Developmental & Comparative anatomy of the CNS

Anatomy of the CNS_ Win2017/18
Athens, 23. Oct 2017

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University of Jena

Aims

This is neither for teaching you comparative anatomy
nor for arguing on what´s right and wrong in science.

This aims to SENSITIZE you to:

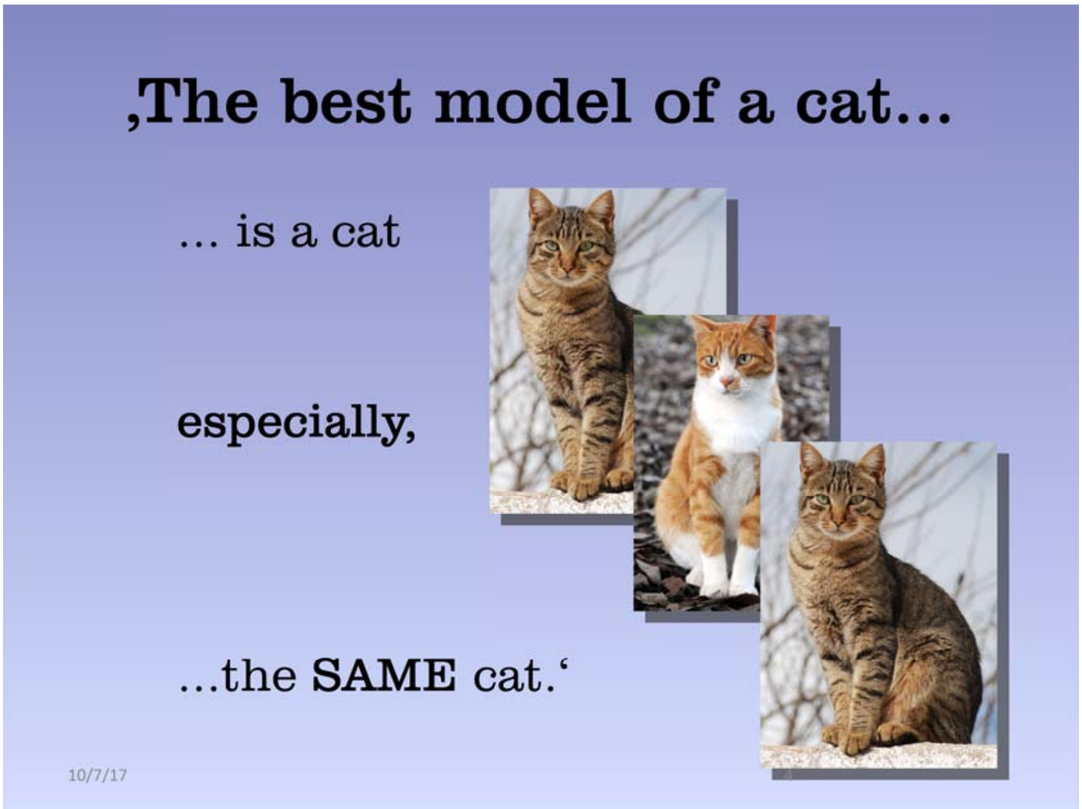
- evolutionary
- developmental
- translational

.... Issues/ perspectives of the CNS research

Objectives

- What is an experimental **animal model**?
- What is it good for (aims of the model)?
- **Selection criteria**
  - Objective … similarity, replicability
    - Driven by desired readout
  - Subjective … availability and accessibility
    - Driven by available sources
- **Evo-Devo** driven models

EVO	for evolution
DEVO	for development


‚The best model of a cat…
… is a cat
especially,
…the SAME cat.‘
10/7/17

Common and *less* common experimental animals in neuroscience

- Rat, mouse, guinea-pig
- Monkeys (Macaque, Rhesus)
- Human beings
  - E.g. for MRI-behavioral studies
- Zebra fish (develpment)
- Zebra finch (neurogenesis)
- Drosophila
- C.elegans
- Cricket
- Bat (space cells)
- Honey bee (behavior!)
- Naked mole rat
  - Prof. Gary Lewin, Pain

Did you ever wonder in which extend ?

Seventh Report from the Commission to the Council and the European Parliament on the Statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union COM(2013)859/final

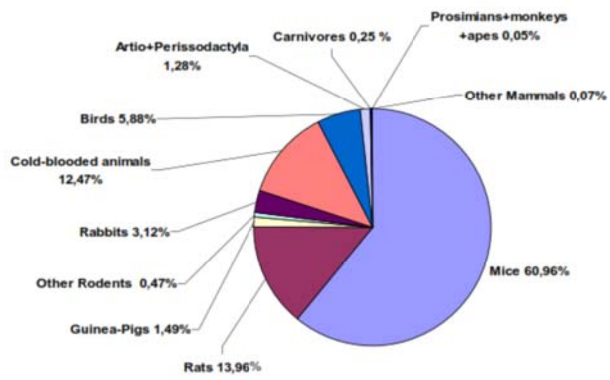
The Seventh Report provides an overview on the number of animals used in the

EU in 2011

for experimental and other scientific purposes. This report includes data from 27 Member States, submitted in the agreed format by all countries.

2013 (7th) report of the EU

Figure 1.1
Percentages of animals used by classes in the Member States

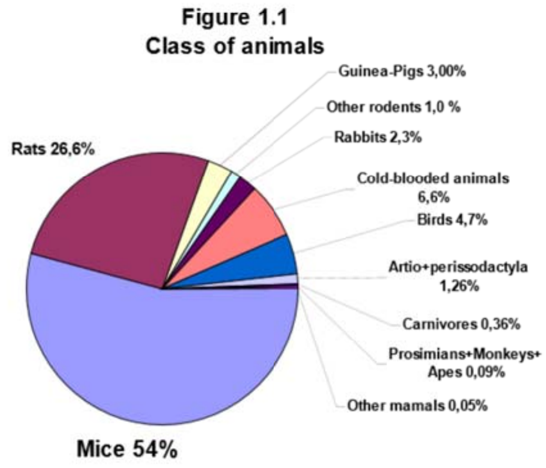


total : **11.000.000 animals in 2011**, all EU members

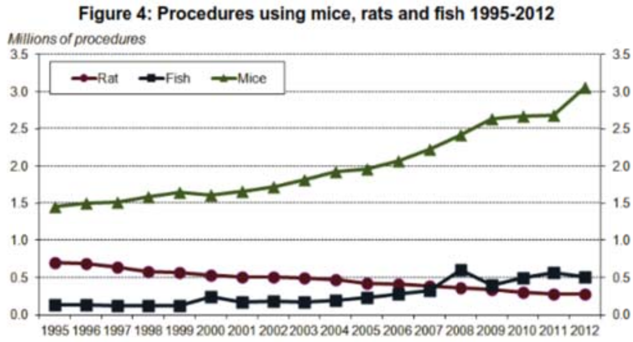
 http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

2003, Third report of the EU

... differences over time



biomedical reserach relies **almost exclusively** on mice



significant tropism towards mice

'Labs often use mice - partly because they are **cheaper** than other animals'

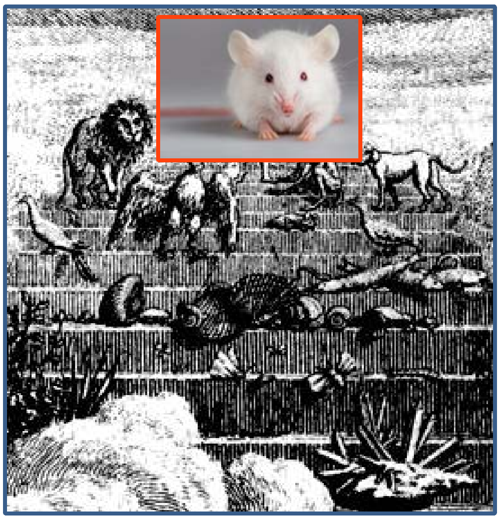
By Laurence Peter
BBC News
4 June 2015

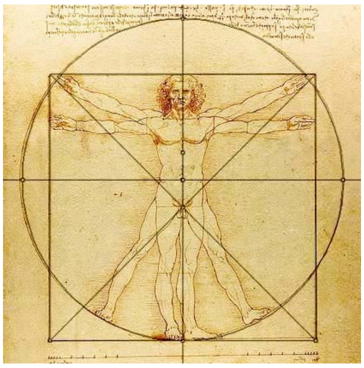
Let´s discuss it later on ...

Evolution revisited

Aristoteles (384-322 BC)
„scala naturae“

Julian Huxley (1942)
´´evolutionary synthesis´´





Of mice and men – are mice relevant models for human disease?

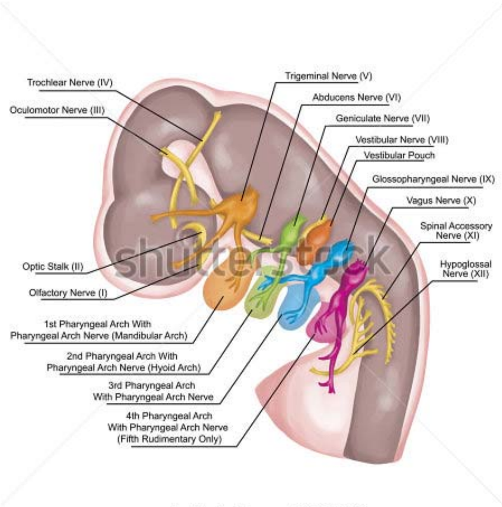
Comparative neuroscience

- Recognize **same** stuctures in different brains
- Compare **similarities** and differences

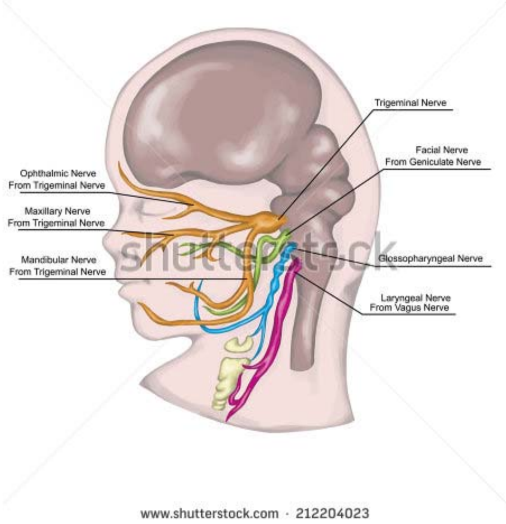
The terminology of ‚**similarity**'

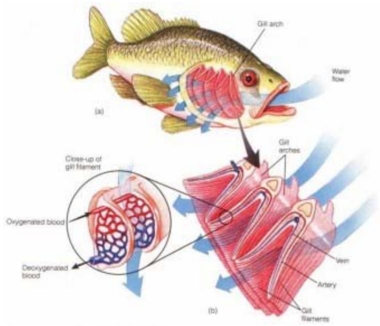
- **Analogy**: similarity of <u>function</u>, irrespective of origin
- **Homology**: similarity of <u>morphology</u>, phyletical and embryogenetical <u>origin</u>, irrespective of function

Origin: Pharyngeal arches



Homology: Gills and branchial nerves





Evo-Devo driven models

- **The *Evo-Devo* field**

- **Evo** = Evolutionary-driven:
  - evolutionary **conservation** (medical-driven models)
- **Devo** = Developmentally-driven:
  - understanding of the generative mechanisms underlying **biological diversity** (Evo-Devo-driven models)

Tzika A. C. & M. C. Milinkovitch, **2008;** Gilbert et al., **1996;**
http://www.lanevol.org/LANE/Evo-Devo.html

10/7/17 17

Gilbert SE, Opitz JM, Raff RA (1996) Dev Biol 173; 357-72

✓Milinkovitch M.C. & A. C. Tzika
Escaping the Mouse Trap; the Selection of New Evo-Devo Model Species
Journal of Experimental Zoology (Mol. Dev. Evol.) 308B: 337–346 (2007)

e-mail

News Coverage

✓Tzika A. C. & M. C. Milinkovitch.
A Pragmatic Approach for Selecting Evo-Devo Model Species in Amniotes
Chapter 7 Pages 119-140 in ‘Evolving Pathways; Key Themes in Evolutionary Developmental Biology’ (A. Minelli & G. Fusco, eds.), Cambridge University Press 2008

e-mail
✓Di-Poï N., Montoya-Burgos J.I., Miller H., Pourquié O., Milinkovitch M.C. & D. Duboule
Changes in Hox genes’ structure and function during the evolution of the squamate body plan
Nature, 464: 99-103 (2010)

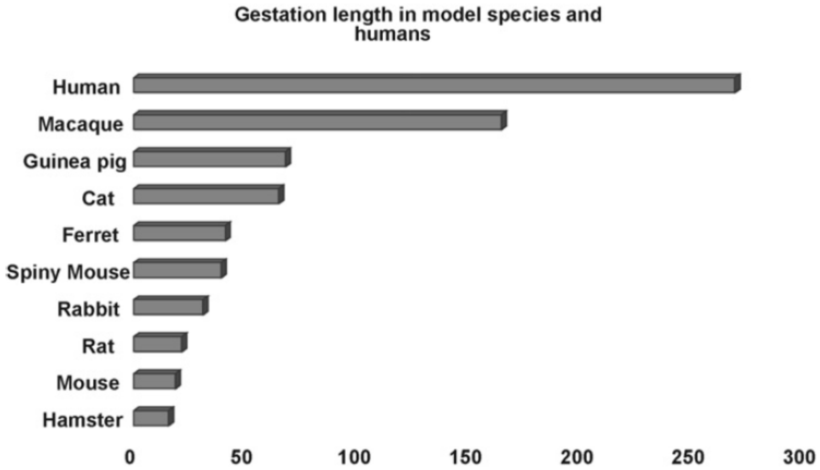
e-mail: Article

e-mail: Supplementary File

Part I
Translating time

Birth is
neither an **offset**
nor an **alignment** point
for developmental matching
of mammals

Gestation length



Clancy et al., **2007** *Neurotoxicology*

Terminology of development
Human

Period	Time intervals
Blastem (conception, gastrulation)	1-16 post-conceptional (PC) day
Embryonal	16th PC day – 8th PC week
Fetal	9th – 28th PC week
Perinatal	29th PC - 1st postnatal (PN) week
Postnatal	2nd-6th PN week

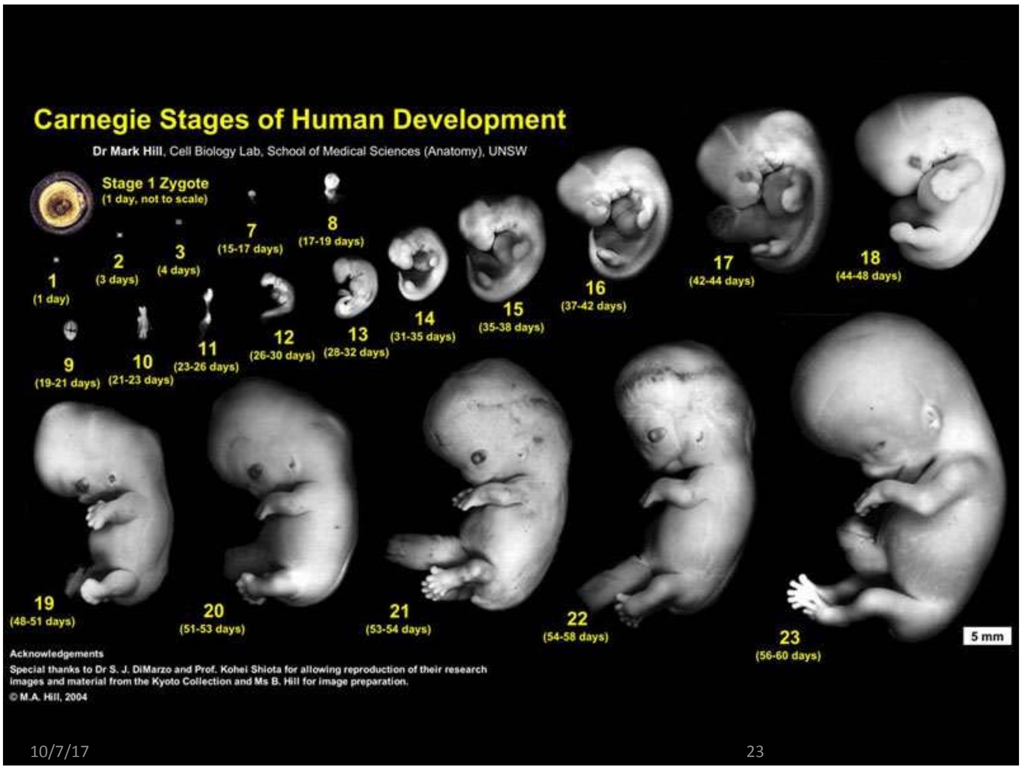
*www.**aap**.org/*

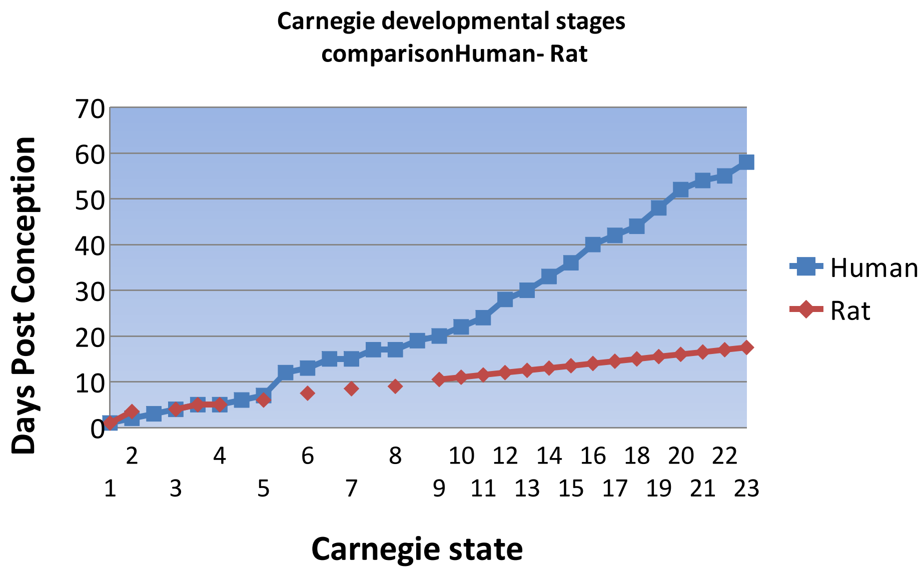
Developmental staging

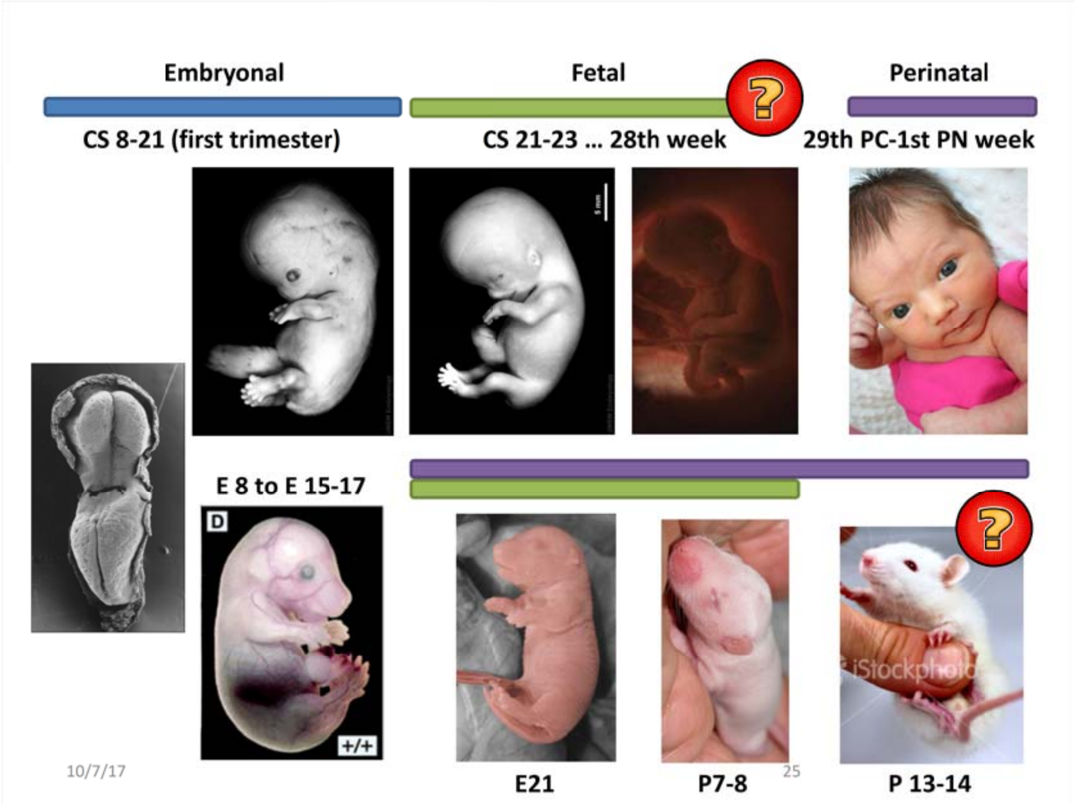
- Vertebrates: **Carnegie** classification system

Individualized staging systems ...

- Rat... **Witschi** classification system
- Mouse... **Thailer** classification system


Carnegie Stages of Human Development
Dr Mark Hill, Cell Biology Lab, School of Medical Sciences (Anatomy), UNSW
Stage 1 Zygote
(1 day, not to scale)
1
(1 day)
2
(3 days)
3
(4 days)
7
(15-17 days)
8
(17-19 days)
9
(19-21 days)
10
(21-23 days)
11
(23-26 days)
12
(26-30 days)
13
(28-32 days)
14
(31-35 days)
15
(35-38 days)
16
(37-42 days)
17
(42-44 days)
18
(44-48 days)
19
(48-51 days)
20
(51-53 days)
21
(53-54 days)
22
(54-58 days)
23
(56-60 days)
5 mm
Acknowledgements
Special thanks to Dr S. J. DiMarzo and Prof. Kohei Shiota for allowing reproduction of their research images and material from the Kyoto Collection and Ms B. Hill for image preparation.
© M.A. Hill, 2004


Carnegie developmental stages
comparisonHuman- Rat
Days Post Conception
70
60
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Carnegie state
Human
Rat



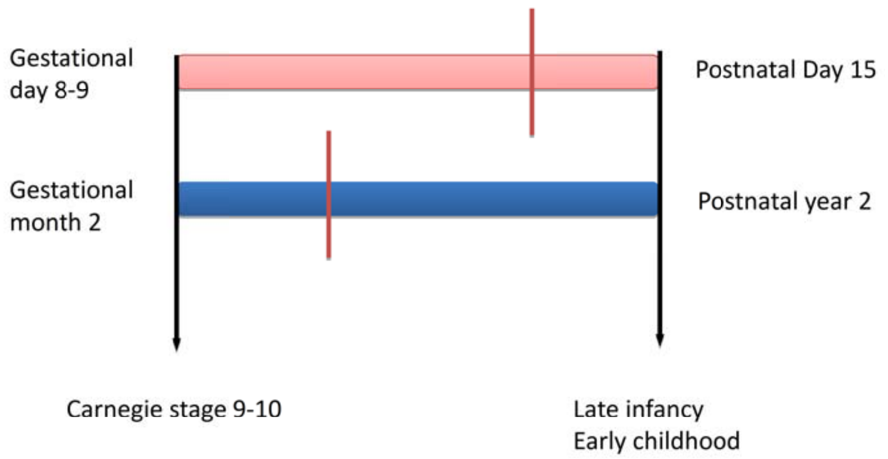
POINT 1: Fetal period is not really translated in rodents !!!!
POINT 2: the PERINATAL period is mixed up with the FETAL period in rat, context – dependtdent on the project. i.e. depends if the protocol extends Postnataly or not, then the same time period is called PERINATAL or FETAL…
POINT 3: EARLY POSTNATAL development of the rat vs human …. Big gap !!! To what does it correspond?
Postnatal 0-10 = INFANCY 1-12 months ?? Ill defined / inaccurate

When is the fetal period in the rat really defined???
OVERLAP between fetal – perinatal period
Ill-defined terminology
Publication – related

	HUMAN	RAT
Perinatal period	0-1 week	??
Infancy	1 week -12 months	PND ??-15
early childhood	2 - 4 years	PND 15 - 25
childhood	4-10 years	PND 55- 35
Peridolescence	10-12 years	PND 35-45
Adolescence	12.5 years	1.5 months
Young adulthood	16 years	2 months
Adulthood - social maturity	18 years	0.5 years
Adulthood - social maturity	30 years	1 year
Late dulthood	45 years	1.5 year
Senescence	60 years	2 years
	75 years	2.5 years
...and so on	90 years	3.0 years
...	105 years	3.5 years
	113 years	3.75 years
	120 years	4.0 years

Rice & Barone, **2000** *Env Health Persp*; Andersen et al., **2002** *Beh Brain Sci*

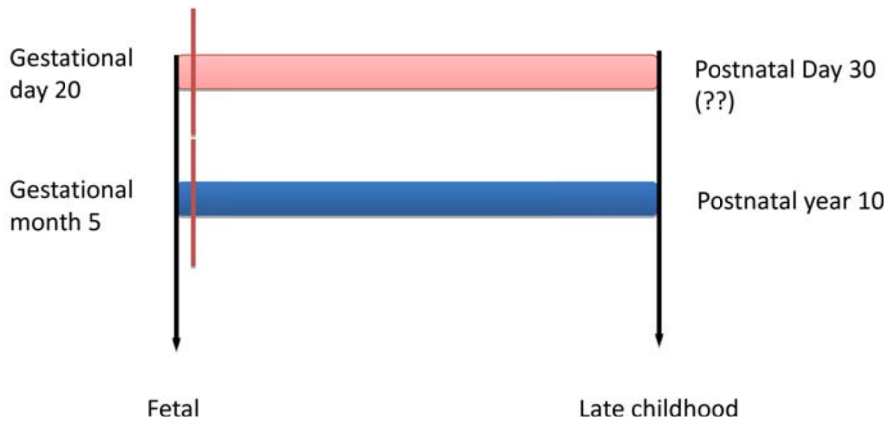
Matching: glial – neuronal proliferation and migration



Rice & Barone, **2000** *Env Health Persp*; Andersen et al., **2002** *Beh Brain Sci*

Rat Human Birth

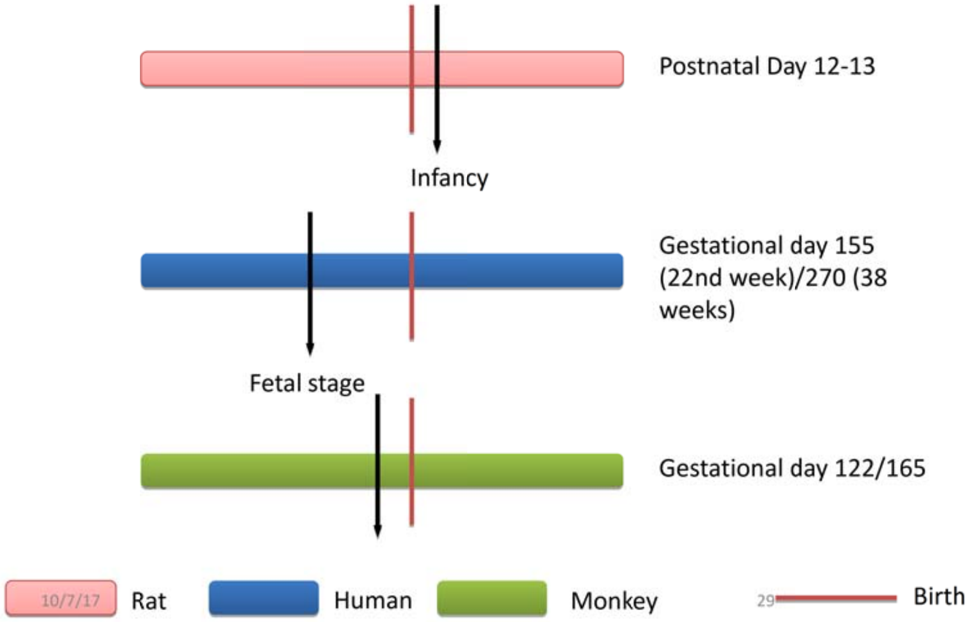
Matching: myelination



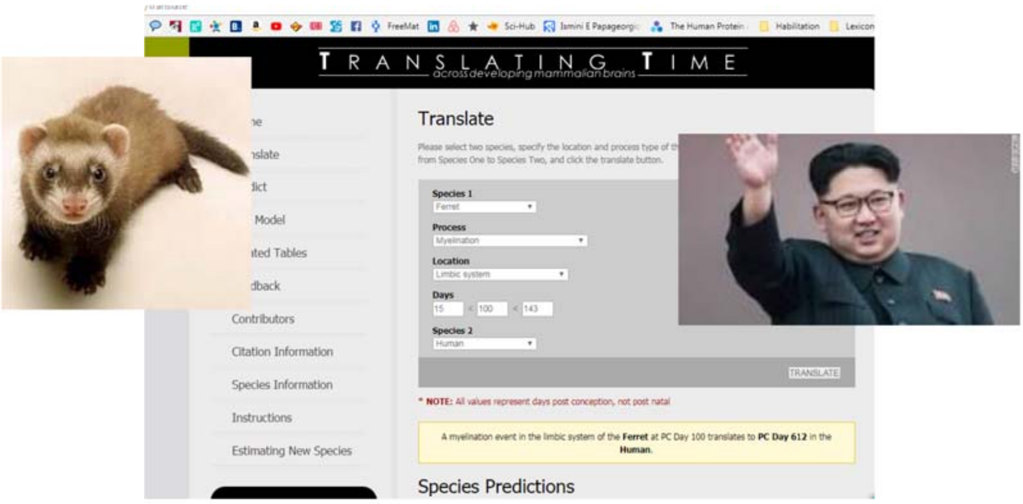
Rice & Barone, **2000** *Env Health Persp*; Andersen et al., **2002** *Beh Brain Sci*

Rat Human Birth

Miss-matching ? : eye opening



http://www.translatingtime.net/



Clancy et al., **2007** *Neurotoxicology* ; Clancy et al., **2001** *Neuroscience*

7368 • The Journal of Neuroscience, April 24, 2013 • 33(17):7368–7383

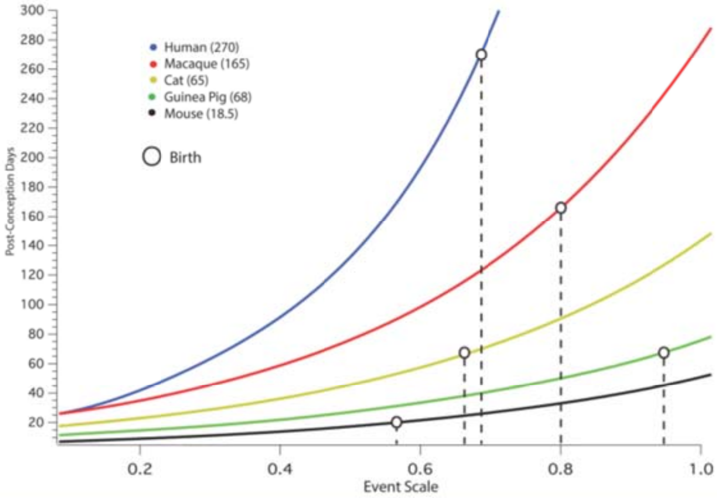
Development/Plasticity/Repair

Modeling Transformations of Neurodevelopmental Sequences across Mammalian Species

Alan D. Workman,[1] Christine J. Charvet,[1] Barbara Clancy,[2] Richard B. Darlington,[1] and Barbara L. Finlay[1]
[1]Behavioral and Evolutionary Neuroscience Group, Cornell University, Ithaca, New York 14853 and [2]Department of Biology, University of Central Arkansas, Conway, Arkansas 72035

A general model of neural development is derived to fit 18 mammalian species, including humans, macaques, several rodent species, and six metatherian (marsupial) mammals. The goal of this work is to describe heterochronic changes in brain evolution within its basic developmental allometry, and provide an empirical basis to recognize equivalent maturational states across animals. The empirical data generating the model comprises 271 developmental events, including measures of initial neurogenesis, axon extension, establishment, and refinement of connectivity, as well as later events such as myelin formation, growth of brain volume, and early behavioral milestones, to the third year of human postnatal life. The progress of neural events across species is sufficiently predictable that a single model can be used to predict the timing of all events in all species, with a correlation of modeled values to empirical data of 0.9929. Each species' rate of progress through the event scale, described by a regression equation predicting duration of development in days, is highly correlated with adult brain size. Neural heterochrony can be seen in selective delay of retinogenesis in the cat, associated with greater numbers of rods in its retina, and delay of corticogenesis in all species but rodents and the rabbit, associated with relatively larger cortices in species with delay. Unexpectedly, precocial mammals (those unusually mature at birth) delay the onset of first neurogenesis but then progress rapidly through remaining developmental events.

7380 • J. Neurosci., April 24, 2013 • 33(17):7368–7383



The position of birth for six placental mammals relative to the event scale.

Workman et al., 2013 J Neuroscience

ttime: an R Package for Translating the Timing of Brain Development Across Mammalian Species

Nagarajan, R., Darlington, R.B., Finlay, B.L. et al. Neuroinform (2010) 8: 201. doi:10.1007/s12021-010-9081-y

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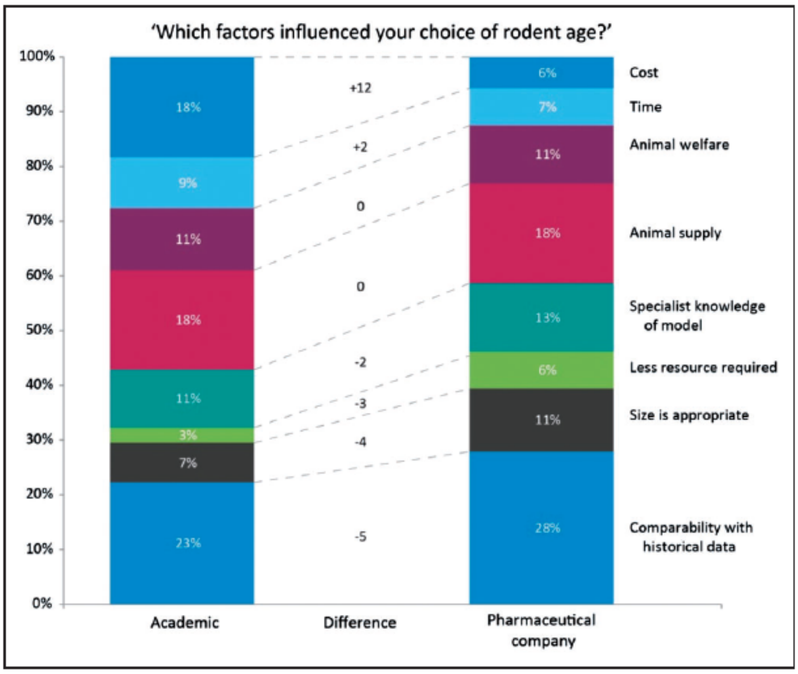
Samuel J Ja
Ilaria Bellan
Alan Holmes
Andrew Rice
Carol Strepl



Jackson et al., 2016 Lab Animals

Summary Part I

- The selection of animal models should be oriented to the scientific question
- Translating developmental time is essential for the result interpretation
- Carnegie scale is based on developmental milestones of the CNS
- Birth is neither a developmental milestone nor an alignment point

Part II
Development of the (C)NS

Models of Human Growth by Scammon, 1930

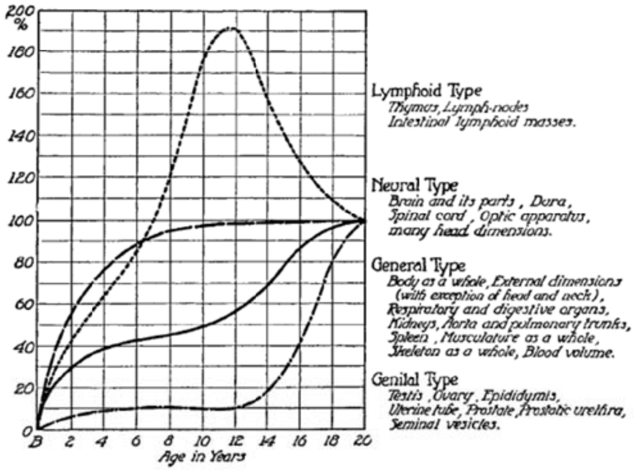
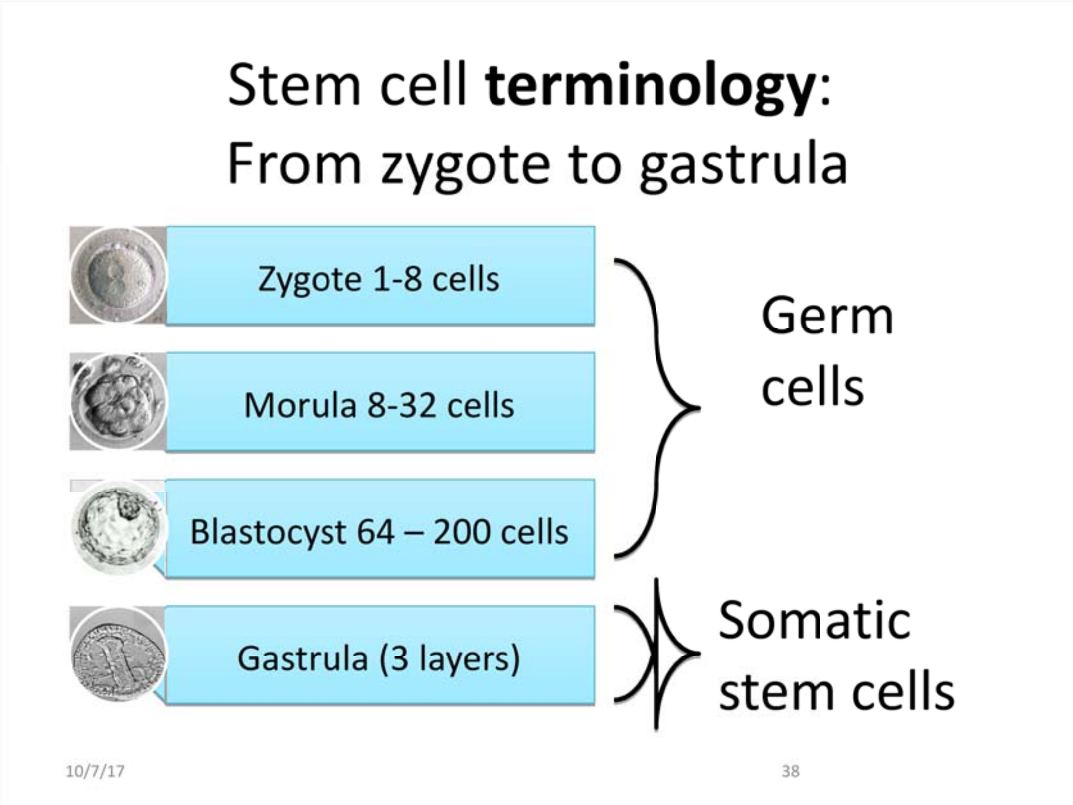


Figure 1.7. Four major types of postnatal growth curves from birth to 20 years, expressed as the percent of the total increment of growth (Scammon, 1930).

Reproduced from: Barry Bogin. Patterns of human growth, 2nd edition. Cambridge University Press 1999


Stem cell **terminology**:
From zygote to gastrula
Zygote 1-8 cells
Morula 8-32 cells
Blastocyst 64 – 200 cells
Gastrula (3 layers)
Germ cells
Somatic stem cells
10/7/17
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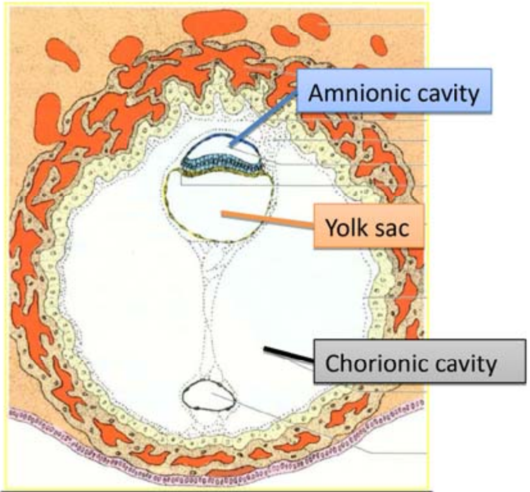
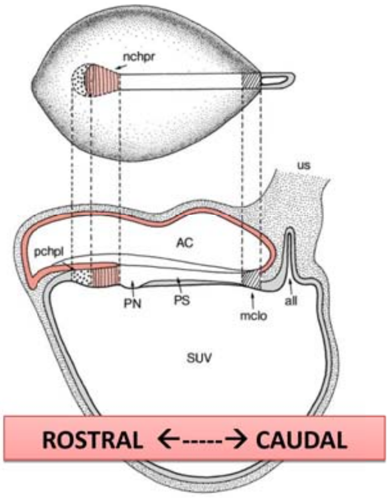
Blastula: 2 germ cell layers

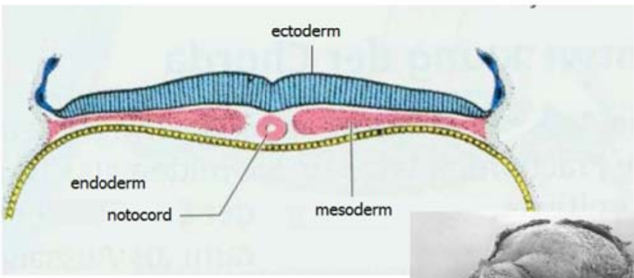


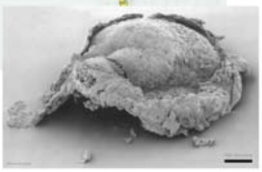


2 Germ cell layers; Rostrocaudal orientation
Epiblast; Hypoblast; **Placode formation**

Clinical Neuroembryology. Donkelaar HJ, Lammens M, Hori A. Springer Verlag 2006

Gastrula: 3 germ-cell layers





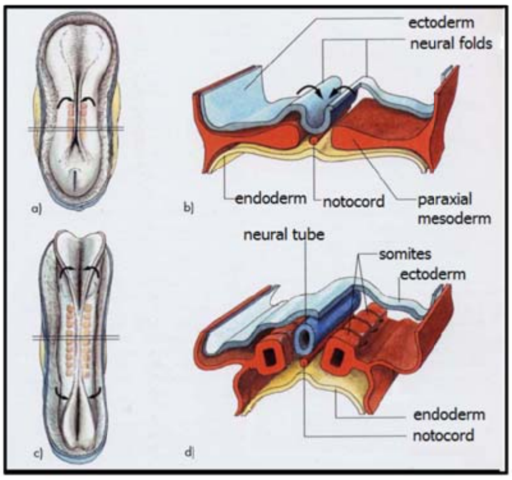
Transverse section of the **placode**

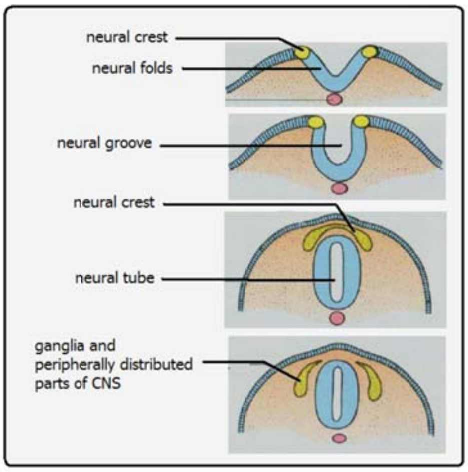
Gastrulation = Carnegie stage 7

Definition of 3 germ cell layers

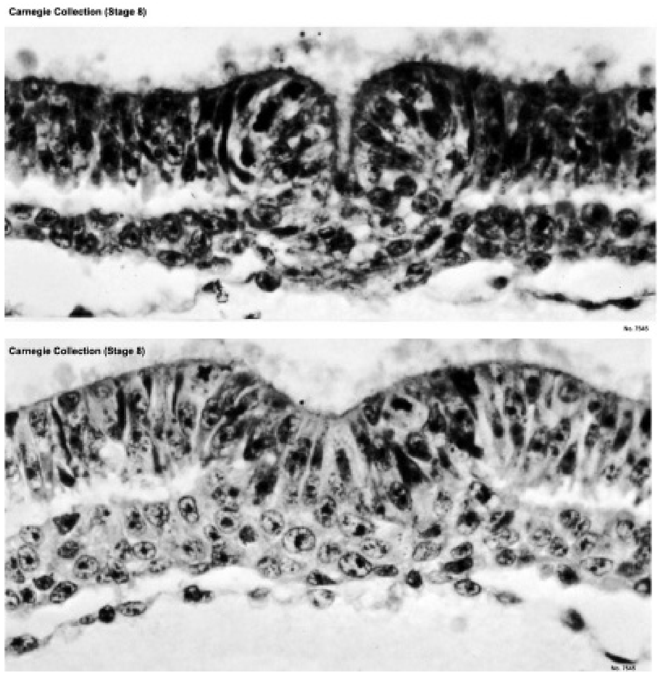
- **Ectoderm**
  - *epithelia* (skin), nervous system (neurons, macroglia)
- **Mesoderm**
  - muscles, bones, blood, liver, spleen, kidneys, nervous system (microglia)
- **Endoderm**
  - *endothelia* (secretory glands, mucosa, respiratory tract, GI tract, blood vessels)

Neural *crest*, neural *tube*





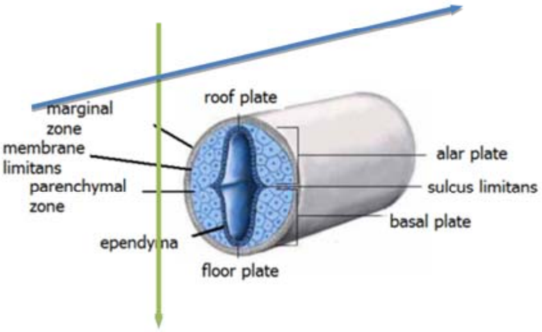
Neural Crest Carnegie stage 8


Carnegie Collection (Stage 8)
Carnegie Collection (Stage 8)

Brain development

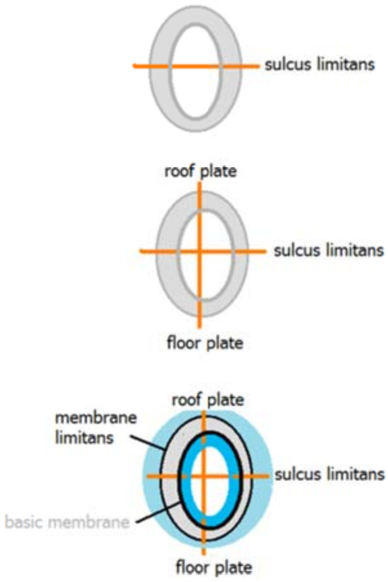
- Dorsoventral
- Rostrocaudal (Anteroposterior)
  - Macroscopic anatomy
  - Microscopic anatomy
  - Genes !!!

Dorsoventral brain development



Tectum: dorsal to sulcus limitans

Tegmentum: ventral to s. limitans



Dorsoventral development:
The Hedgehog (Hg) gene family

- Drosophila prototype gene
  - Hedgehog (*Hh*)
- Mammalian homologues
  - Sonic Hh (*shh*) – Notocord
  - Indian Hh (*ihh*) - Gut
  - Desert Hh (*dhh*) – Sertoli cells

Why ´hedgehog´ ???

Developmental Biology 6th edition by Scott and Gilbert

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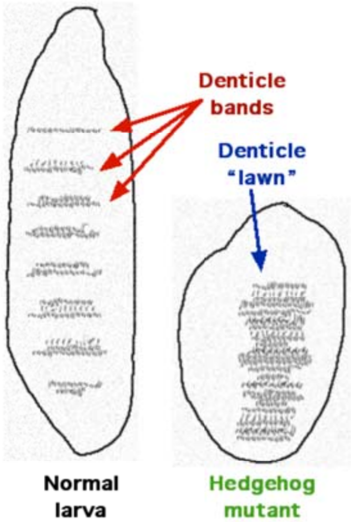
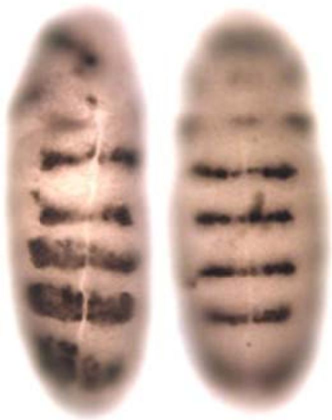
Hh expression pattern: *denticle bands*



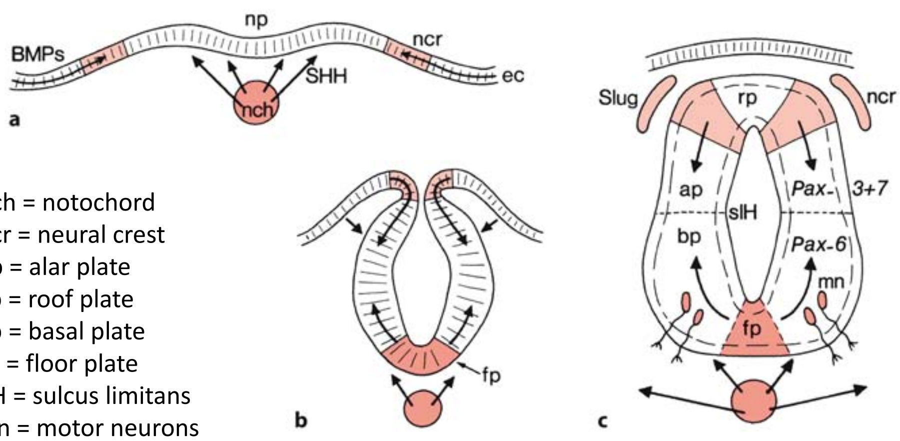


Drosophila larvae

Sonic hedgehog peptide

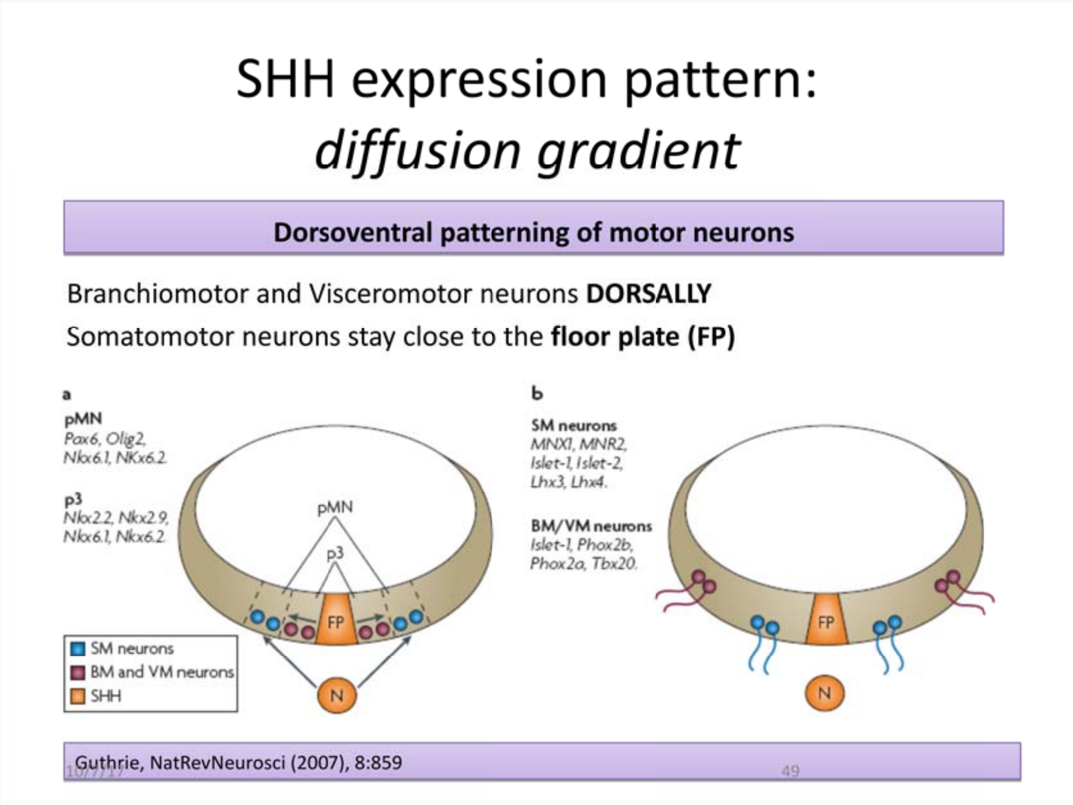
- Paracrine factor
- Produced by the **notocord**
- **„Ventralizing factor“**
- Induces the floor plate
- Concentration gradient THAT
- Shapes the dorsoventral neuronal differentiation
  - Ventral (=close to notocord) = Motor neurons
  - Dorsal = Sensory neurons

Notochord produces SHH



Nch = notochord
Ncr = neural crest
Ap = alar plate
Rp = roof plate
Bp = basal plate
Fp = floor plate
slH = sulcus limitans
Mn = motor neurons

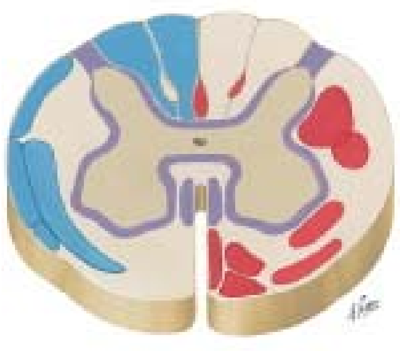
Clinical Neuroembryology. Donkelaar HJ, Lammens M, Hori A. Springer Verlag 2006



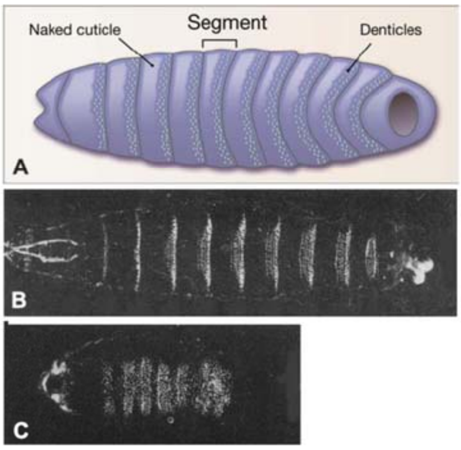
SM = somatomotor
BM = branchiomotor
VM = visceromotor

SHH = Sonic headgehog protein, diffusion gradient

Interactive task



Hh gene defects



***Hh* (-/-) Drosophilas**

´Hedgehog´ larvae

***shh* defect in humans**

Holoprosecephaly spectrum

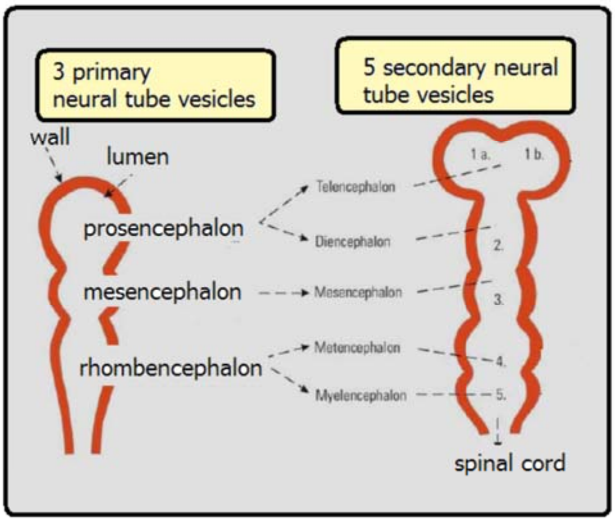
Here: type 3, Cyclopia

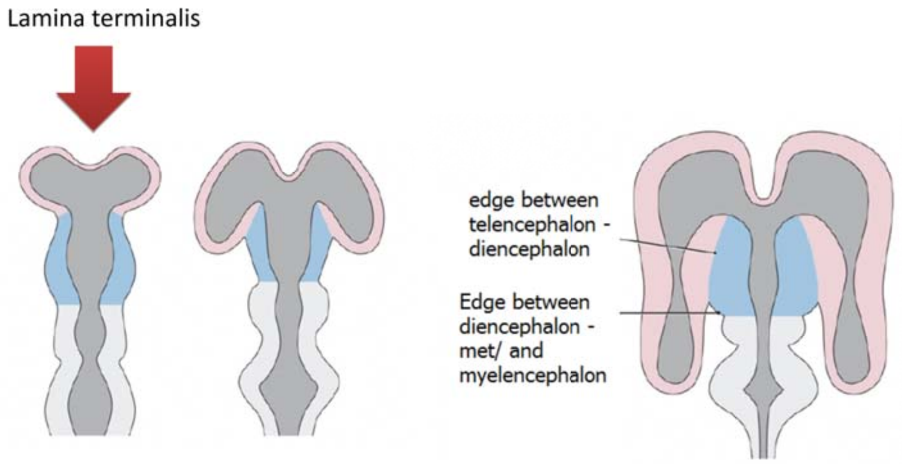
Brink, 2007 *Physiol Rev*; Nusslein-Volhardt & Wieschaus E, **1980** *Nature*

Rostro-caudal brain development
CNS vesicles

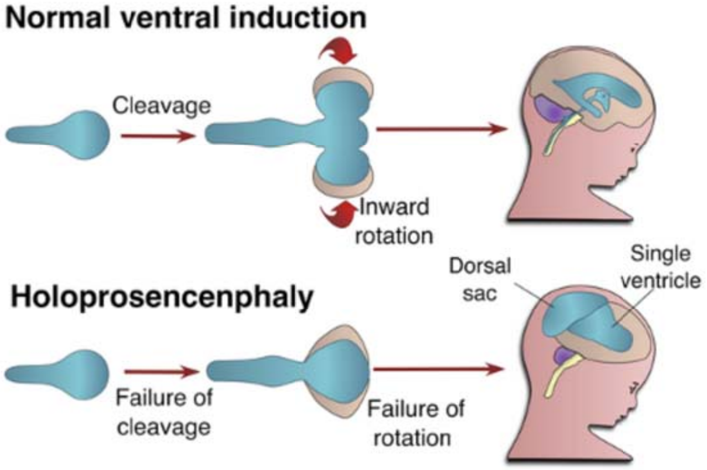
Primary CNS vesicles

Secondary CNS vesicles




Lamina terminalis
edge between telencephalon - diencephalon
Edge between diencephalon - met/ and myelencephalon

Holoprosencephaly



https://www.khanacademy.org/test-prep/mcat/biological-sciences-practice/biological-sciences-practice-tut/e/holoprosencephaly--a-medical-condition-with-devastating-consequences

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At early stages human embryological development, the neural tube begins a process called ventral induction. During ventral induction, the neural tube divides the tube into 3 primary brain vesicles, or subdivisions, that later differentiate into 5 vesicles (Figure 1) . Between the 18th and the 28th day of gestation, the anterior portion of the neural tube, the prosencephalon, divides into two parts (telencephalon and diencephalon - Figure 1). These parts then undergo a cleavage process followed by inward rotation (Figure 2). Under normal circumstances, this would result in a telencephalon and diencephalon divided into two halves each. Incomplete cleavage and failure of rotation of the prosencephalon results in a brain malformation known as holoprosencephaly (Figure 2). Holoprosencephaly is a spectrum of conditions with symptoms varying from mild to severe. In the most severe form, alobar holoprosencephaly, the telencephalon and diencephalon are fused and a single ventricle is formed. In semilobar holoprosencephaly, the diencephalon remains fused but the telencephalon presents a fissure posteriorly. In lobar holoprosencephaly the diencephalon may or may not be fused, but the telencephalon presents a nearly normal fissure. Individuals with the alobar form experience severe mental retardation and seizures that are difficult to treat. The condition is frequently associated with facial malformations (i.e. malformations of the nose, lips and eyes, or in extreme cases cyclopia - fused eyes) and in many cases is fatal due to severe brain malformations. The other two forms result in limited clinical deficits such as cognitive delay and seizures that can be treated; life expectancy in these individuals is not reduced.

Alobar holoprosencephaly

Fusion of cerebral hemispheres

Absence of olfactory tracts

Single ventricle

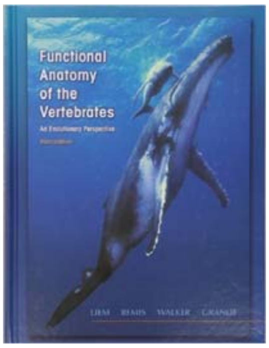
A cyst atop the posterior part of the brain (dorsal sac) may be present

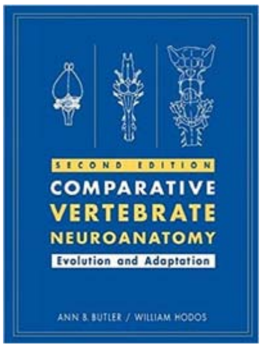
Images by G. Pilu

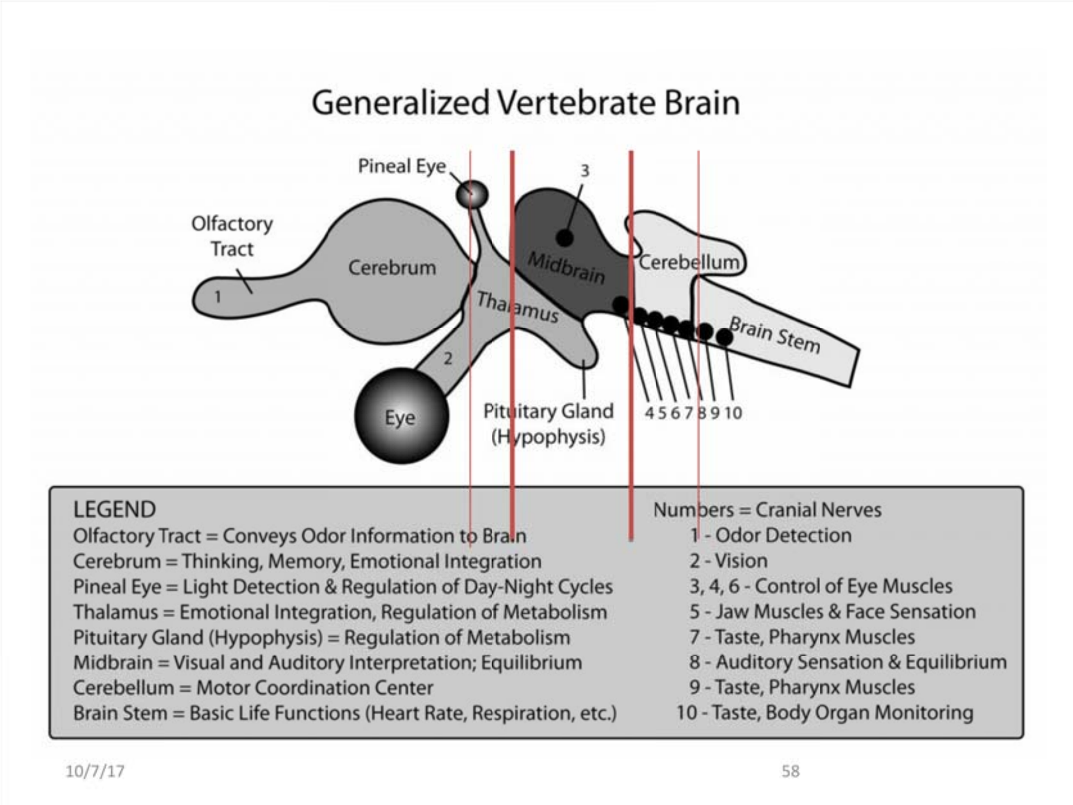
Summary Part II

- 3 germ cell layers define the gastrula
- CNS is an ectodermal structure
- CNS development occurs ventrodorsally and rostrocaudally
- Shh is a ventralizing factor

Part III
Translating ‚Evo‘
Evolution of the CNS







Prosencephalon

Telencephalon (cerebrum)
Diencephalon (thalamus)

Mesencephalon (midbtain)

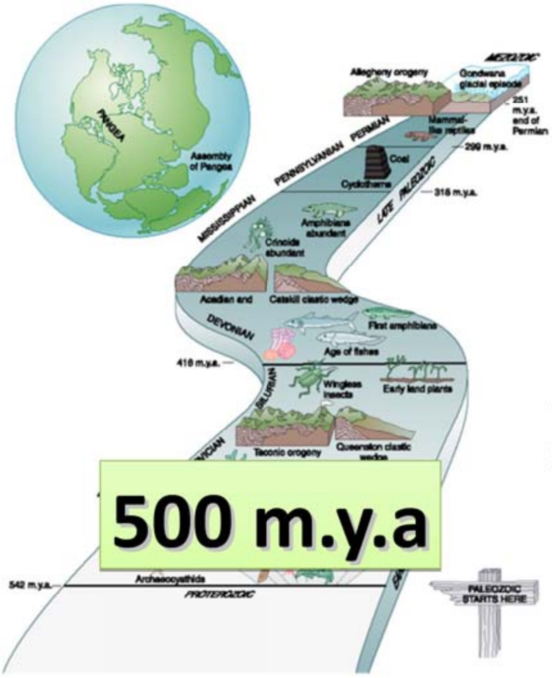
Rhombencephalon

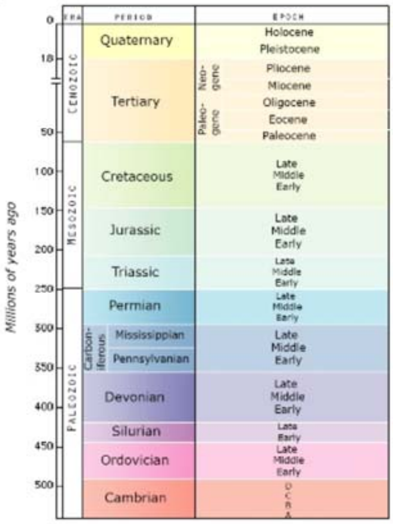
Metencephalon (pons, cerebellum)
Myelenchephalon (medulla oblongata)

Rostrocaudal brain development CNS vesicles

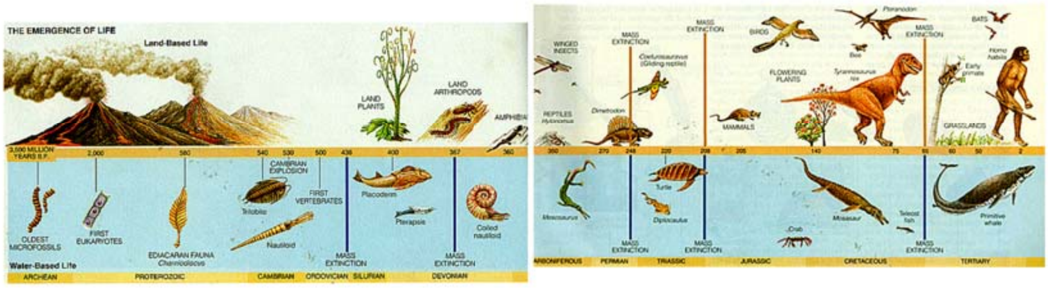
Neural Tube	Primary Vesicles	Secondary Vesicles	Adult Structures
Brain	Prosencephalon	Telencephalon	Rhinencephalon, Amygdala, **Hippocampus**, Cerebrum (Cortex), Basal Ganglia, lateral ventricles
		Diencephalon	Epithalamus, Thalamus, Hypothalamus, Subthalamus, Pituitary, Pineal, third ventricle
	Mesencephalon	Mesencephalon	Tectum, Cerebral peduncle, Pretectum, cerebral aqueduct
	Rhombencephalon	Metencephalon	Pons, Cerebellum
		Myelencephalon	Medulla Oblongata
Spinal Cord			

What is the age of the brain ?





The vertebrate brain

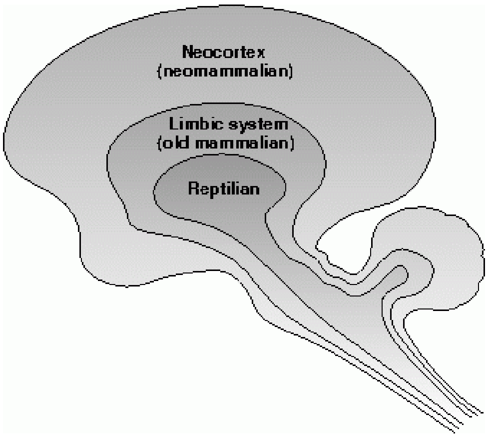


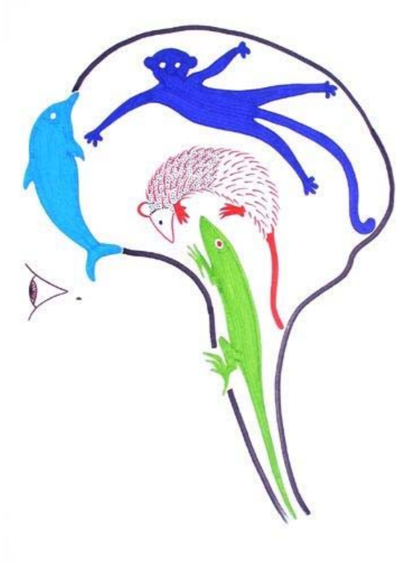
Hindbrain
Midbrain
Cerebellum
~ 500 mil.

Forebrain
Limbic system
~ 300 mil.

Forebrain
mammalian
~ 200 mil.

The “triune“ brain



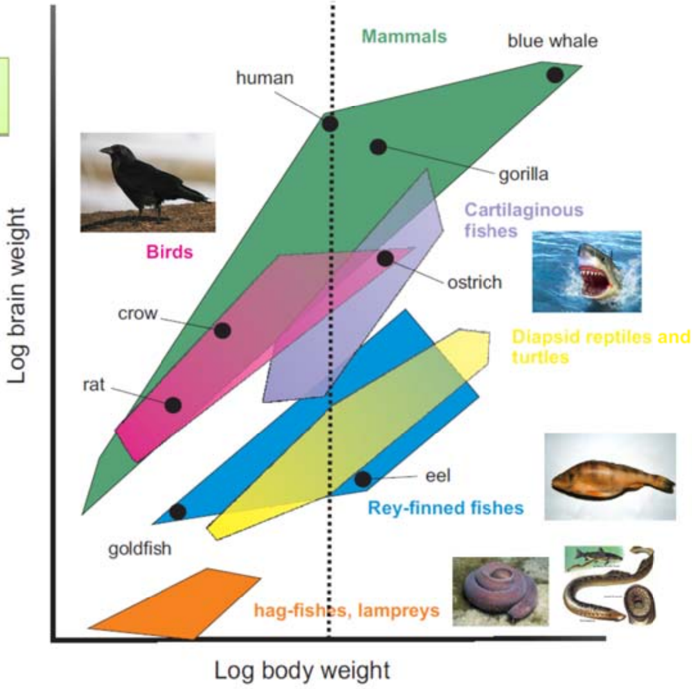


Paul Mc Lean, **1990**

Functional anatomy of the vertebrates 3rd edition. Liem et al.

Isometric evolution
Allometric evolution

(Brain) Size Matters



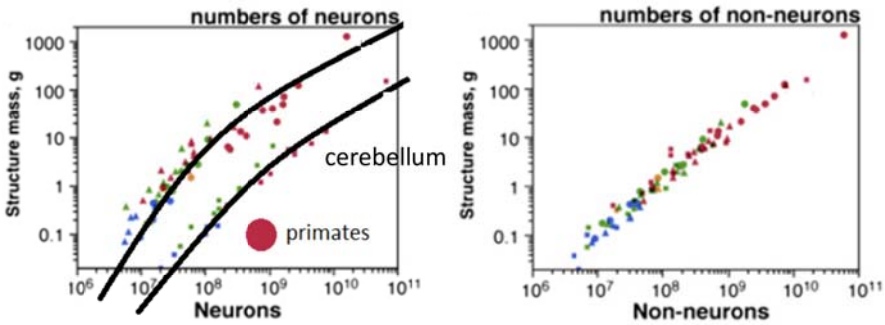
... Or maybe not?

The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost

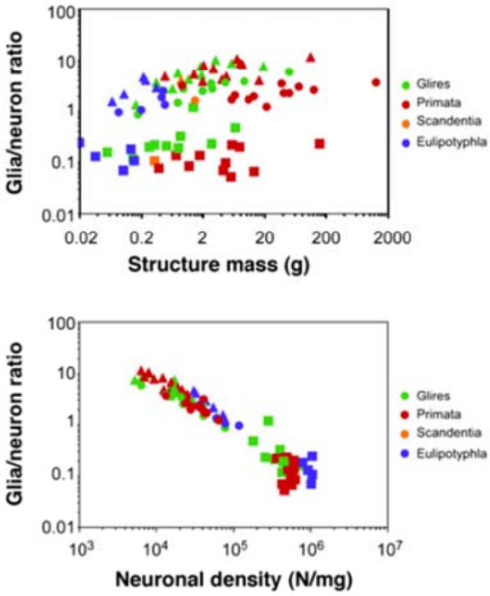
Suzana Herculano-Houzel[1]

Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-902, Rio de Janeiro, Brazil; and Instituto Nacional de Neurociência Translacional, Instituto Nacional de Ciência e Tecnologia/Ministério de Ciência e Tecnologia, 04023-900, Sao Paulo, Brazil

Edited by Francisco J. Ayala, University of California, Irvine, CA, and approved April 12, 2012 (received for review February 29, 2012)



Houzel, PNAS ***2012***



... And the **synaptic density** seems to be constant across species ...

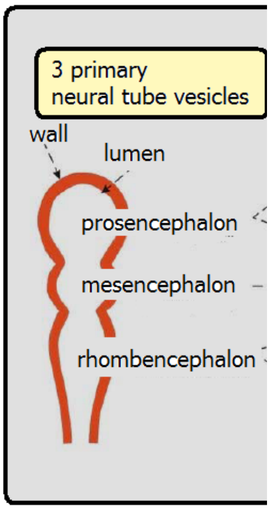
Houzel, PNAS ***2012***

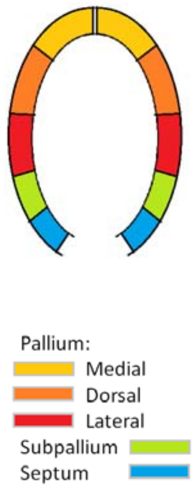
Pallium and subpallium

Primary forebrain developmental structures

Developmental origin of forebrain

- **Pallium**
  - Medial
  - Dorsal
  - Lateral
- **Subpallium**
- **Septum**





Marin and Rubenstein, **2001** *Nat Rev Neuroscience*
Functional anatomy of the vertebrates 3rd edition. Liem et al.

Functional anatomy of the vertebrates 3rd edition. Liem et al.

Pallium

- Lamination properties (*textbook knowledge*)
- Generates the cortex and subcortical nuclei

  - *Cajal Retzius cells*
  - *Reelin gradient = No-Go signal*
  - *Radial migration*
  - *Inside-out pattern: Cortex*
  - *Outside-in pattern: Nuclei*

Functional anatomy of the vertebrates 3rd edition. Liem et al.

Subpallium

- No lamination properties (*textbook knowledge*)
- Generates the basal ganglia
  - *Interneurons !!! GABA-ergic zone*
  - *Tangential migration*

Functional anatomy of the vertebrates 3rd edition. Liem et al.

Pallium and subpallium

Pallium -- Telencephalon

- In **avian brain**: 3-4 layered structure (allocortex)
- In **mammal brain**: 6 layered (isocortical) structure in the middle with 3 layered (allocortical)structure at the margins
  - **Medial** margin = hippocampus
  - **Lateral** margin = amygdala, olfactory allocortex

Subpallium – Diencephalon

- Septum
- Basal ganglia (striatum)
- Hypothalamus – preoptic area
- Thalamus

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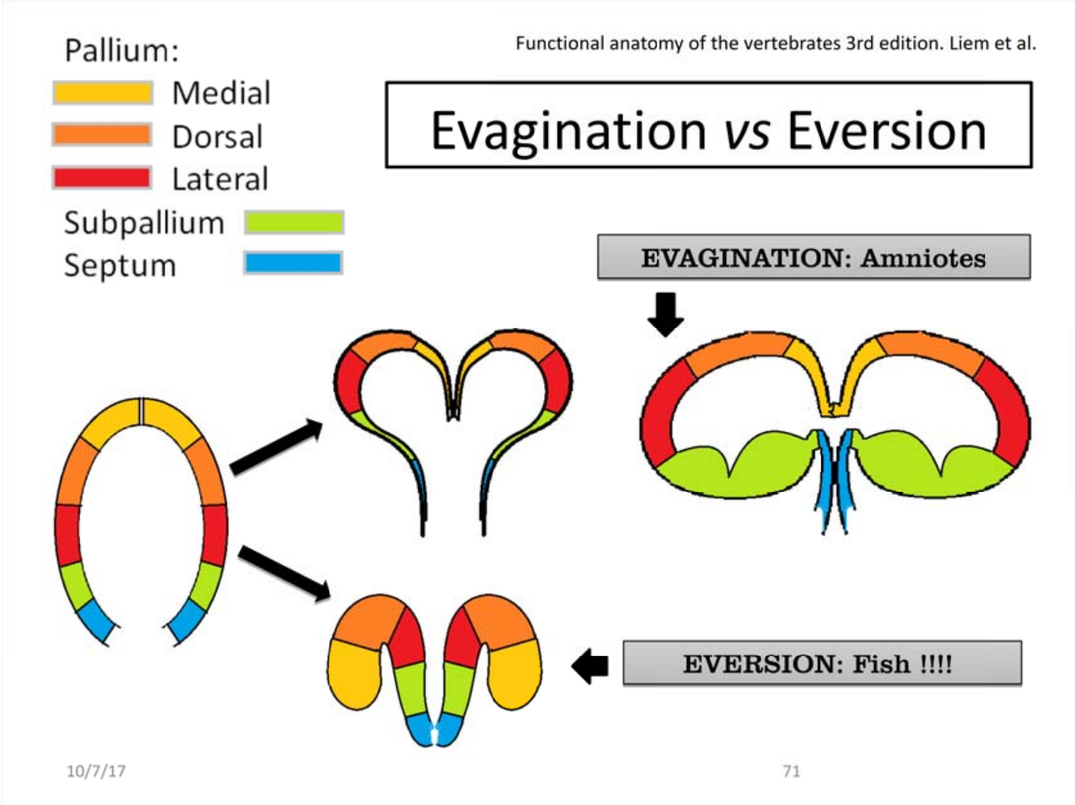
In a neuroanatomy context, the word **pallium** refers to the layers of gray and white matter that cover the upper surface of the cerebrum in vertebrates. The non-pallial part of the telencephalon builds the subpallium. In basal vertebrates the pallium is a relatively simple three-layered structure, encompassing 3-4 histogenetically distinct domains, plus the olfactory bulb. It used to be thought that pallium equals cortex and subpallium equals telencephalic nuclei, but it has turned out, according to comparative evidence provided by molecular markers, that the pallium develops both cortical structures (allocortex and isocortex) and pallial nuclei (claustroamygdaloid complex), whereas the subpallium develops striatal, pallidal, diagonal-innominate and preoptic nuclei, plus the corticoid structure of the olfactory tuberculum. In mammals, the cortical part of the pallium registers a definite evolutionary step-up in complexity, forming the cerebral cortex, most of which consists of a progressively expanded six-layered portion isocortex, with simpler three-layered cortical regions allocortex at the margins. The allocortex subdivides into hippocampal allocortex, medially, and olfactory allocortex, laterally (including rostrally the olfactory bulb and anterior olfactory areas).


Pallium:
Medial
Dorsal
Lateral
Subpallium
Septum
Functional anatomy of the vertebrates 3rd edition. Liem et al.
Evagination vs Eversion
EVAGINATION: Amniotes
EVERSION: Fish !!!!
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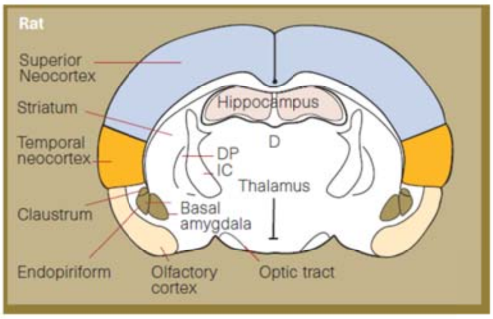
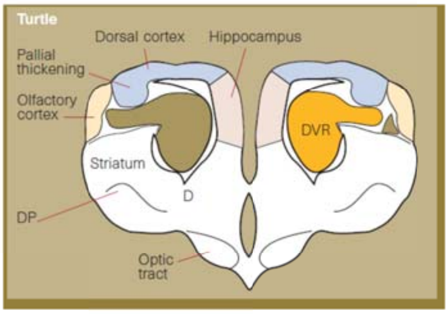
71

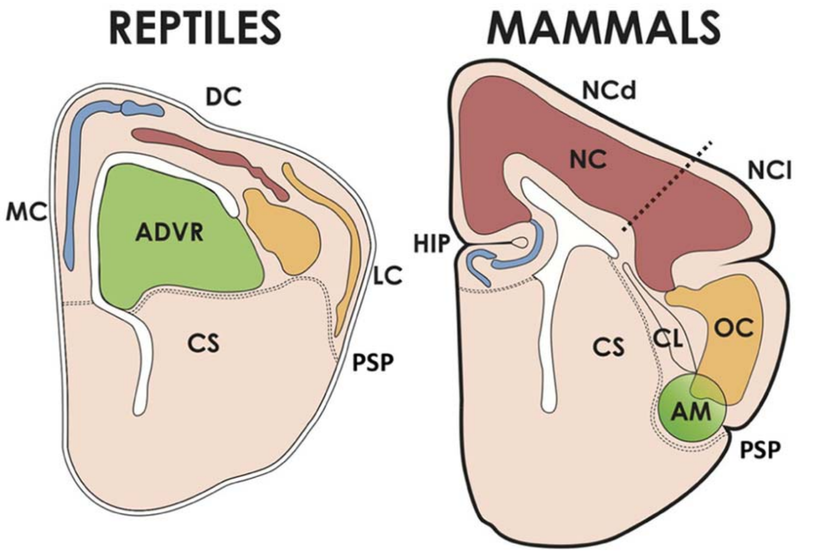
Mammal brain



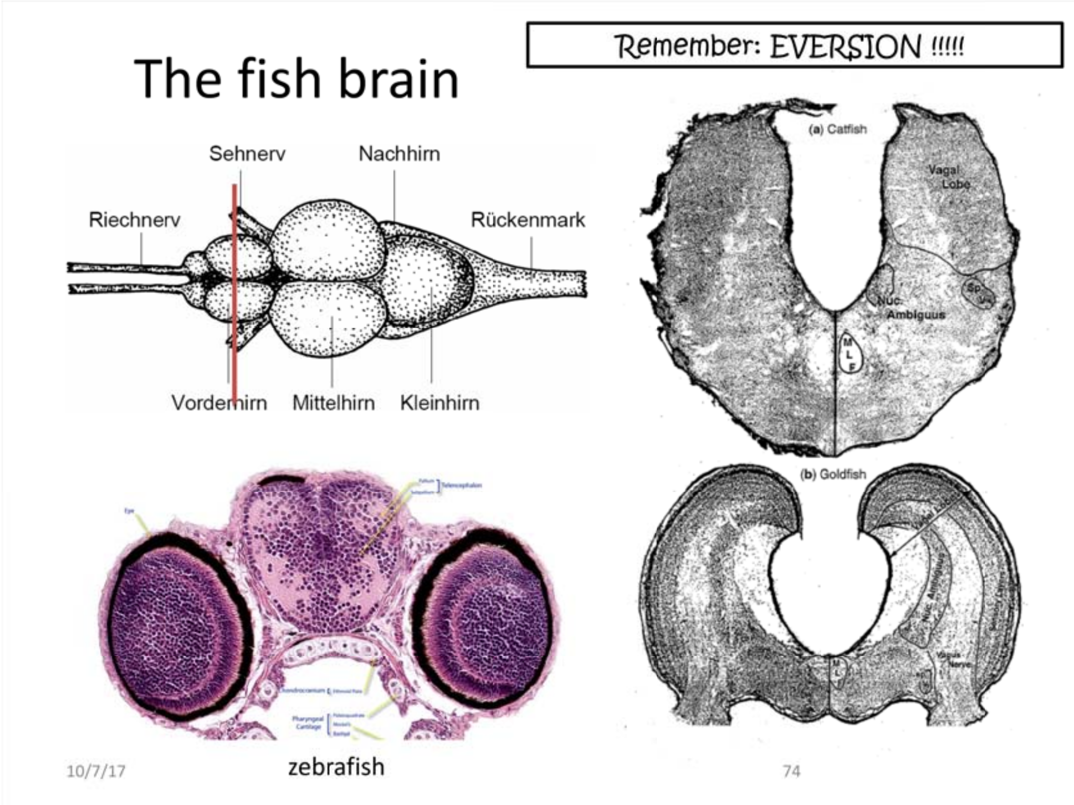
Avian / Reptile brain



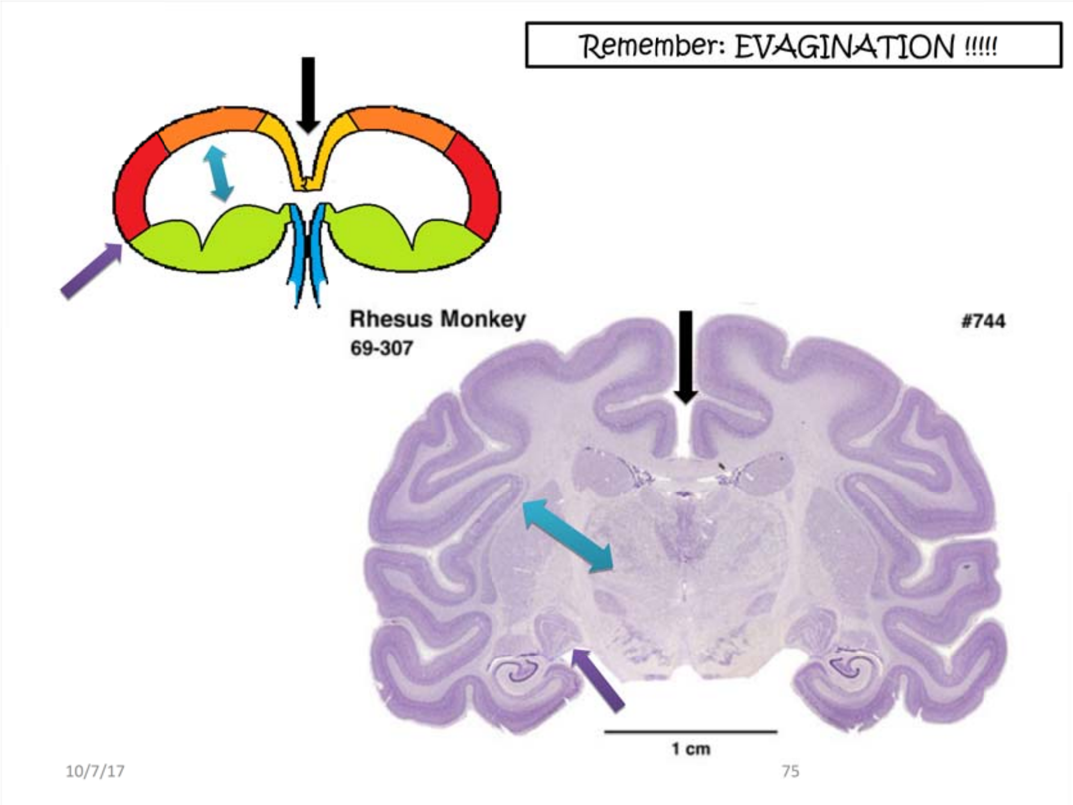
Kaas et al., **1999** *Science*



Aboitiz et al**., 2013** *Front Neuroanatomy*



http://www.catch-release.de/print.php?id=11

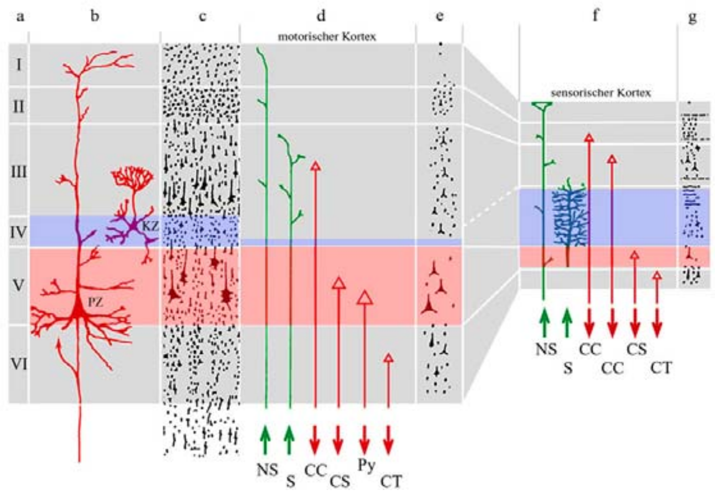

Remember: EVAGINATION !!!!!
Rhesus Monkey
69-307
#744
1 cm
10/7/17
75

Summary Part III

- Human brain is a scaled-up primate brain
- Neuron to glia ratio stays stable across evolution
- Pallium, subpallium and septum are the three primitive structures to organize the brain
- Different anatomical patterns for mammals, reptiles, birds and fish

Part IV
Cortical lamination

Neocortical lamination



http://teaching.thehumanbrain.info/neuroanatomie.php?kap=15

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Der Grundbauplan des Neocortex wird regional variiert. Für die sensiblen Rindengebiete ist das Auftreten der kleinen, dichtgepackten Körnerzellen in den Laminae II und IV typisch ("Verkörnelung"), die im motorischen Kortex weitgehend fehlen; daher ist für den motorischen Kortex die "agranuläre" Rindenstruktur typisch.

Die spezifischen Afferenzen aus dem Thalamus (S) treten hauptsächlich in die Schicht IV ein; unspezifische Fasern (NS) enden in allen Schichten. Der Ursprung der Projektionsfasern liegt vorwiegend in LV, der der Assoziations- und Kommissurenfasern vorwiegend in den Schichten II und III. Abk.: Afferenzen: S: spezifische Afferenzen; NS: nichtspezifische Afferenzen. Efferenzen: Py: Cortico-spinale und cortico-nucleäre (Pyramidenbahnsystem); CS: cortico-subcorticale Fasern (z.B. zu den Basalkernen); CT: cortico-thalamische Fasern; CC: Commissurenfasern.

Lamina	Zellbild	Faserbild	Merkmale
I	Lamina zonalis (molekulare oder plexiforme Schicht)	Tangentialfaserschicht	Synapsenzone, wenig Zellen, Faser- und Gliazellreichtum (Astrozyten)
II	L. granularis ext. (äußere Körnerschicht)		kleine Zellen
III	L. pyramidalis ext. (äußere Pyramidenzellschicht)		
IV	L. granularis int. (innere Körnerschicht)	äußerer Baillager'scher Streifen	
V	L. pyramidalis int. (innere Pyramidenzellschicht)	innerer Baillager'scher Streifen	
VI	L. multiformis (Spindelzellschicht)		Lage der polymorphen Zellen

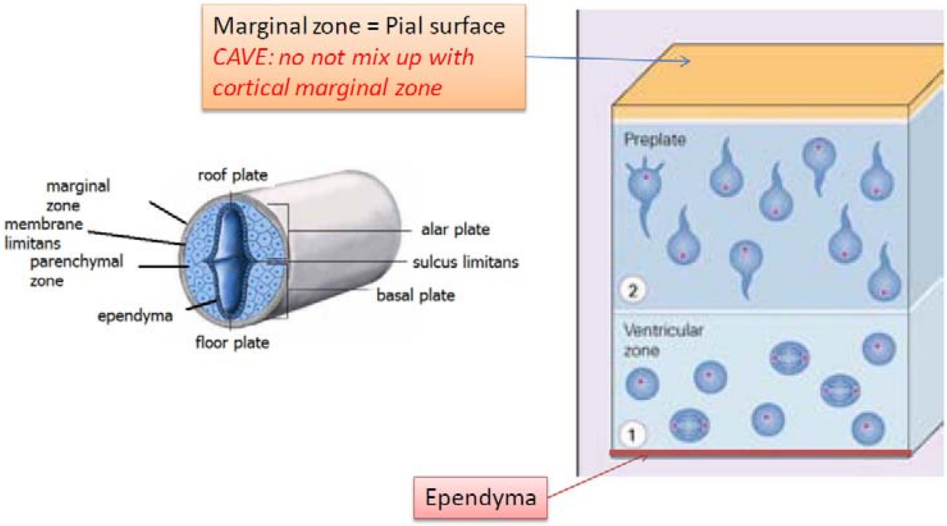
http://teaching.thehumanbrain.info/neuroanatomie.php?kap=15

Classical model

Cerebral neurons (glutamate)	.... Derive from the	Ventricular zone (pallium)	.... via	Radial migation
Interneurons (GABA)		Medial ganglionic eminence (subpallium)		Tangential migration

Kubo et al., **2003** *REVIEW*

Lamination „algorithm“



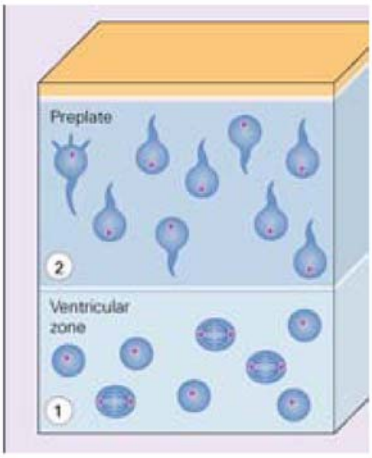
Inside-out Lamination

STEP 1

Ventricular zone = progenitor cells

Formation of **Preplate** *or* **Primordial plexiform layer** = Cajar Rhejius cells and **early** subplate neurons

When?
E 10.5 mouse
GW 4 human



Neuropathology 2nd edition, Ellison and Love **2004**
Kubo et al, **2003**

Inside-out Lamination

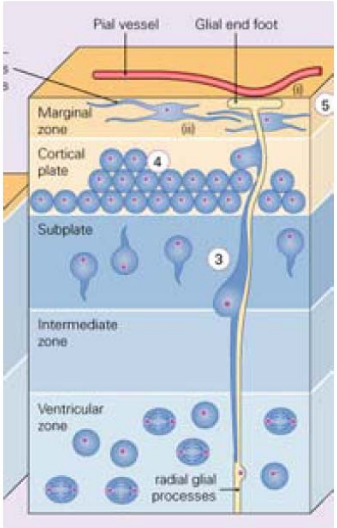
STEP 2

Radial glia (historical name for neuronal progenitors) extend scaffold between Ventricular zone and pial layer

Late Cortical plate neurons migrate radially and split the Preplate into:
-**Subplate (deep)** with early subplate neuron
-**Marginal zone (superficial)** with CR cells

Intermediate zone formation == white matter

When?
E 13 mouse
GW 6 human



Neuropathology 2nd edition, Ellison and Love **2004**
Kubo et al, **2003**

Inside-out Lamination

STEP 3

Marginal zone thinning and CR cell flattening and regression.

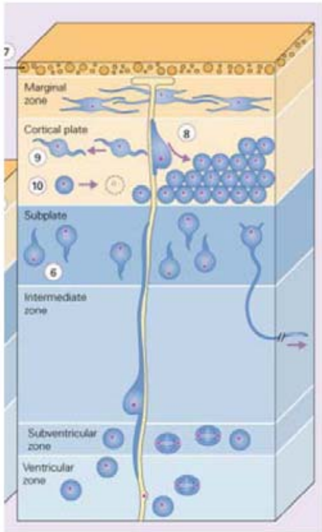
Cortical plate proliferation with VZ-cells migrating radially „**inside out**", i.e.

Younger cells occupy superficial layers

Subventricular zone of neural „progenitors"

Ventricular zone regression

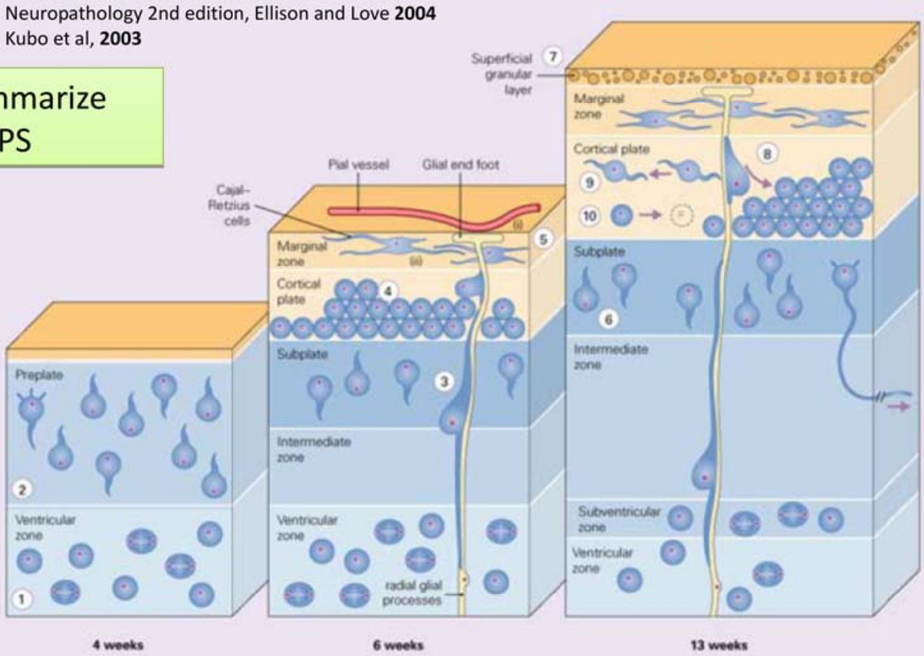
When?
E 18 mouse
GW 13 human



Neuropathology 2nd edition, Ellison and Love **2004**
Kubo et al, **2003**

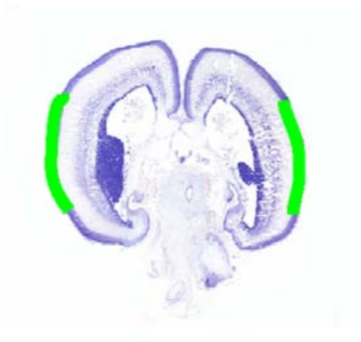
Neuropathology 2nd edition, Ellison and Love **2004**
Kubo et al, **2003**

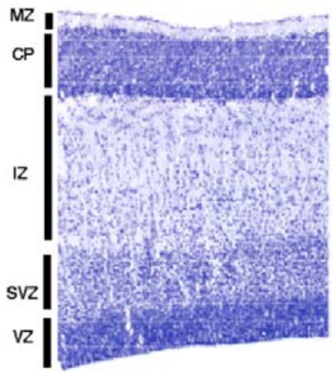
Summarize
STEPS



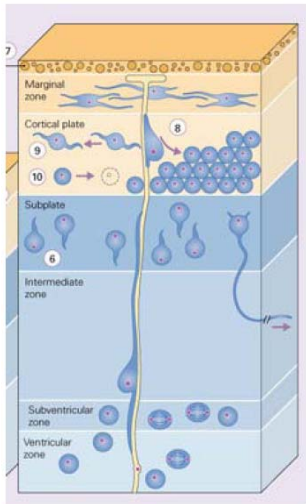
Ellison & Love: Neuropathology 2e © 2004 Elsevier Ltd.

Human embryo @ GW17





Lambert et al., **2011** PLOSone



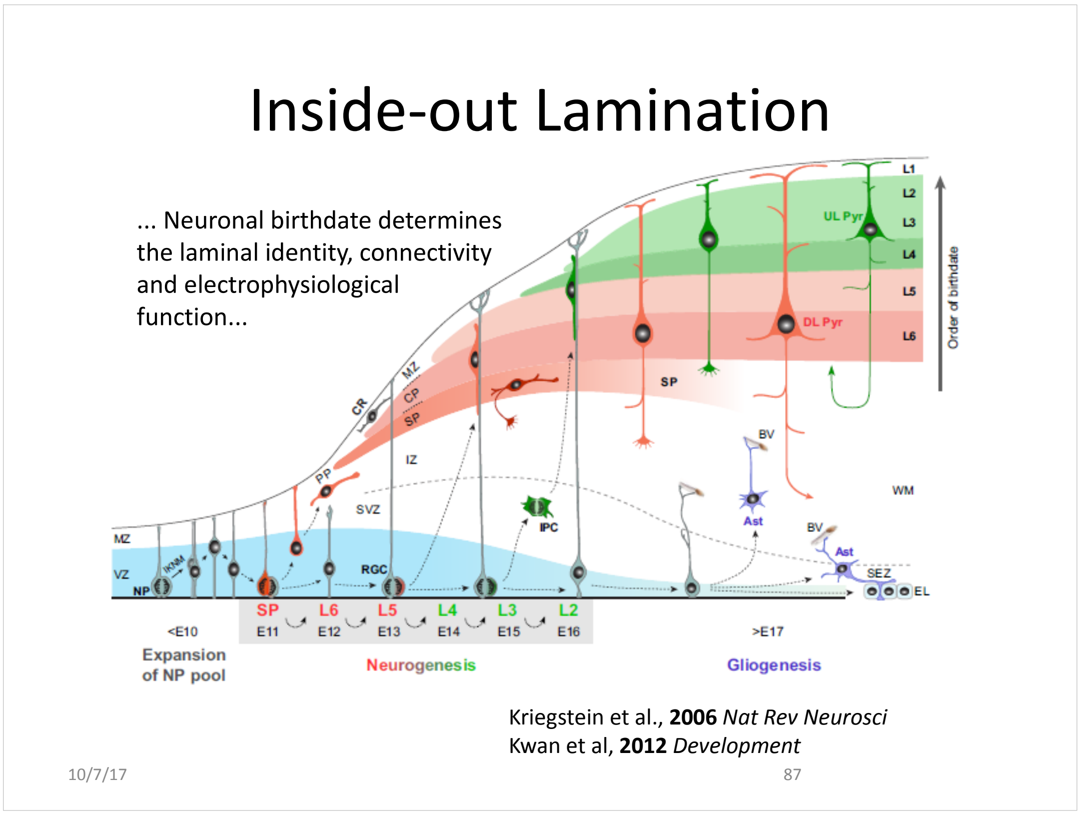
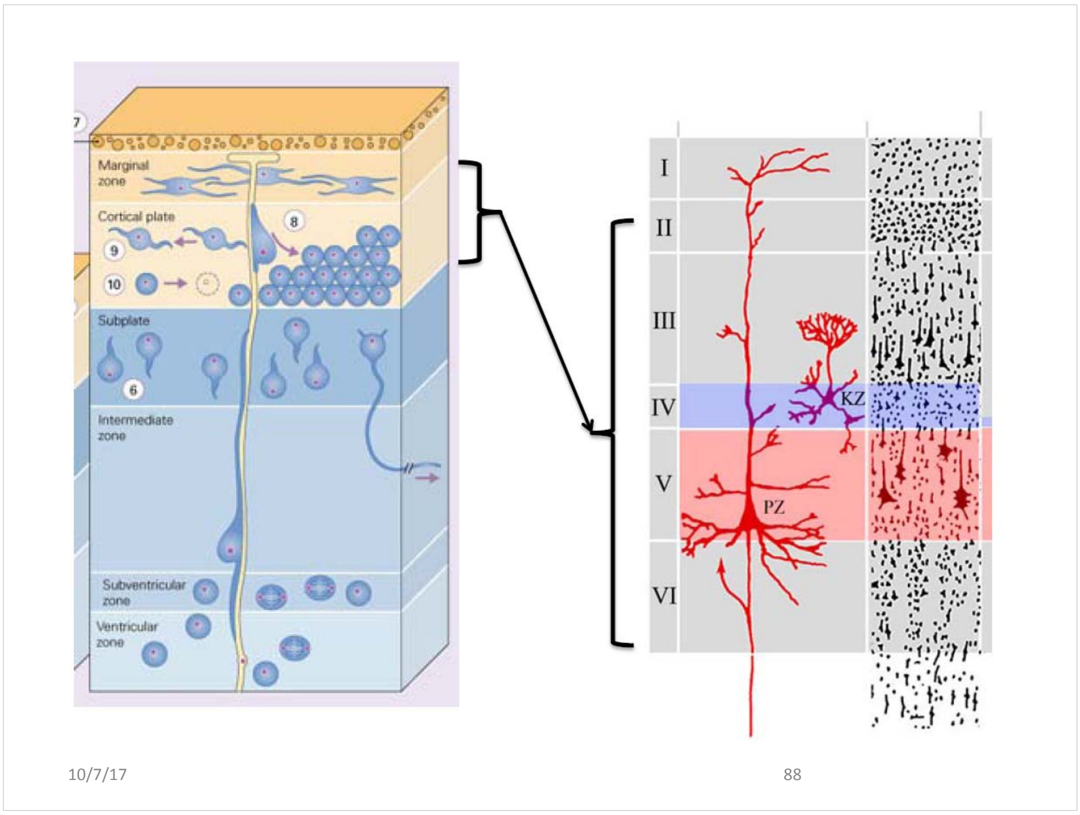


Figure 1 | **Histogenesis of the cerebral cortex.** This schematic drawing provides an approximate
representation of the appearance and relative size of cortical structures between embryonic day (E)12
and E22 in the rat. At the onset of cortical histogenesis, the ventricular zone (VZ, blue), or neuroepithelium,
is the only structure present in the cerebral cortex. Elements of the preplate (PP, yellow)
appear above the VZ between E13 and E14. The subventricular zone (SVZ, dark blue) appears above
the VZ, and beneath the PP after E14. After E16, cortical plate neurons migrate into the PP, splitting
this structure into the superficial marginal zone (MZ) and deeper subplate (SP), and in doing so form
the cortical plate (CP, green). Elements of the intermediate zone (IZ, light blue) invade the cerebral
cortex at E16. The asterisk indicates the stage at which SVZ and IZ elements are intermingled in the
same layer. The cortical layers I – VI and the white matter (WM) are depicted on the right margin of the
scheme. P0, postnatal day 0. The cortical structures were drawn to scale based on unpublished observa
tions (S.N., V.M.-C. and A.K.) and measurements taken from sagittal sections shown in REF. 94 ©
(1991) Raven.



Layers 2-4 derive from cortical plate whereas Layers 5-6 derive from subplate

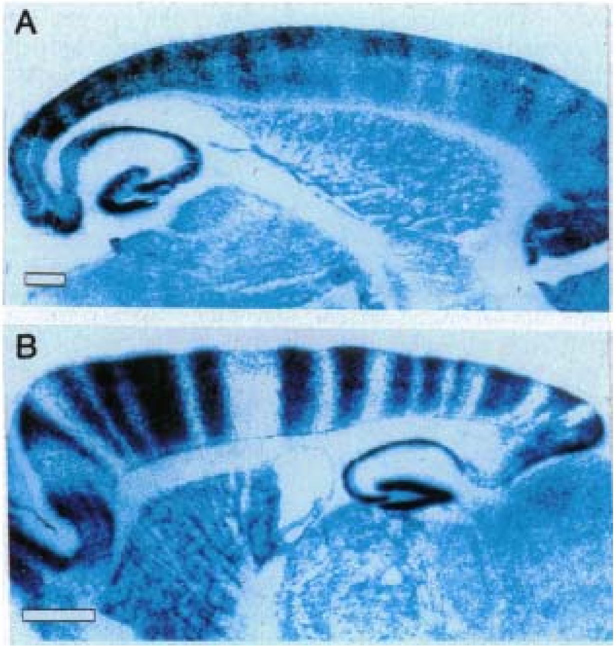
Kwan et al, 2012 REVIEW

Cortical lamination, Radial migration and ***Histogenetic fields***

2 different female rats A and B

lacZ in X chromosome

Different levels of X-lyonization



Rakic **1995**, *PNAS*

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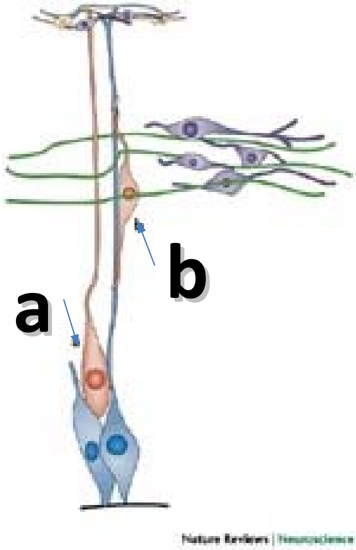
H253 transgenic mice with mixture of beta-gal+ labeled and unlabeled cells forming radial columns running from white matter to the pial surface.
Differential marking is achieved by inserting a lacZ into the one X-chromosome and taking advantage of the X-mosaicism (Lyonization) in female rats.
Scalebar = 200 µm A, 600 µm B

Mechanisms of radial migration

(a)Translocation
- Leading and trailing process
- Trailing process == axon
- Migration along radial glial scaffold

(b)Locomotion
- Leading process attached on pial surface
- Pull soma

2-step migration
- Combination of both mechanisms



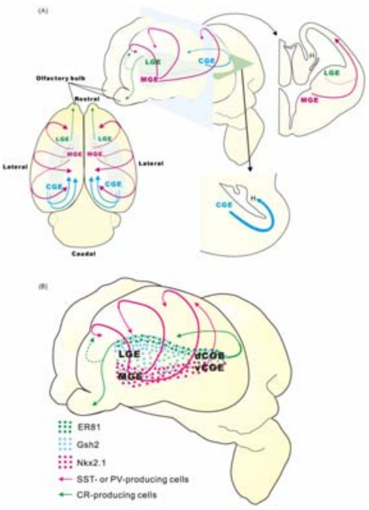
Kubo et al., **2003**; Hatanaka et al., **2016;** Ghashghaei et al, **2007**

And what about

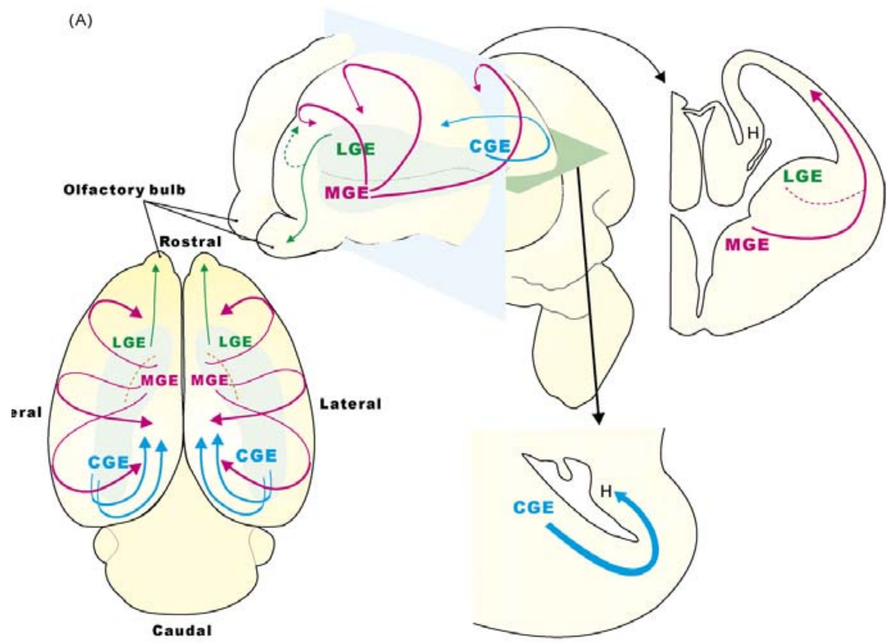
Interneurons ????

Tangential migration: the “intruders”

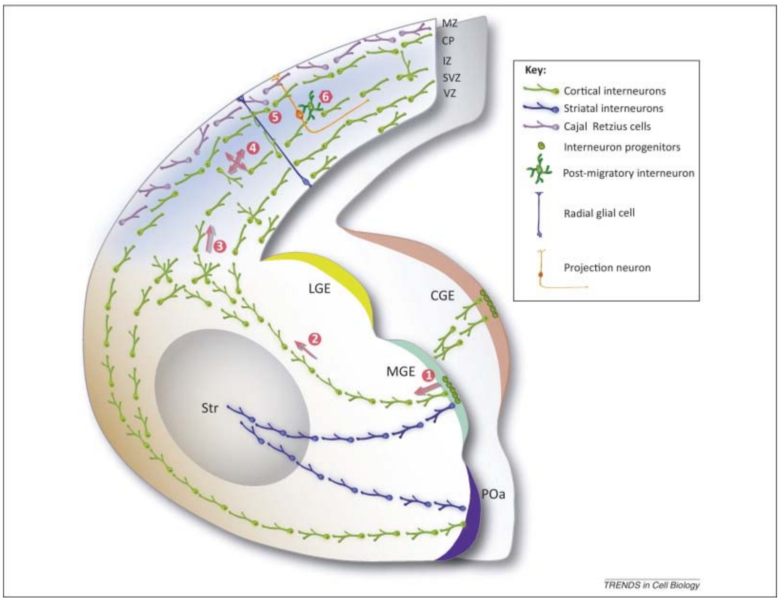
- GABA-ergic interneurons
- **migrate tangentially == across rhombomeres**
- from the medial, lateral and caudal eminence (Subpallium)



Hatanaka et al., **2016**; Nakajima et al., **2007**



(A)
Olfactory bulb
Rostral
LGE
MGE
CGE
H
eral
Lateral
Caudal



Guo and Anton, **2014** *TINS*

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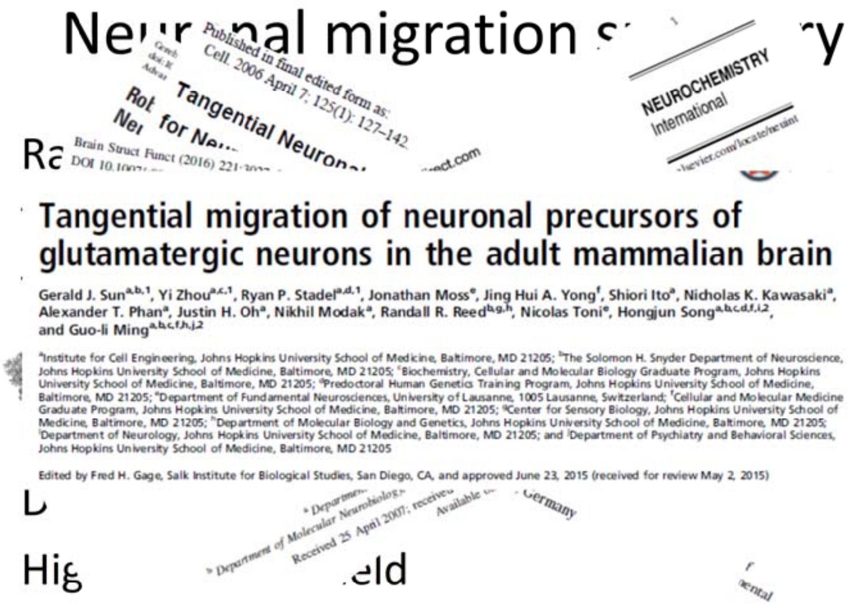
Guidance cues and neuronal migration in the telencephalon. The schema shows a coronal slice of the telencephalon at midembryonic stages, in which the main cortical migrations and their guidance cues are indicated. Interneurons born in the medial ganglionic eminence (MGE) migrate tangentially through the subpallium to reach the cortex. Some of these interneurons enter the striatum (striatal interneurons), whereas others continue toward the cortex (cortical interneurons), sorting out through a mechanism that involves Sema3A and Sema3F. Cortical interneurons advance toward the cortex following a corridor of lateral ganglionic eminence (LGE)-derived cells that express CRD-Nrg1 but not semaphorins. Interneurons are guided toward the cortex by a combination of motogenic (HGF/BDNF) and chemoattractive factors (Ig-Nrg1). Once in the cortex, chemokine signaling (Cxcl12) restricts the migration of interneurons through two streams, the marginal zone (MZ) and the subventricular zone (SVZ). Cajal-Retzius cells also use Cxcl12 to disperse through the MZ in opposite direction to interneurons. Cajal-Retzius cells produce Reelin, which along with other factors such as semaphorins, guide the migration of projection neurons. (CP) cortical plate; (GP) globus pallidum; (IZ) intermediate zone; (MZ) marginal zone; (NCx) neocortex; (PCx) piriform cortex; (Str) striatum; (SVZ/VZ) subventricular/ventricular zones.

Neur…nal migration s… …ry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Cell. 2006 April 7; 125(1): 127–142

Tangential Neuron…

Brain Struct Funct (2016) 221:30…

NEUROCHEMISTRY
International

Tangential migration of neuronal precursors of glutamatergic neurons in the adult mammalian brain

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Department of Molecular Neurobiology … Germany
Received 25 April 2007; received … Available …

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Hatanaka et al., **2016**; Nakajima et al., **2007**

Brain field homology

- Morphogenetic fields
- Histogenetic fields
- Field homology as concept in evolutionary and comparative studies

Brain morphogenetic fields

Functional and anatomical entities defined as:

- Radial migration complex, i.e. Radial histogenetic domains
- Same master control genes, i.e. HOX-domain
- Express same adhesion molecules and homologous cells can cluster
- Express vesicles with the same neurotransmitter content

Kaas, **2006**

Differences between morphogenetic domains

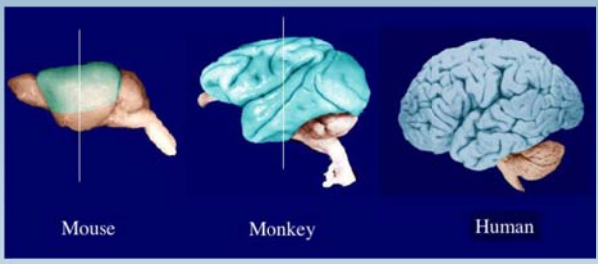
1. Due to field reorganization or repatterning, e.g. HOX mutation
2. Due to immigrant cells, e.g. Tangential migration, NOT NECESSARILY HOMOLOGOUS in all animals
3. Different anatomical location of homologous fields, with impact on the connectivity and the receptor expression

Kaas, **2006**

Summary Part IV

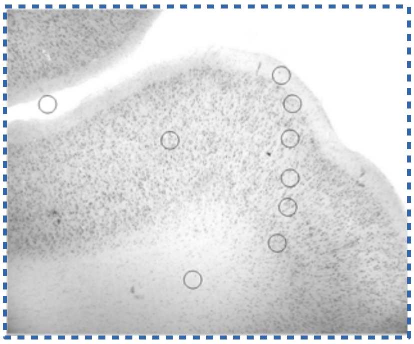
- Cortical lamination is a complex neuron/glia interactive project
- Upside/down model
- Neuronal migration: radial and tangential
- Histogenetic and morphogenetic fields are the developmental CNS units
- Homology between histogenetic fields is not always granted, even if they are defined by the same master gene

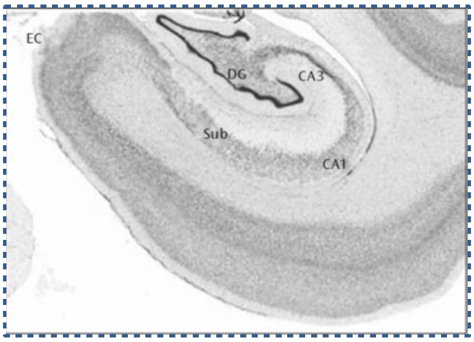
Neocortex (Isocortex)



Neocortex is an evolutionary trait of **mammals**!!!

http://www.nibb.ac.jp/brish/Gallery/cortexE.html

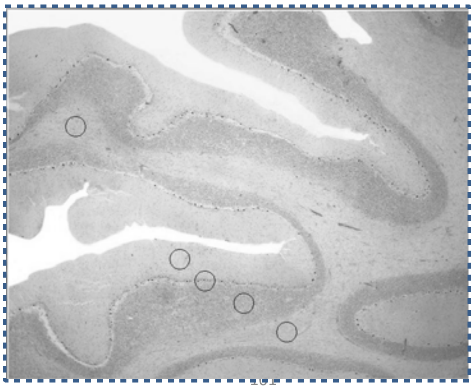




How many types of cortex ?

- Isocortex = 6 layers
  - Neocortex: 6 layers
- Allocortex = 3 layers
  - Paleocortex: 3-5 layers
  - Archicortex: 3 layers

and the Inverted Cortex



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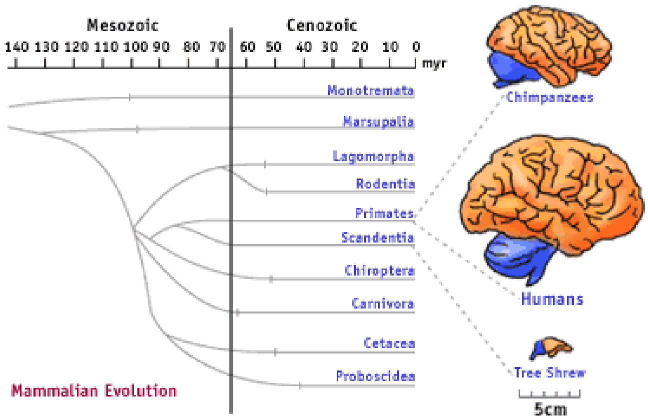
http://www.catch-release.de/print.php?id=11

Neocortex
A mammalian evolution ~ 100 m.y.o.



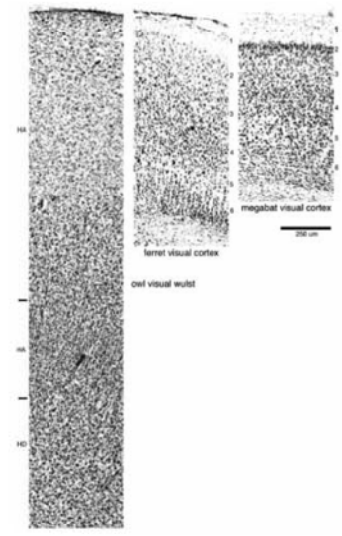
Differences in
cortical lamination between
mammals and birds

avian brains

Birds – reptiles = 3 layered cortex, less laminated

Mammals = 6 layered cortex, highly and strictly laminated

ONCE MORE: Isocortex is a mammalian developmental step



Owl Ferret Bat

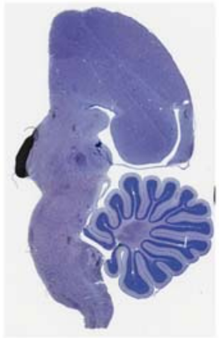
10/7/17 103

Ann B. Butler, Paul R. Manger, B.I.B. Lindahl, Peter Århem. Evolution of the neural basis of consciousness: a bird-mammal comparison (p 923-936).

Cortical evolution

Fish/ amphibian brain

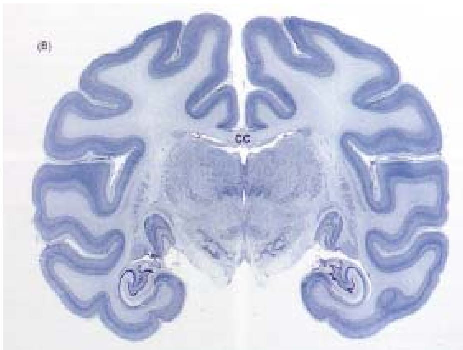
Avian/reptile brain



Mammal brain

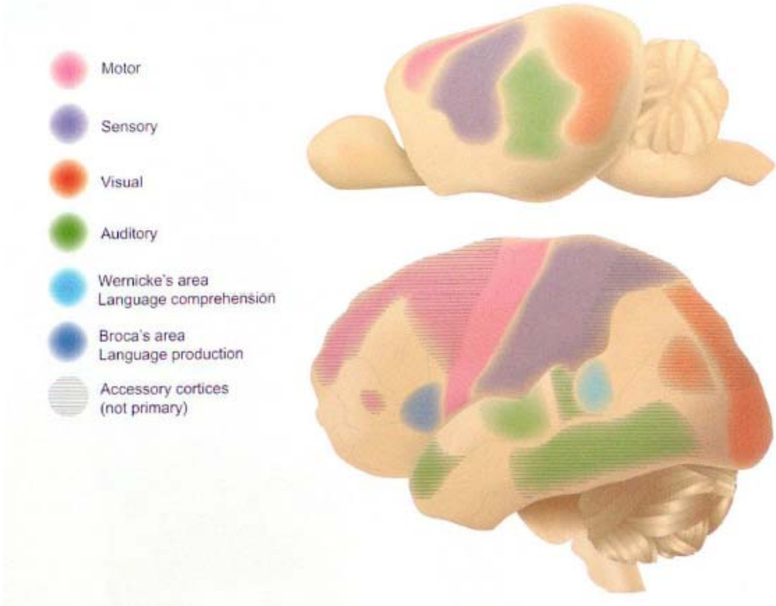
Meso-saggital sections

Comparison of neocortex between **mouse** and **monkey**.



http://www.nibb.ac.jp/brish/Gallery/cortexE.html

Neocortical areas



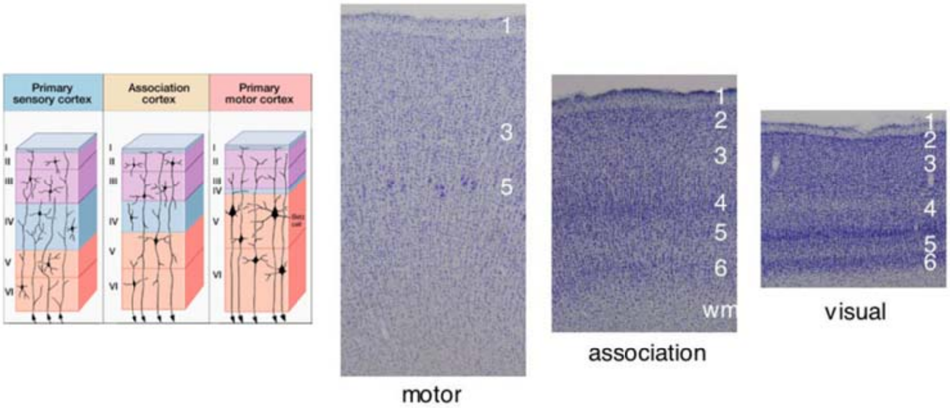
10/7/17 Treuting et al., Comparative anatomy and histology 106

Can you spot **similarities** between Human and Rat anatomical organization ???

Orientate: Sylvian fissure

Additional Question: What is the region between SS and Visual conrtex, which is extensively developed in human brain but not in rats?

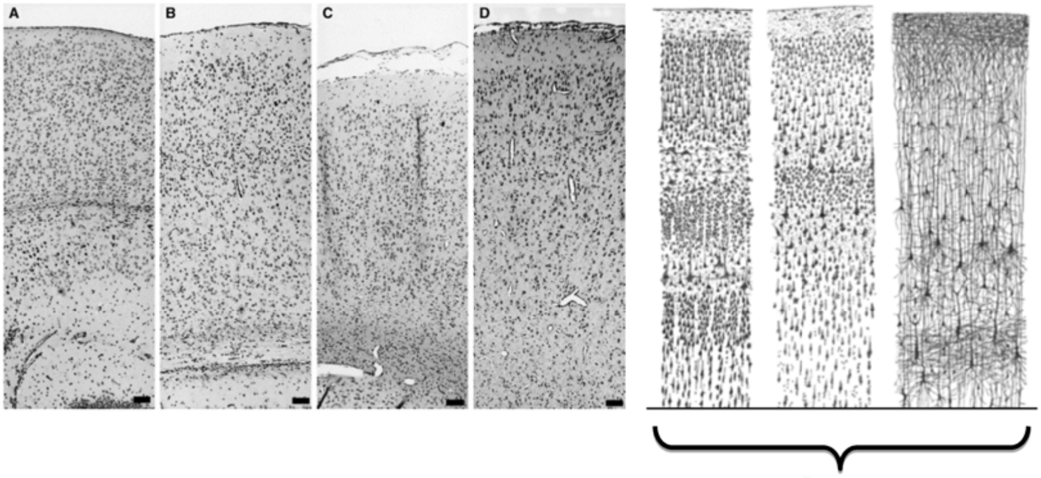
Lamination corresponds to function



Nissl staining of three different areas of the **monkey** neocortex:
primary motor area, temporal association area (area TE) and primary visual

Can you assign any functional significance to those anatomical differences?

Lamination of **mammalian brains**



Rat mouse ferret cat human

visual motor infant

Hutsler et al., 2005; Cajal, 1913

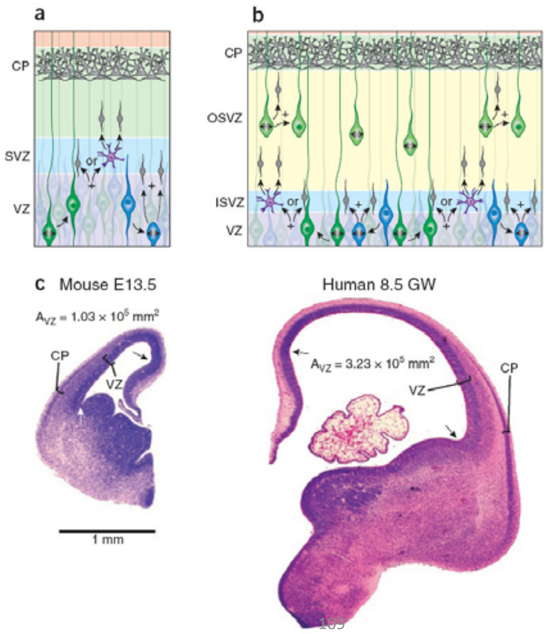
Differences in cortical lamination

Rodent – primate differences in lamination:

Splitting of the subventricular zone in primates

SVZ = Subventricular zone

Inner
Outer



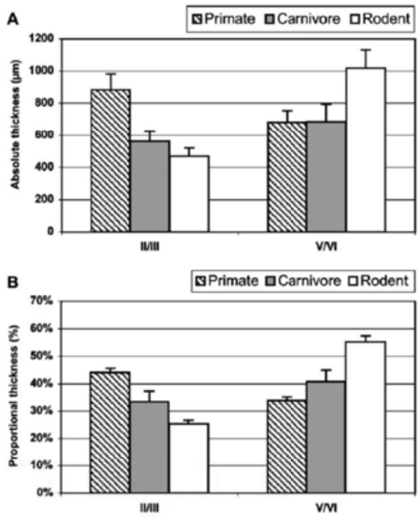
Tyler et al., **2010** *Nature*

Differences in cortical lamination

Layers II/III : Supragranular cortex <u>prominent in **primates**</u>

Layer IV : Granular cortex

Layers V/VI : Subgranular cortex <u>prominent in **rodents**</u>



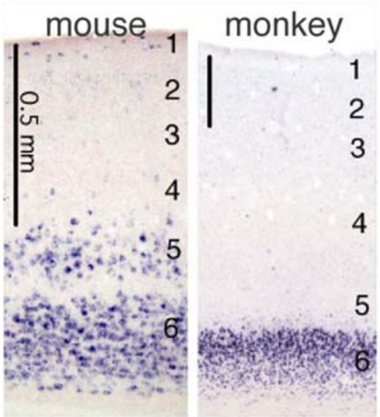
Hutsler et al., **2005**

Anatomical similarities do not necessarily support functional homology

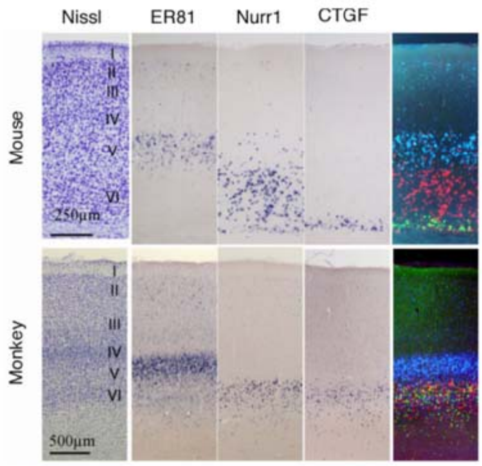
- Electrophysiological and genomic characterization of neocortical neuronal types
  - the **GENSAT project** for neuronal classification
- Gene expression profiling of neocorticals layers

Watakabe, 2006; 2009 *REVIEW*

Differences in cortical lamination
gene expression profiling

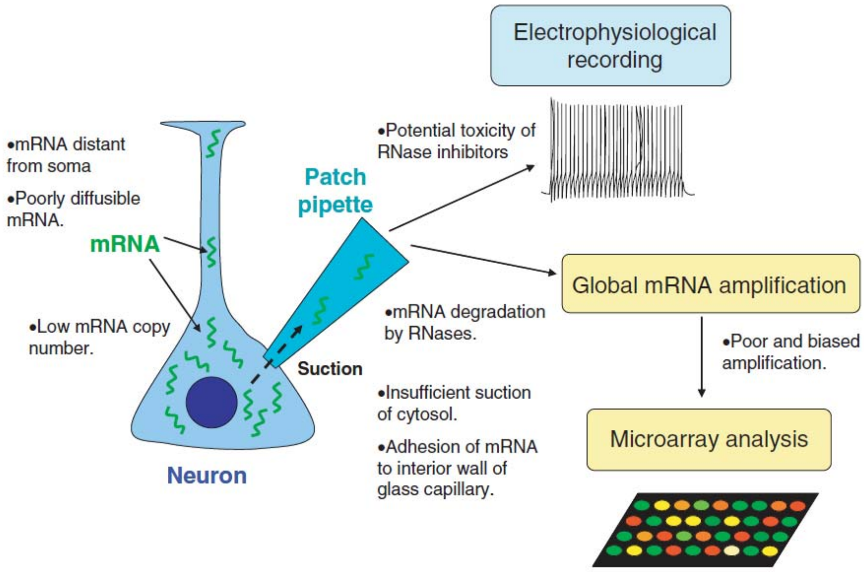


ISH of **Semaphorin 3E (Sema3E)** gene in the mouse and monkey cortex



ISH of four **layer-specific genes** in the mouse and monkey cortex

Elecrophysiological – gene expression profiling



Yano et al., **2006** J Physiol

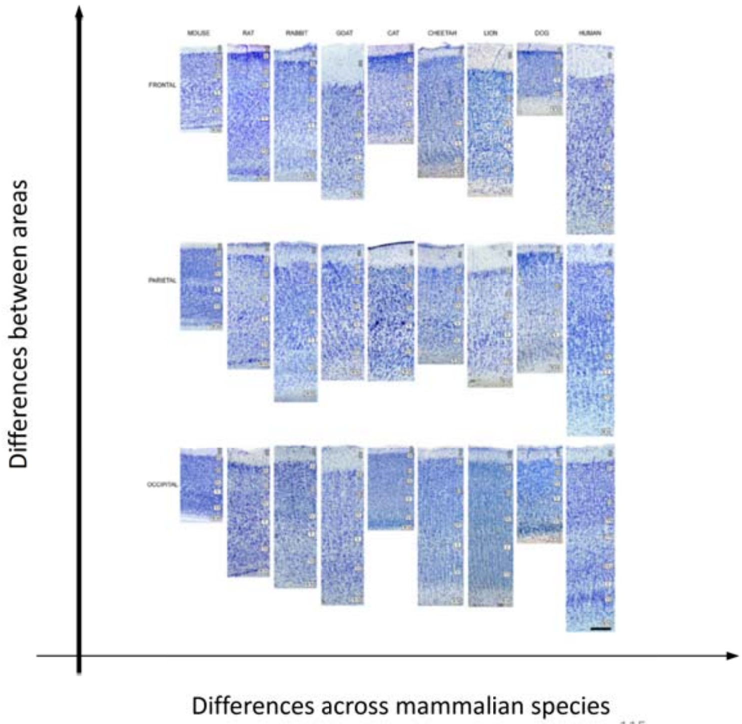
Comparative genomics

Table 5. Orthologous Brain Regions between Species Are More Similar to Each Other than to Different Regions within a Species

Tissue	Human			Mouse	
	Motor Cortex	Caudate	Cerebellum	Anterior Cortex	Striatum
Human caudate	1.20	—	—	—	—
Human cerebellum	1.67	1.73	—	—	—
Mouse anterior cortex	1.00	1.27	1.46	—	—
Mouse striatum	1.26	1.00	1.54	1.44	—
Mouse cerebellum	1.43	1.50	1.29	1.75	1.81

10/7/17

Yano et al., **2006** J Physiol


MOUSE
RAT
RABBIT
GOAT
CAT
CHEETAH
LION
DOG
HUMAN
FRONTAL
PARIETAL
OCCIPITAL
Differences between areas
Differences across mammalian species

Summary Part V

- Lamination corresponds to function
- Splitting of the subventricular zone is a mammalian developmental trait
- Orthologous brain regions between species are more similar than different brain regions within a species

  {translation}

  A cats leg is more similar to a human leg that to the nose of the same cat

Thanks for your attention