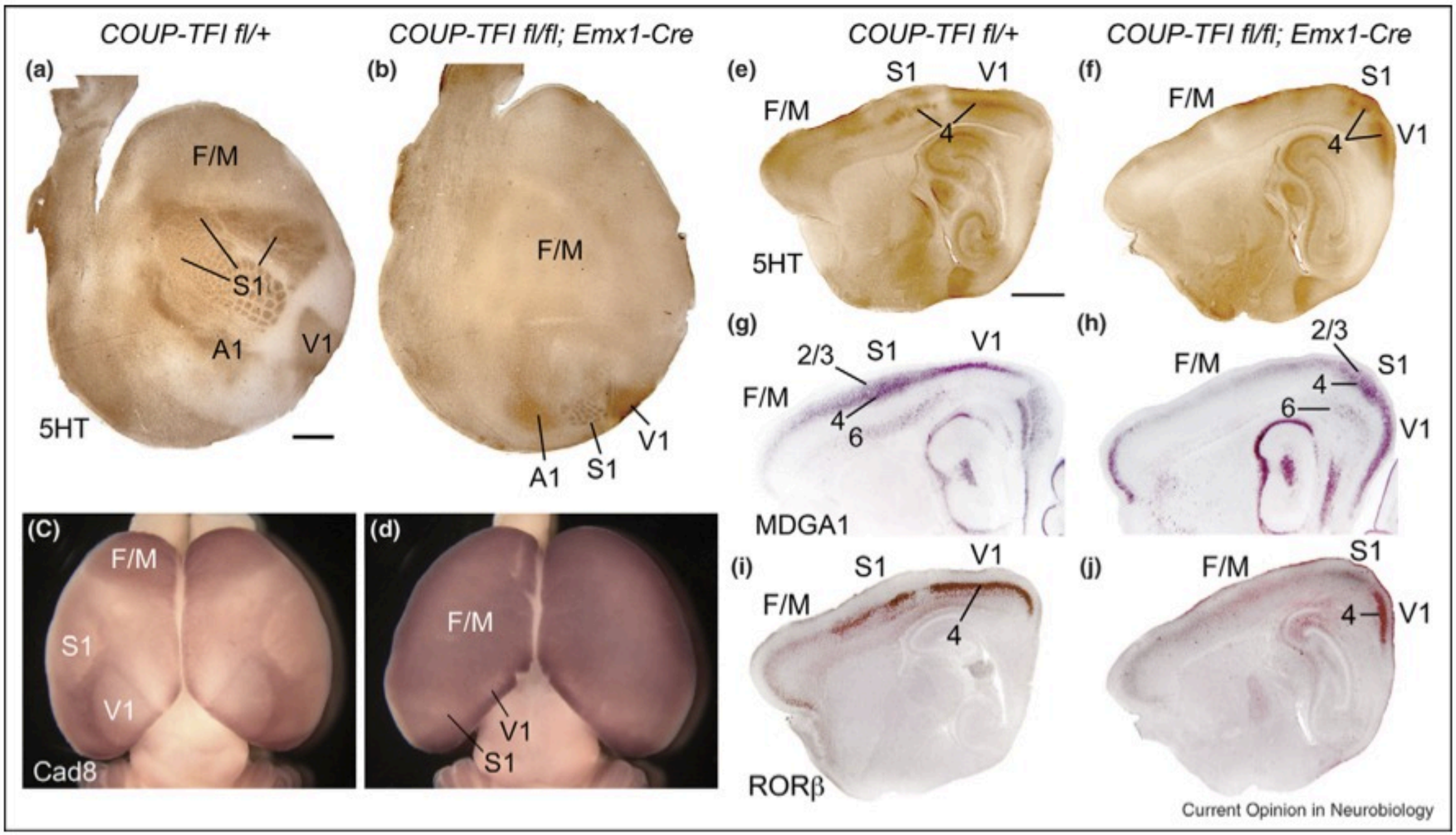


- *the same set of transcription factors is expressed by progenitors across the entire cortex*
- *the <u>level</u> of expression of a transcription factor is a defining parameter*
- ***"Cooperative Concentration Model"***
- *Only in some cases, the TCA connections are preserved (emx2, pax6, not Coup?)*

Changes to location of primary sensory areas

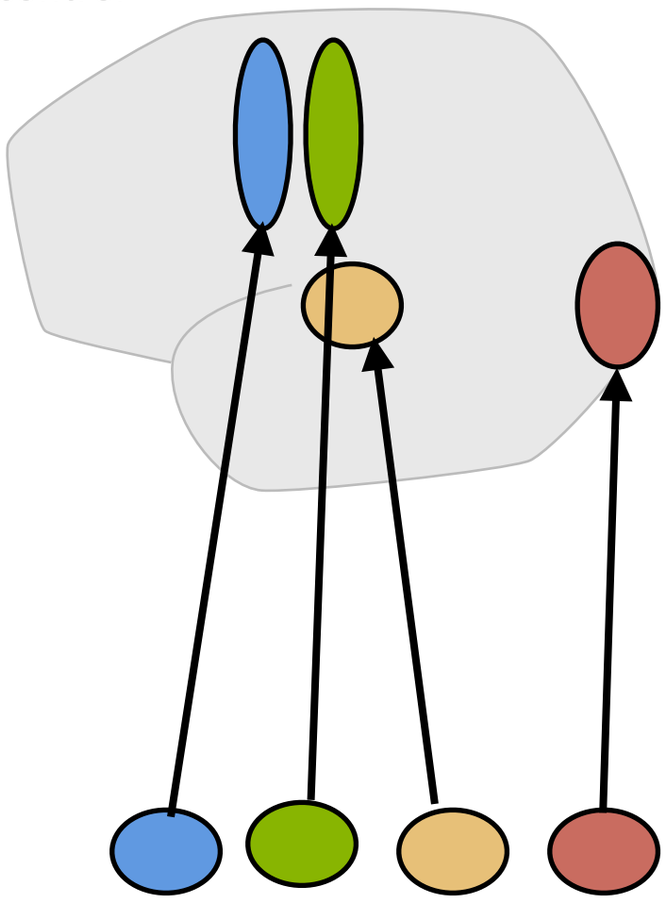
Wild type

(conditional COUP-TF1 KO)

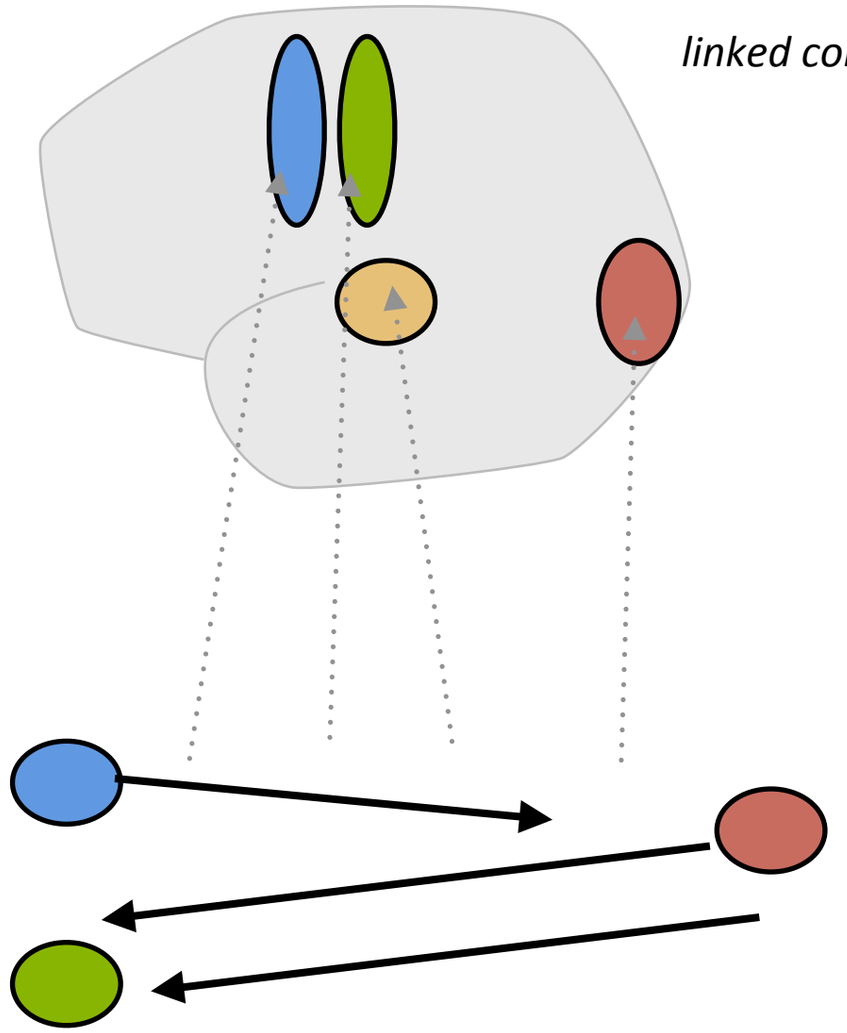


underlying generative model

independent control



linked control

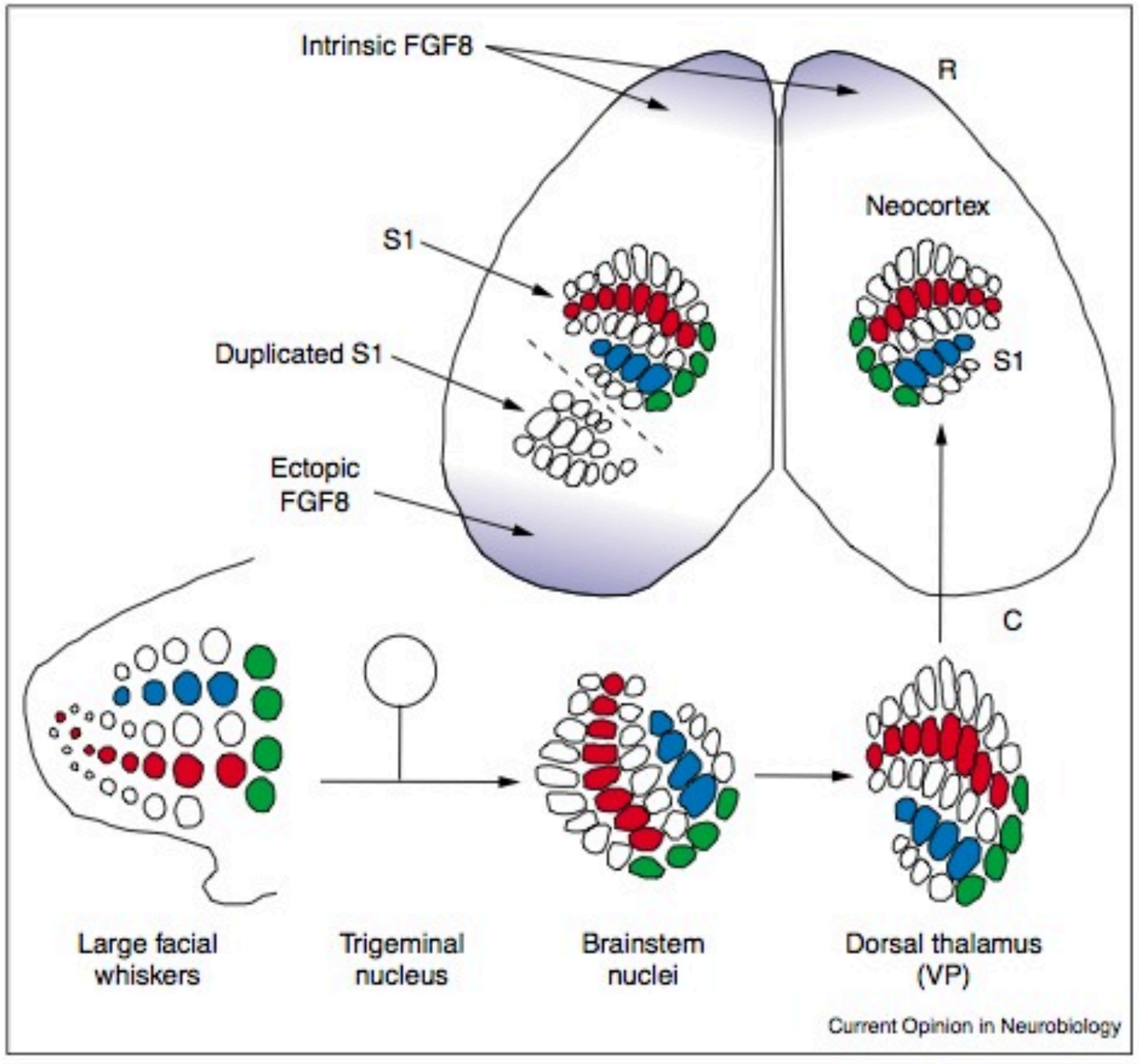


1. relative sizes of areas will be correlated

2. implications of "gene duplication"

e.g. V1 --> V2

Extra S1 with ectopic FGF8



Development of barrels in the somatosensory area. Vibrissae-related maps are found in the trigeminal complex of the brainstem, which receives input from the trigeminal ganglion. These brainstem nuclei in turn project to the contralateral VP nucleus of the dorsal thalamus. VP axons project to S1. Note the preservation of topography shown in different colors. When FGF8 is ectopically expressed in the caudal part of the neocortical primordium by *in vivo* electroporation, a partial duplication of the S1 barrel-field is observed [9**]. Barrel formation is dependent upon an orderly TCA input from the VP [45]. Therefore, the ectopic source of FGF8 is expected to influence the areal targeting of TCAs, such that those arising from the appropriate subset of barreloids in the VP duplicate their orderly projections to two discrete sites in the CP.
C: caudal; R: rostral.

- with ectopic FGF8, you get a second (mirrored) barrel field

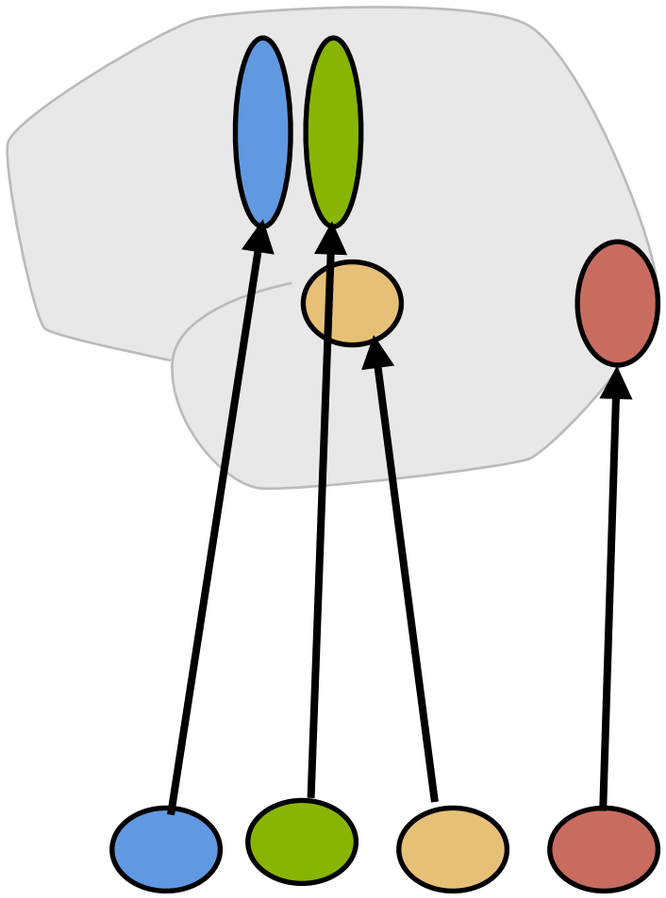
- this has appropriate TCA input from VP

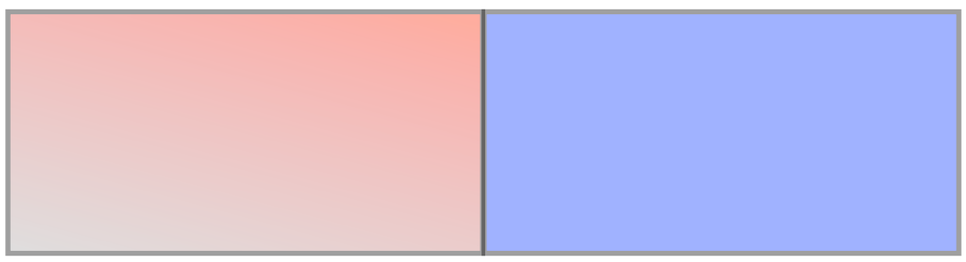
- suggests FGF8 influences the targeting of TCAs

O'Leary & Nakagawa 2002

underlying generative model

independent control





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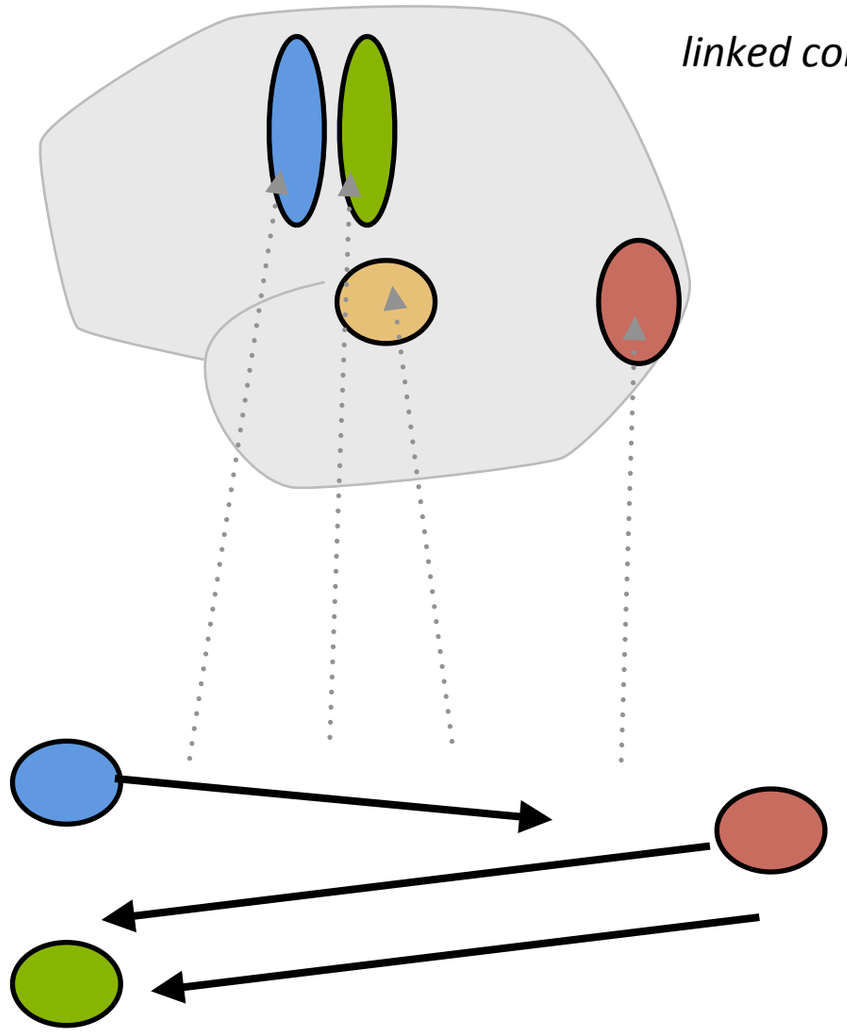
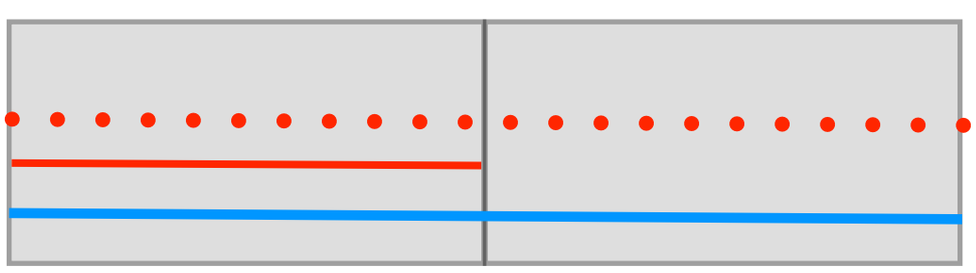




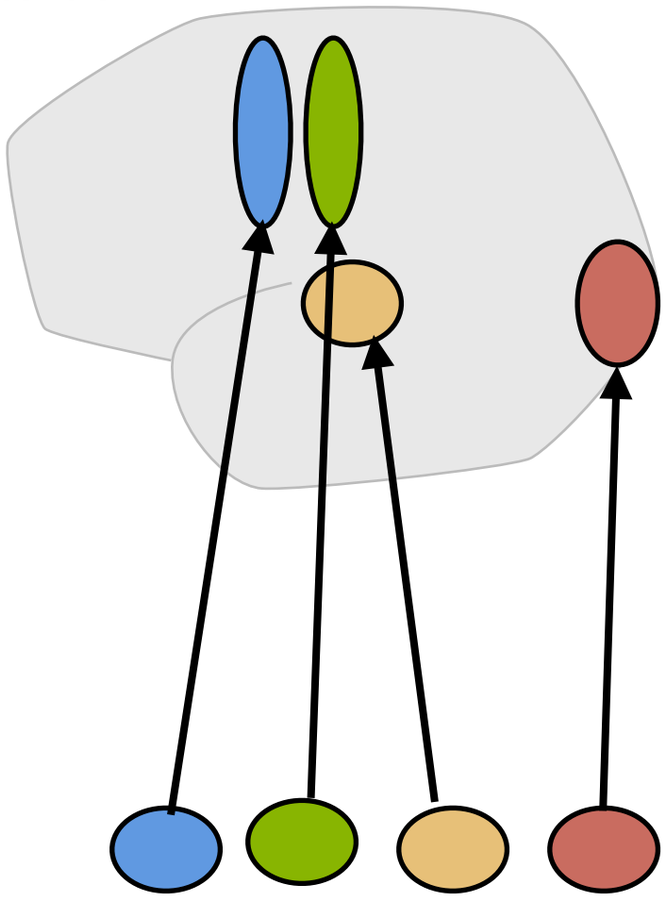
3. activity dependent refinement or are we missing some area-specific genes?

4. relationship to laminar organization

5. link to butler, compartments/embryonic zones

implication

independent control



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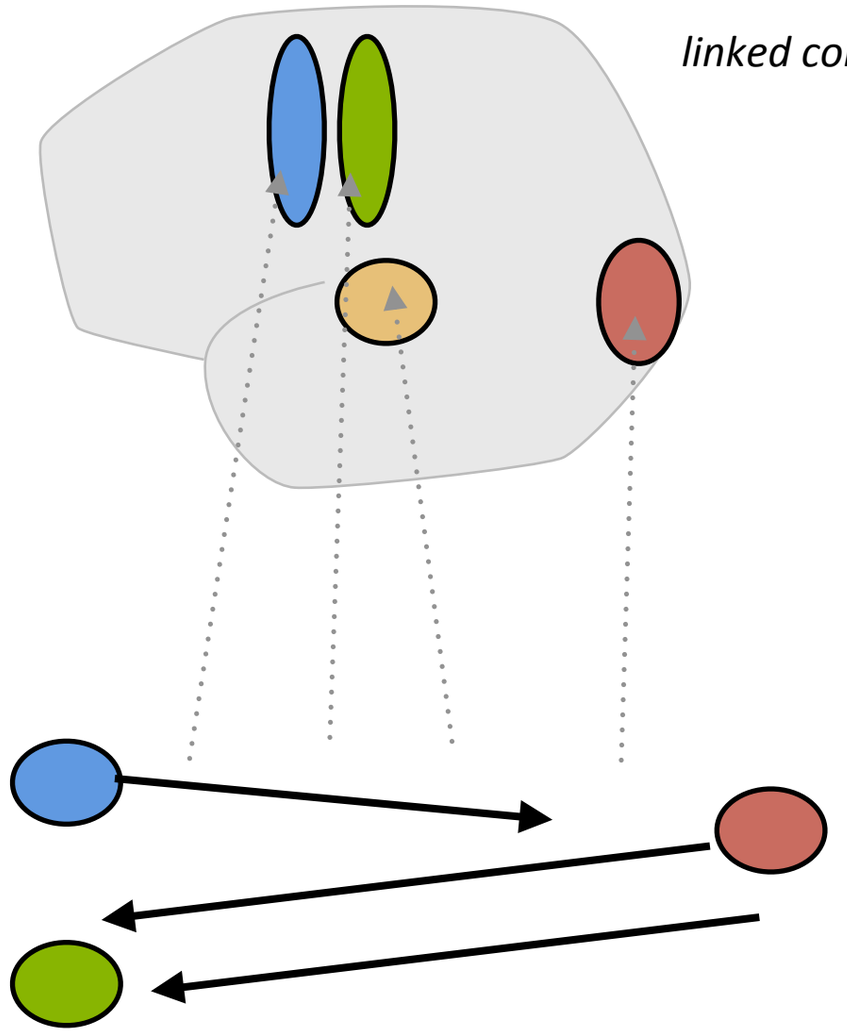


Correlated variability across individuals is a clue to the underlying causal mechanisms

Cortical Area Size and Behavior

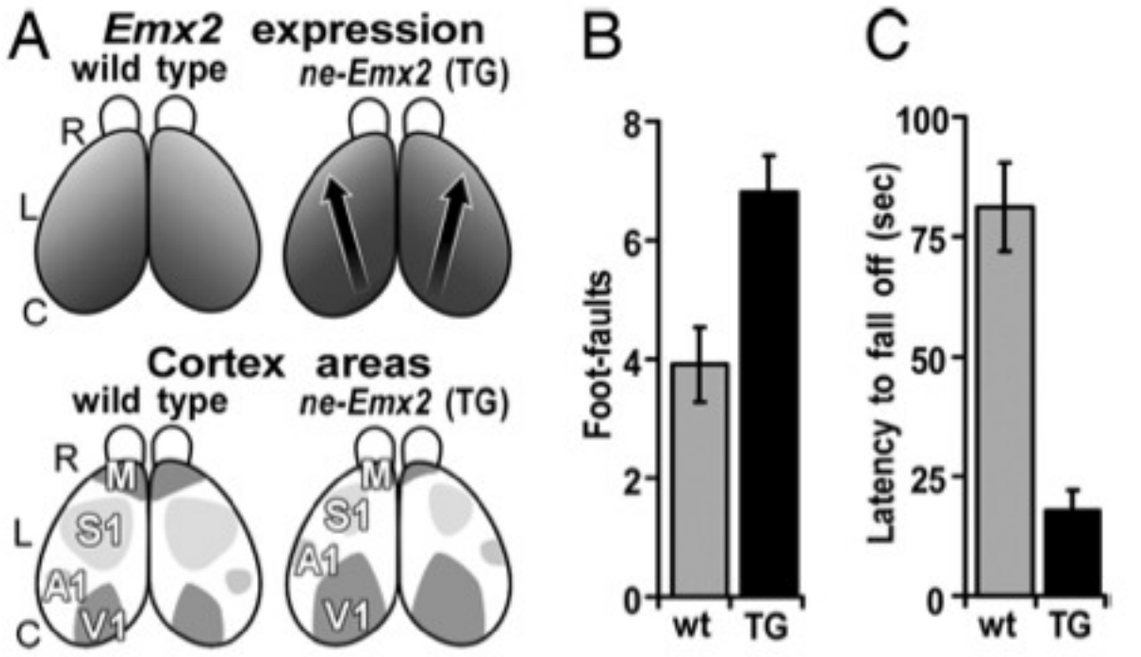
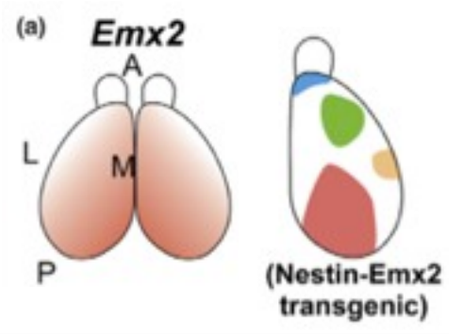


Fig. 1. Reduction in sizes of sensorimotor areas in *ne-Emx2* mice correlates with diminished performance on tests of tactile and motor behaviors. (*A*) Dorsal views of mouse neocortex to show relative levels of graded *Emx2* expression and area patterning in wt and *ne-Emx2* transgenic (TG) mice. R, rostral; L, lateral; C, caudal. (*Upper*) *Emx2* expression in embryonic cortex. Arrows indicate shifts in area patterning. Darker shading indicates higher *Emx2* expression. (*Lower*) Size and position of primary sensory areas, somatosensory (S1), visual (V1), auditory (A1), and motor area (M), in adult cortex. Compared with wt, M and S1 are reduced in size in *ne-Emx2* mice. Overall cortical size is the same as in wt. (*B*) Grid walk. Mice walk over a wire mesh grid, and performance is analyzed (16). Analysis was done by counting the number of errors in foot placement (foot-faults) per 20 steps. The wt made significantly fewer foot-faults (3.9 ± 0.6, $n = 11$) than *ne-Emx2* (TG) mice (6.8 ± 0.6, $n = 11$) (Student's t test, $P = 0.0034$). In addition, *ne-Emx2* mice often fall off the grid, a behavior never seen in wt (see SI Movie 1). (*C*) Rotarod. Mice were placed on a rotating rod that smoothly accelerated from 5 to 70 rpm over 3 min, and the latency to fall off was measured as described (17). *ne-Emx2* (TG) mice show a significantly reduced performance (average fall-off latency = 17.8± 4.4 s, $n = 11$) compared with wt (average fall-off latency = 81.2 ± 9.2 s, $n = 11$; Student's t test $P =$ 4.29E-06) (see SI Movie 2).

over express EMX2 → *smaller S1* → *worse at sensory and motor tasks*

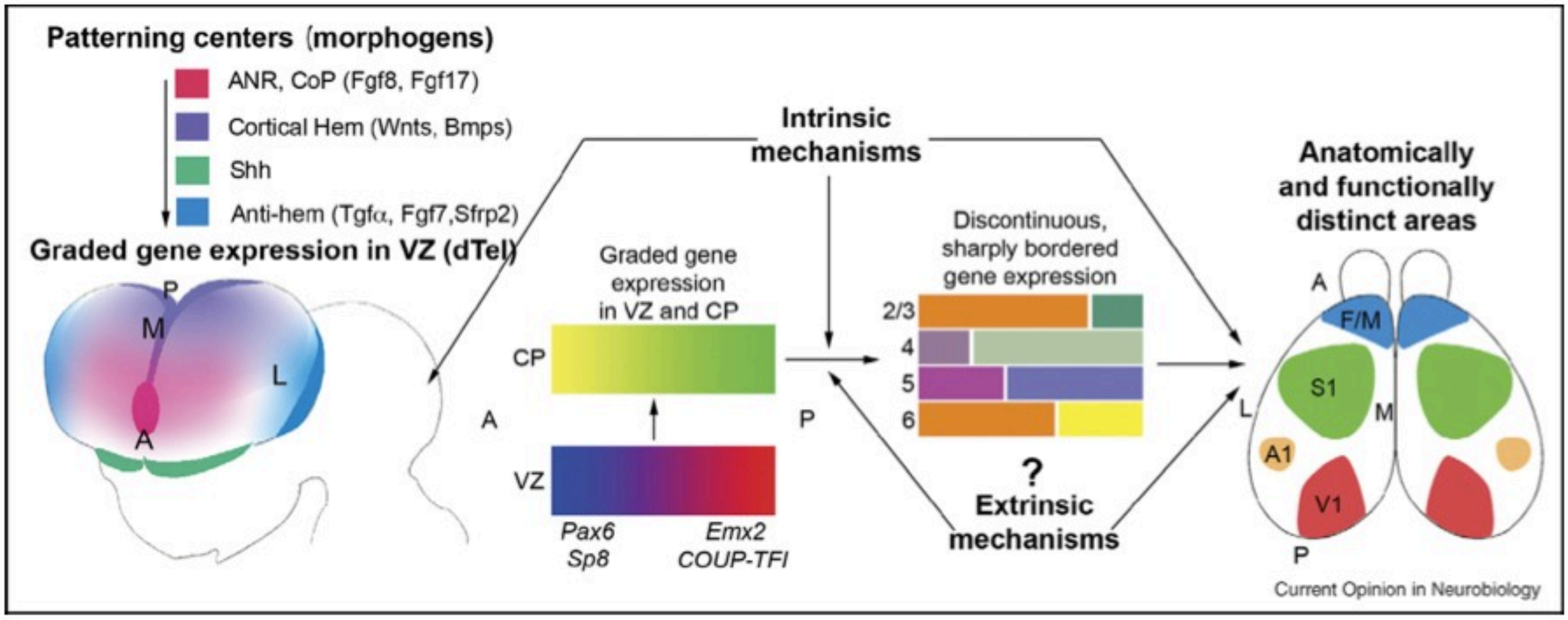
1- grid walk: count foot placement errors

2- time to fall off a rotating rod



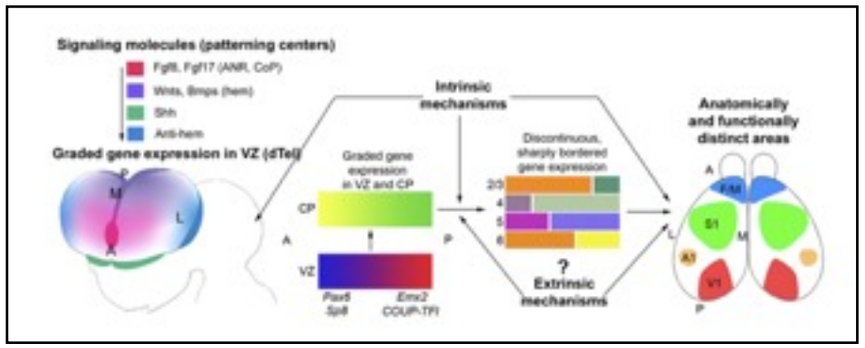
... but also less good with a bigger S1... Leingartner 2007 PNAS

return to the diagram

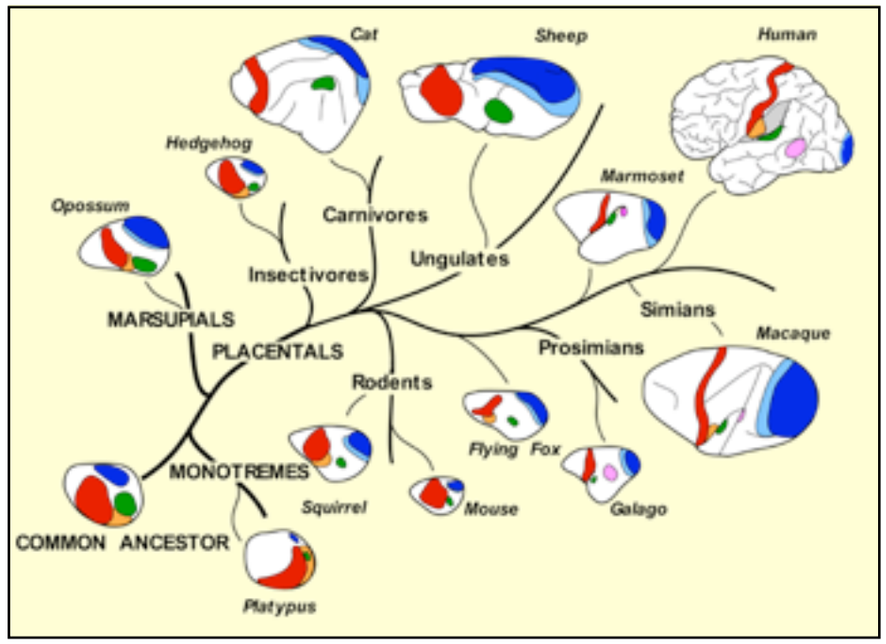


So far, this is the kind of sensory field variability we see...

Patterning the Cortex & Arealization



Dennis O'Leary



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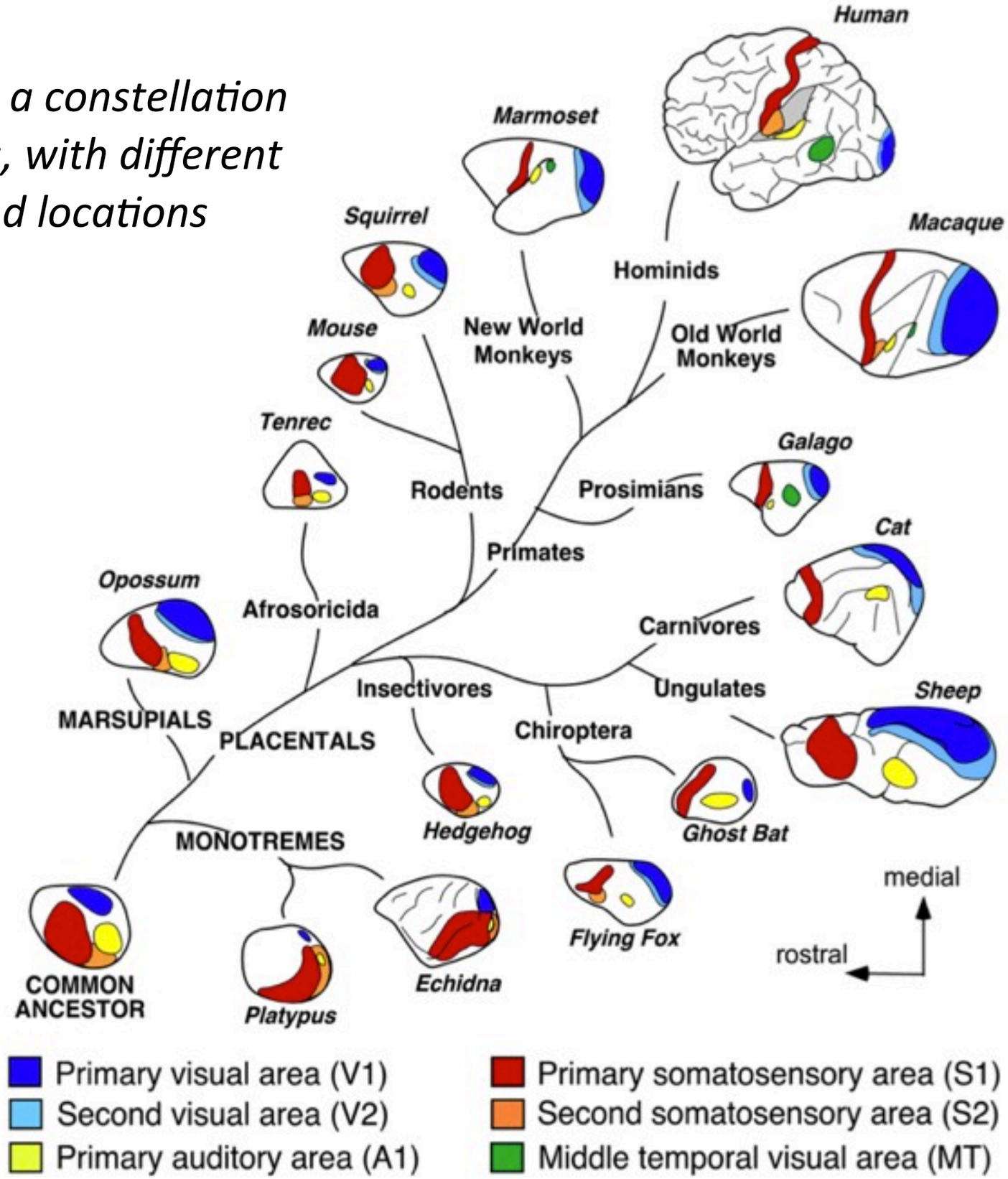
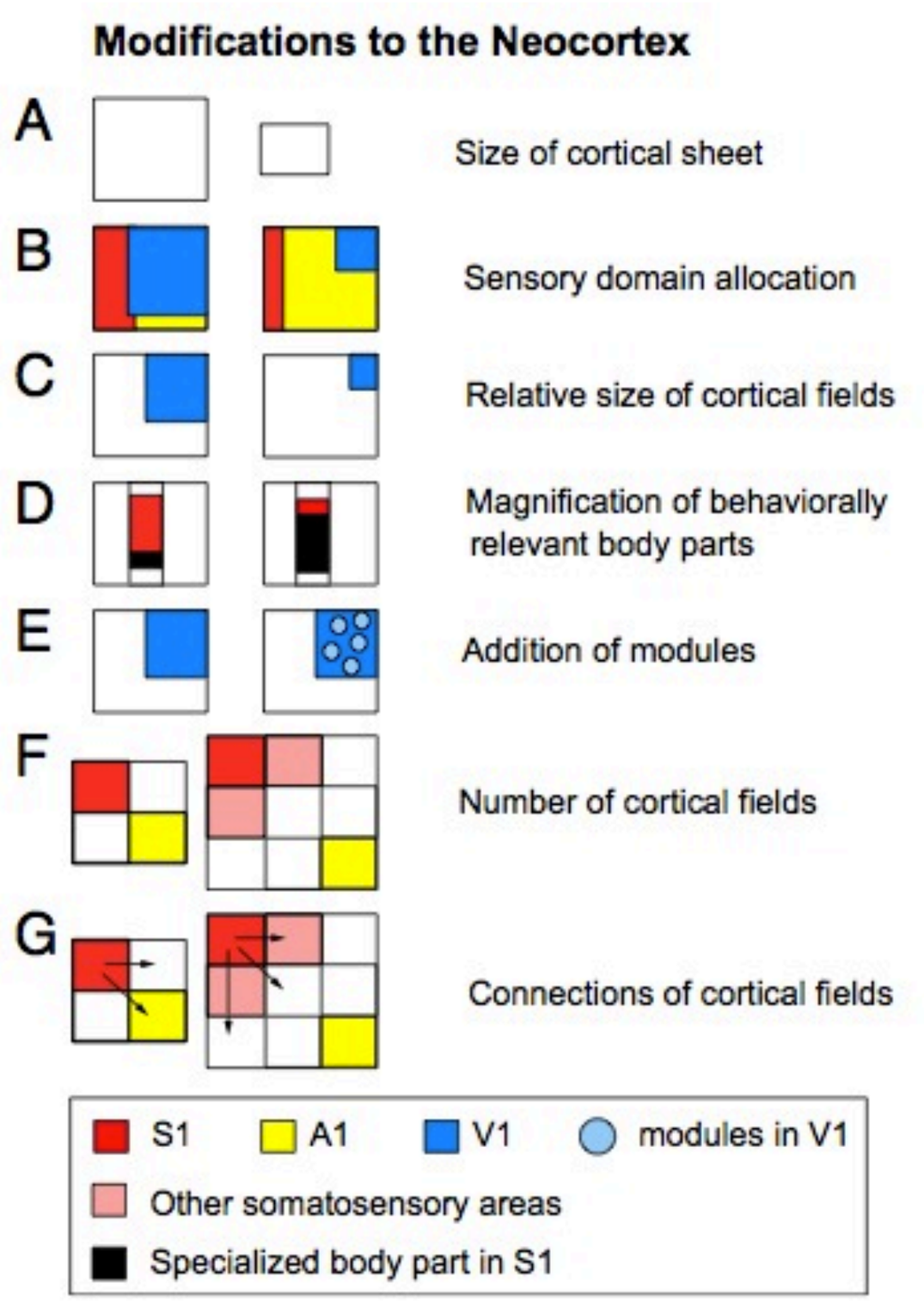
Preserved Cortical Fields

All species have a constellation of cortical fields, with different relative sizes and locations



variability in sensory domain allocation

Types of cortical variability



Specalizations - extreme cases of varibility

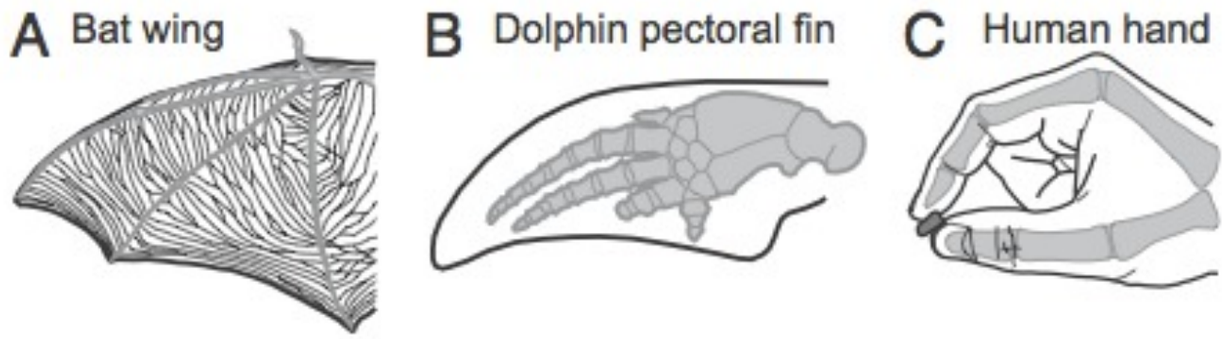
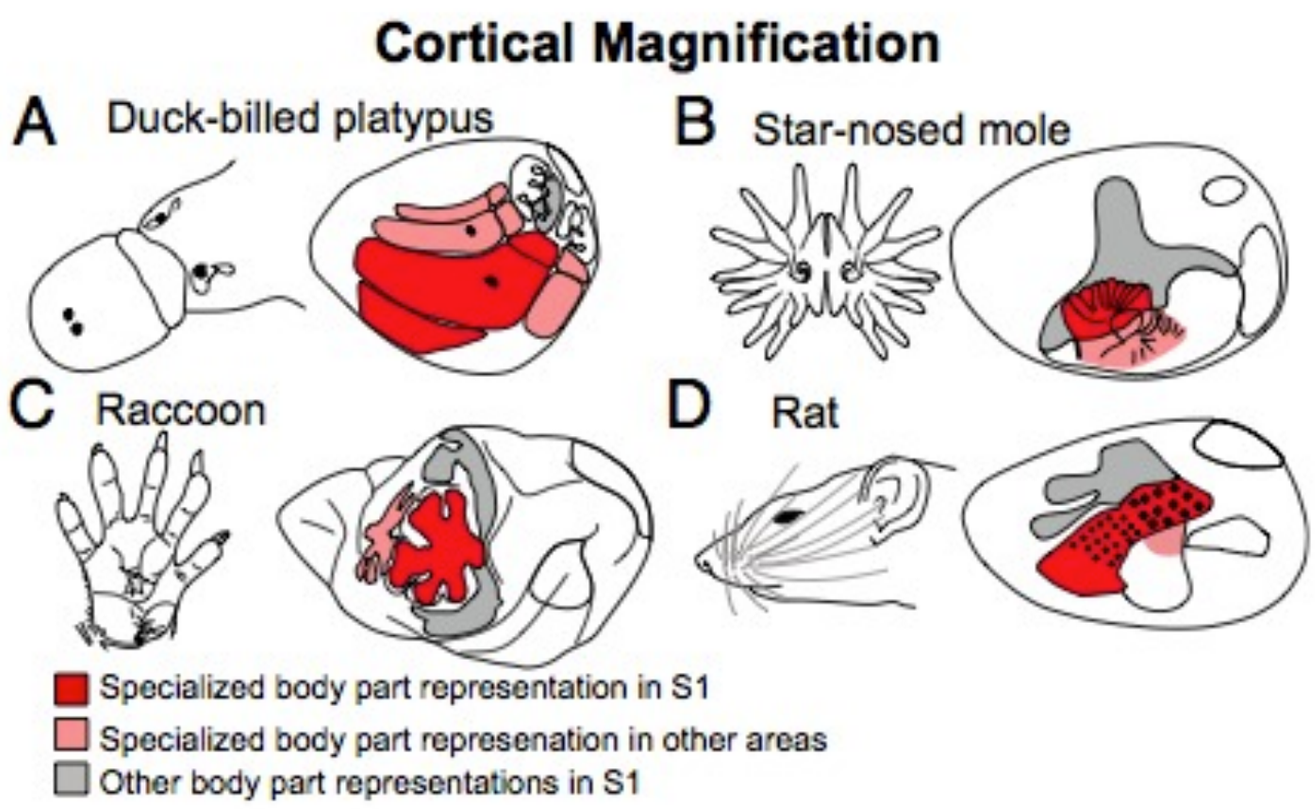


Fig. 4. (*A*) Wing of a bat, (*B*) pectoral fin of a dolphin, and (*C*) hand of a human are examples of homologous morphological structures. Although they are used for very different purposes, they are organized around the same basic skeletal frame (in gray).



Within-species variance of cortical organization

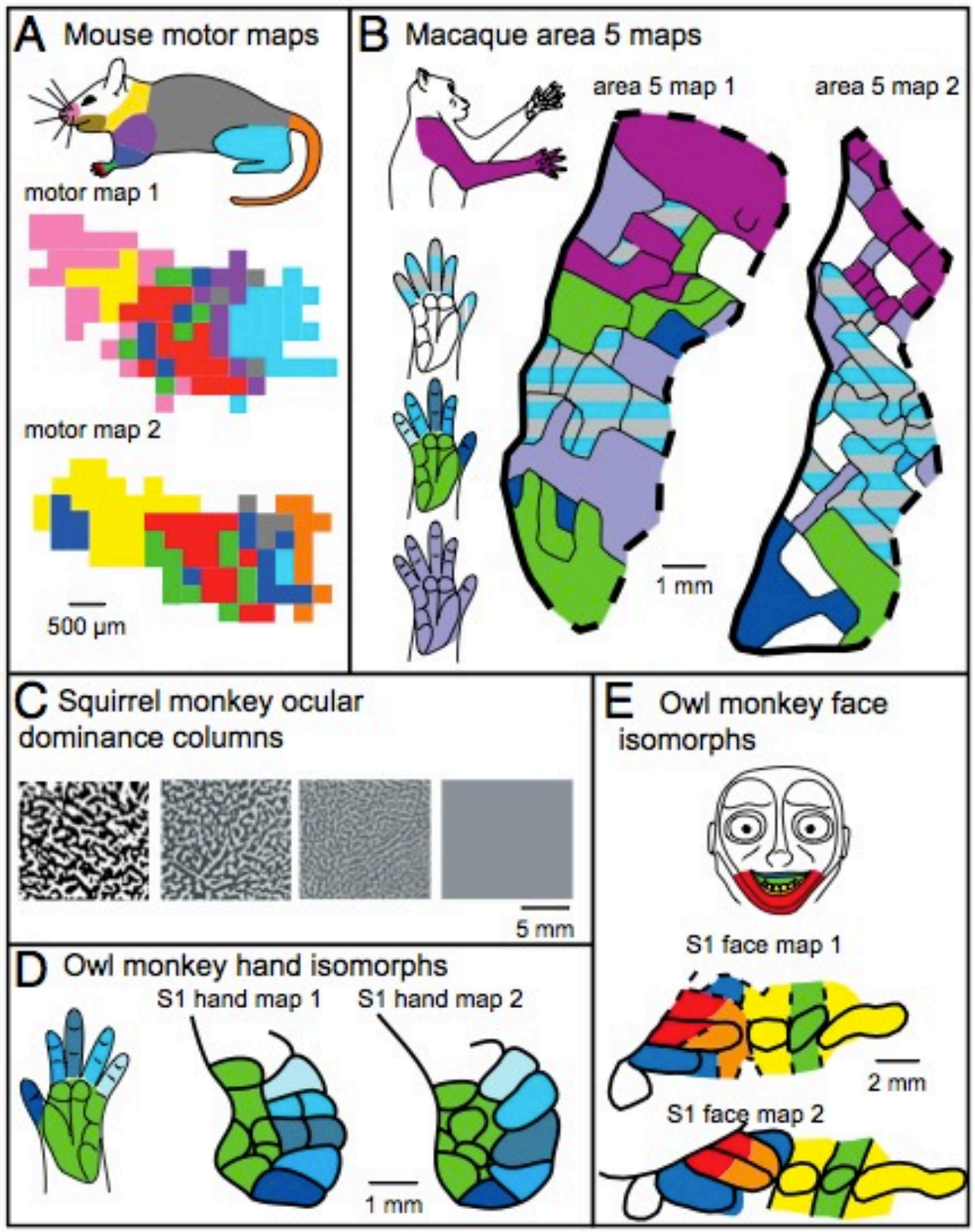
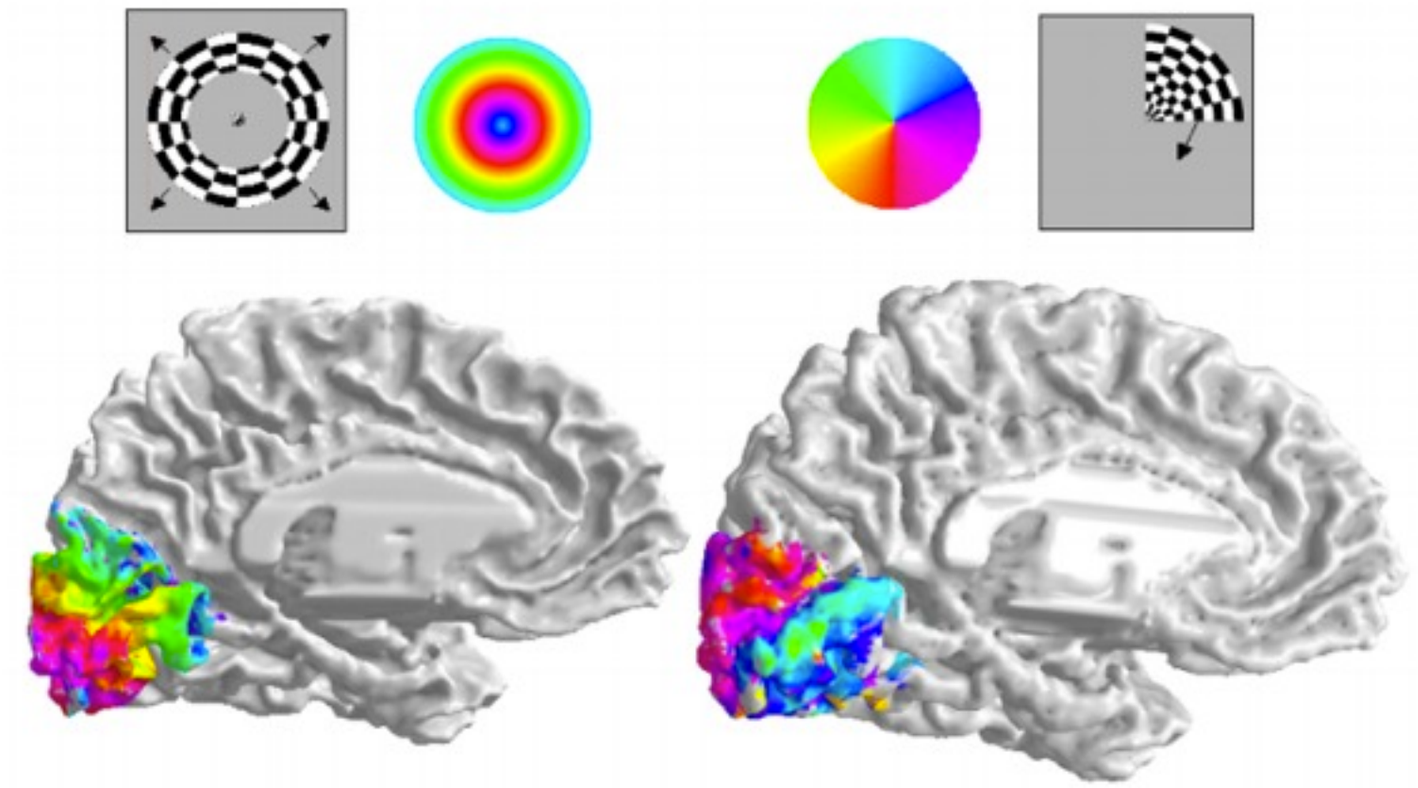


Fig. 5. Examples of intraspecies variability for (*A*) motor cortex in mice (adapted from ref. 41), (*B*) area 5 in macaque monkeys (adapted from ref. 24), (*C*) ocular dominance columns in squirrel monkeys (adapted from ref. 47), (*D*) S1 architectonic isomorphs in the owl monkey face representation (adapted from ref. 45), and (*E*) hand representation (adapted from ref. 46). In mice, motor maps are grossly topographically organized but are locally fractured. *A* depicts motor maps from two different individual mice. Each small square represents a microstimulation location that evoked a movement of a particular body part, color-coded according to the colored mouse body at top. In macaques (*B*), maps of posterior parietal area 5 are highly variable and are fractured. Area 5 also demonstrates an extreme magnification of the forelimb. Color codes of the hand and arm correspond to their representations in cortical maps. In squirrel monkeys (*C*) ocular dominance columns vary from highly distinct (leftmost square) to nonexistent (far right square). Finally, the myeloarchitectonically distinct modules of the face (*D*) and hand (*E*) representations in S1 of owl monkeys vary in their specific size and shape between individual animals. Color codes of the hand and face correspond to their representations in cortical maps.

** this is a clue to where the joints are... what is preserved and what is variable...*

Variance across species / Variance within species



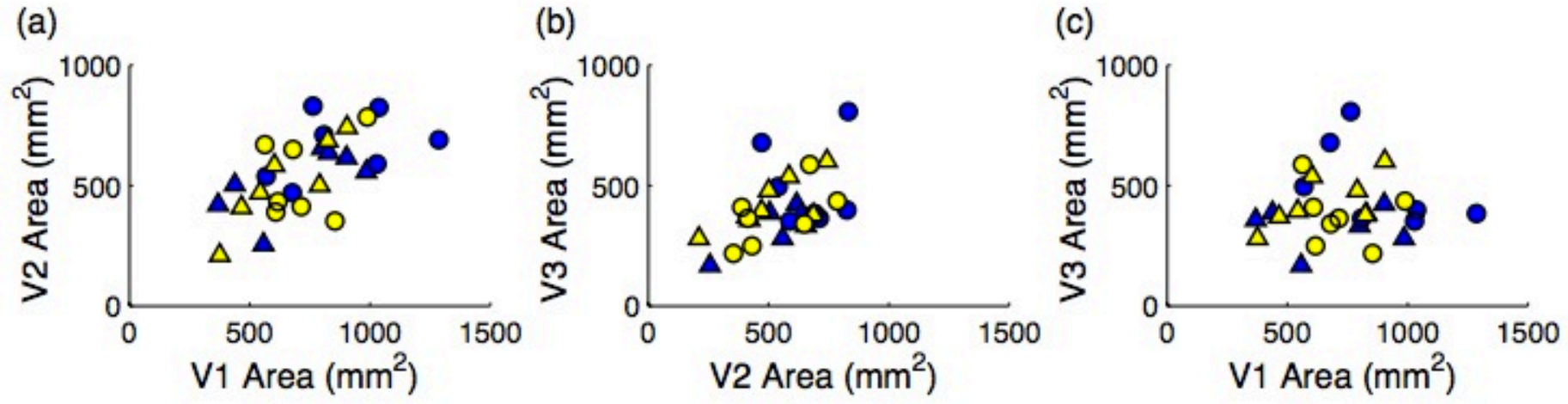
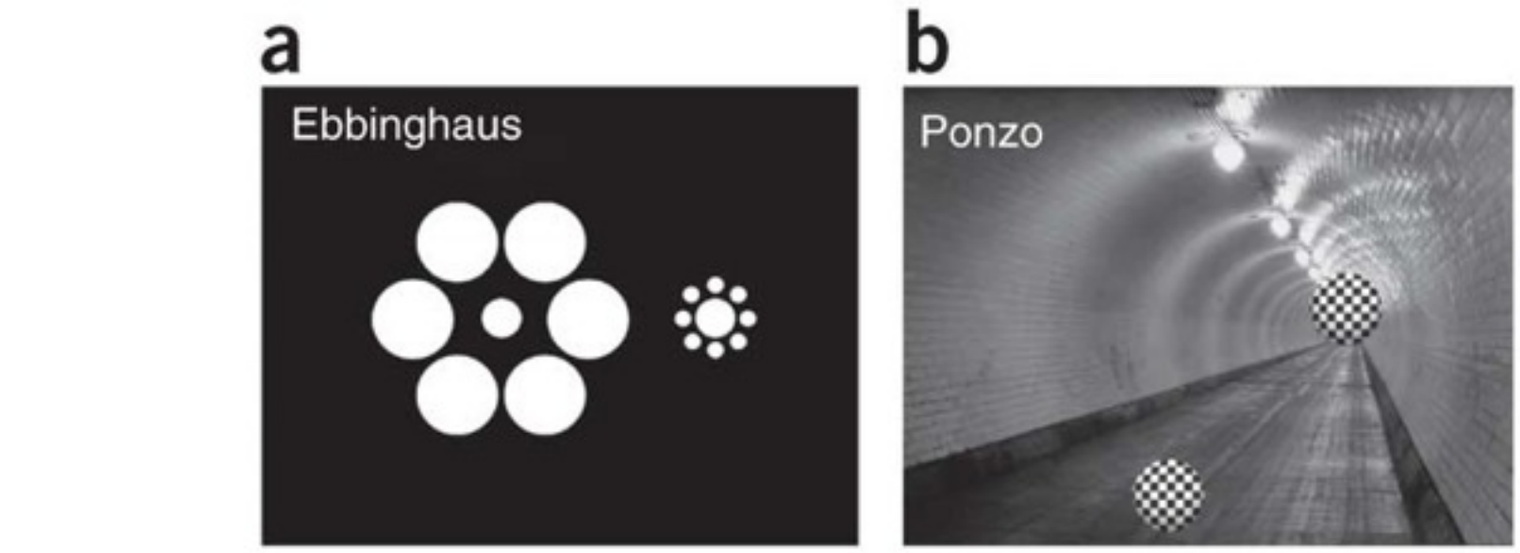
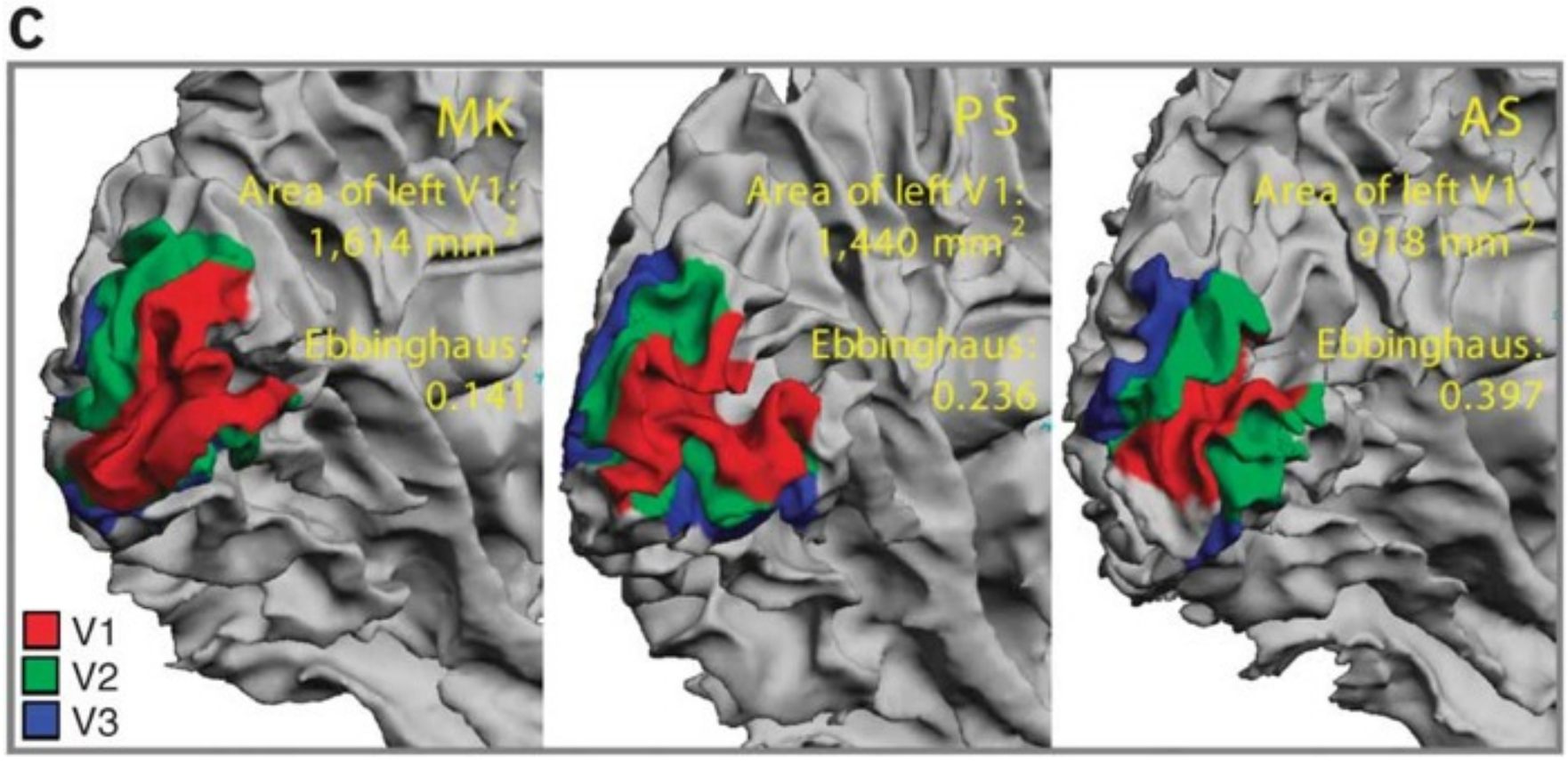


Figure 2. V1 surface area correlates with V2 surface area (a), but V3 surface area is only weakly correlated with V2 surface area (b) and there is no significant correlation with V1 surface area (c). Note that these are measurements of quarter-field cortical representations. Triangles are ventral regions and circles are dorsal regions; yellow symbols are right hemisphere data and blue symbols are left hemisphere data.

V1 Surface Area predicts illusion magnitude



"A **larger area of V1 devoted to a particular portion** of the visual field would then necessarily be accompanied by a **lesser influence of contextual effects** mediated by anatomical structures with a fixed spatial scale. "

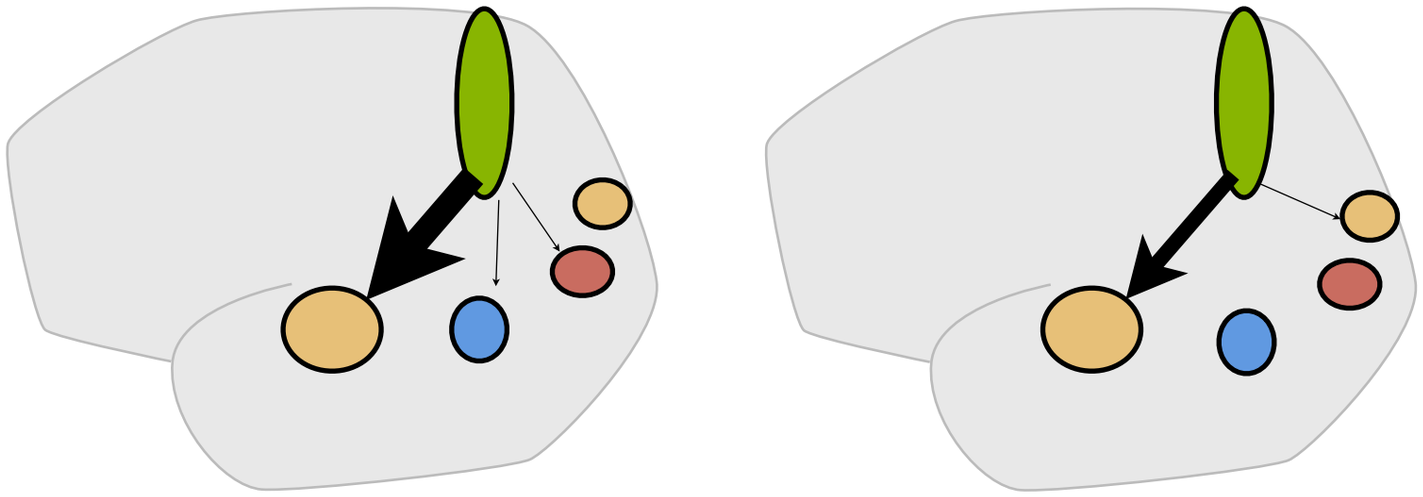


bigger V1
smaller illusion

small V1
bigger illusion

Schwartzkoff 2011 Nature

Connections



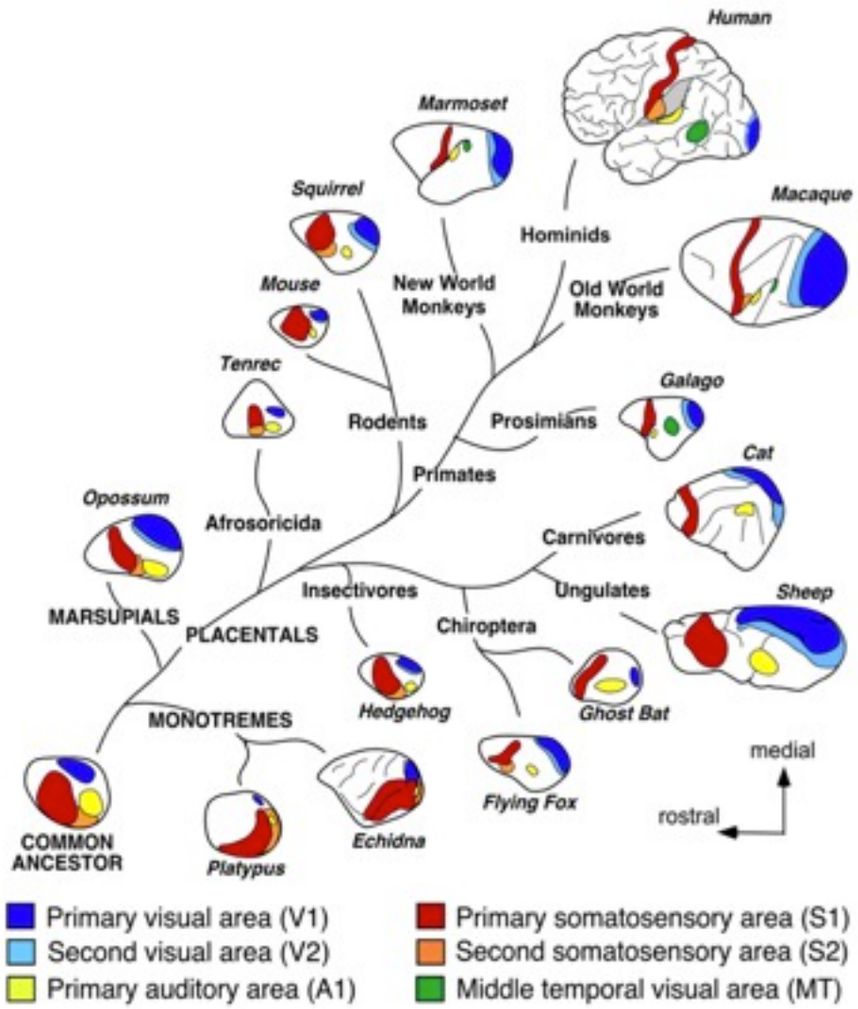
1. change in density

2. novel sparse other structures

- a fair amount of variation in regional location, less variation in projections

- what does this imply about the underlying generative model

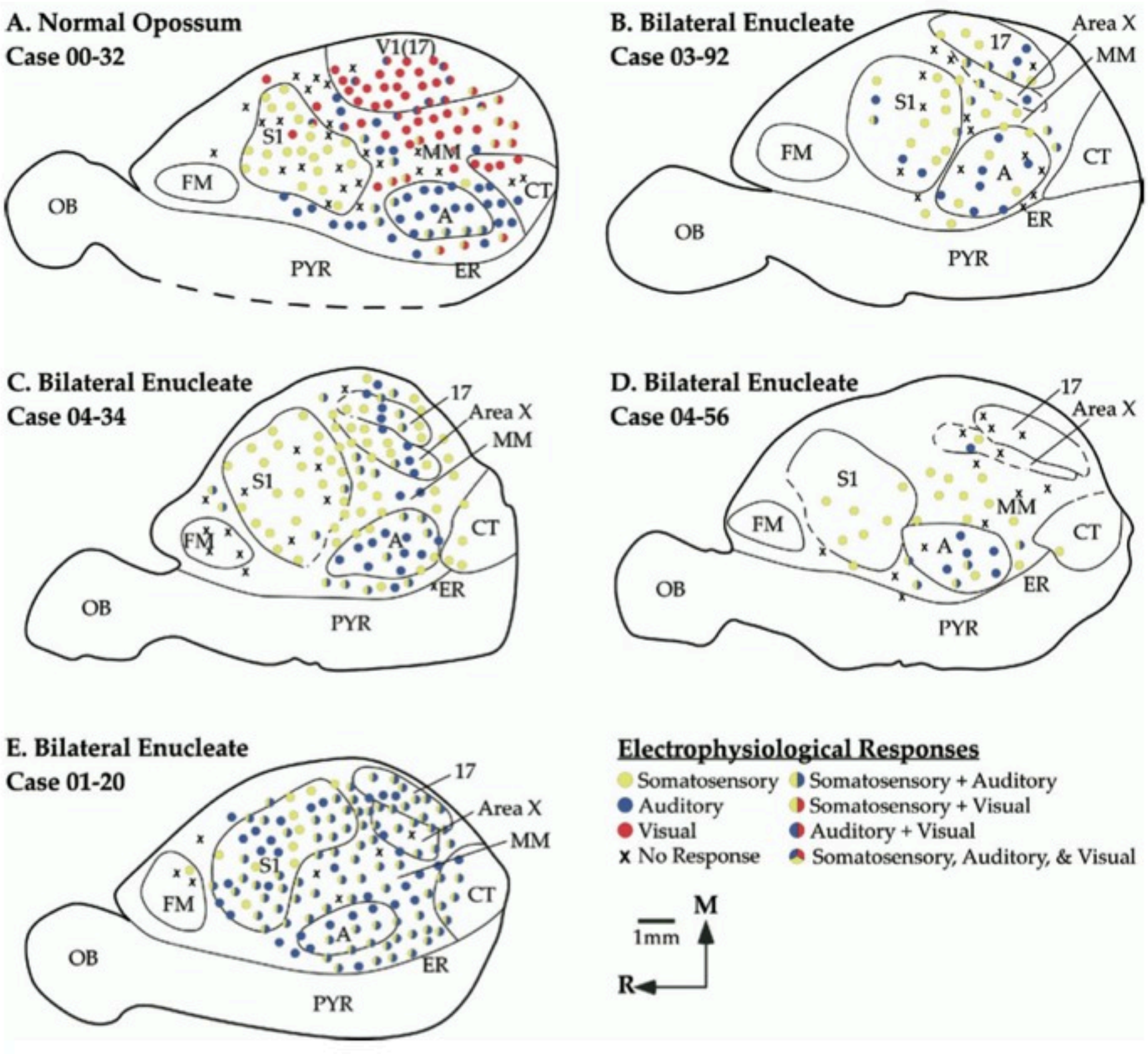
The main claim



while the exact size and connectivity is refined by activity, there is a core constellation of fields is genetically specified

- *blind mole rat*
- *congential blindness/deafness*
- *enucleation*

Takes on somatorsensory + auditory responsiveness



Normal + Extra thalamic and cortical connections

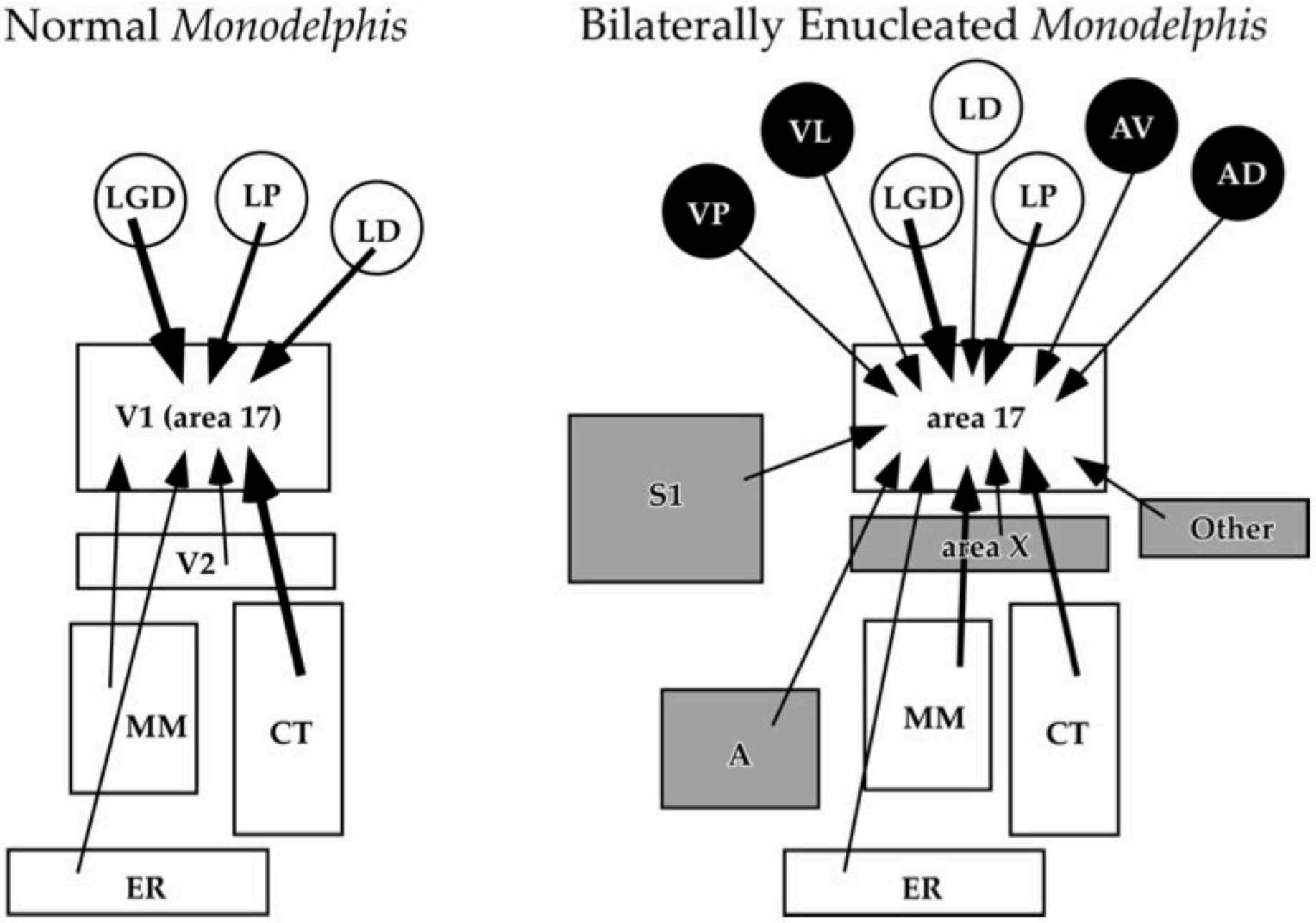
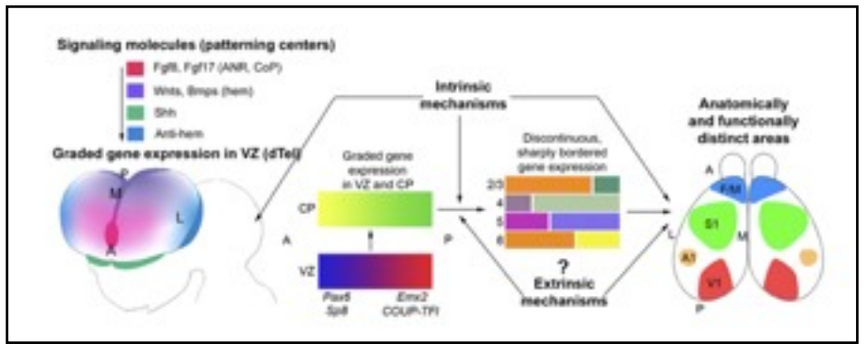
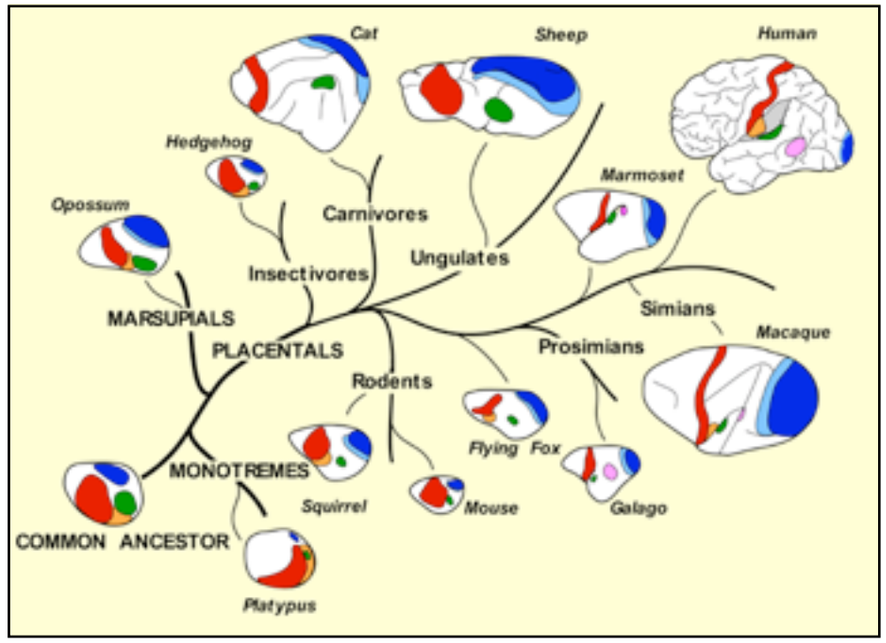


Fig. 8. A summary of the thalamic (circles) and cortical (boxes) connections of area 17 in a normal (left) and bilaterally enucleated (right) opossum. In normal animals, thalamocortical projections are restricted to LGD, LP, and LGD. Corticocortical connections of area 17 in normal animals are predominantly from visual areas V2 and CT, and from ER. In bilaterally enucleated animals, normal projections from LGD, LP, and LD of the thalamus can be identified; however, a large number of abnormal connections are also observed from VP, VL, AV, and AD. Like the thalamus, the normal pattern of corticocortical connections exist in bilateral enucleated animals; however, additional projections (shaded boxes) from S1, A, MM, area X, and other regions of the cortex have been identified as well. The thickness of arrows roughly denotes the density of connections. Abbreviations defined in Table 1.

Patterning the Cortex & Arealization



Dennis O'Leary



Leah Krubitzer

1. Patterning from a developmental perspective

... more embryology 101
... implications for generative models of cortical organization

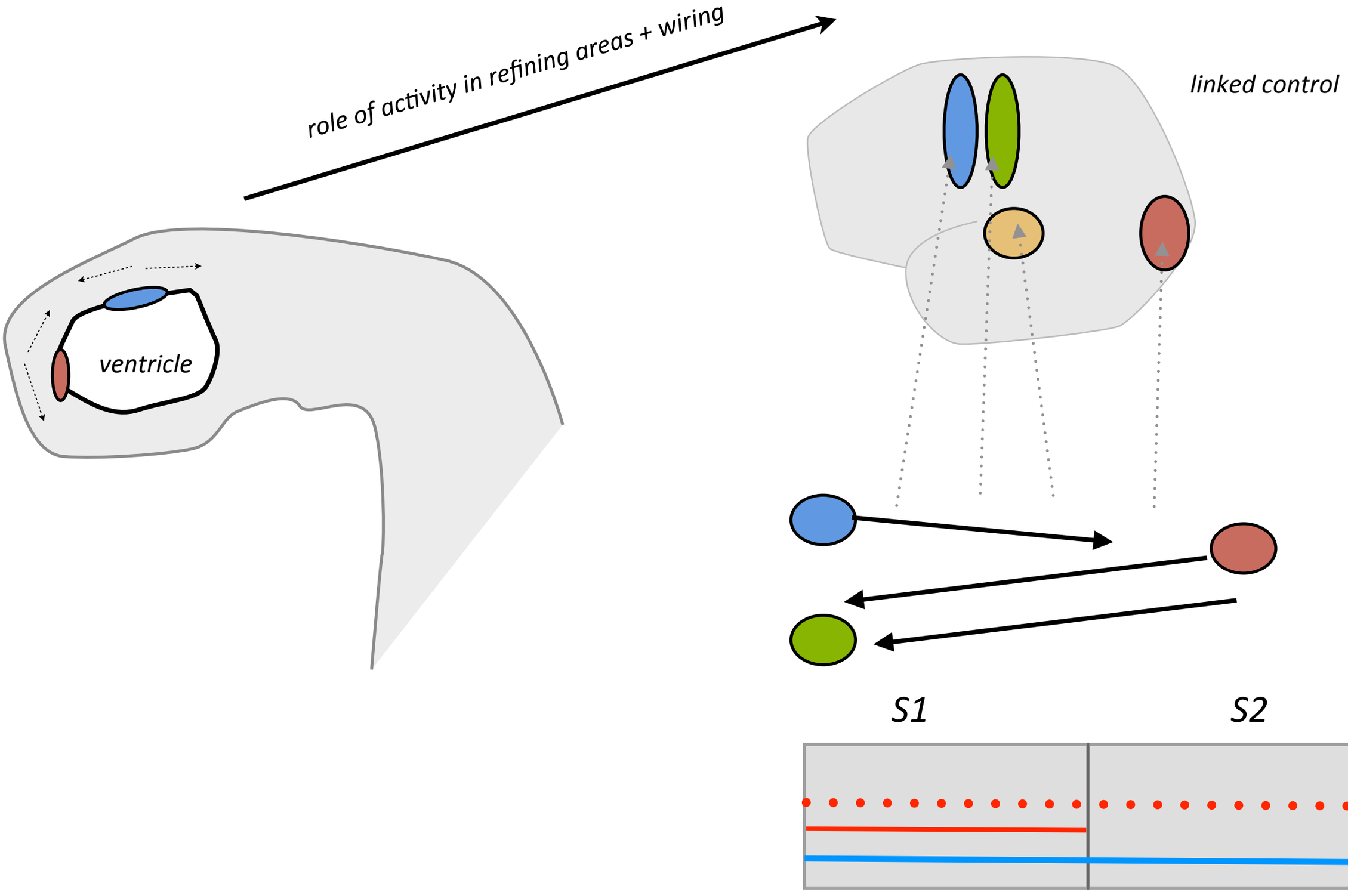
2. Patterning similarities across species and an evolutionary perspective

... leveraging variability within and across species

Broad related question: What's an area?

In understanding the process by which the cortex gets patterned, is there any insight to be drawn about what a good 'unit' or module is? a cortical area? a cortical field/zone? a prosomere? how big is it?

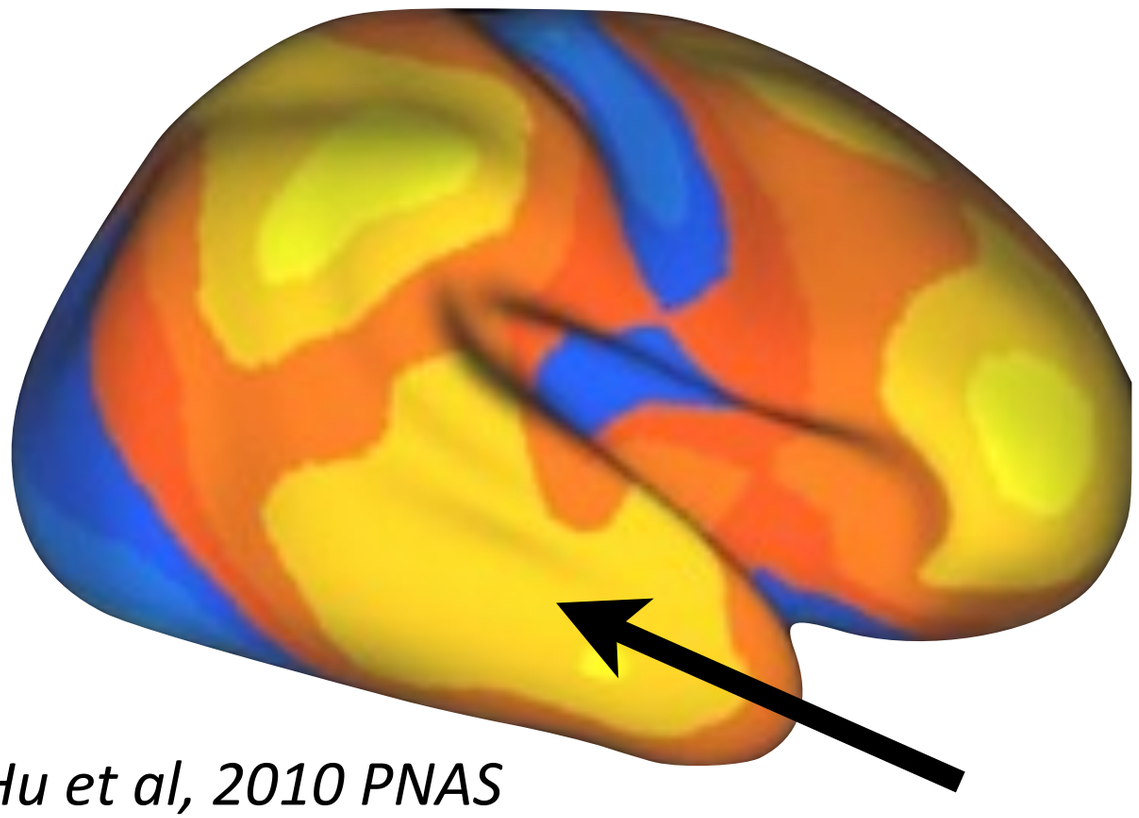
back to the models



link this to “areas” and “pathways” and “subfields”

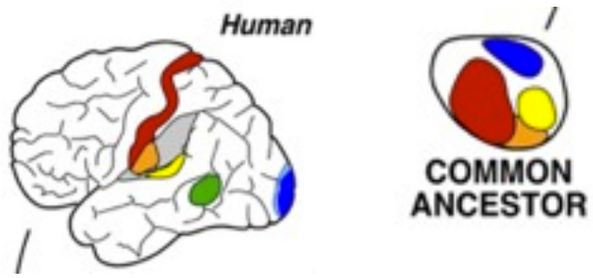
expansion between monkeys and humans

Areas of expansion in the human cortex during infancy and childhood, top, closely match areas of change in the human brain when compared with the brains of apes and monkeys. Yellow areas expanded the most, followed by orange, red, blue and light blue areas.

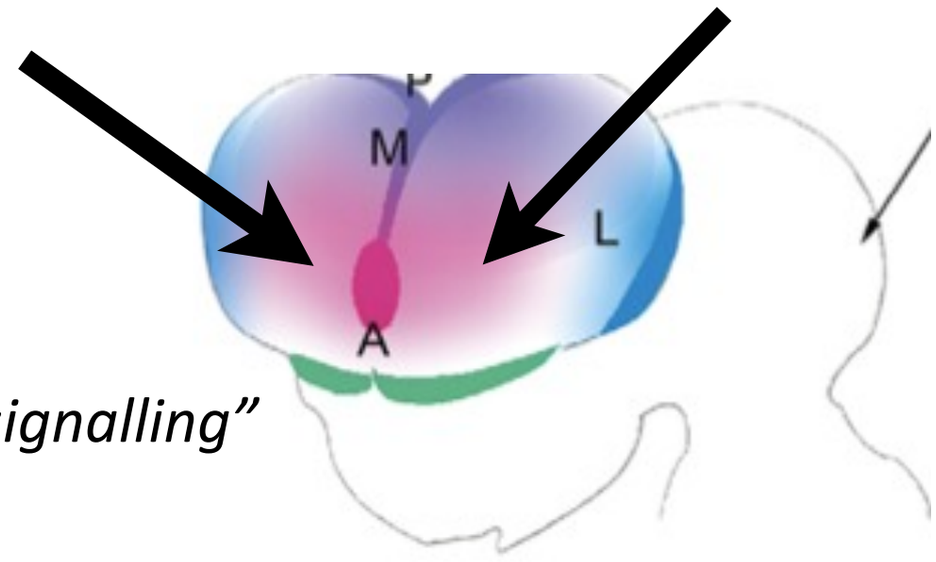


Hu et al, 2010 PNAS

60 mya the cortex was highly constrained by these gradients AND most of cortex was sensory

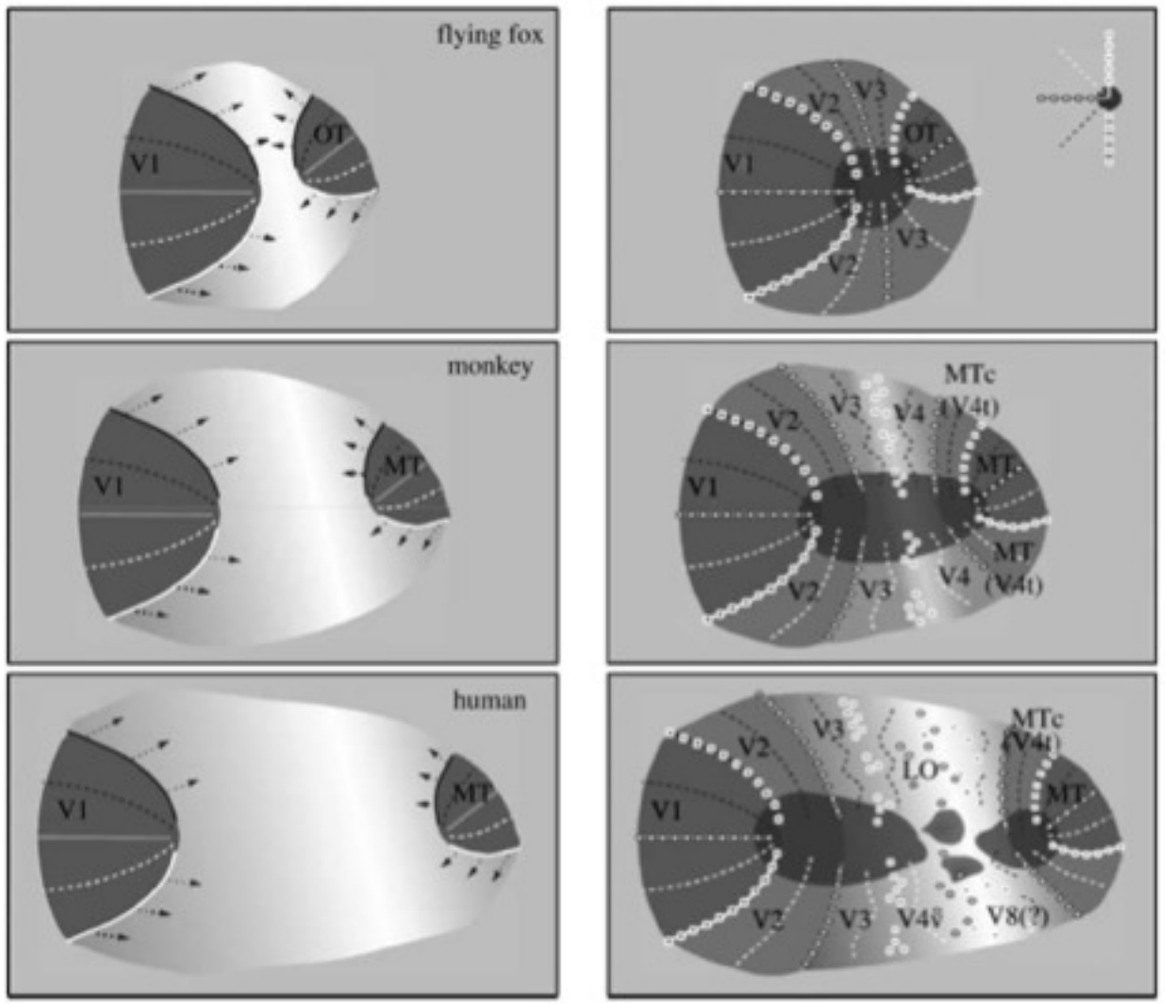


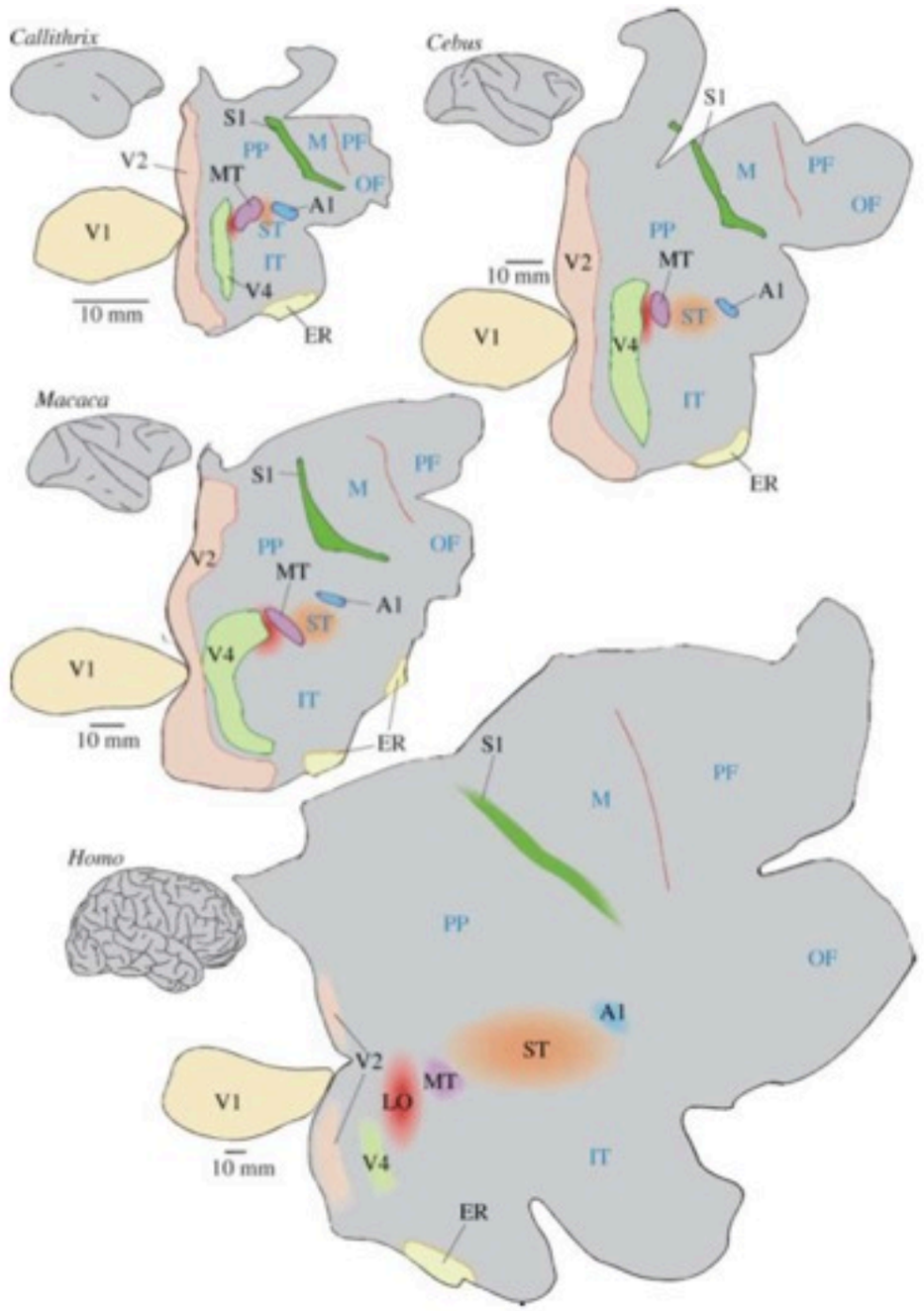
suggests a few fixed anchors?



"extra cortex without as much signalling"

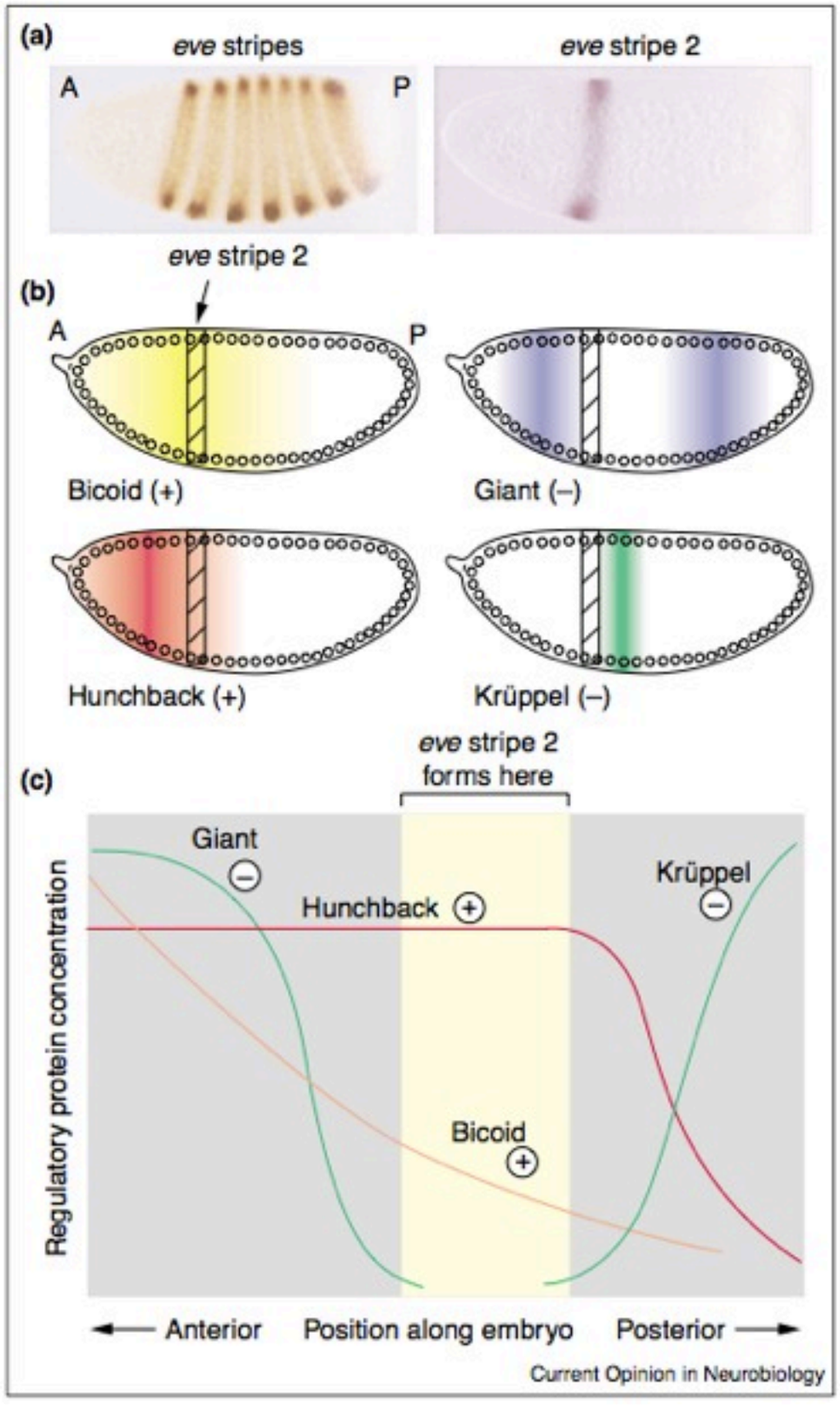
Increase in cortex size, increase in areas



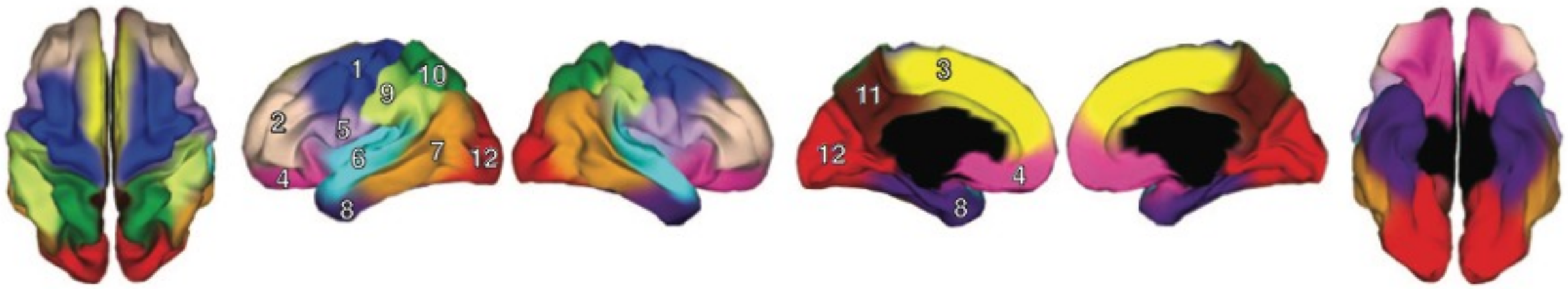


Rosa 2005

discrete zones from continuous gradients

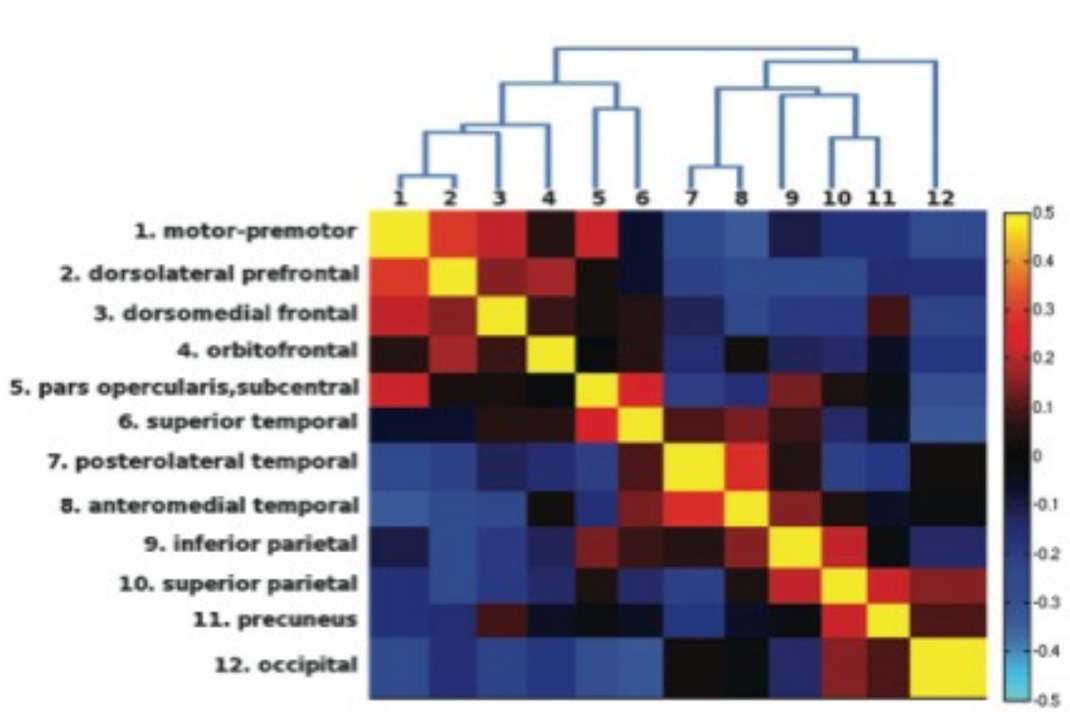


Correlated zones of expansion/contraction



mouse brain (*11*). In effect, we sought to develop a brain atlas of human cortical surface area that was based entirely on genetic correlations, rather than a priori structural or functional information.

To delineate the genetic patterning of the cortical area, we measured relative surface areal expansion using cortical surface reconstruction and spherical atlas mapping developed by Dale and colleagues (*12*–*14*). We divided the area measured at each location by the total surface area in order to account for global effects. Using the twin design, which compares monozygotic and dizygotic twins, we then estimated genetic correlations between different points on the cortical surface. These genetic correlations represent shared genetic influences on relative areal expansion between cortical regions (*15*). Details of these methods have been previously described (*8*, *16*). After computing pairwise genetic correlations, we used an unsupervised pattern recognition method—fuzzy cluster analysis (*17*)—to demarcate the genetic topography of cortical surface area based on the genetic correlations of relative surface area measures. To determine the appropriate number of clusters, we computed the widely used silhouette coefficient.



Chen 2012 Science