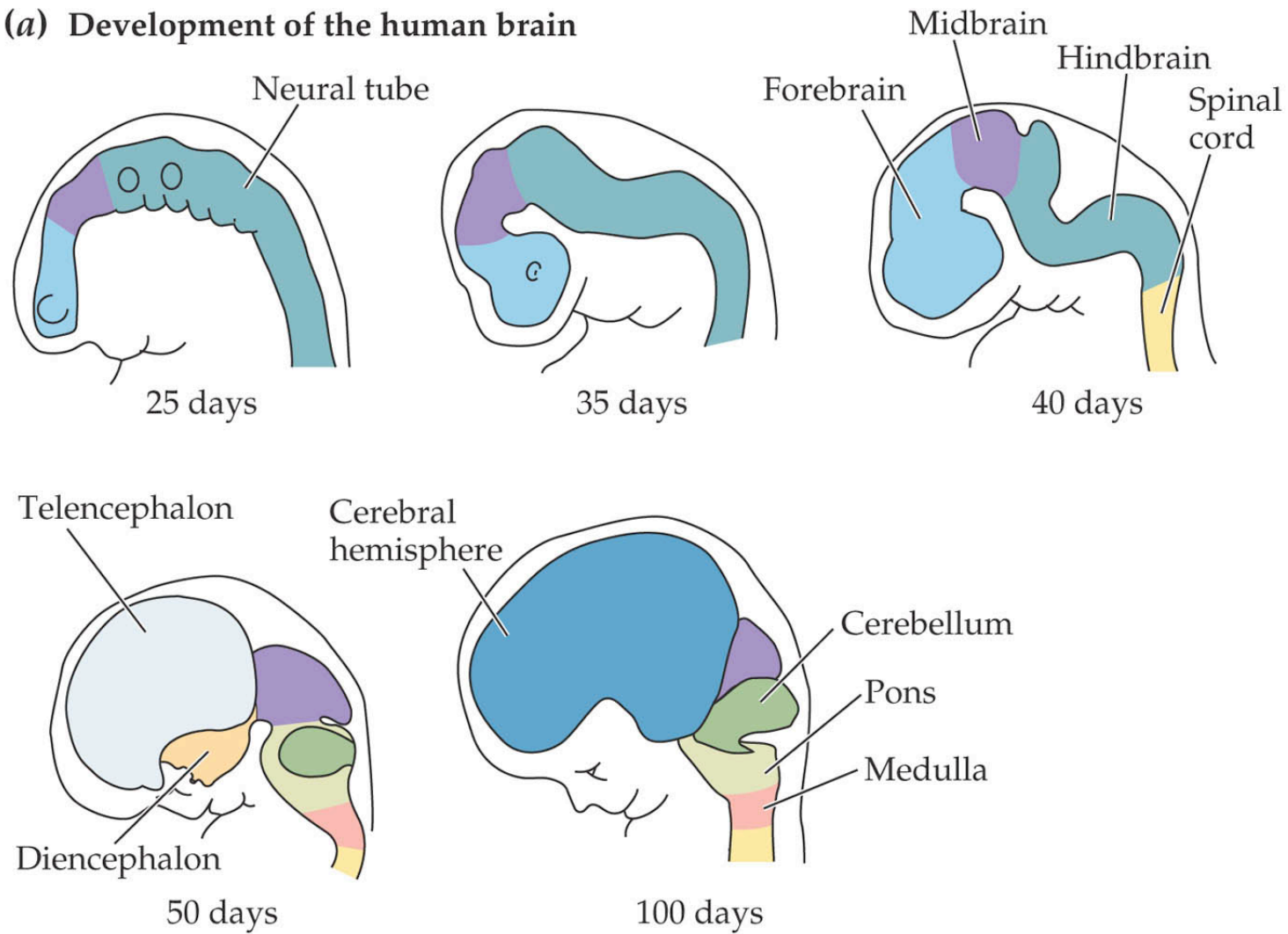


Patterns of Vertebrate Neurogenesis and the Paths of Vertebrate Evolution

Finlay et. al, 1998

Samantha Podurgiel
February 15, 2011

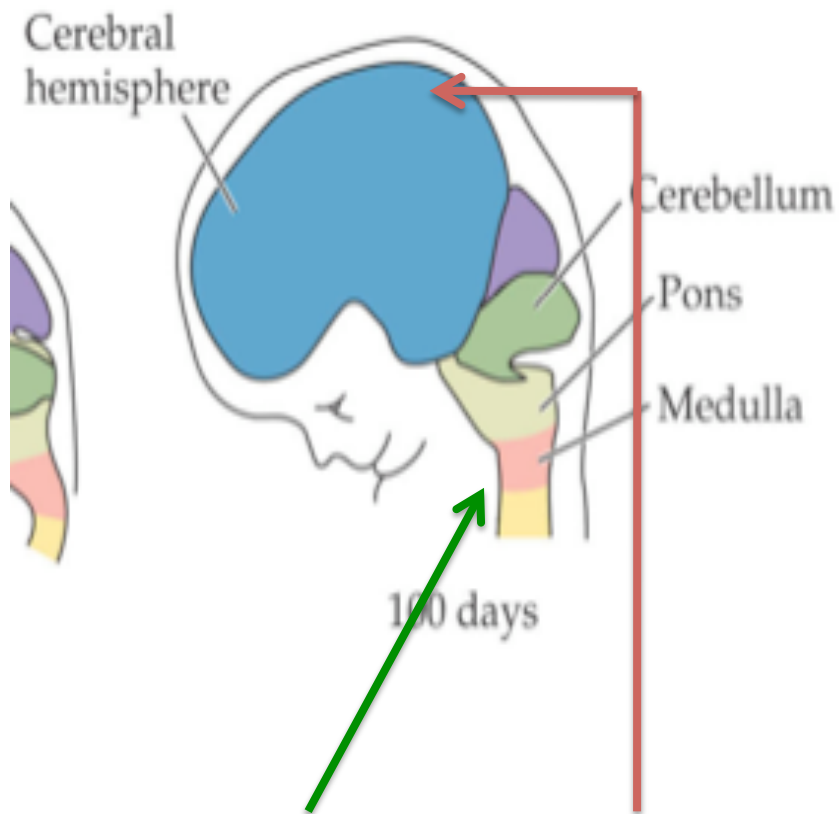
(a) Development of the human brain



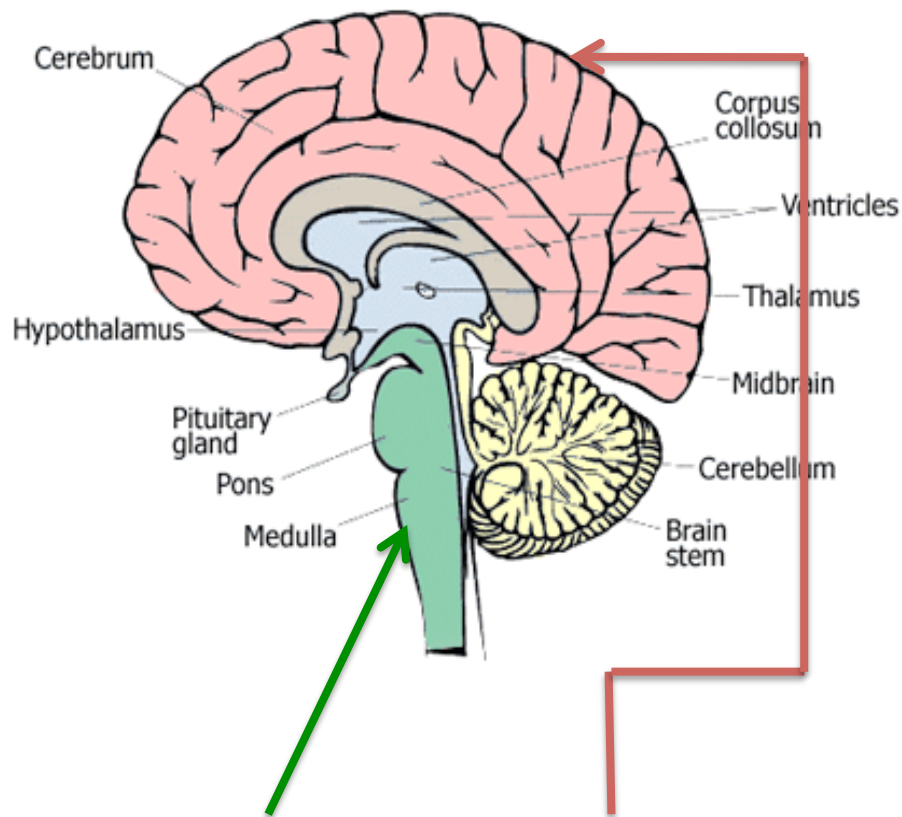
The developmental “gradient” of the neural tube moves from lower to higher. The hindbrain develops first, then the midbrain, and finally the forebrain

movie

Later structures are larger!

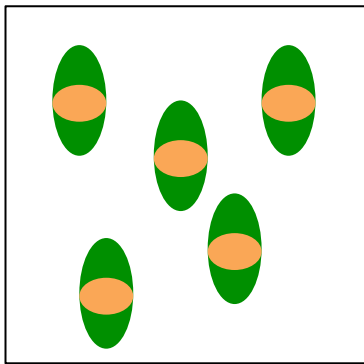


Medulla vs. Cortex

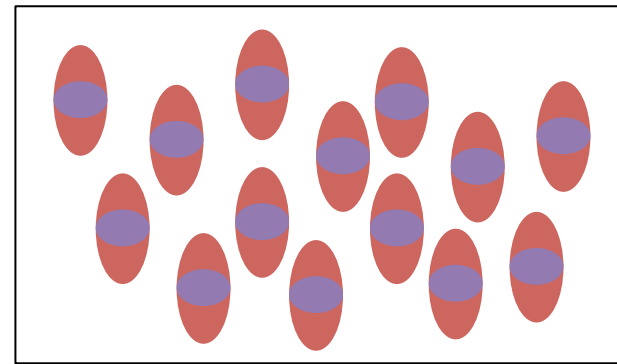


Medulla vs. Cortex

Structures that develop later have more time for their progenitor cells to divide, which results in an increased amount of cells, and thus a larger structure

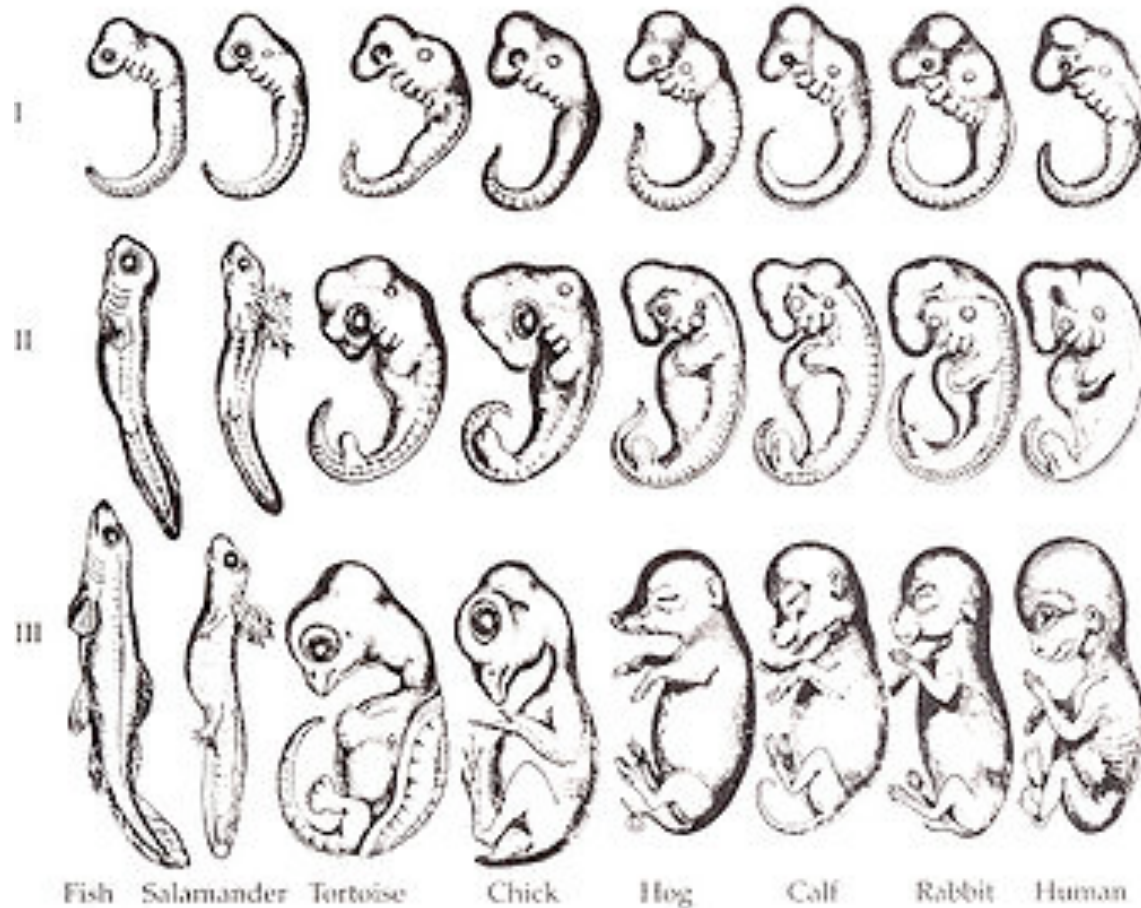


Medulla, smaller precursor pool



Cortex, larger precursor pool

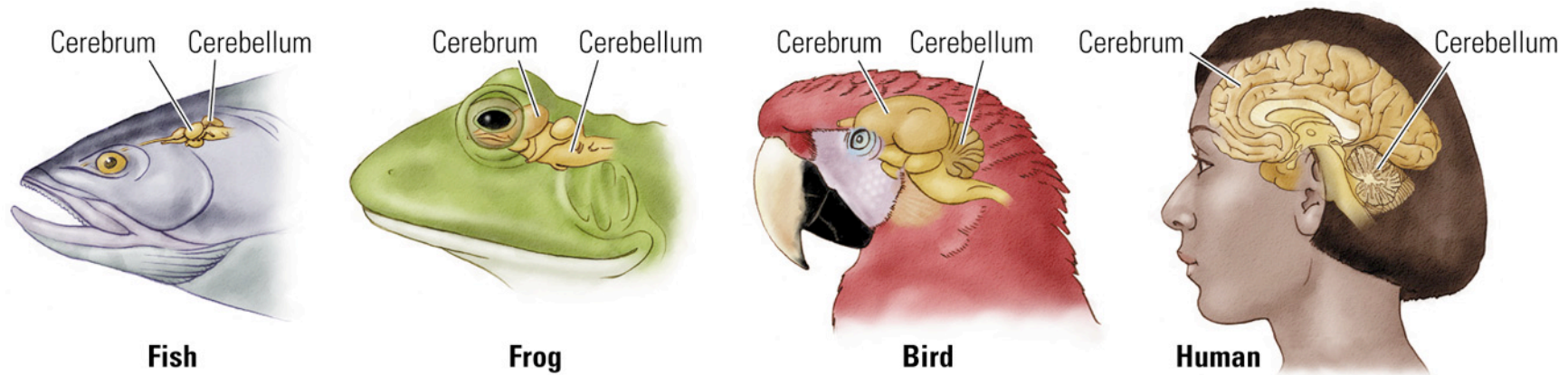
“Ontogeny (development) recapitulates phylogeny (evolution).”



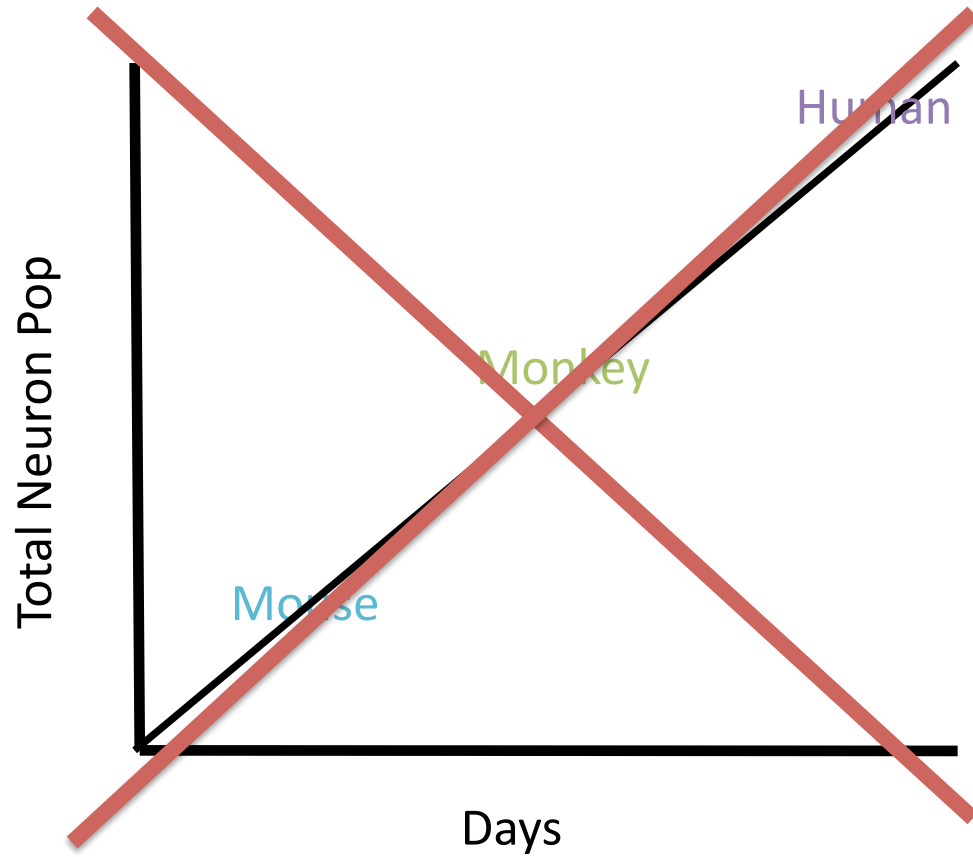
We can look across different species (a **phylogenetic** comparison) as a function of those we believe to be “higher” (more evolved, more intelligent) versus “lower” (older, less intelligent).

Such comparisons show that the “lower” structures in the brain (pons, medulla, cerebellum) -- structures that regulate the most basic of functions (breathing, heart rate, automatic movement, etc.) -- are *not all that different across lower to higher species*.

In contrast, “higher” structures (thalamus, callosum, cortex) -- structures that modulate processing of speech and language, decision making, etc. -- are *far more elaborate and complex in “higher” species*. Reptiles, fish, and amphibians generally have a very minimal, small cortex.



These **phylogenetic** comparisons suggest that higher brain structures are more recent products of evolution.



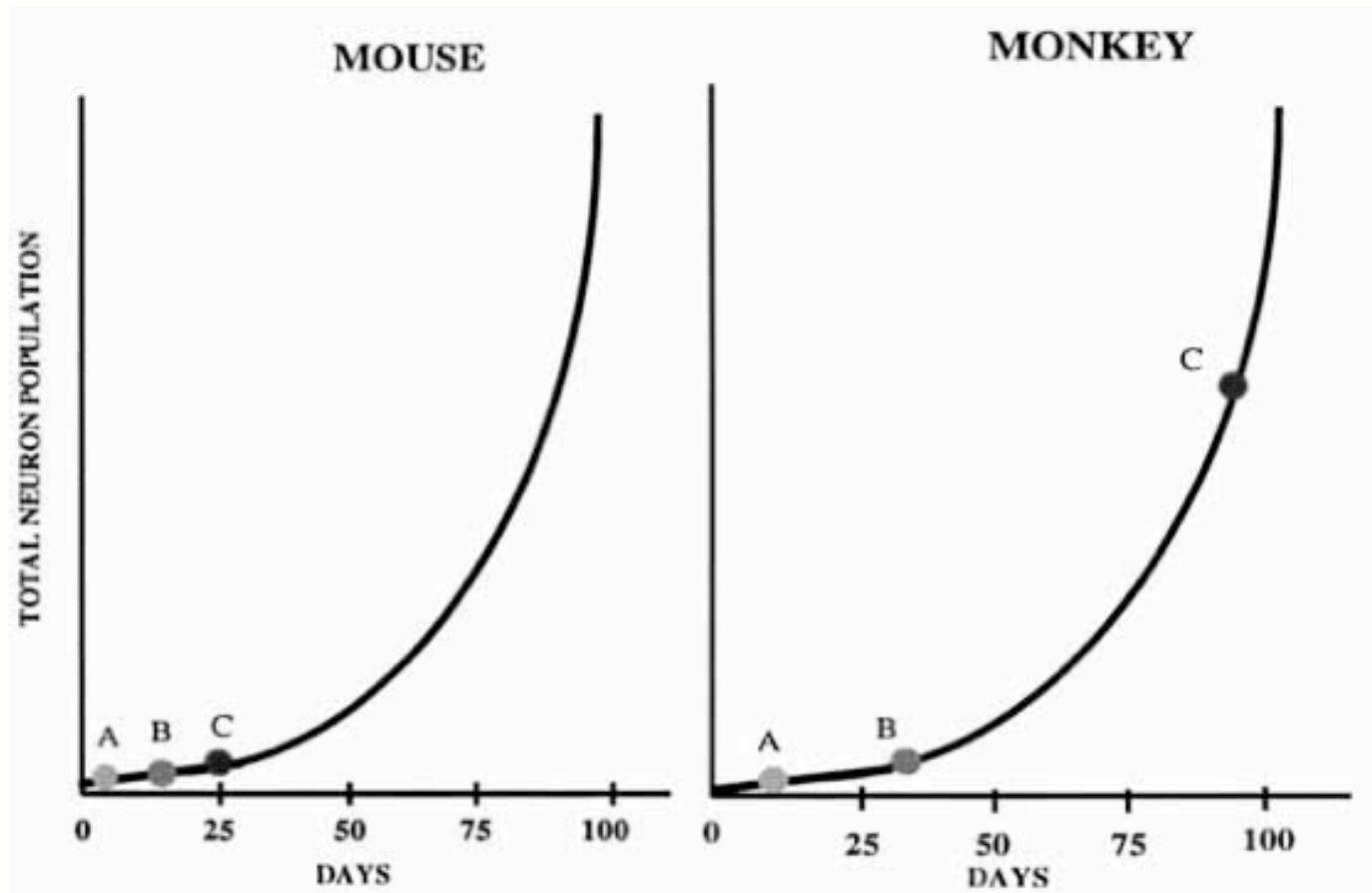
Evolution is nonlinear, humans don't simply have large mice brains

Late Makes Large!

Some components of the brain increase in size across species at a slower rate than the whole brain enlarges: **MEDULLA**

Some components of the brain increase in size at approximately the same rate as the whole brain: **DIENCEPHALON**

Some components of the brain increase in size at a greater rate than the whole brain enlarges: **ISOCORTEX**



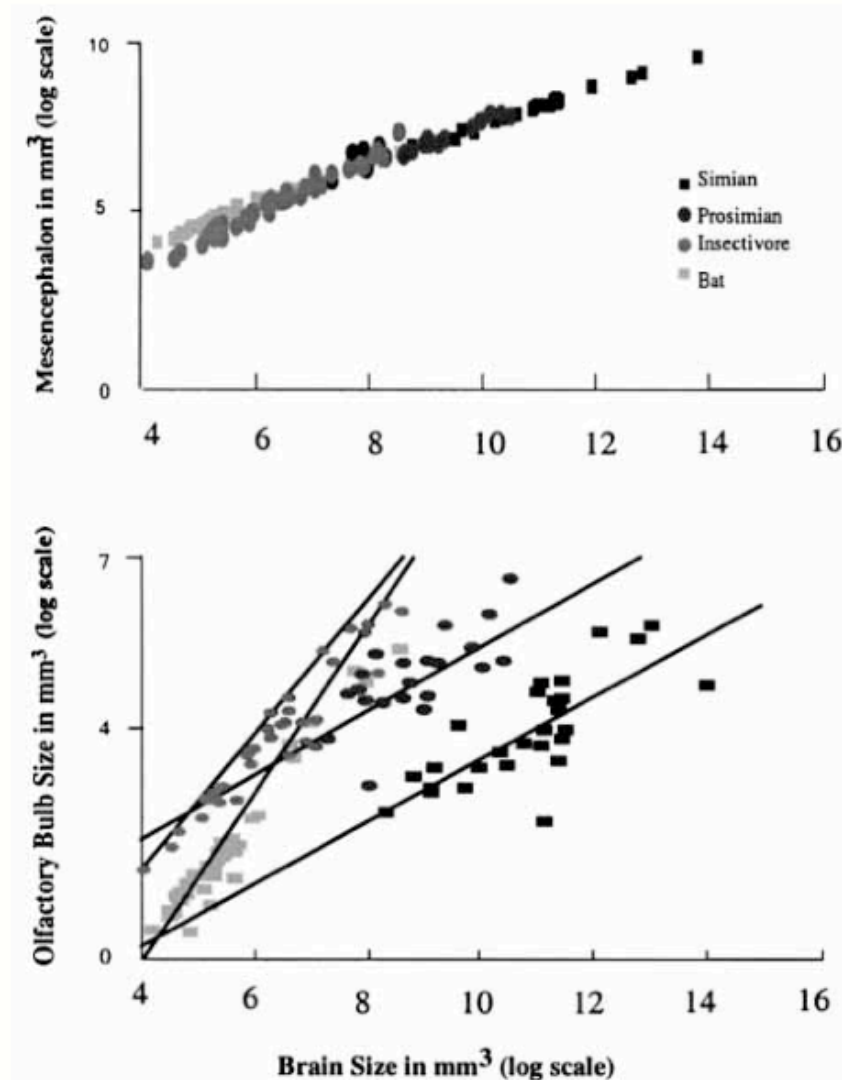
Late means large: Eventual size of a structure generated **early (A)**, **intermediate (B)** or **late (C)** in the order of neurogenesis for a species with a short period of neurogenesis and a small brain (mouse), and one with a long period of neurogenesis and a large brain (monkey). In the long-development species, the precursor pool for late-generated structures has a longer time to multiply and becomes disproportionately large

A “late makes large” caveat: Limbic Structures

Many researchers have recognized that olfactory bulbs scale very poorly with brain size

Figure: comparison of scaling of mesencephalon size versus olfactory bulb size for 131 primates, prosimians, insectivores, and bats: **each family and subfamily have distinct slopes and intercepts**

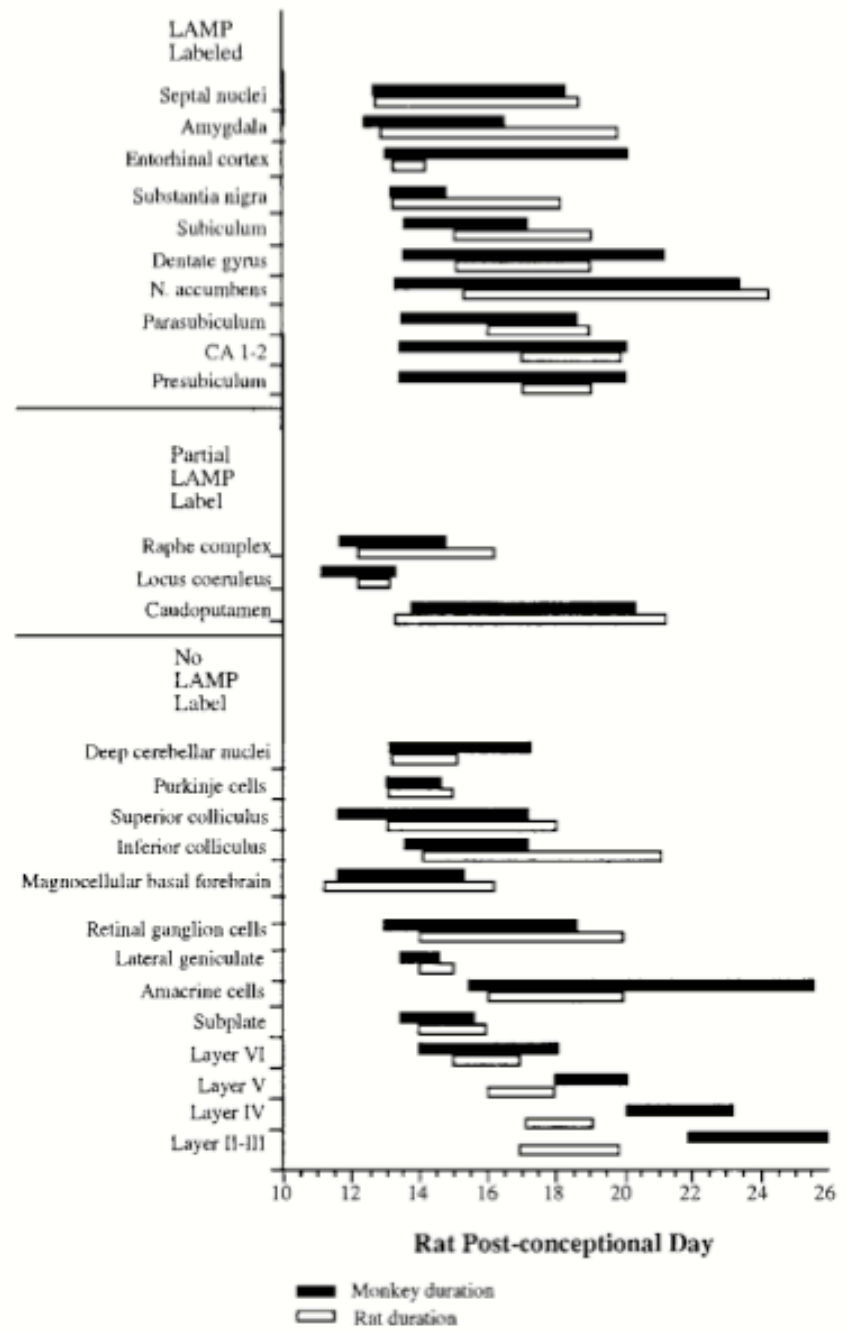
What about other limbic structures?



The Limbic Factor:

This figure shows a number of events in neurogenesis, both limbic and non-limbic, with monkey PC days adjusted to the rat developmental period using expression of LAMP protein indicative of limbic system membership

Express LAMP protein = member of limbic system

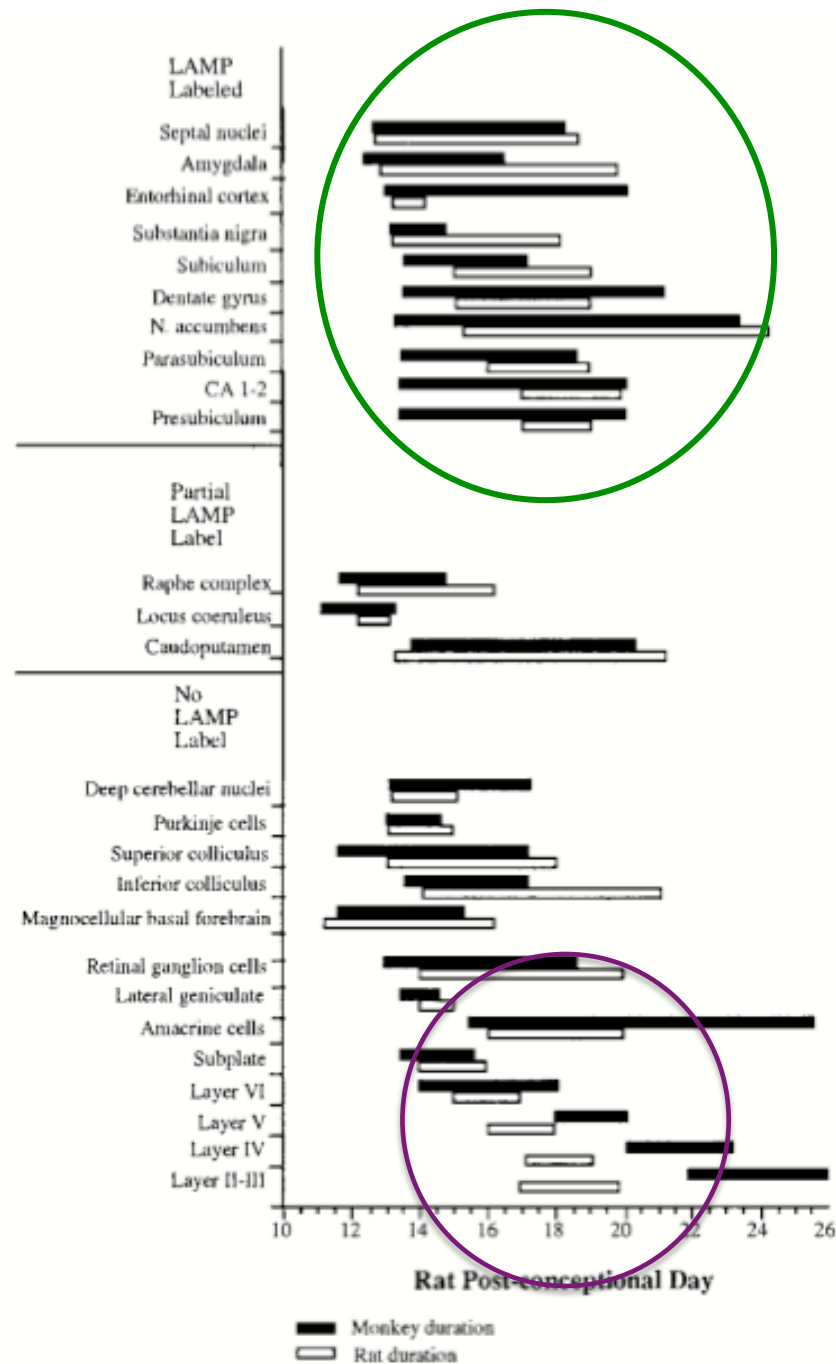


The Limbic Factor:

The onset of terminal neurogenesis is advanced and almost synchronous in LAMP-containing structures in monkeys compared to rats.

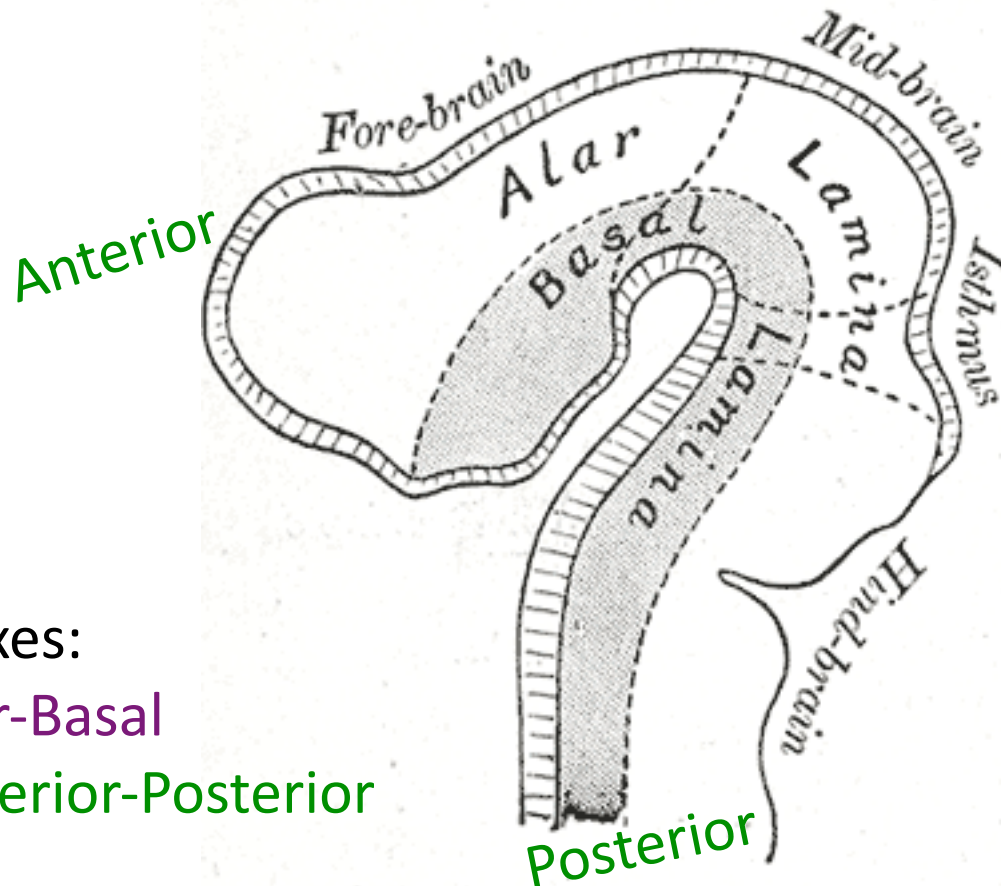
Therefore, the number of cells in the precursor pool would be reduced, and result in smaller structures (For limbic system structures in primates).

Conversely, isocortical neurogenesis appears to be progressively delayed in monkeys compared to rats, particularly for the upper layers.



The Prosomeric Model:

A model of segmentation with respect to the original neural tube



2 axes:

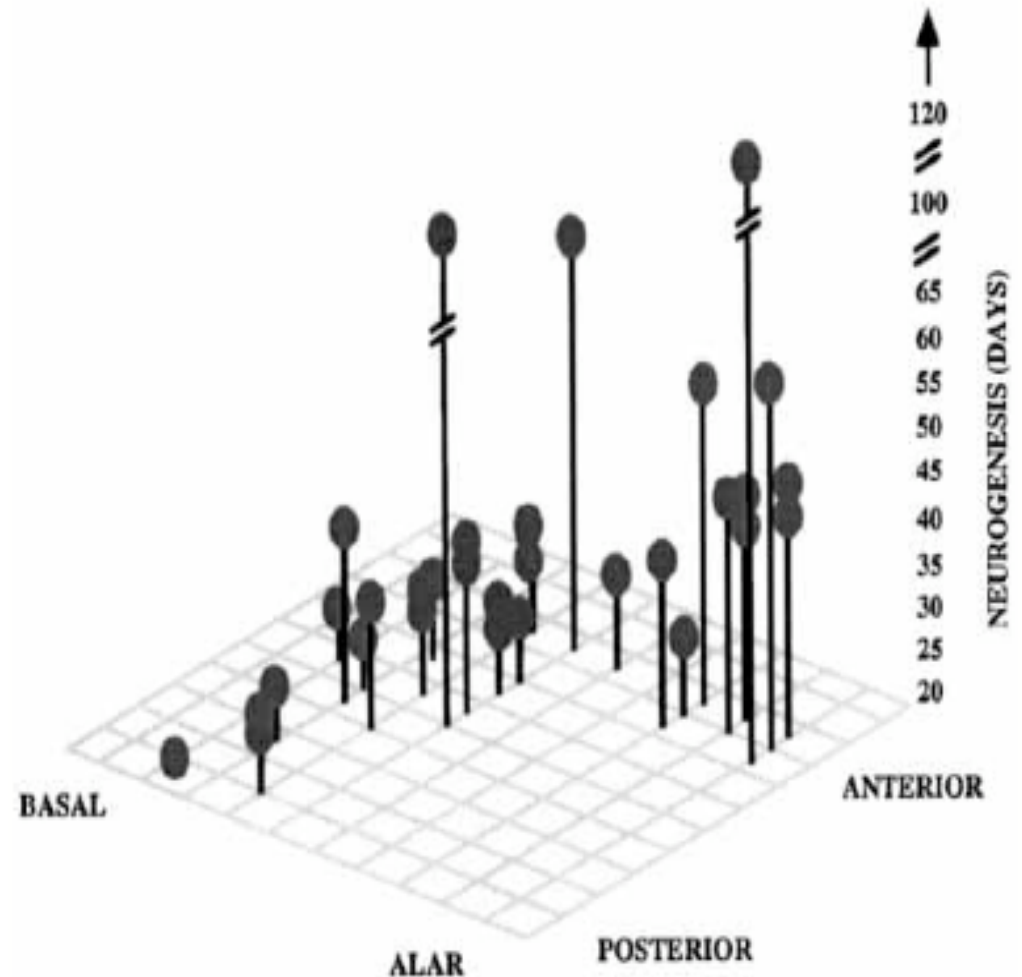
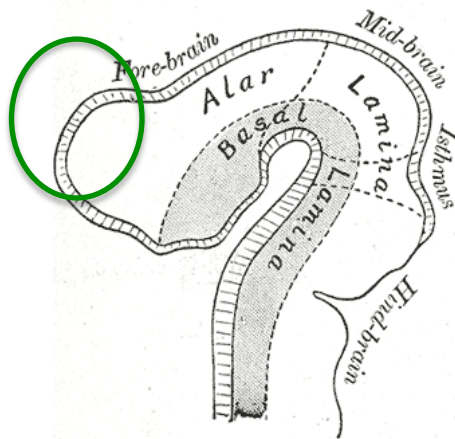
Alar-Basal

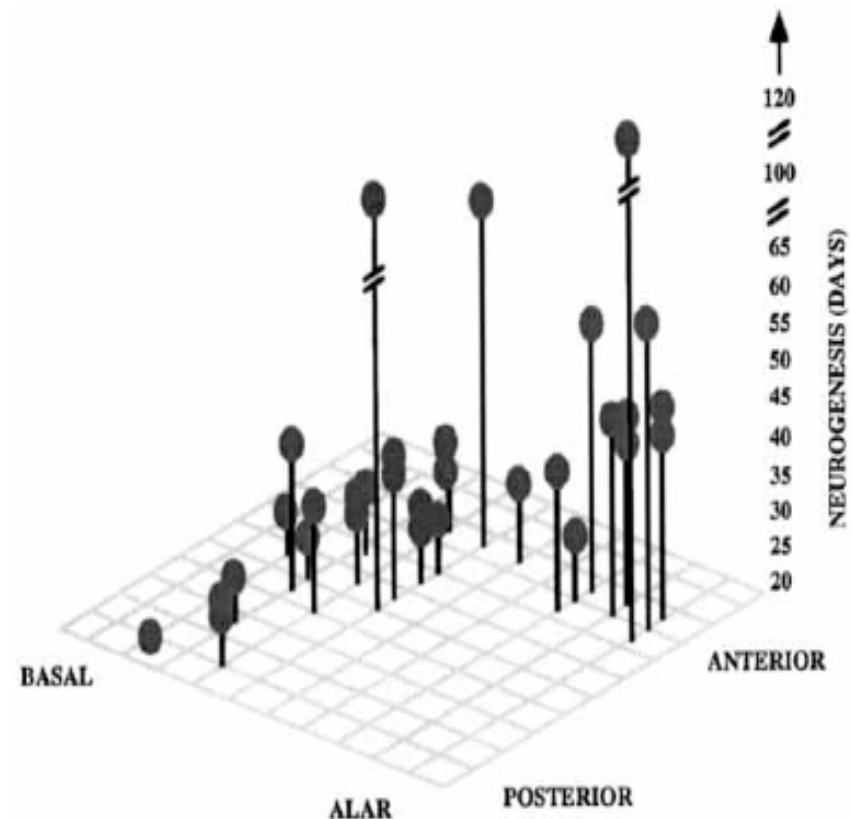
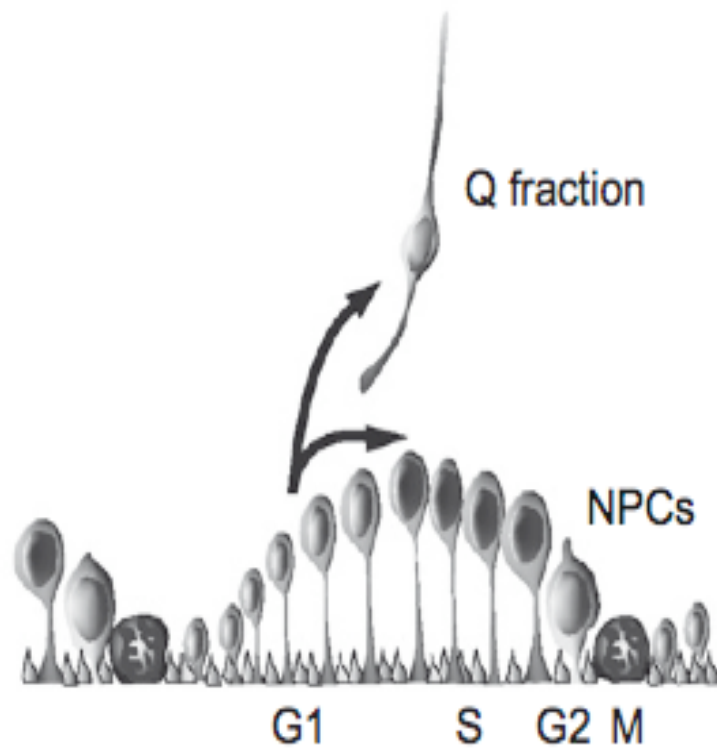
Anterior-Posterior

Everything that arises from a single location on the neural tube is a single point in an analysis of prosomere-based patterns of neurogenesis

Figure: The total duration of terminal neurogenesis plotted on anterior/posterior and alar/basal axes

There is a strong relationship between position on the prosomeric axes and duration of neurogenesis: *the more alar and anterior, the more protracted neurogenesis is*



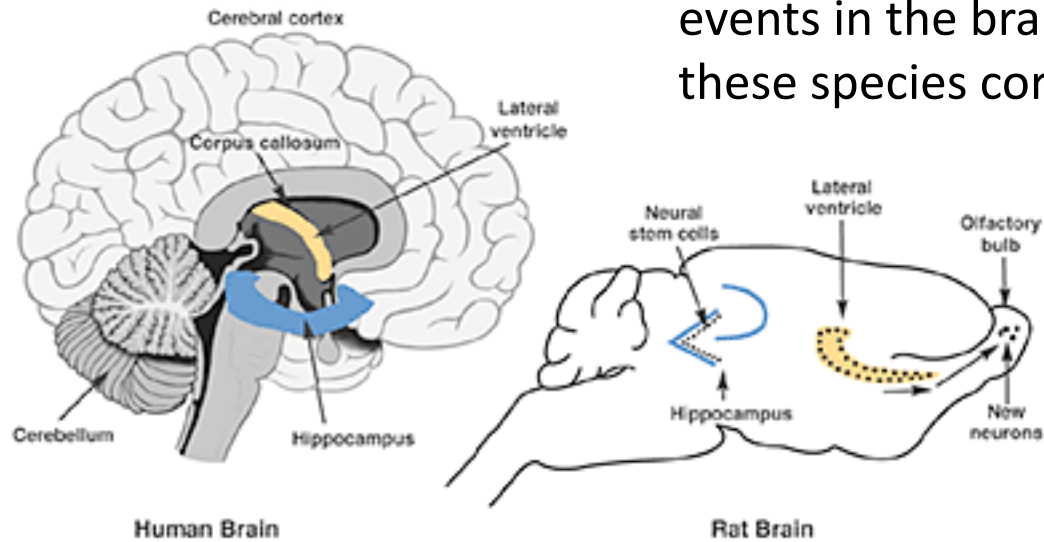


Q fraction stays **lower longer** in the **alar** and **anterior** positions, which allows the precursor pool in these regions to proliferate at a higher rate, producing larger structures as the duration of embryogenesis is extended



In research labs we study the rat brain in hopes of making implications about the human brain

How do developmental events in the brains of these species correlate?



The Finlay/Darlington Model: *A prediction of developmental time across mammalian species*



$$Y = \ln (\text{PC days} - 4.34)$$

$Y = \text{species factor} + \text{neural events factor} + \text{primate factor}$

18 PC days in Mouse neurodevelopment equates to 45.4 PC days in Cat neurodevelopment



4.34: constant that accounts for the fact that early events take about the same amount of time in all eutherian mammals

Neural events factor: each neural event is assigned an event score

-Later events, higher scores

Species factor: each species is assigned a species score

-Slower developing species, higher scores

Primate factor: adjust for systemic variability in primate cortical and limbic systems

-Limbic/cortical components of rodent and human brains mature at different rates

-Adds .248683 to estimated Y-score of every primate cortical events

-Subtracts .079280 from the estimated Y-score of every primate limbic event

$$Y = \ln (\text{PC days} - 4.34)$$

$$Y = \text{Neural events factor} + \text{Species factor} + \text{Primate Factor}$$

Putting the model to use: www.translatingtime.com

The image shows a screenshot of the website www.translatingtime.com. At the top, the title "TRANSLATING TIME" is displayed in large, spaced-out letters, with the subtitle "across developing mammalian brains" underneath. Below the title, there is a navigation menu on the left with links: "Homepage", "Translate", "The Model", "Related Tables", "Provide Feedback", and "Contacts". In the center, there is a button labeled "TRANSLATE NEURODEVELOPMENTAL TIME ACROSS MAMMALIAN SPECIES" which is circled in blue. To its right is another button labeled "PREDICT NEURODEVELOPMENTAL EVENTS". Above these buttons, the text "MAKE SELECTION BELOW" is visible. Below the navigation and buttons, there is a paragraph of text explaining the website's purpose: "Because clinicians and researchers rely on neurodevelopment data obtained from a variety of non-human species, it is essential to be able to relate studies across the different experimental animals, and ultimately to humans, in an easily accessible format. This web site is based on a mathematical model originally described by Finlay and Darlington (Science, 268:1578-84) that predicts post conception (PC) dates using log transformations. It integrates hundreds of empirically-derived neural events to translate neurodevelopmental time across hamsters, mice, rats, rabbits, spiny mice, guinea pigs, ferrets, cats, rhesus monkeys and humans." To the right of this paragraph is a section titled "Citation Information" with the text: "If you use any information from this website, please [click here](#) for citation details". At the bottom of the page, there are three columns of information: "Site Created By:" listing Barbara Clancy, Ph.D., Brandon M. Kersh, and James R. Hyde; "Contributors:" listing Steve Jennings, Ph.D., Dan Berleant, Ph.D., Roger Hall, Nathan Crabtree, and Josh Hanna; and "Supported By:" listing the NCTR (National Center for Translational Research), Arkansas INBRE, and NSF (National Science Foundation). Logos for UCA, UA LR, and I I A M S C are also visible.

TRANSLATING TIME

across developing mammalian brains

1 Species One

- Hamster
- Mouse
- Rat
- Rabbit
- Spiny mouse
- Guinea pig
- Ferret
- Cat
- Macaque
- Human

MIN ← Range → MAX
12.1 ↔ 43.3

2 Days Post Conception (Species one)

12.1 < 30 < 43.3

TRANSLATE

R Results

30 PC days in *Rabbit* neurodevelopment equates to 49.9 PC days (8.9 PN days) in *Ferret* neurodevelopment

GO BACK

3 Species Two

- Hamster
- Mouse
- Rat
- Rabbit
- Spiny mouse
- Guinea pig
- Ferret
- Cat
- Macaque
- Human

MIN ← Range → MAX
18.1 ↔ 73.5

i Species One Info

Species: *Oryctolagus cuniculus*
Family: Leporidae
Order: Lagomorpha
Gestation: 31
Species Score(SP): 1.143898
Data Range: 12.1 ↔ 43.3

i Species Two Info

Species: *Mustela putorius furo*
Family: Mustelidae
Order: Carnivora
Gestation: 41
Species Score(SP): 1.718129
Data Range: 18.1 ↔ 73.5

T R A N S L A T I N G T I M E

across developing mammalian brains

1 Species One

- Hamster
- Mouse
- Rat
- Rabbit
- Spiny mouse
- Guinea pig
- Ferret
- Cat
- Macaque
- Human

MIN ← Range → MAX

15.2 ↔ 58.6

2 Days Post Conception (Species one)

15.2 < 25 < 58.6

3 Species Two

- Hamster
- Mouse
- Rat
- Rabbit
- Spiny mouse
- Guinea pig
- Ferret
- Cat
- Macaque
- Human

MIN ← Range → MAX

34.5 ↔ 197.9

TRANSLATE

R Results

25 PC days in *Guinea pig* neurodevelopment equates to

Human neurodevelopment as follows:

- Cortical Events: 78.1 PC days
- Limbic Events: 57.5 PC days
- Non-cortical/limbic Events: 61.8 PC days

GO BACK

*Why do primates have 3 predictions? [The Model](#)

i Species One Info

Species: *Cavia porcellus*
Family: Cavidae
Order: Rodentia

Gestation: 68.5
Species Score(SP): 1.476369
Data Range: 15.2 ↔ 58.6

i Species Two Info

Species: *Homo sapiens*
Family: Hominidae
Order: Primates

Gestation: 270
Species Score(SP): 2.5
Data Range: 34.5 ↔ 197.9

T R A N S L A T I N G T I M E

across developing mammalian brains

MAKE SELECTION BELOW

Homepage
Translate
The Model
Related Tables
Provide Feedback
Contacts

TRANSLATE
NEURODEVELOPMENTAL
TIME ACROSS
MAMMALIAN SPECIES

PREDICT
NEURODEVELOPMENTAL
EVENTS

Because clinicians and researchers rely on neurodevelopment data obtained from a variety of non-human species, it is essential to be able to relate studies across the different experimental animals, and ultimately to humans, in an easily accessible format. This web site is based on a mathematical model originally described by Finlay and Darlington (Science, 268:1578-84) that predicts post conception (PC) dates using log transformations. It integrates hundreds of empirically-derived neural events to translate neurodevelopmental time across hamsters, mice, rats, rabbits, spiny mice, guinea pigs, ferrets, cats, rhesus monkeys and humans.

Citation Information

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Supported By:



TRANSLATING TIME

across developing mammalian brains

adultlike cortical innervation of dLGN
amygdala – peak of neurogenesis
anterior commissure appears
anterior olfactory nucleus – peak of neurogenesis
AV, AM, AD nuclei – peak of neurogenesis
axons in optic stalk
CA 1, CA 2 – peak of neurogenesis
caudoputamen – peak of neurogenesis
claustrum – peak of neurogenesis
cochlear nuclei – peak of neurogenesis
complete separation of layer V (S1)
cones – peak of neurogenesis
corpus callosum appears
cortical axons innervate dLGN
cortical axons reach dLGN
cranial motor nuclei – peak of neurogenesis
cranial sensory nuclei – peak of neurogenesis
deep cerebellar nuclei – peak of neurogenesis
dentate gyrus – peak of neurogenesis
dLGN – peak of neurogenesis
dLGN– end of neurogenesis
dLGN– start of neurogenesis
entorhinal cortex – peak of neurogenesis
external capsule appears
eye opening

Hamster
Mouse
Rat
Rabbit
Spiny mouse
Guinea pig
Ferret
Cat
Macaque
Human

Predict

Abbreviations used on this site,
[Click Here](#)

TRANSLATING TIME

across developing mammalian brains

Results of your Event Prediction

corpus callosum appears predicted to occur at:

73.4 days post conception

Species:

Gestation: days post conception

Eye opening: days post conception

Brain region (if primate):

GO BACK

Some Key Points:

1. Late makes large: Applies to both development and evolution
2. Primate limbic structures are an exception
3. Prosomeric model: the more alar and anterior, the more protracted neurogenesis is
4. Barbara Finlay used these, and other factors to put together a model for converting PC days across various mammalian species:

$$Y = \text{Neural events factor} + \text{Species factor} + \text{Primate Factor}$$

Thank you!

