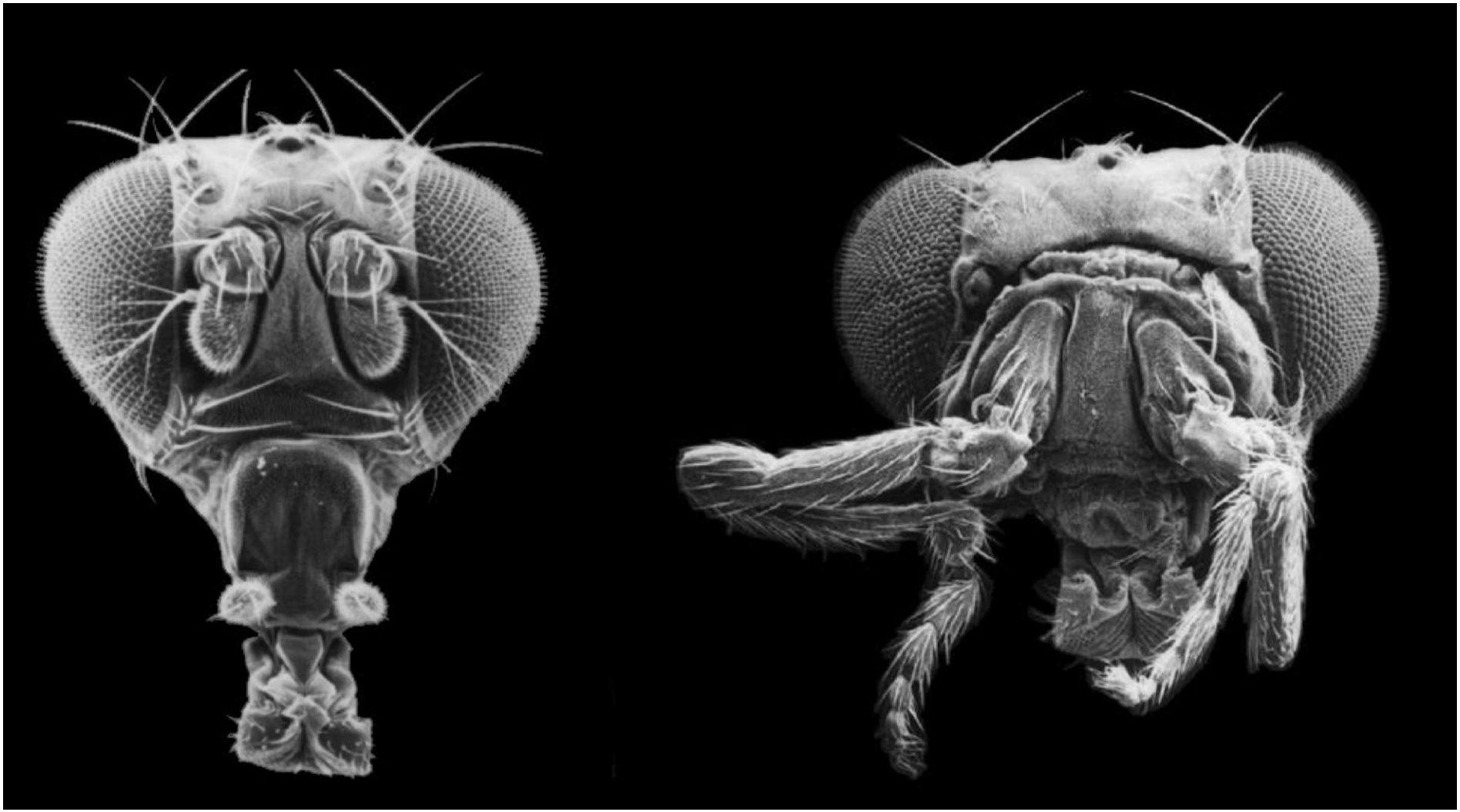
PONTS ET CHAUSSEES

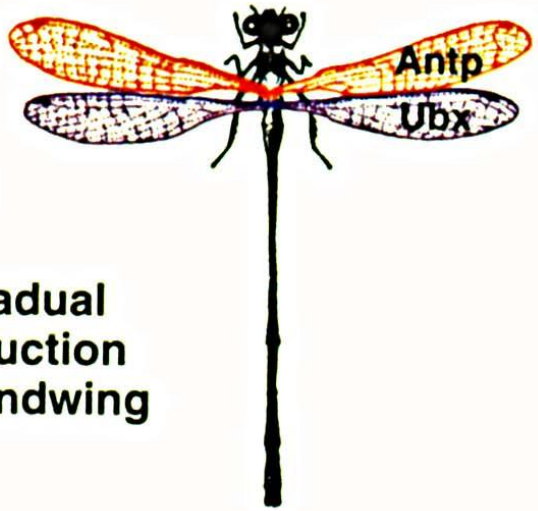
2009

QUELQUES REPÈRES CHRONOLOGIQUES

Bactéries	-3500M
Protozoaires	-1000M
Métazoaires	-600M (expansion)
Agnathes	-500M
Gnathostomes	-400M
Tétrapodes et insectes	-360M
Radiation des reptiles	-280M
Dinosaures	-250M
Premiers oiseaux	-150M
Extinction des dinosaures	-70M
FIN DU SECONDAIRE	
Grande radiation des mammifères, oiseaux, insectes	
Evolution des premiers primates	
FIN DU TERTIAIRE	-1,8M



FOUR-WINGED ANCESTOR
wing pairs identical

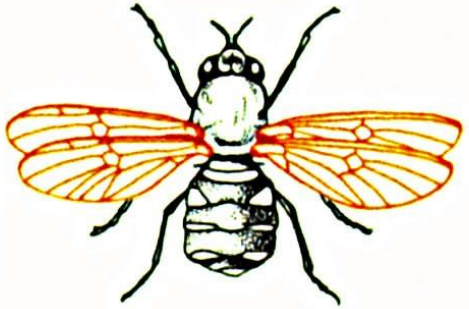


evolution of Ubx-regulated gene set

gradual reduction of hindwing

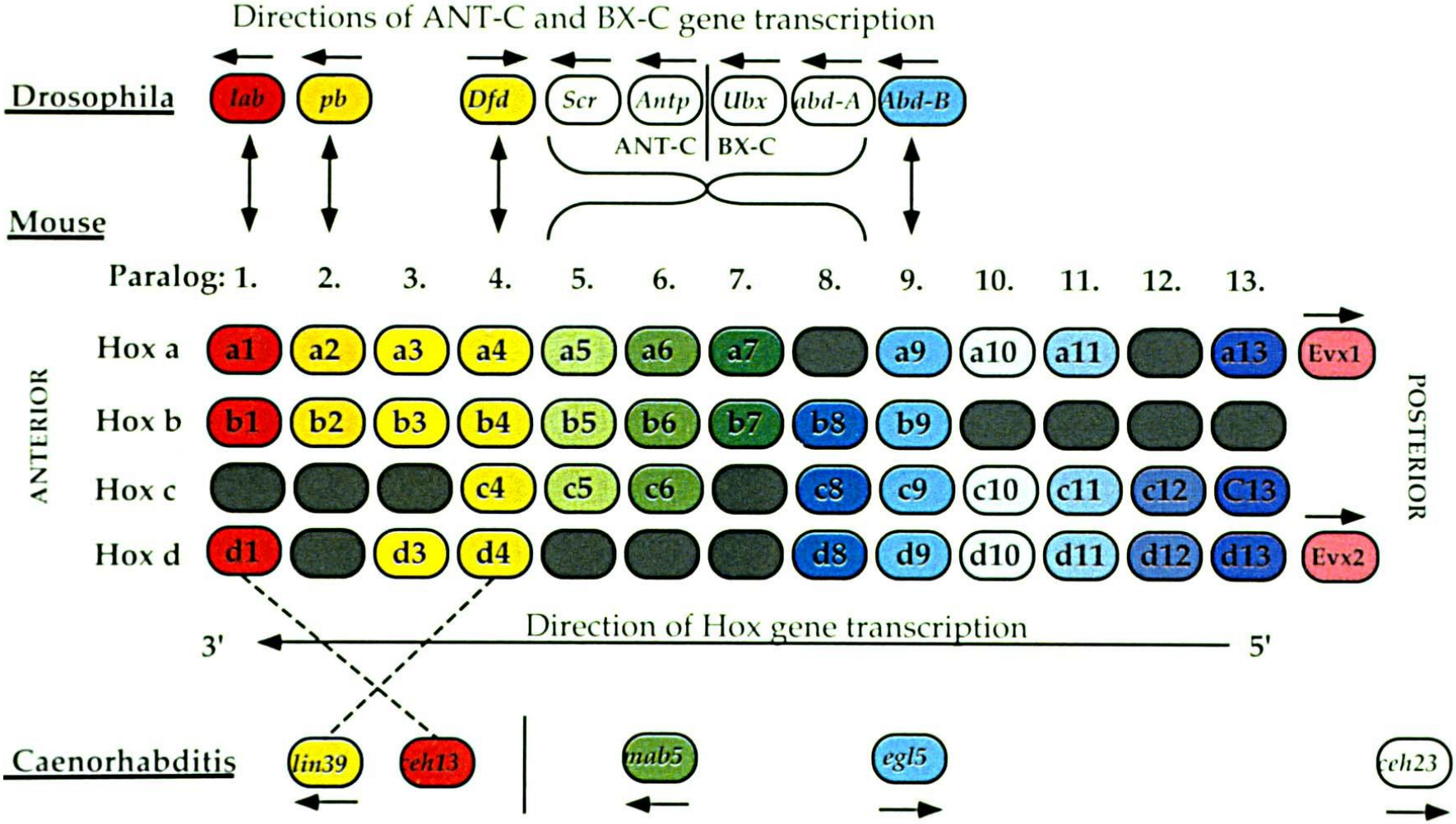
DIPTERA

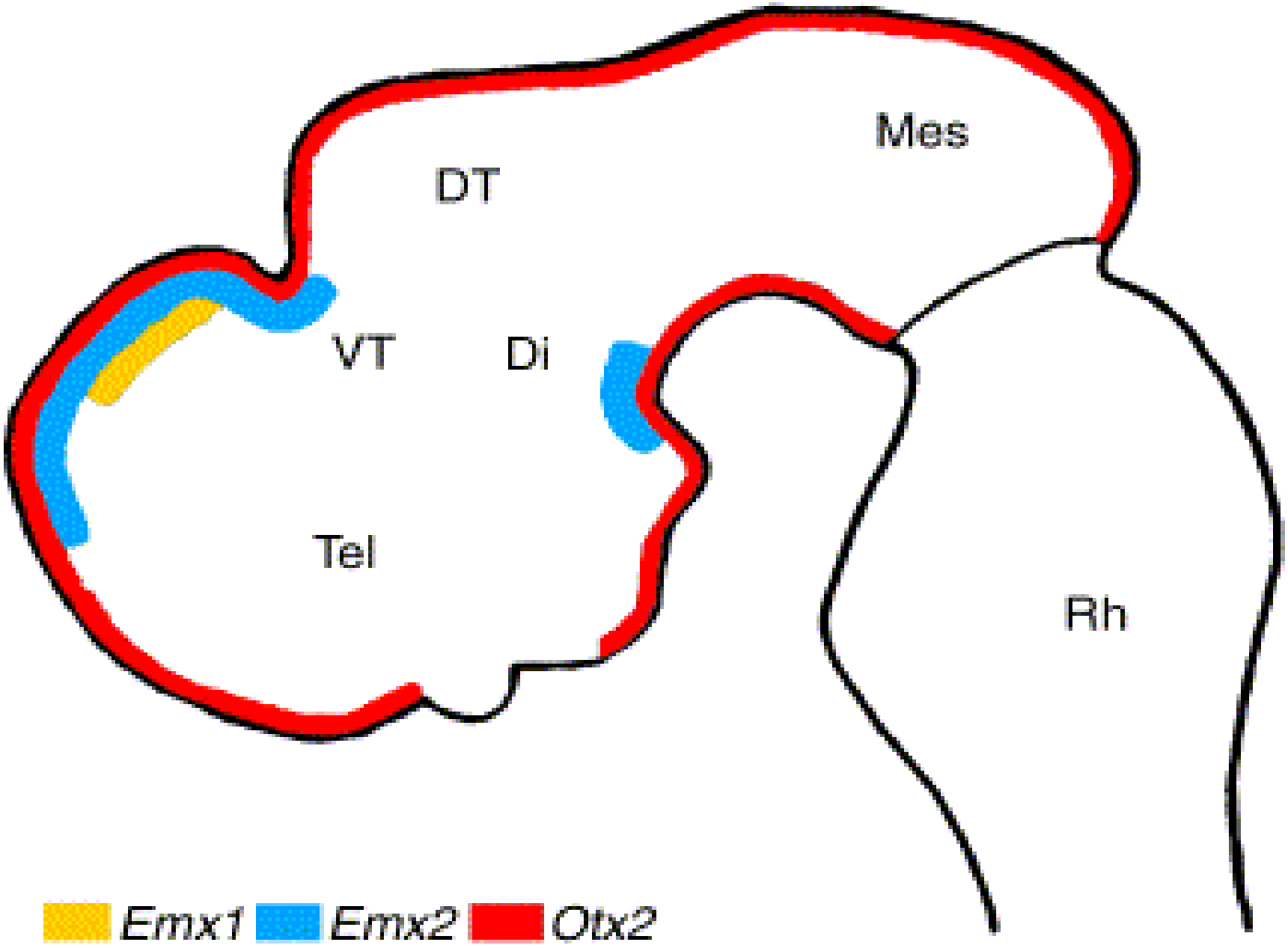
Ubx mutation, entire Ubx-regulated gene set expressed as in forewing



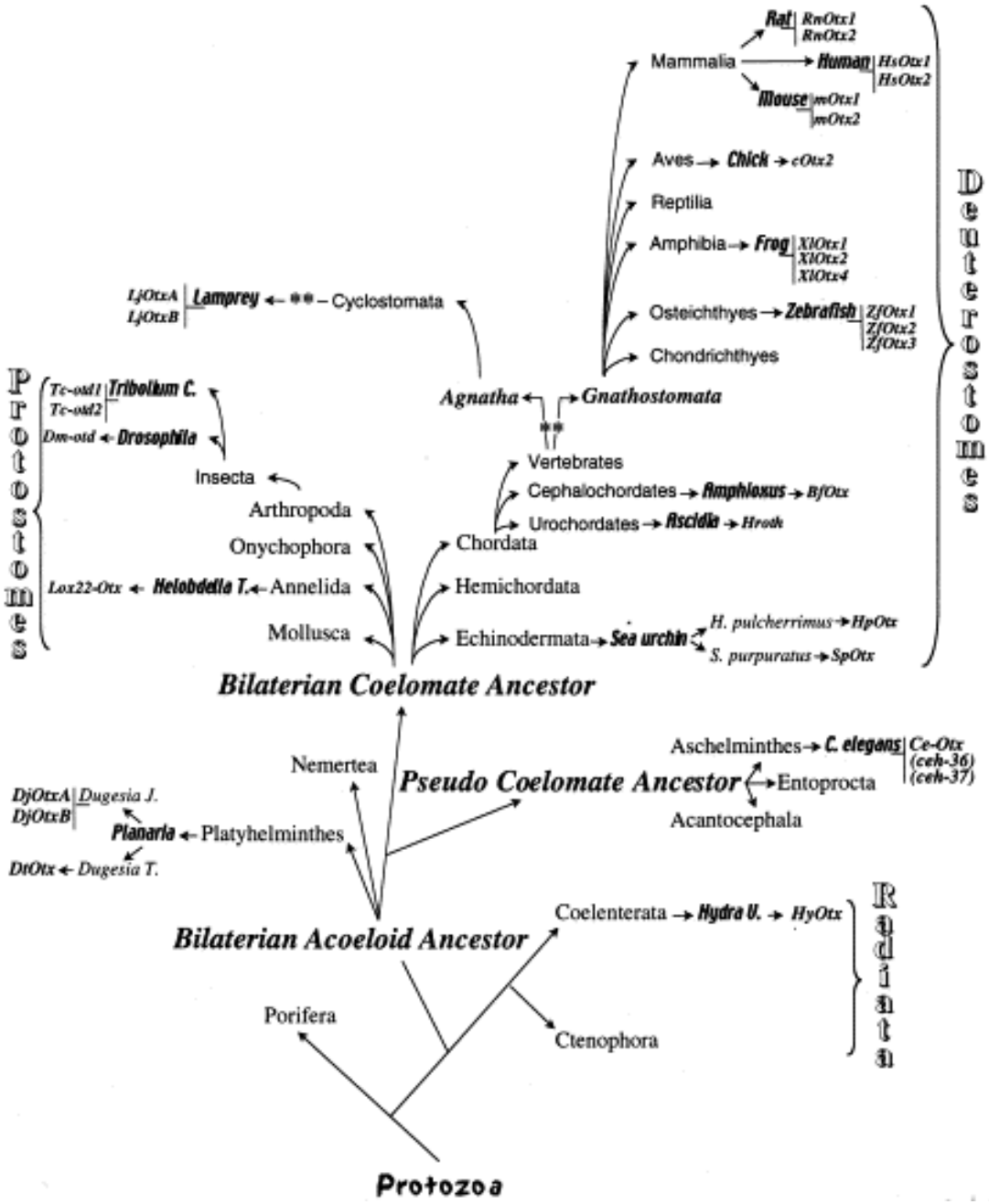
Ubx mutant

The HOX and HOM Complexes

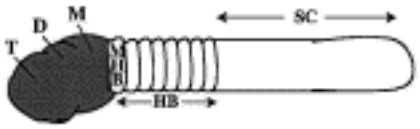




Trends in Neurosciences


Rat
RnOtx1
RnOtx2
Mammalia
Human
HsOtx1
HsOtx2
Mouse
mOtx1
mOtx2
Aves
Chick
cOtx2
Reptilia
Amphibia
Frog
XlOtx1
XlOtx2
XlOtx4
Osteichthyes
Zebrafish
ZfOtx1
ZfOtx2
ZfOtx3
Chondrichthyes
Deuterostomes
LjOtxA
LjOtxB
Lamprey
Cyclostomata
Agnatha
Gnathostomata
Tc-otd1
Tc-otd2
Tribolium C.
Dm-otd
Drosophila
Protostomes
Insecta
Vertebrates
Cephalochordates
Amphioxus
BfOtx
Urochordates
Ascidia
Hroth
Arthropoda
Onychophora
Chordata
Lox22-Otx
Helobdella T.
Annelida
Hemichordata
Mollusca
Echinodermata
Sea urchin
H. pulcherrimus
HpOtx
S. purpuratus
SpOtx
Bilaterian Coelomate Ancestor
Aschelminthes
C. elegans
Ce-Otx
(ceh-36)
(ceh-37)
Nemertea
Pseudo Coelomate Ancestor
Entoprocta
Acantocephala
DjOtxA
DjOtxB
Dugesia J.
Planaria
Platyhelminthes
DtOtx
Dugesia T.
Bilaterian Acoeloid Ancestor
Coelenterata
Hydra V.
HyOtx
Radiata
Porifera
Ctenophora
Protozoa

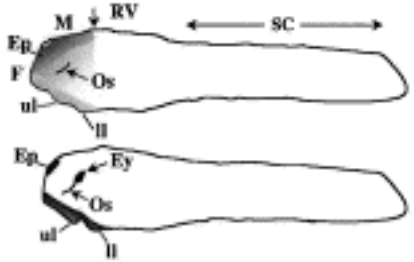
Otx1 + Otx2



Mouse
(gnatostomes)

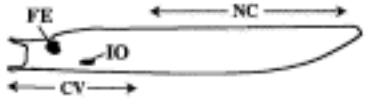
LjOtxA

LjOtxB



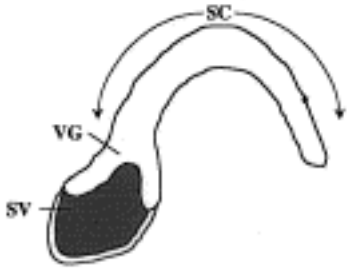
Lamprey
(agnates)

AmphiOtx



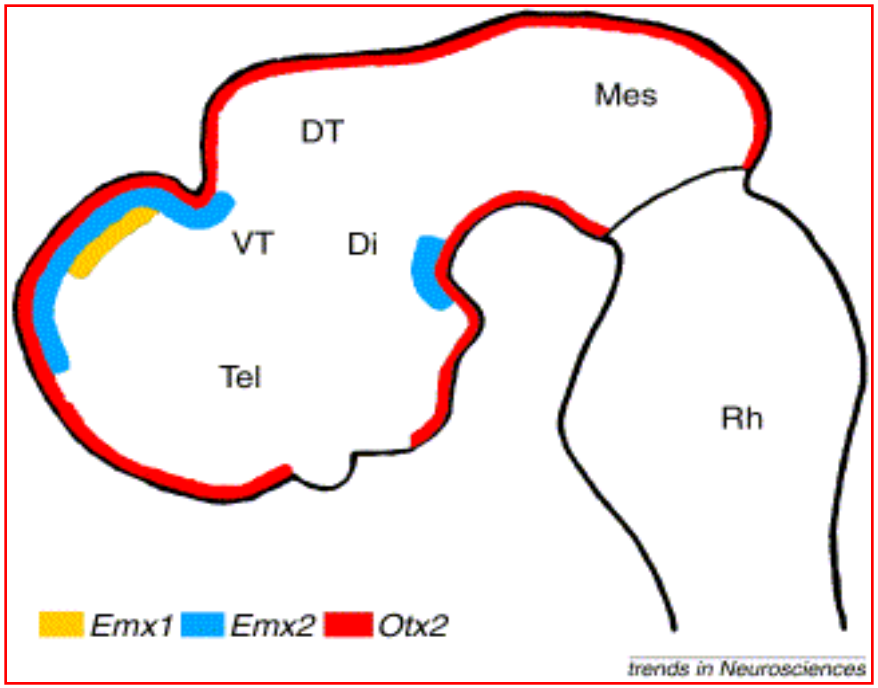
Amphioxus
(cephalochordates)

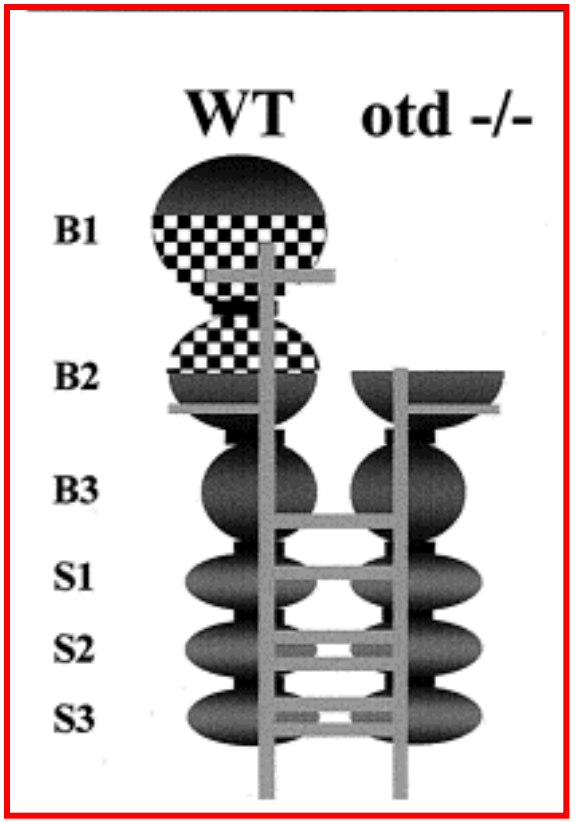
HrothOtx

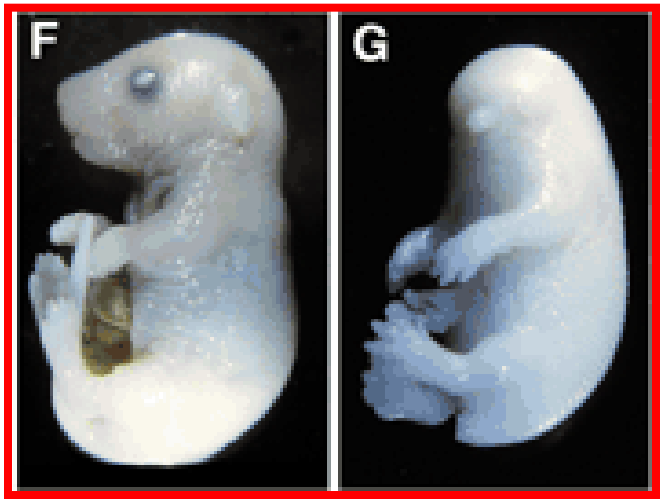


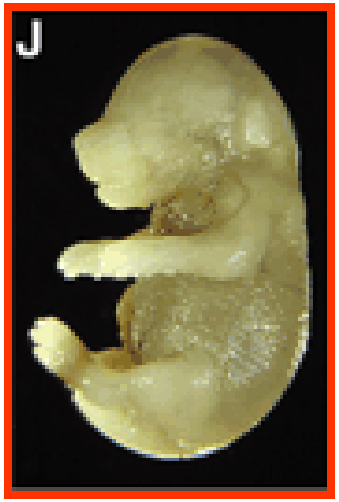
Ascidia
(urochordates)

HOMEOGENE FUNCTIONAL CONSERVATION IN EVOLUTION



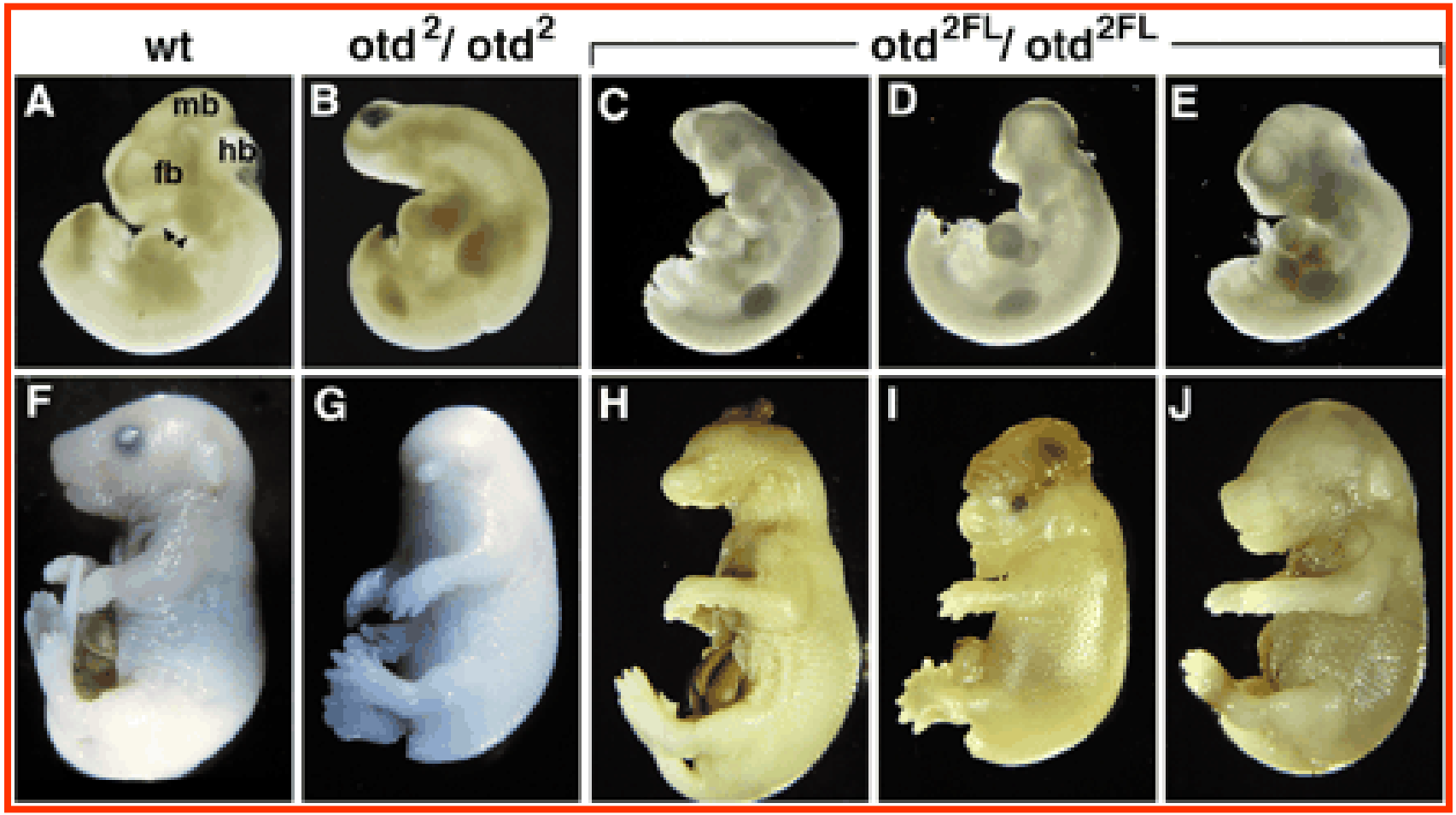


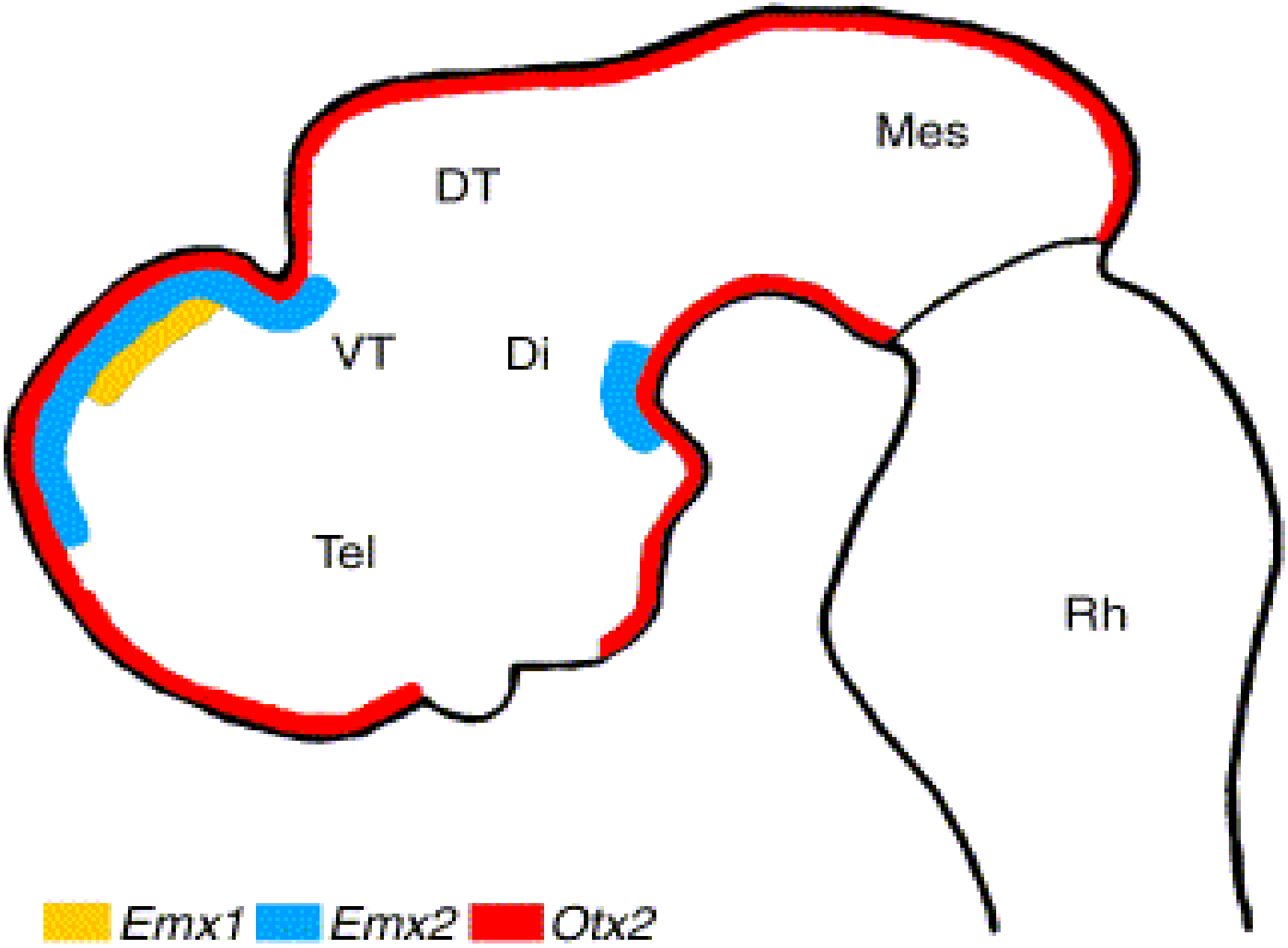




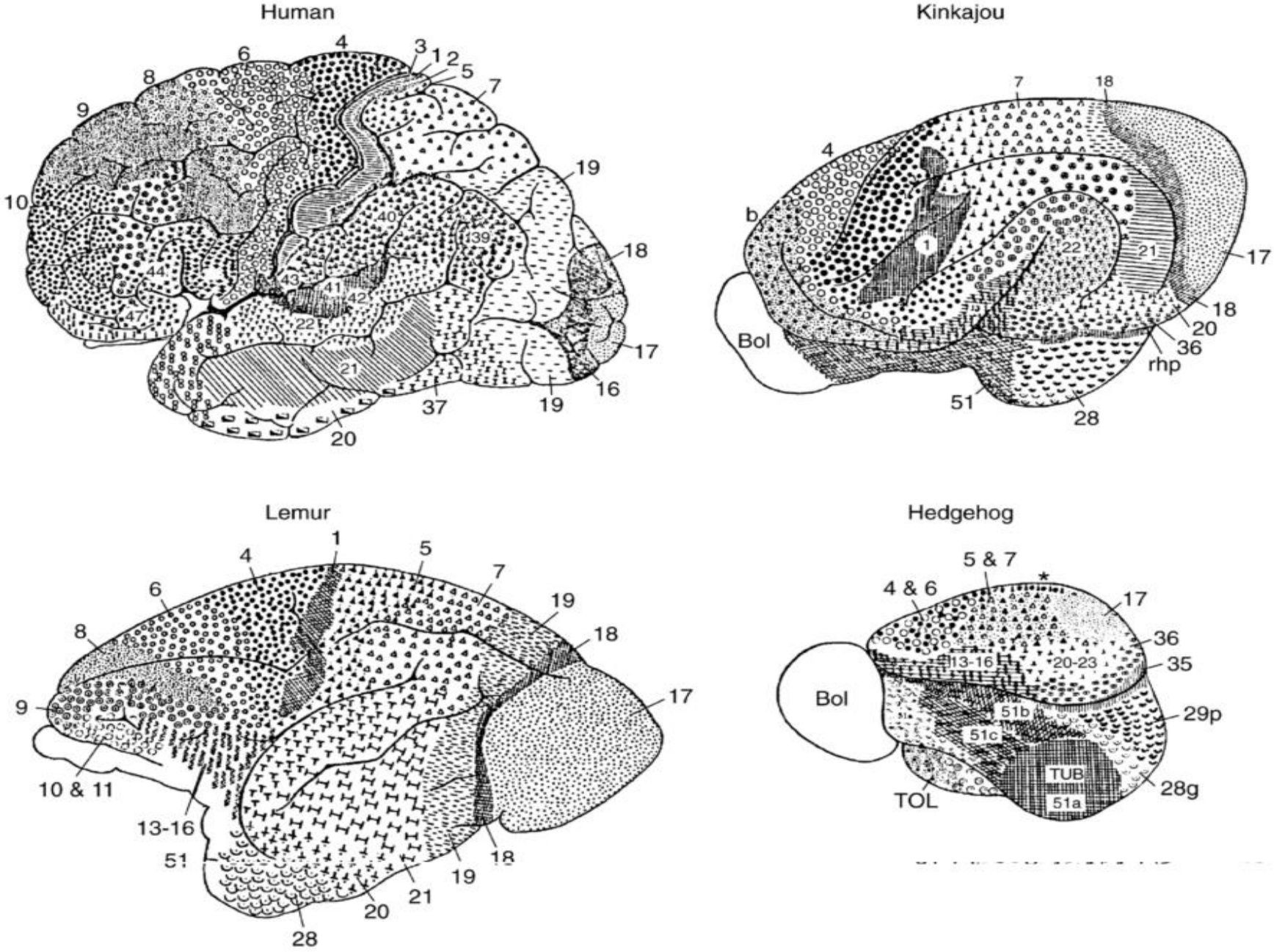
Boncinelli, Simeone & Col.

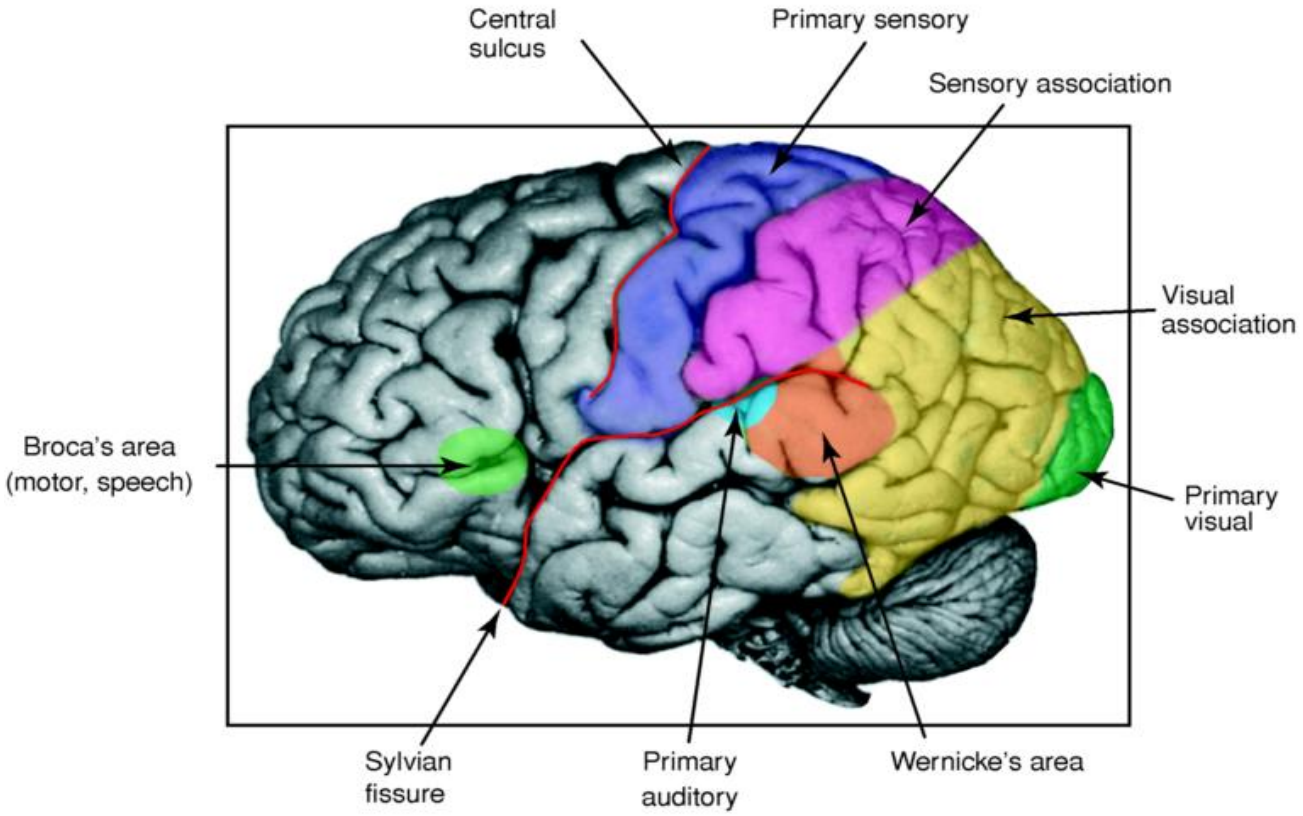
Otd dans Otx2 avec ou sans séquences flanquantes (FL)





Trends in Neurosciences





Primer

Evolution of the neocortex

Jon H. Kaas

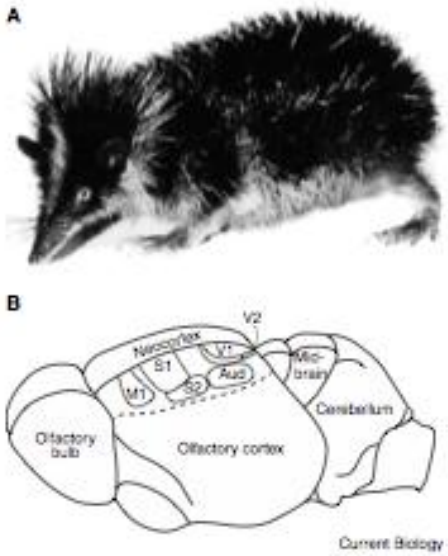
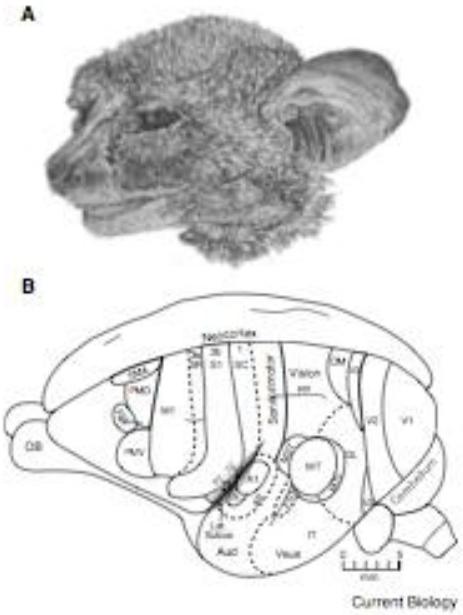


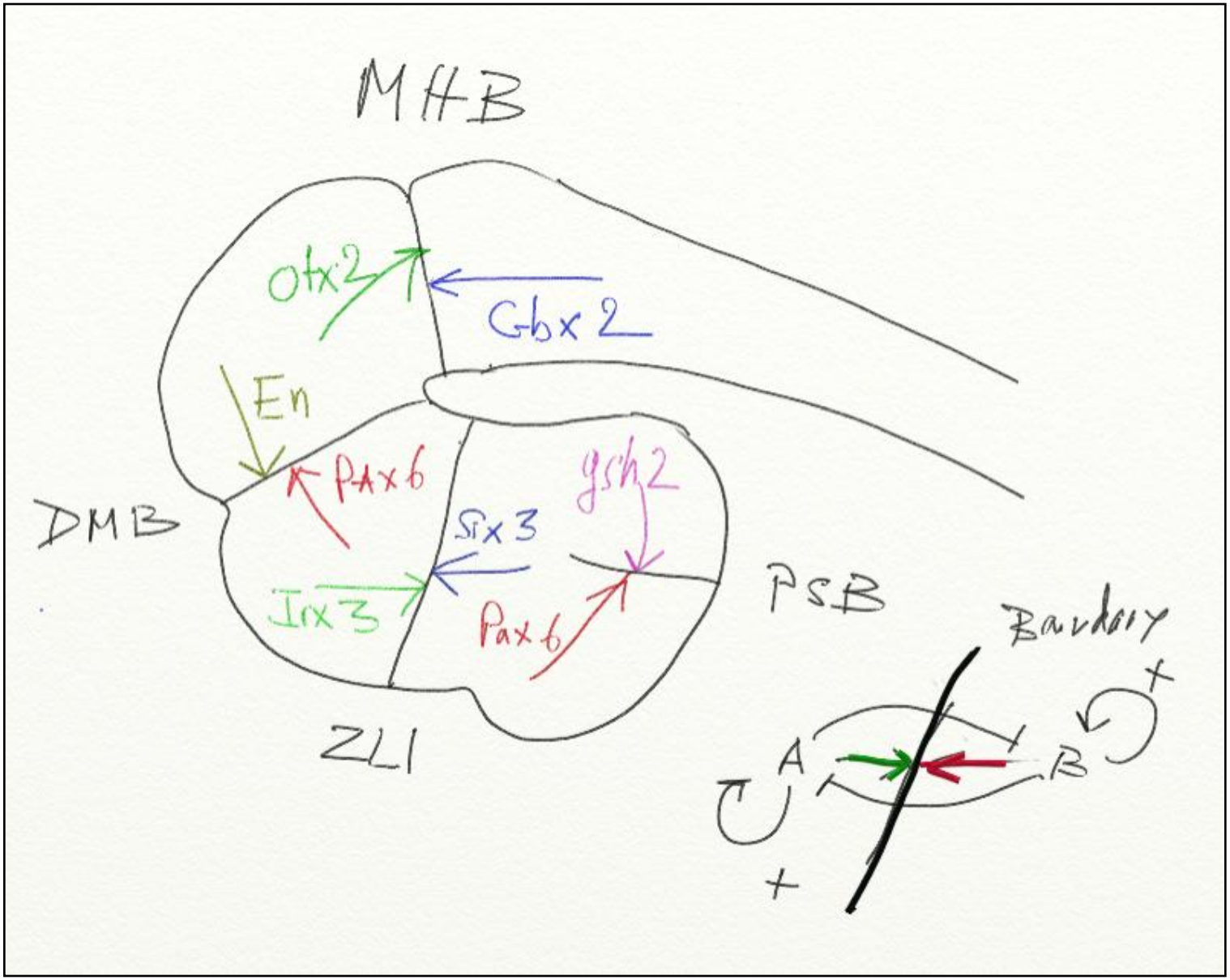
Figure 1. The tenrec brain as a model for the brains of early mammals.

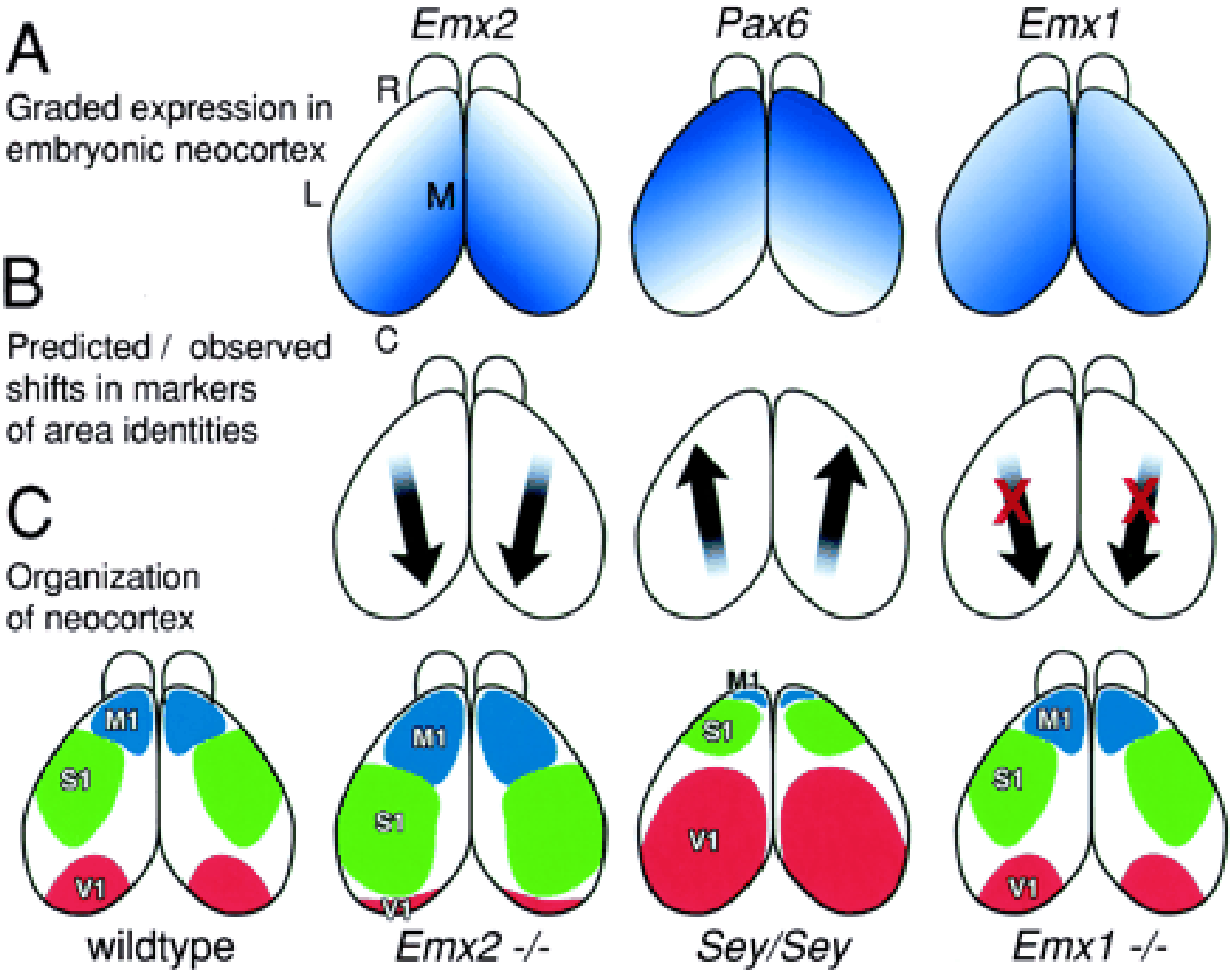
(A) A small Afrotherian mammal, the Madagascar tenrec (Echinops telfairi) sharing many characteristics with the earliest mammals. (B) A dorsolateral view of the tenrec brain with major parts and subdivisions of neocortex. Neocortex is small and subdivided into few cortical areas, mainly primary and secondary visual (V1 and V2) and somatosensory (S1 and S2) areas, a primary motor area (M1) and an auditory field (Aud).

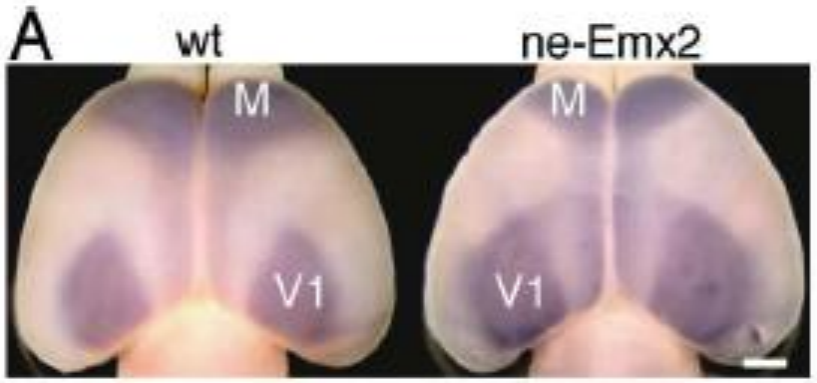
Figure 2. The galago brain.

(A) The cat sized prosimian primate, Galago garnetti (also known as Otolemur garnetti). The brain of this prosimian may help us understand the evolution of primate brains. (B) A dorsolateral view of a galago brain. The somatosensory areas include area 3b, area 1 or the caudal somatosensory area (SC), area 3a or the rostral somatosensory area (SR), the second area (S2), the parietal ventral area (PV) and other areas buried in the lateral sulcus. Visual areas include the first (V1) second (V2) and third (V3) visual areas, the dorsomedial visual area (DM), the dorsolateral visual area (DL), the middle temporal visual area (MT), the medial superior temporal area (MST), and the fundal area of the superior temporal sulcus (FST).



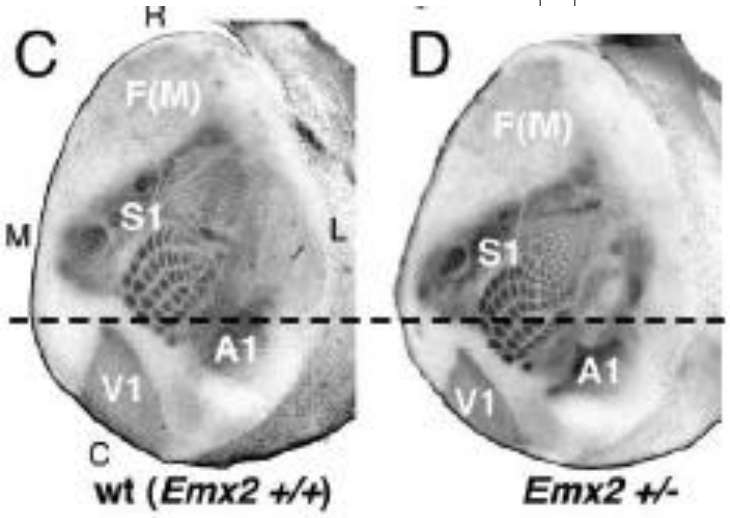

MHB
Otx2
Gbx2
En
Pax6
Six3
gsh2
Irx3
Pax6
DMB
PSB
ZLI
Boundary
A
B
+
+


A
Graded expression in embryonic neocortex
Emx2
Pax6
Emx1
R
L
M
B
Predicted / observed shifts in markers of area identities
C
C
Organization of neocortex
M1
S1
V1
wildtype
Emx2 -/-
Sey/Sey
Emx1 -/-



1 extra emx2 copy

Visual cortex



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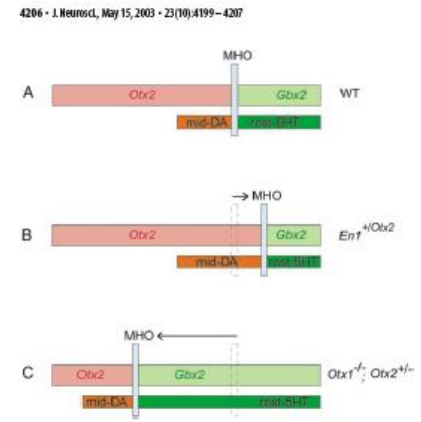
Somatosensory cortex

Hamasaki et al. Neuron, vol 43, p359-372, 2004

OTX/GBX Equilibrium in making the isthmus



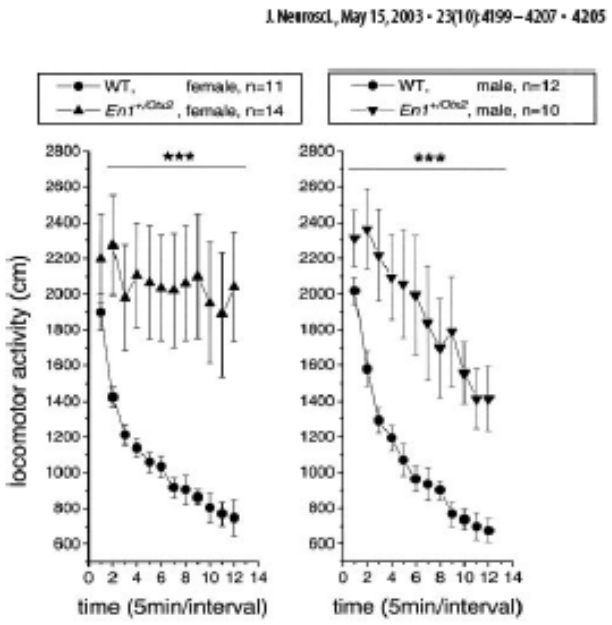
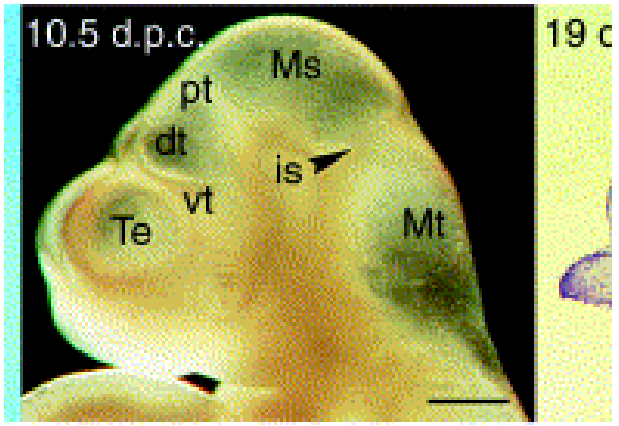
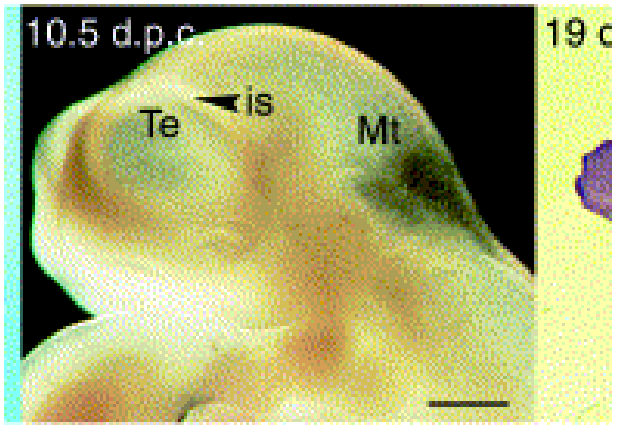


Figure 6. *En1*$^{+/Otx2}$ mutants are hyperactive. Locomotor activity of *En1*$^{+/Otx2}$ mice in an open field is shown. *En1*$^{+/Otx2}$ mice and their wild-type (WT) littermates were placed in an open field, and locomotor activity was monitored by video-tracking. *En1*$^{+/Otx2}$ mice showed enhanced locomotor activity (factor genotype, $^{***}p < 0.00001$) independent of gender ($p = 0.57$).

Wild type

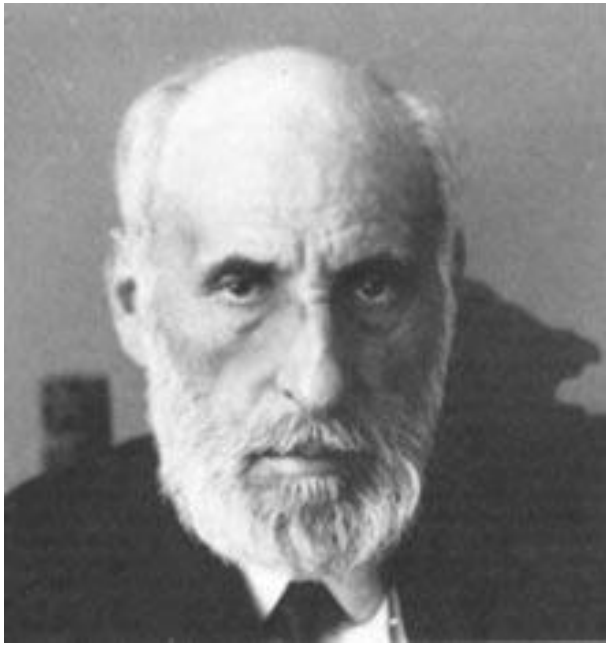


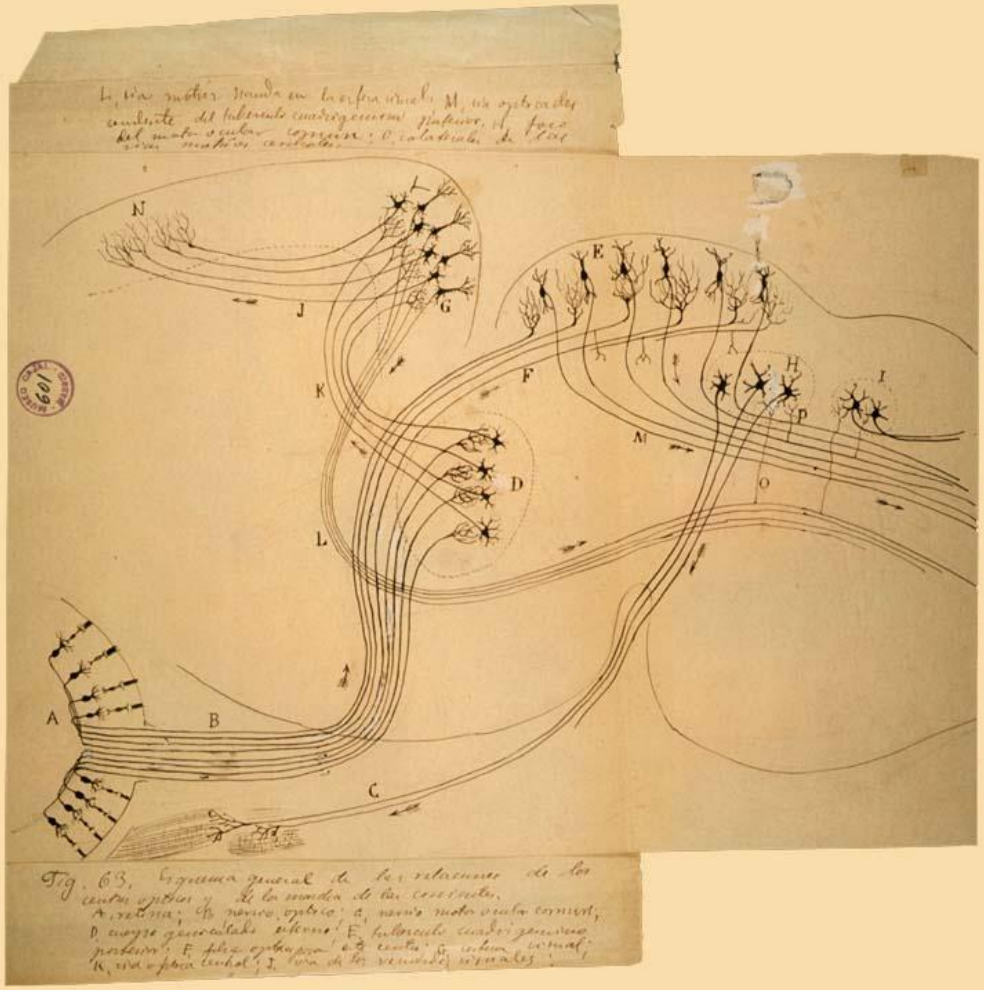
Otx1–/–; Otx2+/–



Wurst & Colleagues

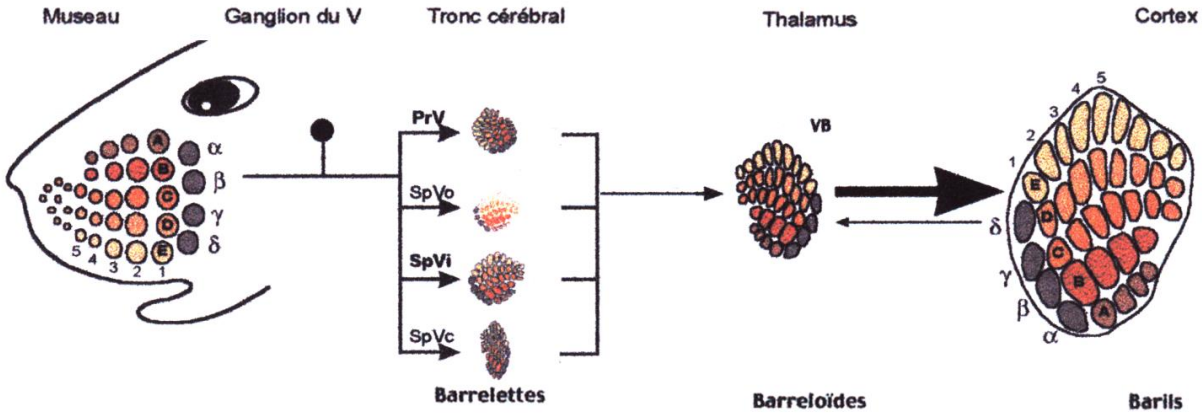
Fig. 18. The Author at the Beginning of his Career. Notice the sullen and unsociable expression.



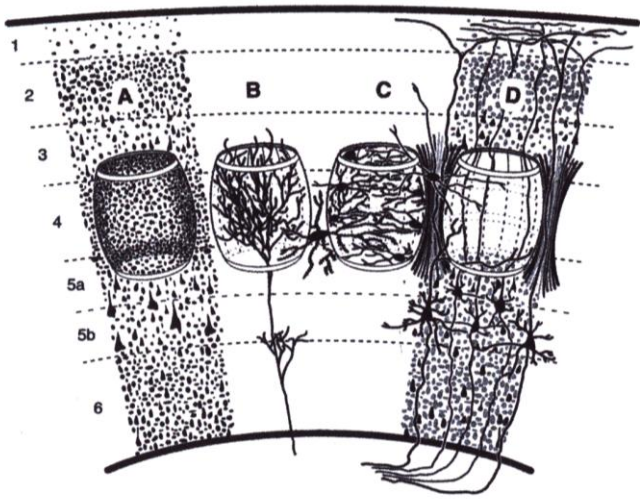


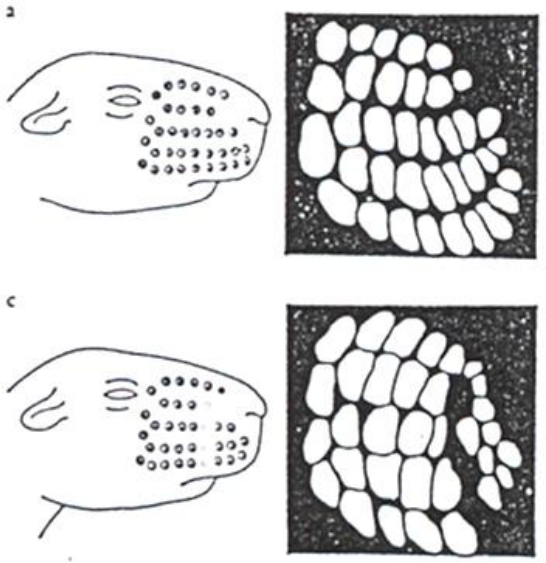
"Schematic of the afferent and efferent pathways of the optic centers". A, retina; B, optic nerve; C, fibers from the oculomotor nucleus; D, lateral geniculate nucleus; E, colliculus; F, optic fibers; G, visual cortex; K, central optic pathway; J, pathway of visual association fibers; L, motor pathway arising from the visual cortex; M, superior colliculus; H, oculomotor nucleus; O, collaterals of the cerebral motor pathways. Modified from a photograph taken from the original (34X28cm). Drawn on sheet/paper. P.Y. 1901. S.R. y Cajal Institute - CSIC - Madrid, Spain.

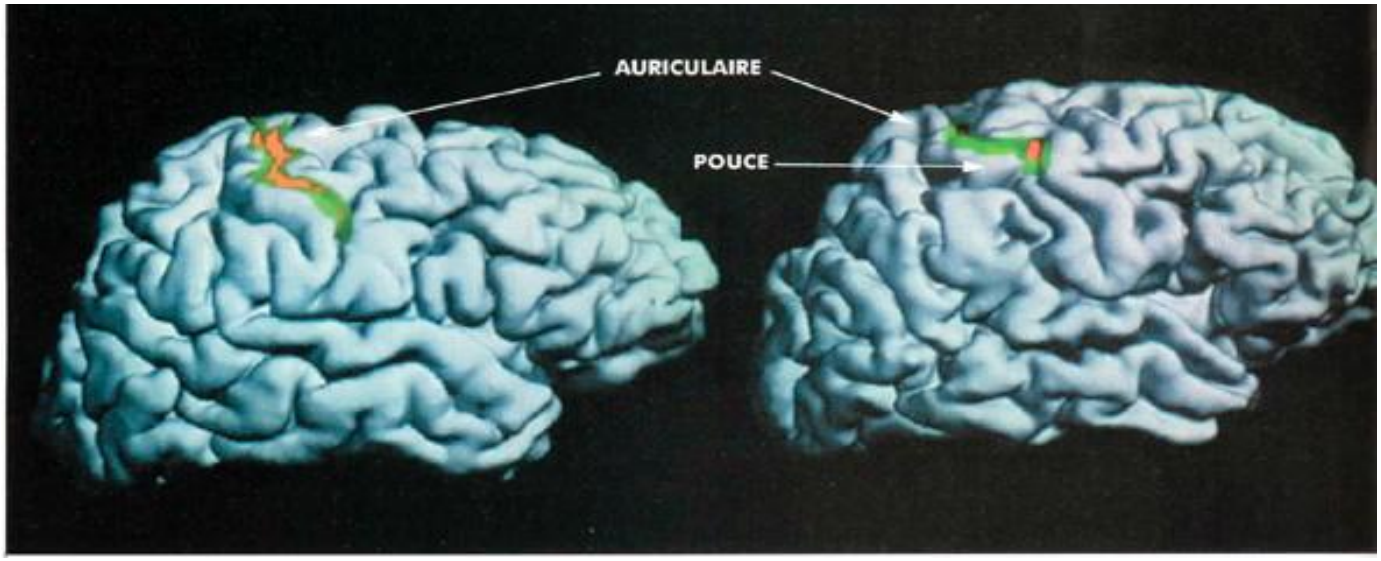
A

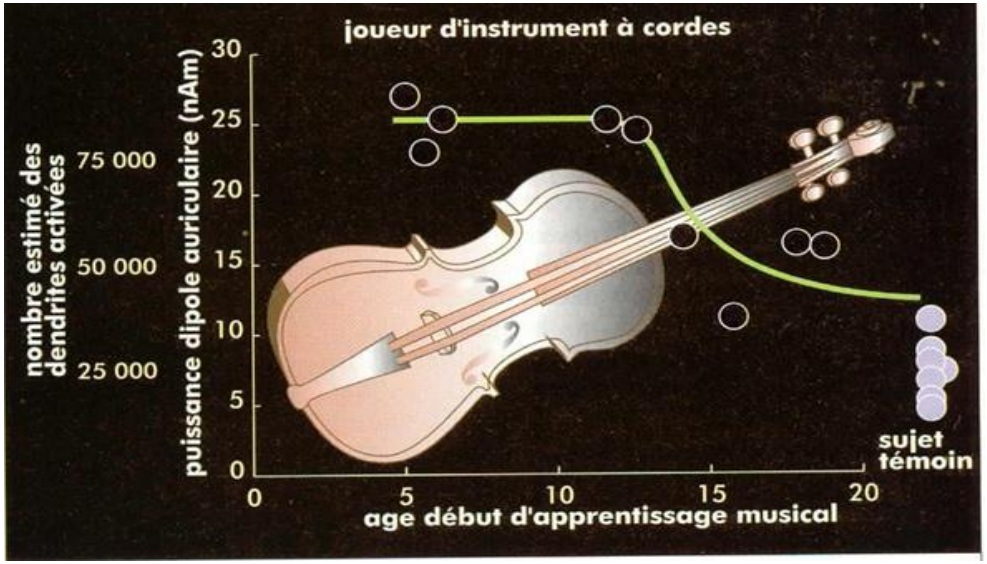

Museau
Ganglion du V
Tronc cérébral
Thalamus
Cortex
PrV
SpVo
SpVi
SpVc
VB
Barrelettes
Barreloïdes
Barils

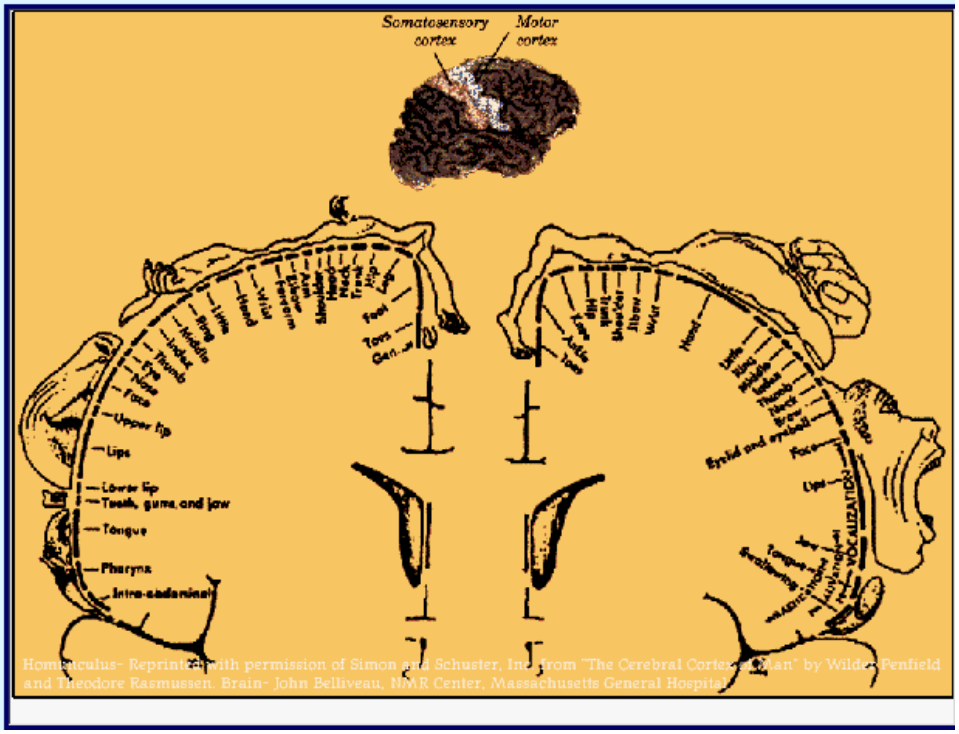
B


A
B
C
D

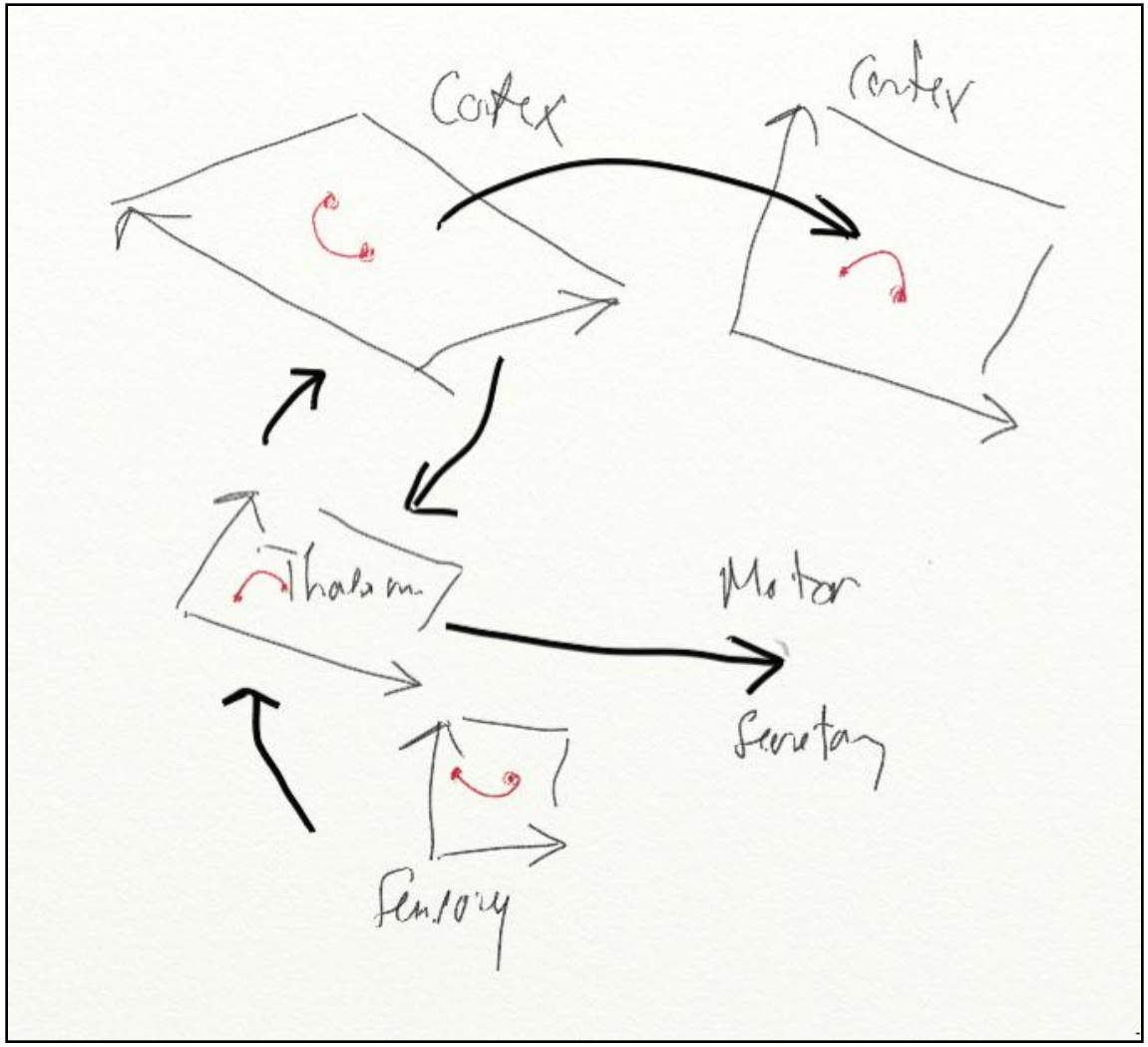


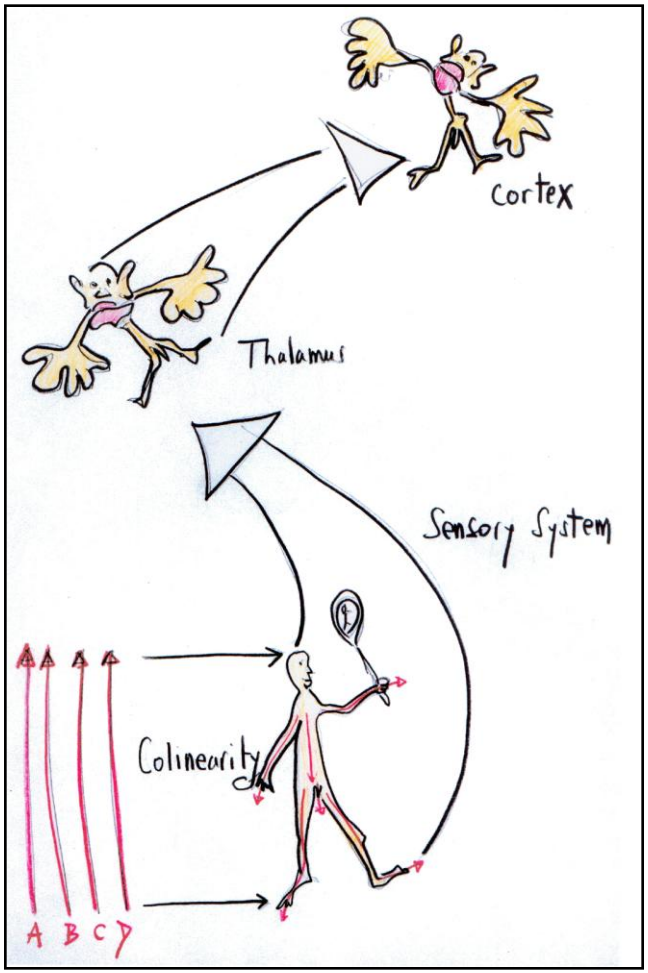

AURICULAIRE
POUCE

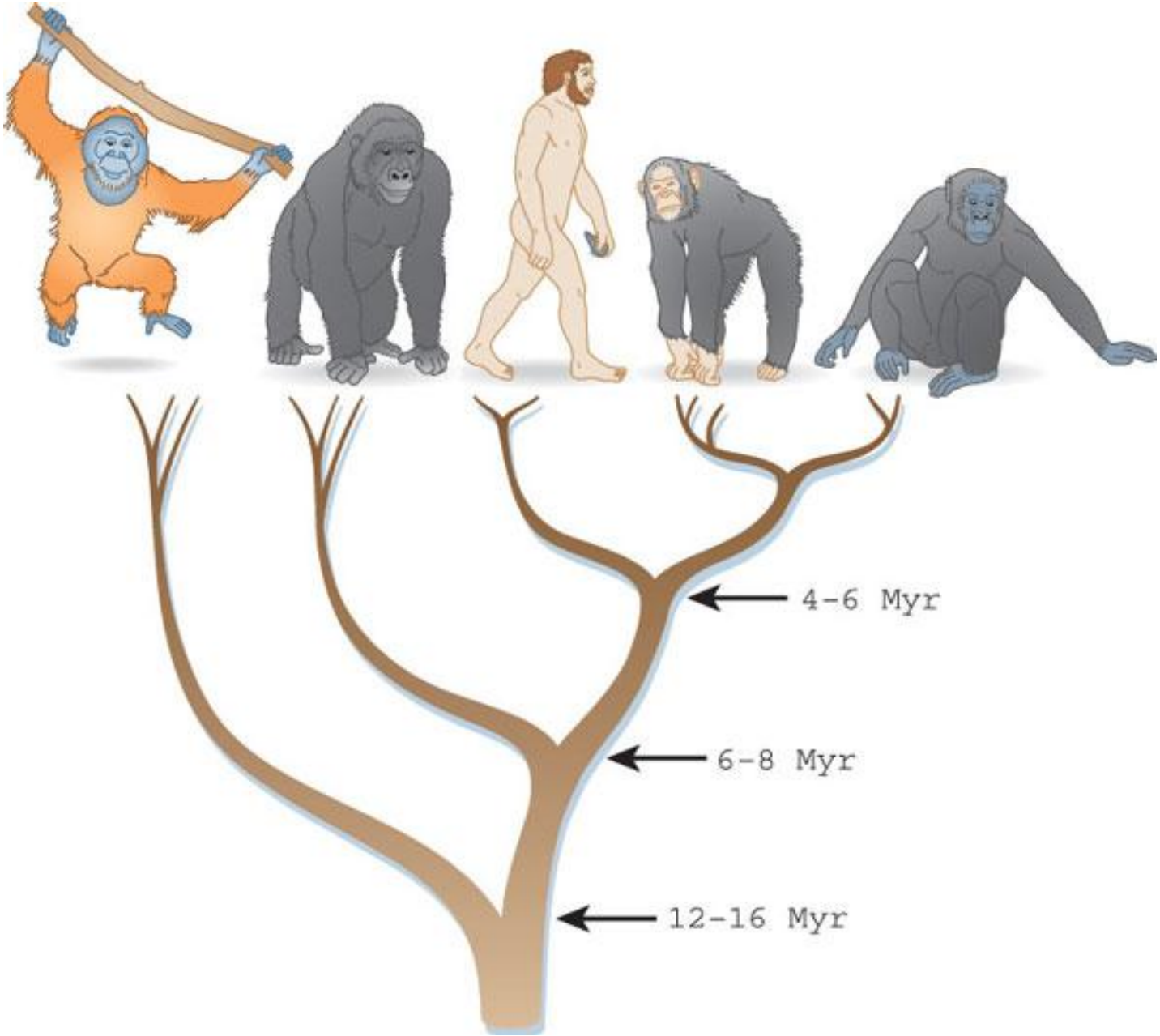

joueur d'instrument à cordes
nombre estimé des dendrites activées
75 000
50 000
25 000
puissance dipole auriculaire (nAm)
30
25
20
15
10
5
0
0
5
10
15
20
age début d'apprentissage musical
sujet témoin



Homunculus- Reprinted with permission of Simon and Schuster, Inc., from "The Cerebral Cortex of Man" by Wilder Penfield and Theodore Rasmussen. Brain- John Belliveau, MMR Center, Massachusetts General Hospital


Cortex
Cortex
Thalamus
Motor
Sensory
Sensory

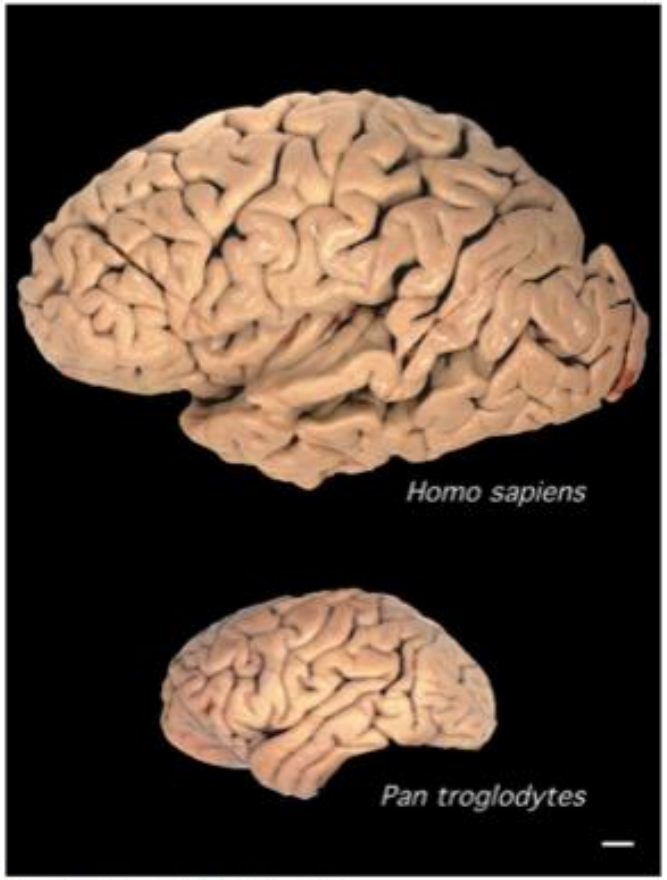

Cortex
Thalamus
Sensory System
Colinearity
A B C D



Svante Pääbo Nature, vol 241, p409-412, 2003

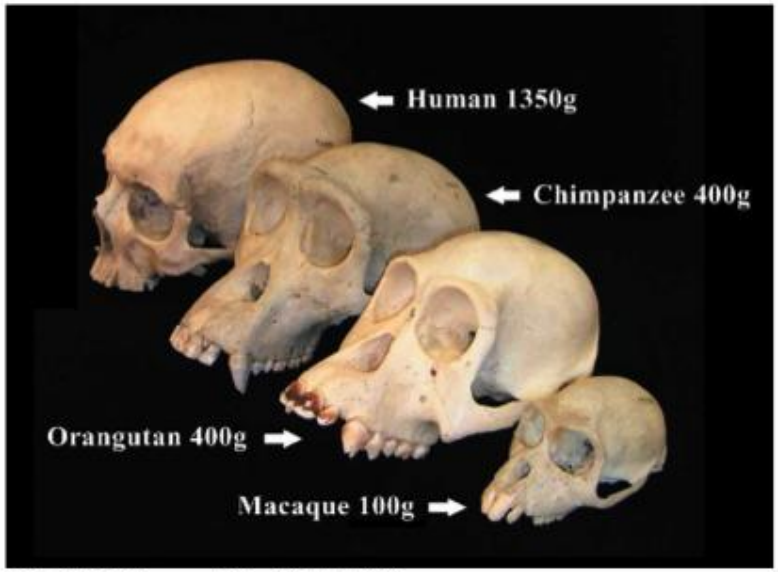
Molecular Insights into Human Brain Evolution

Jane Bradbury



DOI: 10.1371/journal.pbio.0030050.g001

Figure 1. Comparison of a Human and a Chimpanzee Brain
Scale bar = 1 cm.
(Image: Todd Preuss, Yerkes Primate Research Center)



DOI: 10.1371/journal.pbio.0030050.g003

Figure 3. Primate Brain Sizes
These skulls are from the Harvard Museum of Comparative Zoology.
(Image: Christopher Walsh, Harvard Medical School)

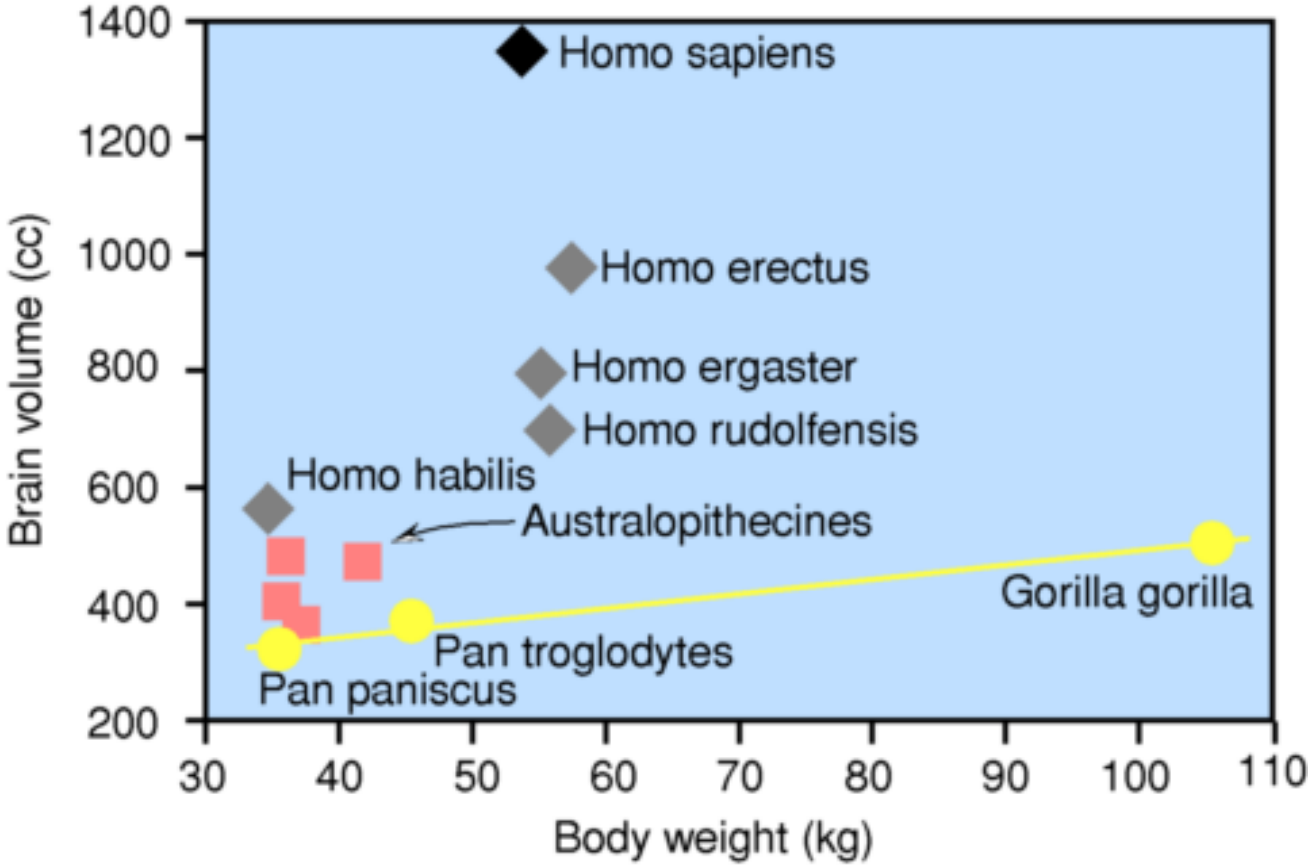
HOMINOÏDES

Hyalobatidés	Hyalobatinés	Siamang et Gibbon
Pongidés	Ponginés	Orang outan
Hominidés	Paninés	Gorille et Chimpanzé
Homininés	Homo	

HOMINIDÉS

		Cerveau (cm3)	Taille (m)
Australopithèques	-2,5/-0,750 (Lucy)	300-400	1,10
Homo habilis (outils)	-1,8M/-0,750M	600-700	1,30-1,50
Homo erectus	-1,2M/-0,120M	800-1000	1,50-1,70
Anténéandertaliens (feu)	-0,750/-0,100M	1100-1400	1,60-1,70
Néandertaliens (sépultures)	-0,120/-0,035M	1200-1740	1,65-1,70
Homo sapiens (art)	-0,120M	1450-1650	1,60-1,80

An excess of 900 cm3 (unknow causes, tragic consequences)



Cellular scaling rules for primate brains

Suzana Herculano-Houzel, Christine E. Collins, Peiyan Wong, and Jon H. Kaas

PNAS 2007;104;3562-3567; originally published online Feb 20, 2007;
doi:10.1073/pnas.0611396104

Primates are usually found to have richer behavioral repertoires and better cognitive abilities than rodents of similar brain size. This finding raises the possibility that primate brains differ from rodent brains in their cellular composition. Here we examine the cellular scaling rules for primate brains and show that brain size increases approximately isometrically as a function of cell numbers, such that an 11× larger brain is built with 10× more neurons and ≈12× more nonneuronal cells of relatively constant average size. This isometric function is in contrast to rodent brains, which increase faster in size than in numbers of neurons. As a consequence of the linear cellular scaling rules, primate brains have a larger number of neurons than rodent brains of similar size, presumably endowing them with greater computational power and cognitive abilities.

allometry | brain size | evolution | number of neurons | number of glia

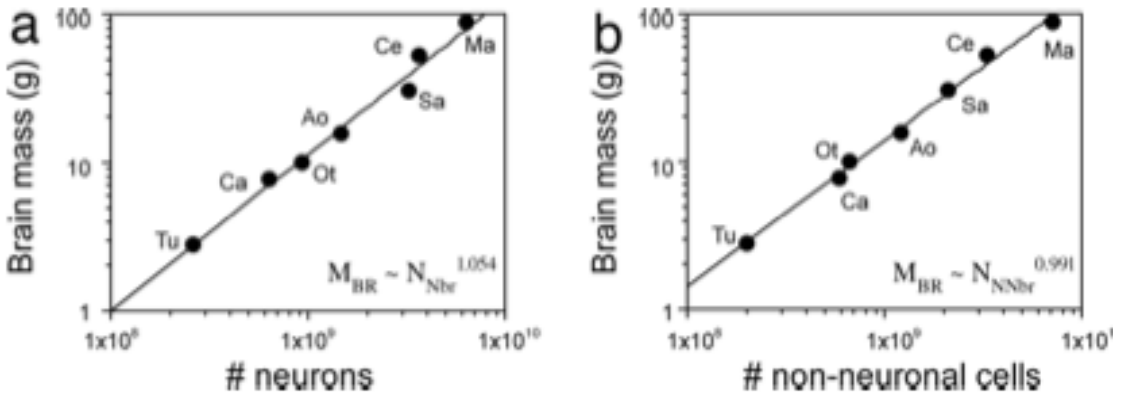


Table 1. Comparative cellular composition of the brain of the tree shrew and six primate species

Species	Body mass, g	Brain mass, g	Total neurons, $\times 10^6$	Total nonneurons, $\times 10^6$
Tree shrew	172.5 ± 3.5	2.752 ± 0.011	261.40	199.65
Marmoset	361.0 ± 1.4	7.780 ± 0.654	635.80 ± 115.73	590.74 ± 70.81
Galago	946.7 ± 102.6	10.150 ± 0.060	936.00 ± 115.36	666.59 ± 63.50
Owl monkey	925.0 ± 35.4	15.730	1,468.41	1,195.13
Squirrel monkey	n.a.	30.216	3,246.43	2,075.03
Capuchin monkey	3,340.0	52.208	3,690.52	3,297.74
Macaque monkey	3,900.0	87.346	6,376.16	7,162.90
Variation, macaque/marmoset	10.8×	11.2×	10.0×	12.1×

Species ordered by increasing brain size. Values are mean ± SD. n.a., not available.

NATURE REVIEWS | NEUROSCIENCE VOLUME 7 | NOVEMBER 2006 | 883

Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion

Arnold Kriegstein, Stephen Noctor and Verónica Martínez-Cerdeño

Abstract | The dramatic evolutionary expansion of the cerebral cortex of *Homo sapiens* underlies our unique higher cortical functions, and therefore bears on the ultimate issue of what makes us human. Recent insights into developmental events during early proliferative stages of cortical development indicate how neural stem and progenitor cells might interact to produce cortical expansion during development, and could shed light on evolutionary changes in cortical structure.

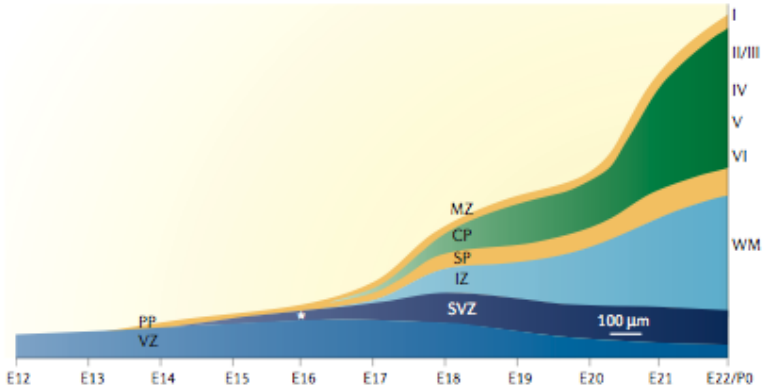


Figure 1 | **Histogenesis of the cerebral cortex.** This schematic drawing provides an approximate representation of the appearance and relative size of cortical structures between embryonic day (E)12 and E22 in the rat. At the onset of cortical histogenesis, the ventricular zone (VZ, blue), or neuroepithelium, 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 observations (S.N., V.M.-C. and A.K.) and measurements taken from sagittal sections shown in REF. 94 © (1991) Raven.

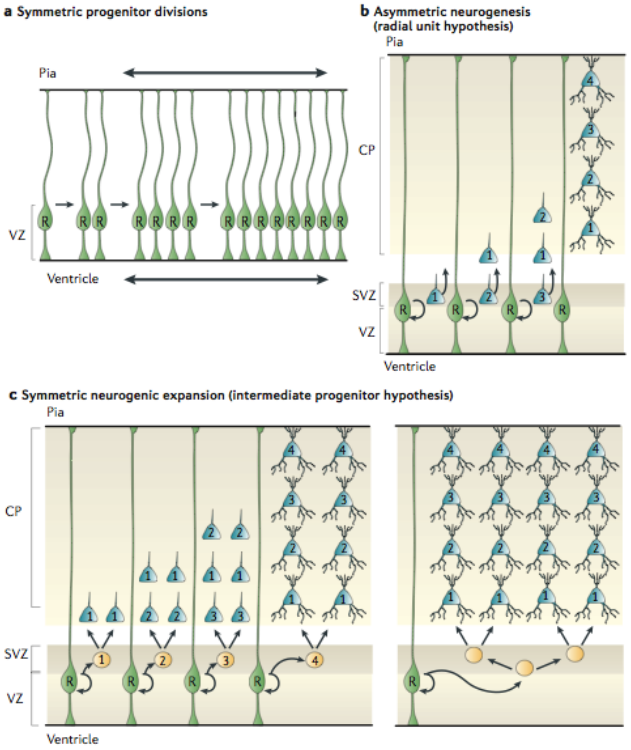


Figure 2 | **Patterns of cell division in the embryonic cortex.** Schematic drawings illustrating division patterns observed in the embryonic cortex during development. **a** | Symmetric progenitor divisions in the ventricular zone (VZ) increase the founder cell (radial glia (R), green) population. cells and produce g in a radial array ntermediate pro- f cells of the same the same cortical Z before terminal rated for a given mbered cells 1–4 ns.

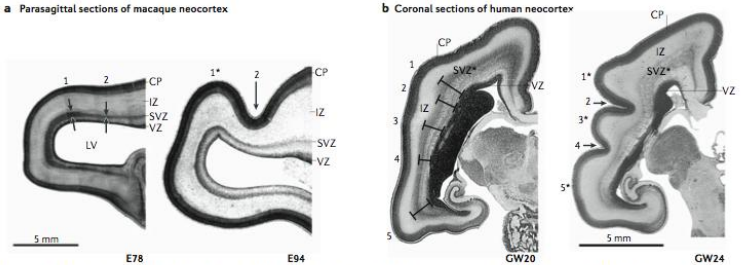
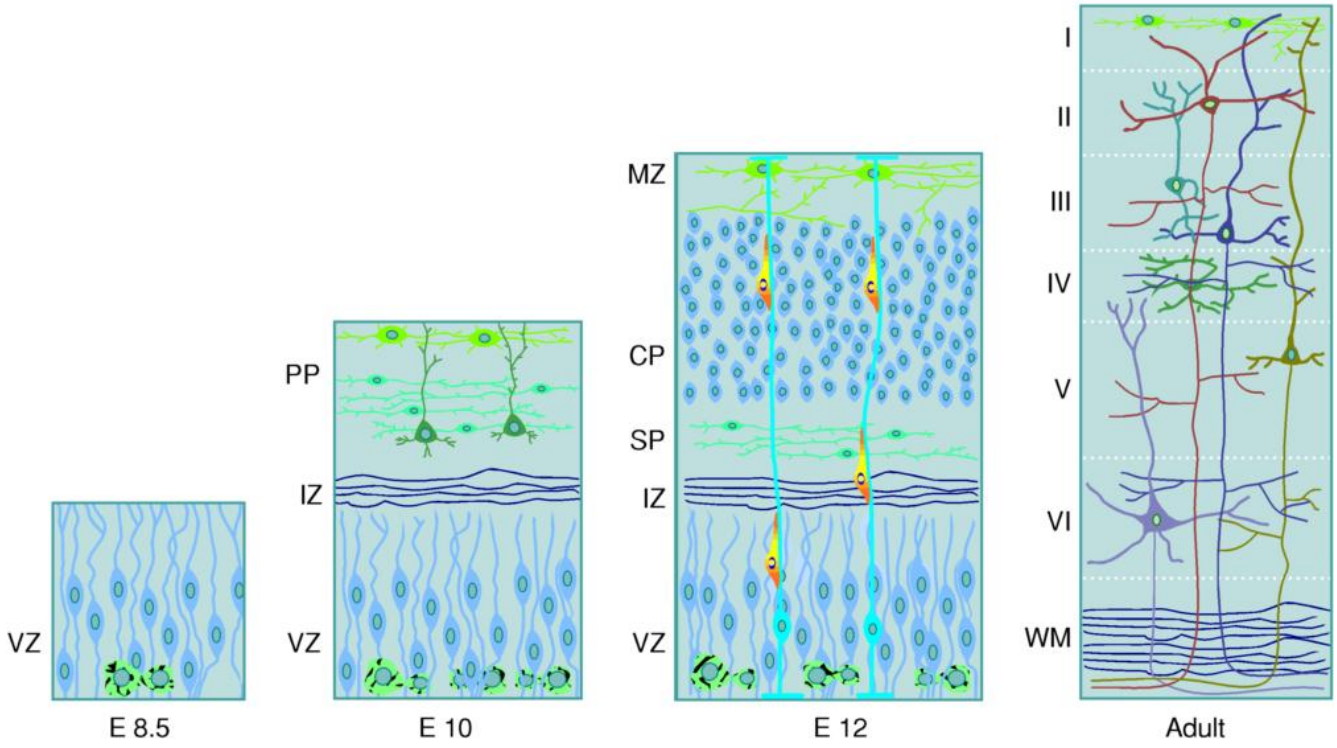
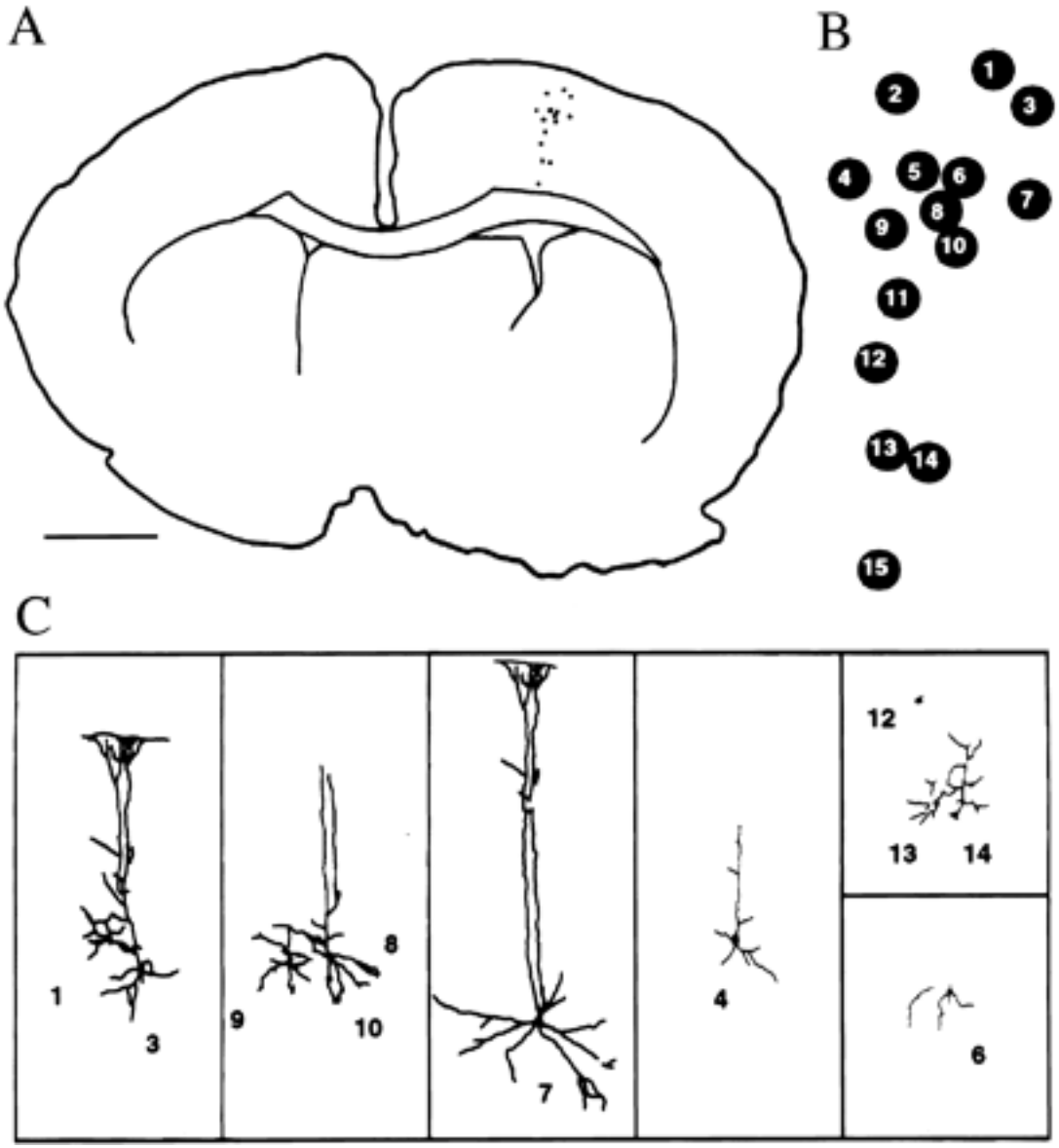


Figure 3 | **SVZ size predicts sites of gyral and sulcal formation.** The subventricular zone (SVZ) is thicker in areas underlying gyrus formation and thinner in areas underlying sulcus formation. **a** | Parasagittal sections of the macaque occipital lobe. In embryonic day (E) 78 macaque cortex, a thickened SVZ (indicated by black arrows under 1) presages the gyral formation that can be seen just over 2 weeks later at E94 (1*). By contrast, a much thinner SVZ (indicated by black arrows under 2) is located under a region of sulcal formation (2, arrow). **b** | Similar features are observed in coronal sections of the developing human cortex. At gestational week (GW) 20, areas of thickened SVZ (indicated by brackets under 1, 3 and 5) presage gyral formation that can be seen in the same region of the cortex four weeks later at GW24. By contrast, areas of thinner SVZ (indicated by brackets under 2 and 4) are located under regions of sulcal formation that are observed four weeks later at GW24. CP, cortical plate; IZ, intermediate zone; LV, lateral ventricle; SVZ*, encompasses stratified transitional fields 1–6; VZ, ventricular zone. Panel **a** modified, with permission, from REF. 56 © (2002) Oxford Univ. Press. Panel **b** modified, with permission, from REF. 63 © (2005) Taylor & Francis.

FIG 16.6

INSIDE OUT MIGRATION

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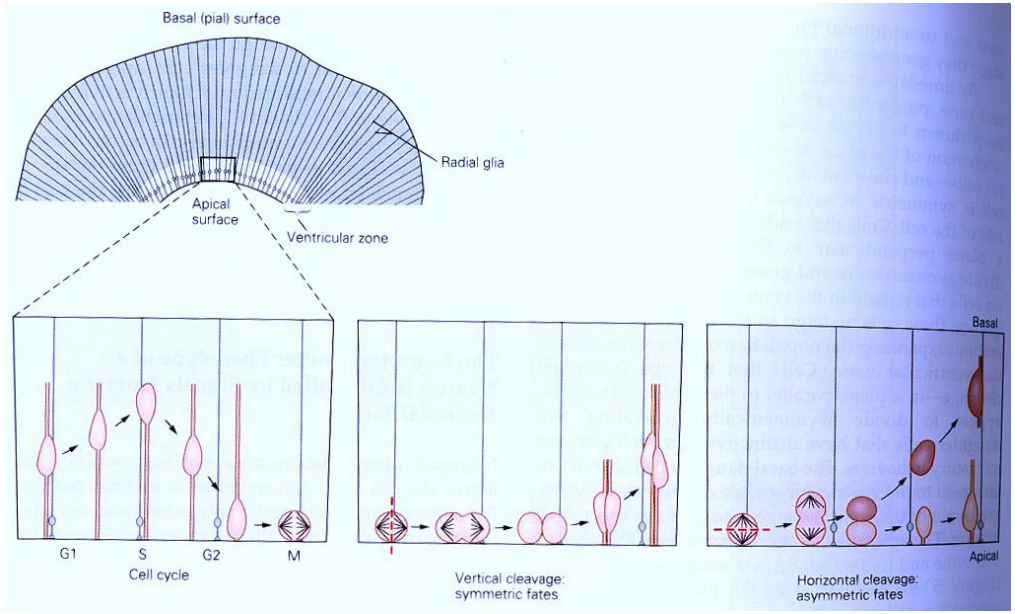
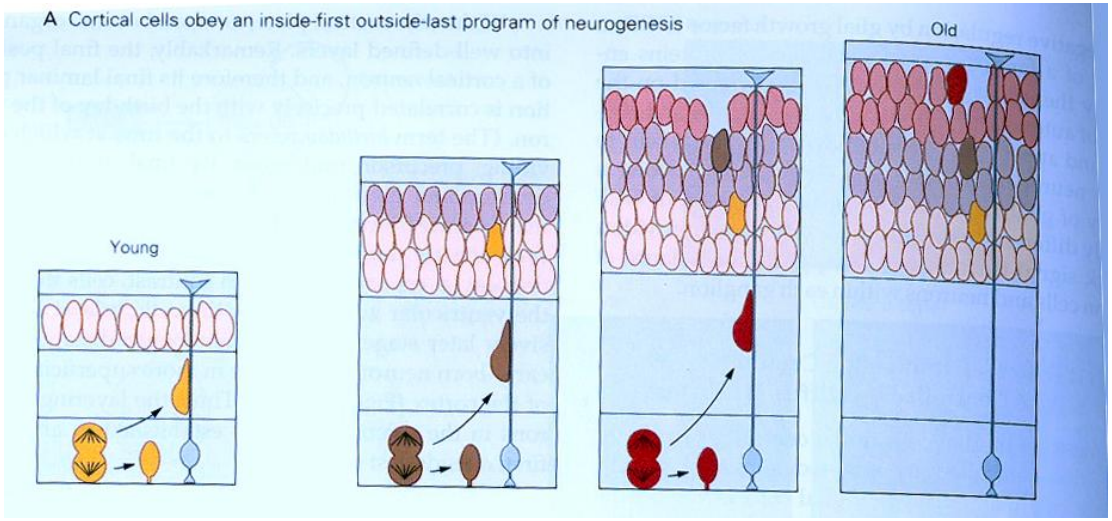
Production des cellules nerveuses: la zone ventriculaire



Migration radiaire et développement « inside-out » du cortex



Development of the human cerebral cortex: Boulder Committee revisited

Irina Bystron[*‖], *Colin Blakemore*[*] *and Pasko Rakic*[§]

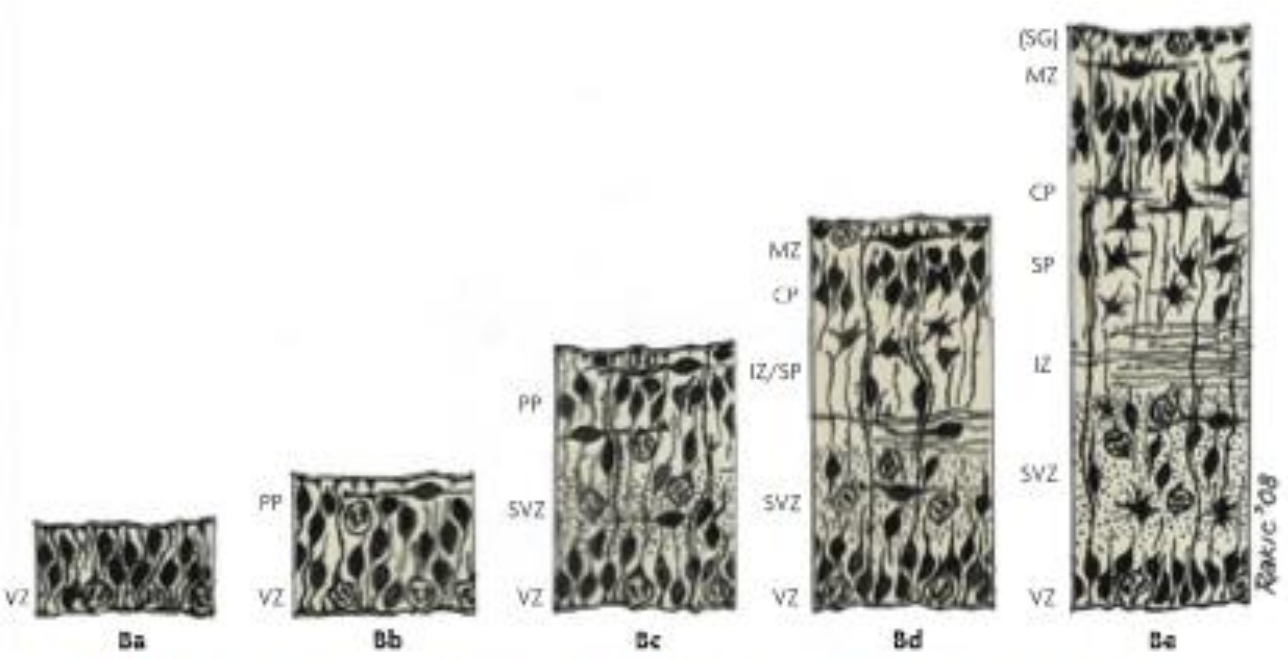


Figure 1 | **The Boulder Committee's 1970 schematic model of human neocortical development, and a proposed revision. A** | The Boulder Committee's original summary diagram of neocortical development. **B** | Our revised version. Comparison of these two illustrations summarizes our redefinition of the sequence of events and the formation of transient compartments, including the preplate (PP) and the intermediate and subplate zones (IZ and SP). The panels in part **B** correspond to the following approximate ages (for the lateral part of the dorsal telencephalon): **a**: embryonic day (E) 30; **b**: E31–E32; **c**: E45; **d**: E55; **e**: gestational week 14. CP, cortical plate; I & IZ, intermediate zone; M & MZ, marginal zone; S & SVZ, subventricular zone; (SG), subpial granular layer (part of the MZ); V & VZ, ventricular zone. Part **A** reproduced, with permission, from REF. 4 © (1970) Wiley.

nature Vol 437|1 September 2005|doi:10.1038/nature04103

PROGRESS

Molecular insights into human brain evolution

Robert Sean Hill[1] & Christopher A. Walsh[1]

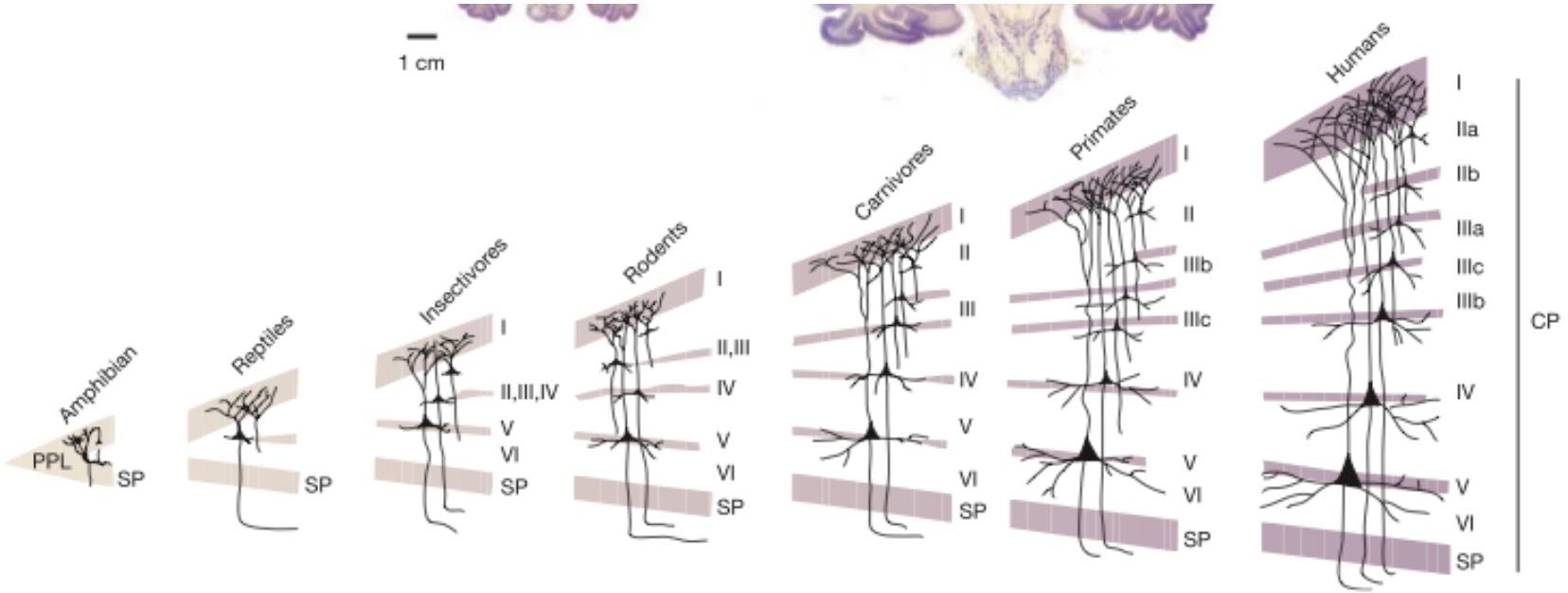
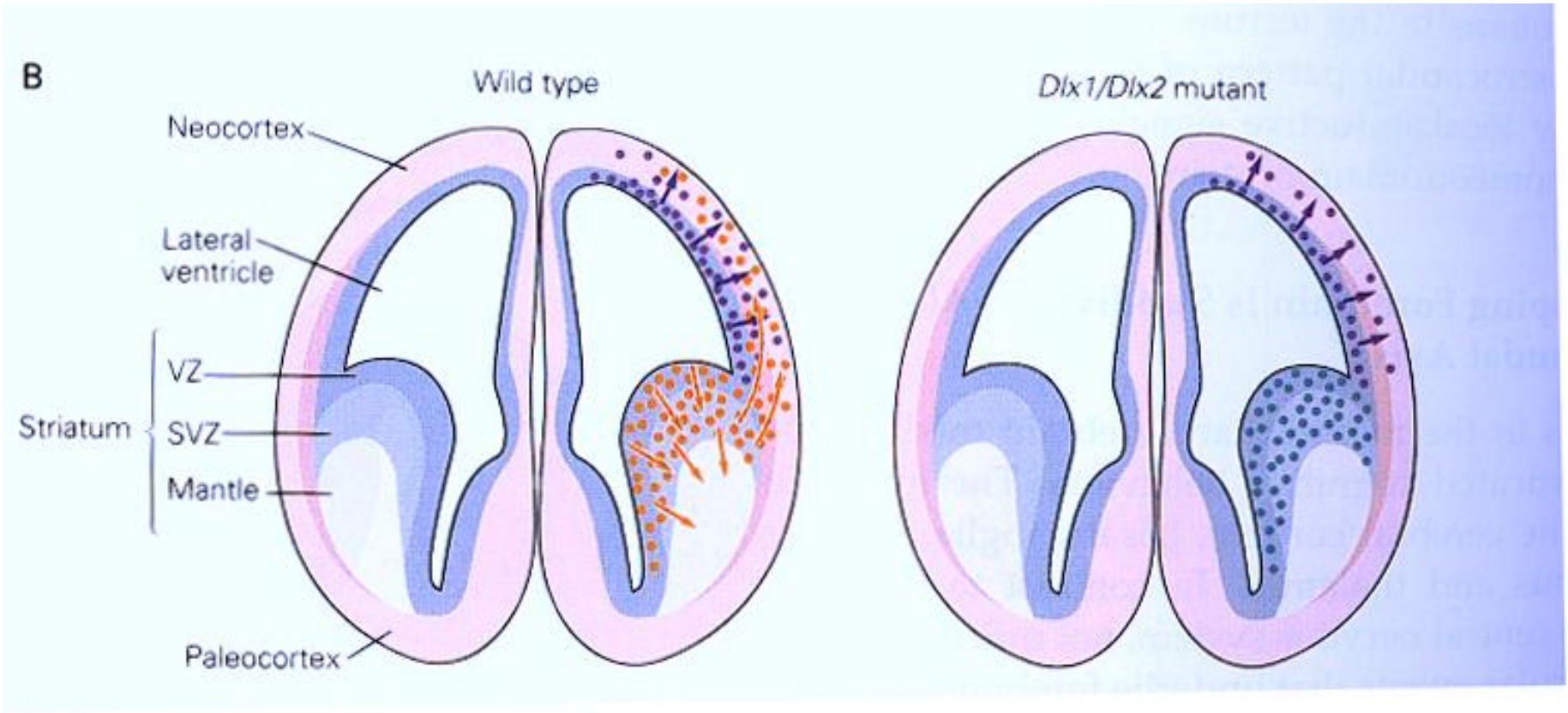


Figure 1 | Differences in cerebral cortical size are associated with differences in the cerebral cortex circuit diagram. The top panel shows side views of the brain of a rodent (mouse), a chimpanzee and a human to show relative sizes. The middle panel shows a cross-section of a human and chimpanzee brain, with the cellular composition of the cortex illustrated in the bottom panel (adapted from ref. 5). The cerebral cortex derives from two developmental cell populations: the primordial plexiform layer (PPL) and the cortical plate (CP). The primordial plexiform layer seems to be homologous to simple cortical structures in Amphibia and Reptilia, and appears first temporally during mammalian brain development. The cortical plate develops as a second population that splits the primordial plexiform layer into two layers (layer I at the top and the subplate (SP) at the bottom; numbering follows the scheme of ref. 31). Cortical-plate-derived cortical layers are added developmentally from deeper first (VI, V) to more superficial (III, II) last. Cortical-plate-derived cortical layers are progressively elaborated in mammals with larger brains (for example, insectivores have a single layer II/III/IV that is progressively subdivided into II, III, IV, then IIa, IIb, and so on), so that humans have a larger proportion of these late-derived neurons, which project locally or elsewhere within the cortex. Images from the top and middle panels are from the Comparative Brain Atlas (http://www.brainmuseum.org).

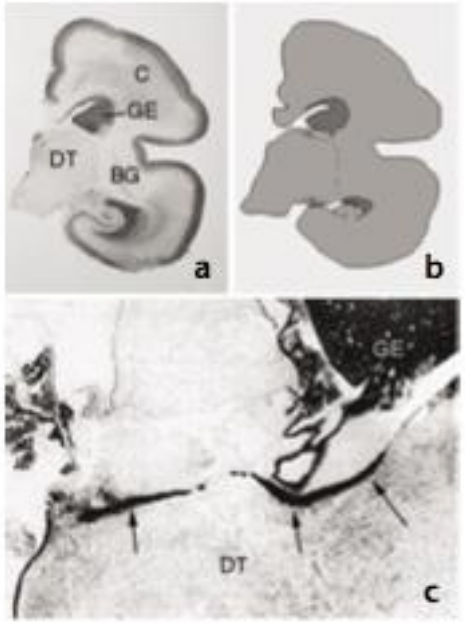
Migration tangentielle des interneurones GABAergiques corticaux



Telencephalic origin of human thalamic GABAergic neurons

nature neuroscience • volume 4 no 9 • september 2001

Kresimir Letinic and Pasko Rakic



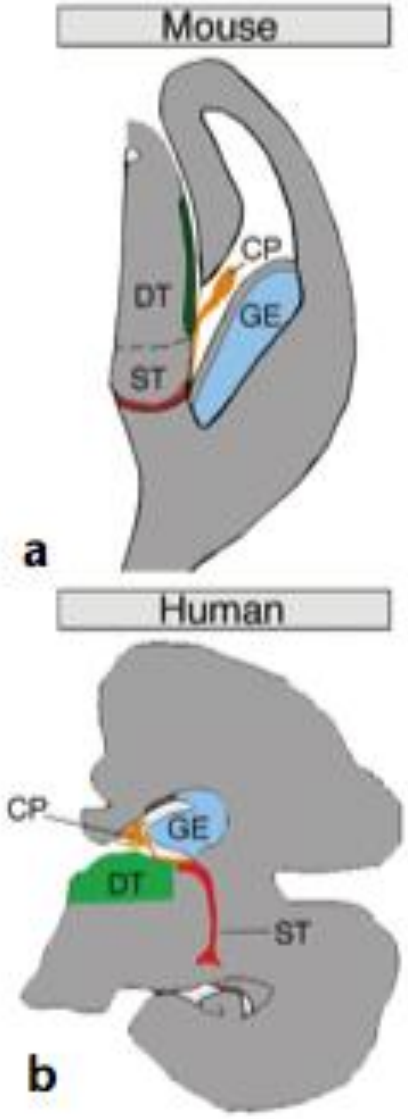
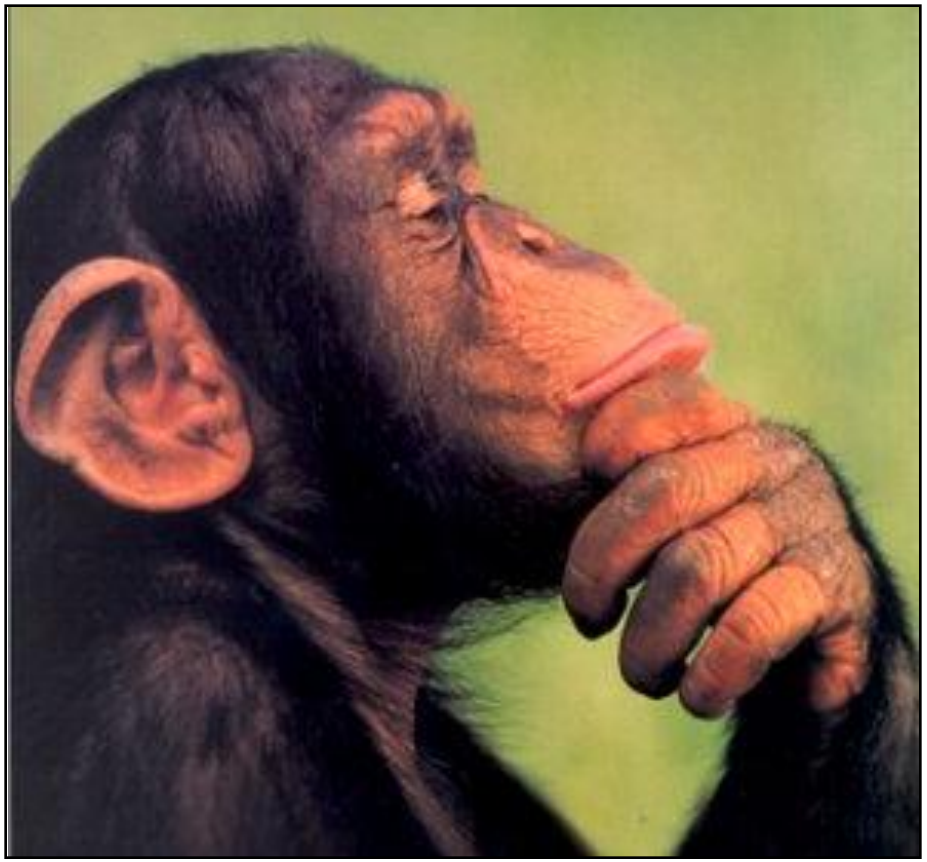
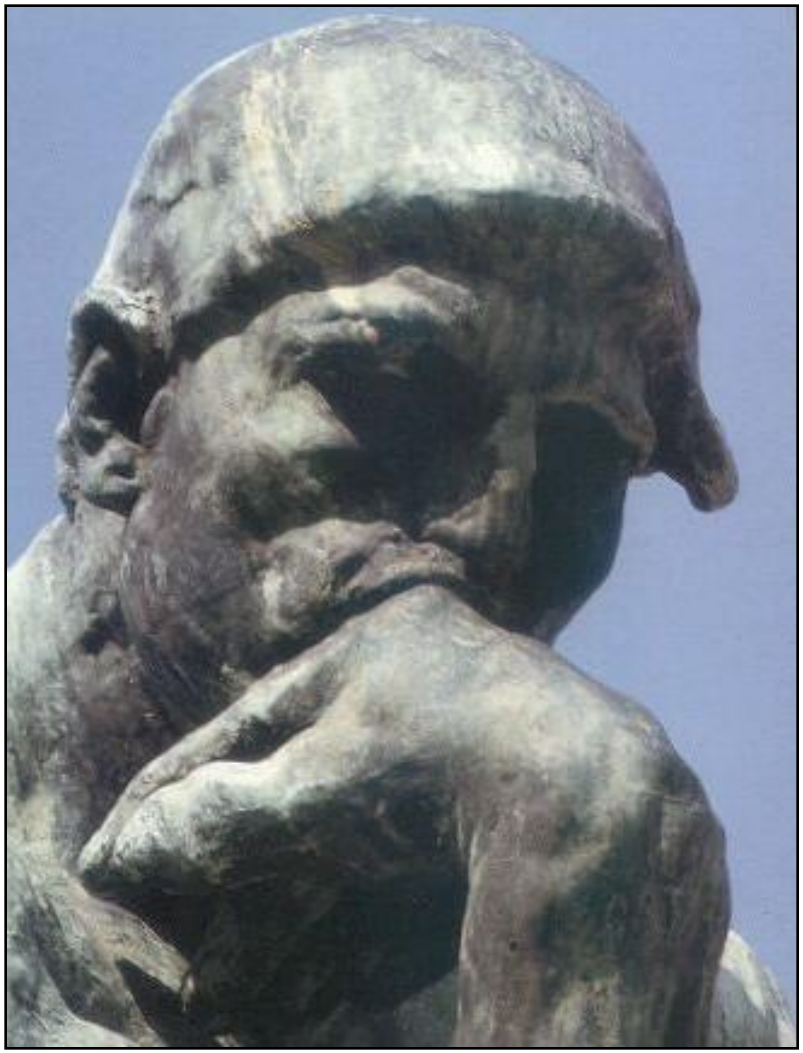
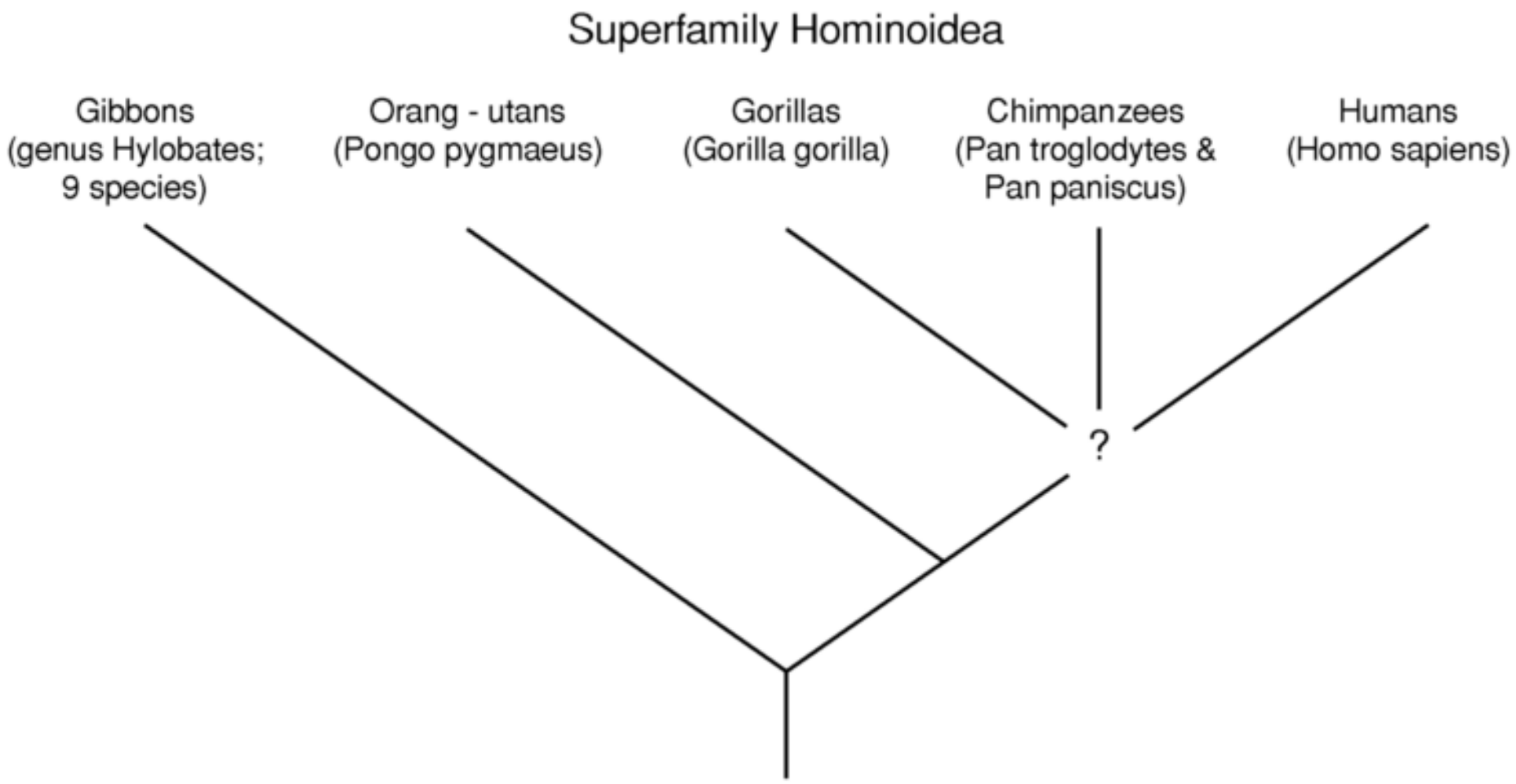


Fig. 1. Localization of the GE–DT migratory stream in the fetal human forebrain. (**a**) Nissl-stained coronal section through a 20-week-old human forebrain shows the localization of major telencephalic structures. C, cortex; BG, basal ganglia. (**b**) Diagram of section in (**a**) illustrating the GE–DT migratory stream (arrows). (**c**) Low magnification image of migratory stream in a Nissl-stained section (arrows).







Neanderthal

416 Cell 134, 416–426, August 8, 2008 ©2008 Elsevier Inc.

A Complete Neandertal Mitochondrial Genome Sequence Determined by High-Throughput Sequencing

Richard E. Green,[1,*] Anna-Sapfo Malaspinas,[2] Johannes Krause,[1] Adrian W. Briggs,[1] Philip L.F. Johnson,[3] Caroline Uhler,[4] Matthias Meyer,[1] Jeffrey M. Good,[1] Tomislav Maricic,[1] Udo Stenzel,[1] Kay Prüfer,[1] Michael Siebauer,[1] Hernán A. Burbano,[1] Michael Ronan,[5] Jonathan M. Rothberg,[6] Michael Egholm,[5] Pavao Rudan,[7] Dejana Brajković,[8] Željko Kućan,[7] Ivan Gušić,[7] Mårten Wikström,[9] Liisa Laakkonen,[10] Janet Kelso,[1] Montgomery Slatkin,[2] and Svante Pääbo[1]

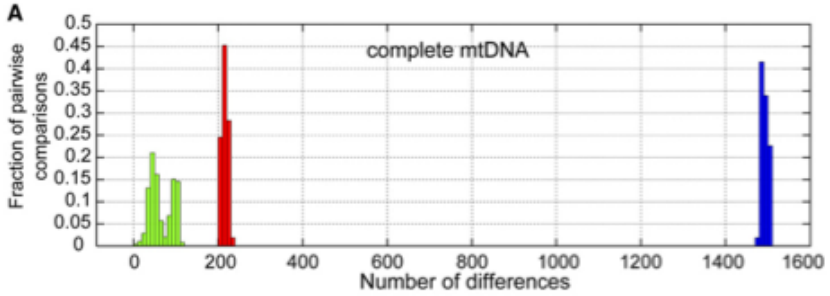


Table 1. Number of Synonymous and Nonsynonymous Substitutions in Each Protein-Coding mtDNA Gene Assigned to the Neandertal or Extant Human Lineage by Parsimony with the Chimpanzee as an Outgroup

	Neandertal		Extant Human	
Gene	Synonymous	Nonsynonymous	Synonymous	Nonsynonymous
ND1	4	2	5	2
ND2	6	1	3	1
COX1	8	0	8	0
COX2	0	0	3	4
ATP8	2	1	3	0
ATP6	3	3	1	2
COX3	1	1	3	1
ND3	1	1	5	1
ND4L	3	1	1	0
ND4	5	0	9	0
ND5	7	5	6	4
ND6	1	1	1	0
CYTB	3	4	9	3
Total	44	20	57	18

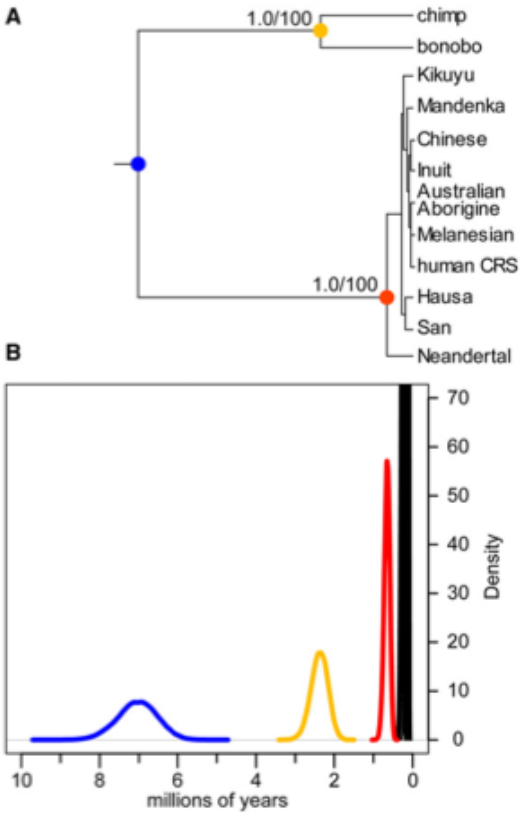


Figure 3. Phylogenetic Tree and Divergence Time Estimate of mtDNA Sequences

(A) Bayesian phylogenetic tree of complete mtDNA sequences of the Neandertal, 10 extant humans, one chimpanzee, and one bonobo. Identical topologies for the Neandertal and chimpanzee/bonobo split are produced by each tree-building method. The Bayesian posterior probability and the bootstrap support values are shown for two internal nodes.

(B) Posterior distribution of divergence times at each internal node using a 6–8 Mya for the ape/hominid divergence (blue node). The extant human divergences are shown in black, the Neandertal/human divergence in red, the chimpanzee/bonobo divergence in yellow, and the ape/hominid in blue.

Vol 437|1 September 2005|doi:10.1038/nature04023

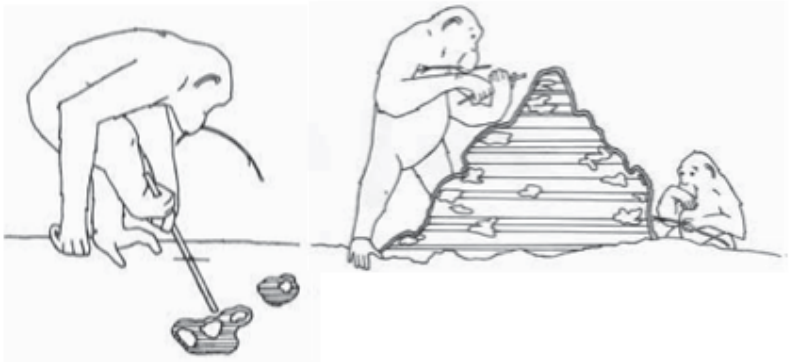
The second inheritance system of chimpanzees and humans

Andrew Whiten[1]

Half a century of dedicated field research has brought us from ignorance of our closest relatives to the discovery that chimpanzee communities resemble human cultures in possessing suites of local traditions that uniquely identify them. The collaborative effort required to establish this picture parallels the one set up to sequence the chimpanzee genome, and has revealed a complex social inheritance system that complements the genetic picture we are now developing.

Box 3 | A tool-set for harvesting termites

At many study sites, chimpanzees harvest termites using a single probing tool inserted into the sides of the insects' mounds. This skill has recently been shown to be acquired much earlier in young females, which spend more time than males closely observing the proficient fishing of their mothers[41]. Such evidence suggests that this skill is acquired by social learning. Recently, a study in the Goualougo Triangle, Republic of Congo, described chimpanzees approaching termite mounds already armed with appropriate tools, sometimes two different ones[23]. The first is a stout stick (left), which is thrust into the ground using both hands and often a foot, puncturing a tunnel into the nest about 30 cm beneath the ground. A more delicate probe is then inserted into the tunnel to extract termites; this probe is first prepared by biting it to length, manually stripping the leaves and pulling it through the teeth to create an effective 'brush-tip'. This brush-tip method, like the use of the puncturing stick, is not known for chimpanzees harvesting termites elsewhere in Africa. The drawing on the right shows a female ready with such a probe in her mouth, and holding a third tool-type used for perforating termite mounds. Images drawn by D. Morgan from a video by C. Sanz and D. Morgan.



Box 2 | The different social conventions of neighbours

The 'grooming hand-clasp' was the first social custom to be identified in chimpanzees, routine at Mahale but absent at Gombe, just 100 km away. Recently, it was discovered that although the Mahale K community (photographed, but now extinct) used the originally described palm-to-palm convention (left), members of the neighbouring M community typically show a different, wrist-to-wrist hand-clasp (right)[39]. Moreover, the relative status of the groomers is apparent in the placement of the hands. Gwekulo, an adult female that transferred from the K to the M community, was observed to adopt the preferred wrist-to-wrist pattern of her new partners some of the time, but also to influence them to occasionally make palm-to-palm contact; however, she made delicate adjustments to do so, flexing her elbow in the local customary way, rather than keeping it straight, which was the norm in K community[40].

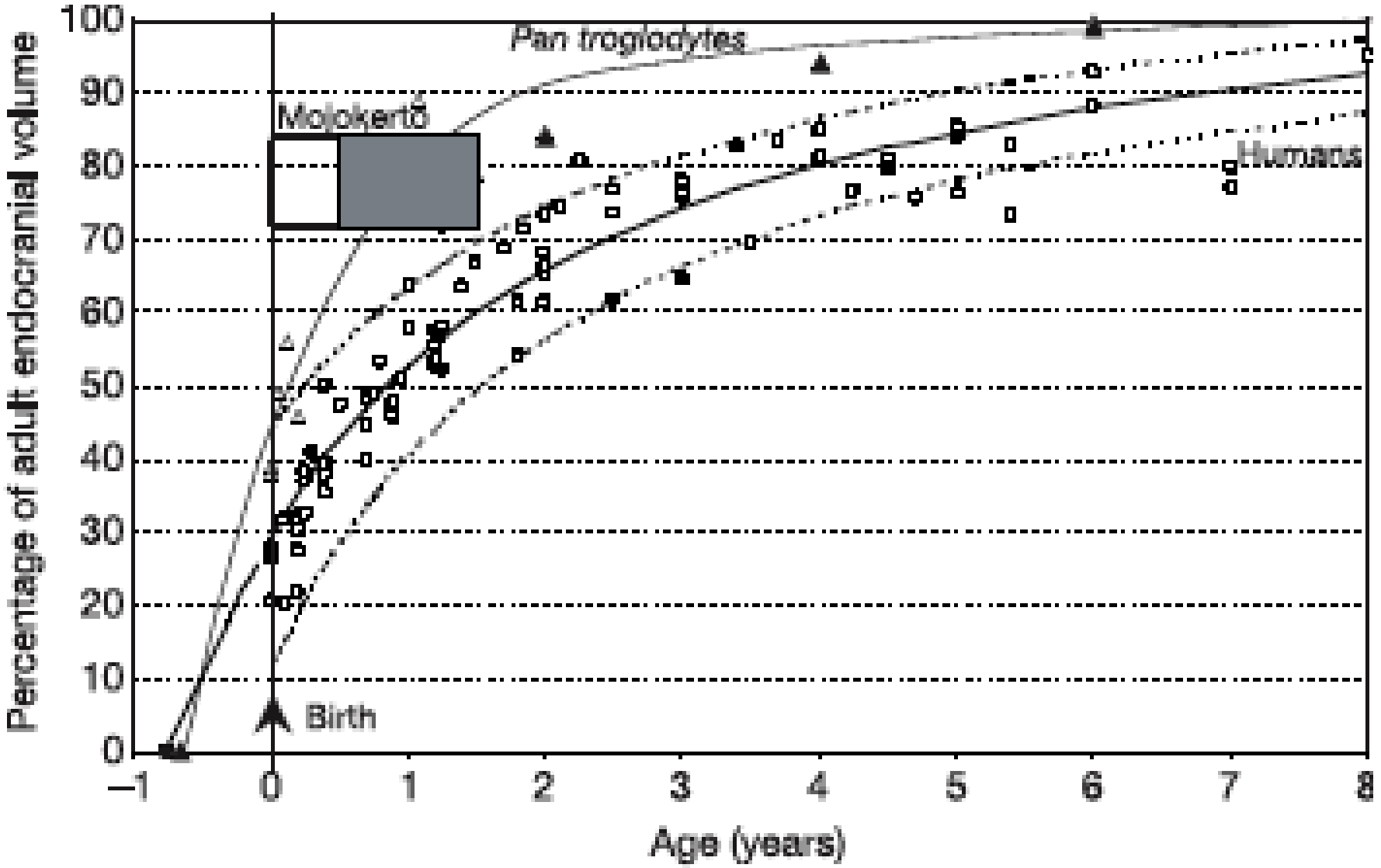
Box 2 Figure | Hand-clasp styles. Left, palm-to-palm (drawing by D. Bygott). Right, wrist-to-wrist (courtesy of M. Nakamura).

Early brain growth in *Homo erectus* and implications for cognitive ability

Nature, 431, p 299, 2004

H. Coqueugniot[1], J.-J. Hublin[2], F. Veillon[3], F. Houët[1] & T. Jacob[4]

Epigenetics, critical periods ?



NEWS & VIEWS

EVOLUTIONARY BIOLOGY

Human brain gene wins genome race

Chris P. Ponting and Gerton Lunter

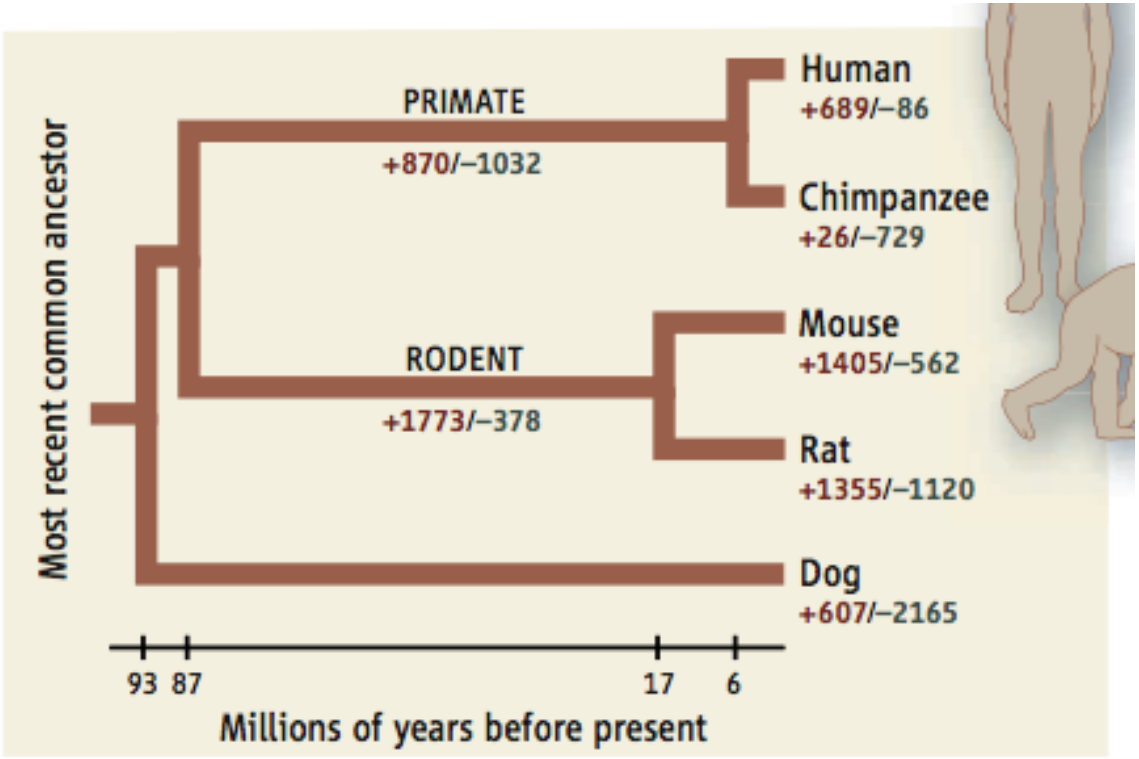
The differences in brain size and function that separate humans from other mammals must be reflected in our genomes. It seems that the non-coding 'dark matter' of genomes harbours most of these vital changes.

29 JUNE 2007 VOL 316 SCIENCE

Relative Differences: The Myth of 1%

–JON COHEN

Genomewise, humans and chimpanzees are quite similar, but studies are showing that they are not as similar as many tend to believe



The 6.4% difference. Throughout evolution, the gain (+) in the number of copies of some genes and the loss (–) of others have contributed to human-chimp differences.

Ponctual mutations
Insertion deletions
Splice modifications
Enhancer/promoter modifications
Gene copies and gene deletion
Non-coding elements
…..

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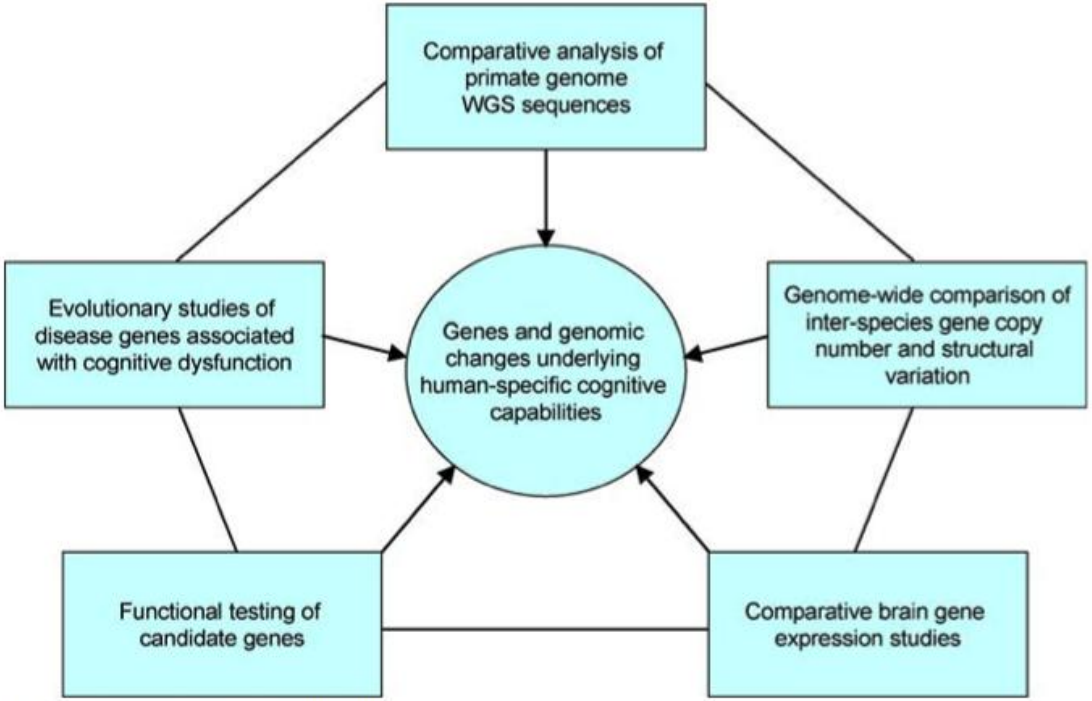
Review

The Jewels of Our Genome: The Search for the Genomic Changes Underlying the Evolutionarily Unique Capacities of the Human Brain

James M. Sikela



DOI: 10.1371/journal.pgen.0020080.g004

Figure 4. Strategies for Identification of Genes and Genomic Changes Underlying the Evolution of Human-Specific Cognitive Capabilities

Listed are various strategies that, either independently or in combination, have the potential to identify gene or genomic changes and pathways relevant to the evolution of human-specific cognitive abilities.

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PLoS GENETICS

Review

The Jewels of Our Genome: The Search for the Genomic Changes Underlying the Evolutionarily Unique Capacities of the Human Brain

James M. Sikela

Table 1. Single-Gene Studies Potentially Related to the Evolution of Human Cognitive Abilities

Gene	Unique Evolutionary Feature	Reference
FOXP2	Implicated in language deficit	[14]
ASPM	Implicated in change in brain size	[64]
MCPH1	Implicated in change in brain size	[68]
PDYN	Human-specific alteration of regulatory region	[15]
GLUD2	Implicated in ape brain evolution	[69]
COX8	Potentially related to increased energy demand of brain	[70]
CMAH	A sialic acid hydroxylase activity lost in human lineage	[71]

Table 2. Comparative Brain Gene Expression Studies

Tissue	Species Compared	Reference
Cerebral cortex	Human, chimp, rhesus	[72]
Anterior cingulate cortex	Human, chimp, gorilla, macaque	[73]
Brain frontal cortex	Human, chimp, orangutan, macaque	[74]
Prefrontal cortex	Human, chimp, macaque, marmoset	[75]
Brain, several others	Human, chimp	[22]
Brain regions	Human, chimp	[21]

Molecular evolution of *FOXP2*, a gene involved in speech and language

Wolfgang Enard*, Molly Przeworski*, Simon E. Fisher†, Cecilia S. L. Lai†, Victor Wiebe*, Takashi Kitano*, Anthony P. Monaco† & Svante Pääbo*

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NATURE | VOL 418 | 22 AUGUST 2002 | www.nature.com/nature

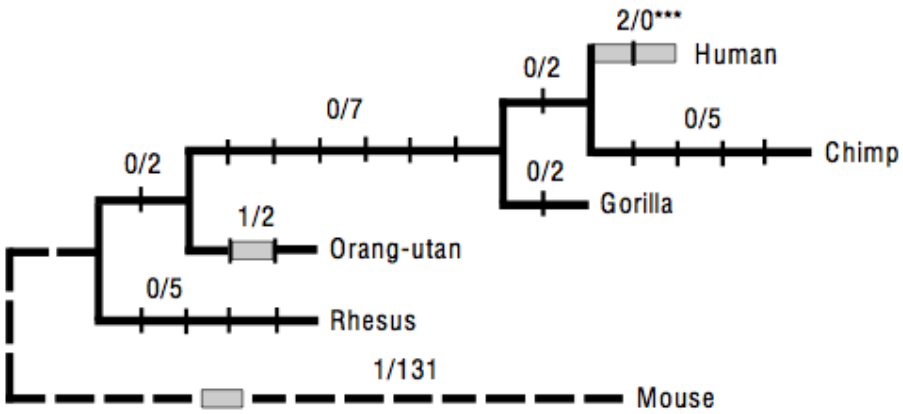


Figure 2 Silent and replacement nucleotide substitutions mapped on a phylogeny of primates. Bars represent nucleotide changes. Grey bars indicate amino-acid changes.

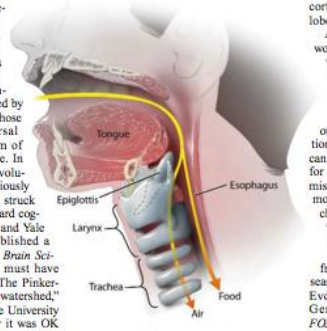
Individuals with disruption of *FOXP2* have multiple difficulties with both expressive and receptive aspects of language and grammar, and the nature of the core deficit remains a matter of debate[18–20]. Nevertheless, a predominant feature of the phenotype of affected individuals is an impairment of selection and sequencing of fine orofacial movements[18], an ability that is typical of humans and not present in the great apes. We speculate that some human-specific feature of *FOXP2*, perhaps one or both of the amino-acid substitutions in exon 7, affect a person's ability to control orofacial movements and thus to develop proficient spoken language. If this speculation is true, then the time when such a *FOXP2* variant became fixed in the human population may be pertinent with regard to the evolution of human language. We estimated this time point using a likelihood approach. Under a model of a randomly mating population of constant size, the most likely date since the fixation of the beneficial allele is 0, with approximate 95% confidence intervals of 0 and 120,000 years. Our point-estimate of 0

27 FEBRUARY 2004 VOL 303 SCIENCE

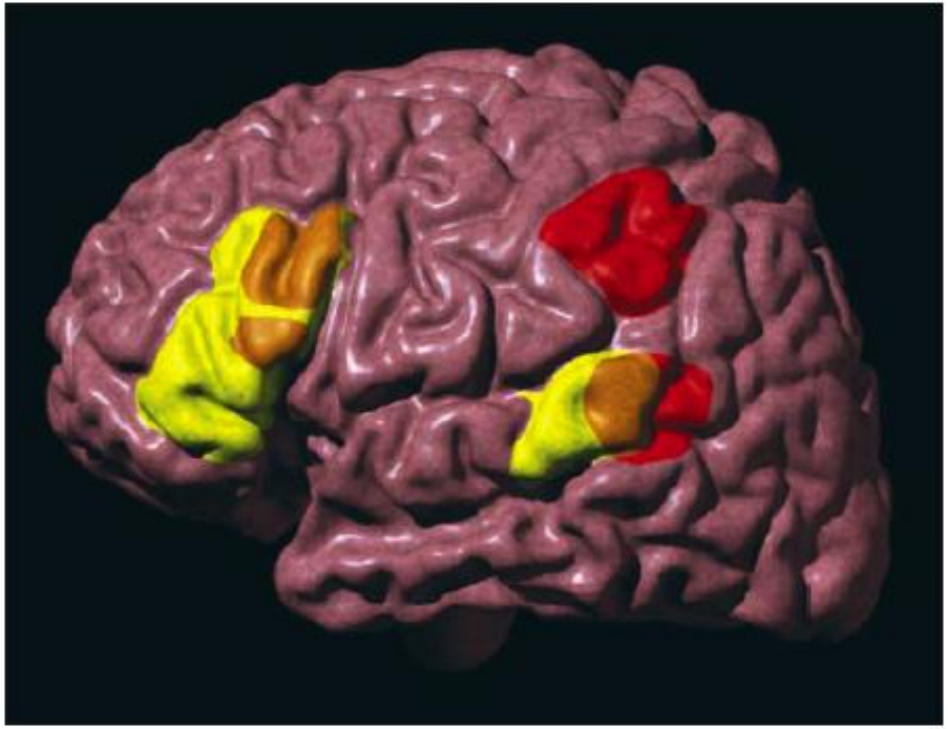
The Origin of Speech

–CONSTANCE HOLDEN

How did the remarkable ability to communicate in words first evolve? Researche probing the neurological basis of language are focusing on seemingly unrelate abilities such as mimicry and movement



Dangerous talk. Side view of human vocal tract shows that because of our lowered larynx, food and drink must pass over the trachea, risking a fall into the lungs if the epiglottis is open.



Wired for imitation? Classic language areas—Broca's and Wernicke's (yellow)—overlap (orange) with areas critical for imitation (red).

Current Biology 18, 354–362, March 11, 2008 ©2008 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2008.01.060

Impaired Synaptic Plasticity and Motor Learning in Mice with a Point Mutation Implicated in Human Speech Deficits

Matthias Groszer,[1] David A. Keays,[1] Robert M.J. Deacon,[2] Joseph P. de Bono,[3] Shweta Prasad-Mulcare,[4] Simone Gaub,[5] Muriel G. Baum,[6] Catherine A. French,[1] Jérôme Nicod,[1] Julie A. Coventry,[1] Wolfgang Enard,[7] Martin Fray,[8] Steve D.M. Brown,[8] Patrick M. Nolan,[8] Svante Pääbo,[7] Keith M. Channon,[3] Rui M. Costa,[4] Jens Eilers,[6] Günter Ehret,[5] J. Nicholas P. Rawlins,[2] and Simon E. Fisher[1,*]

Hand and mouth. Chimps gesture with both face and hands to help express themselves.

Human specific loss of olfactory receptor genes

Yoav Gilad*†‡, Orna Man†, Svante Pääbo*, and Doron Lancet‡

Table 2. Relative rates of OR gene silencing

	Human	Chimp	Gorilla	Orang	Rhesus
Fraction of OR pseudogenes, %	54	32	28	32	36
Gene silencing rate relative to the mean*	3.28	0.92	0.72	0.89	0.66
FET†	0.00003	1	0.675	0.871	0.213
Gene silencing rate relative to mean, human excluded‡	4.29	1.20	0.94	1.17	0.87
FET	0.00001	0.771	1	0.715	0.757

3324–3327 | PNAS | March 18, 2003 | vol. 100 | no. 6

*Gene silencing rate on a specific lineage relative to the mean rate of the entire phylogeny.

†*P* values for Fisher's exact tests (FET) for the difference between the mean rate of OR pseudogene accumulation and the lineage-specific rates.

‡All specific lineages rates are relative to a mean rate, which is calculated excluding the human lineage.

Evolution of primate gene expression

Philipp Khaitovich, Wolfgang Enard, Michael Lachmann and Svante Pääbo

Abstract | It has been suggested that evolutionary changes in gene expression account for most phenotypic differences between species, in particular between humans and apes. What general rules can be described governing expression evolution? We find that a neutral model where negative selection and divergence time are the major factors is a useful null hypothesis for both transcriptome and genome evolution. Two tissues that stand out with regard to gene expression are the testes, where positive selection has exerted a substantial influence in both humans and chimpanzees, and the brain, where gene expression has changed less than in other organs but acceleration might have occurred in human ancestors.

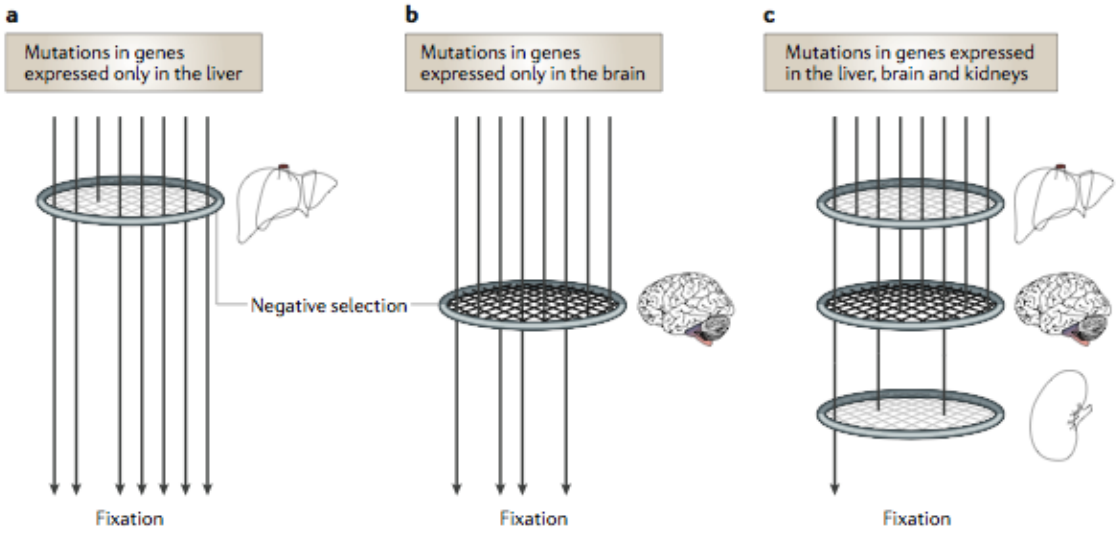


Figure 2 | **Negative selection adds up across tissues.** Each panel shows several mutations that affect expression levels of genes only in the liver (**a**), only in the brain (**b**), or in the brain, liver and kidneys (**c**). As there are more constraints acting in the brain than in the liver, more mutations are weeded out by negative selection in the brain than in the liver. For genes expressed in several tissues (**c**) a mutation needs only to be detrimental in one tissue to be weeded out by negative selection. Therefore, even more mutations are weeded out by negative selection, leading to the tendency for genes that are expressed in more tissues to be less diverged between species[29]. The same scenario would also apply for mutations that affect the protein sequence of genes[105].

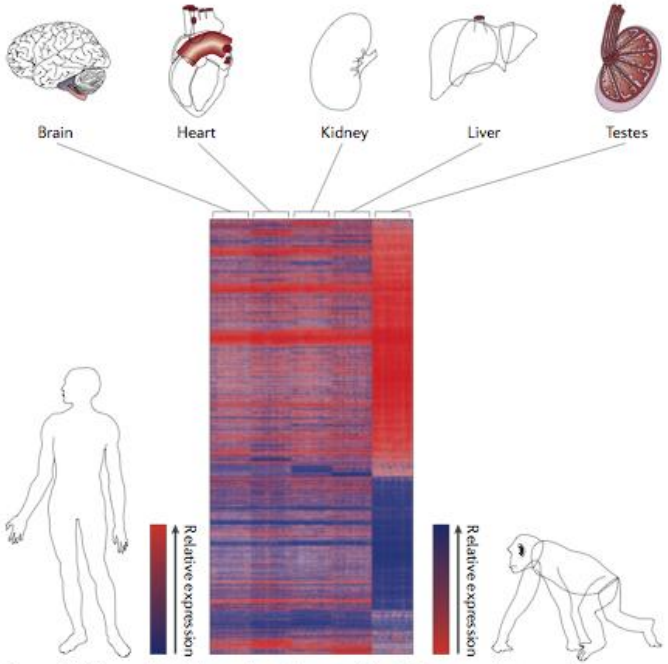


Figure 3 | **Hierarchical clustering of expression differences between humans and chimpanzees in five different tissues.** All probe sets differently expressed between humans and chimpanzees in at least one tissue are shown (data from REF. 29). Genes in red are more highly expressed in humans than in chimpanzees and genes in blue represent the reverse. Note that the testes exhibit many more differences than the other four tissues. Expression profile reproduced from REF. 29 © (2005) American Association for the Advancement of Science.

Tissue/cell specific regulatory elements
Mixture of cell types (particularly in the brain)
Deep sequencing versus µarrays

Conservation and evolution of gene coexpression networks in human and chimpanzee brains

Michael C. Oldham*†‡, Steve Horvath§¶, and Daniel H. Geschwind†‡‖

PNAS | November 21, 2006 | vol. 103 | no. 47 | 17973–17978

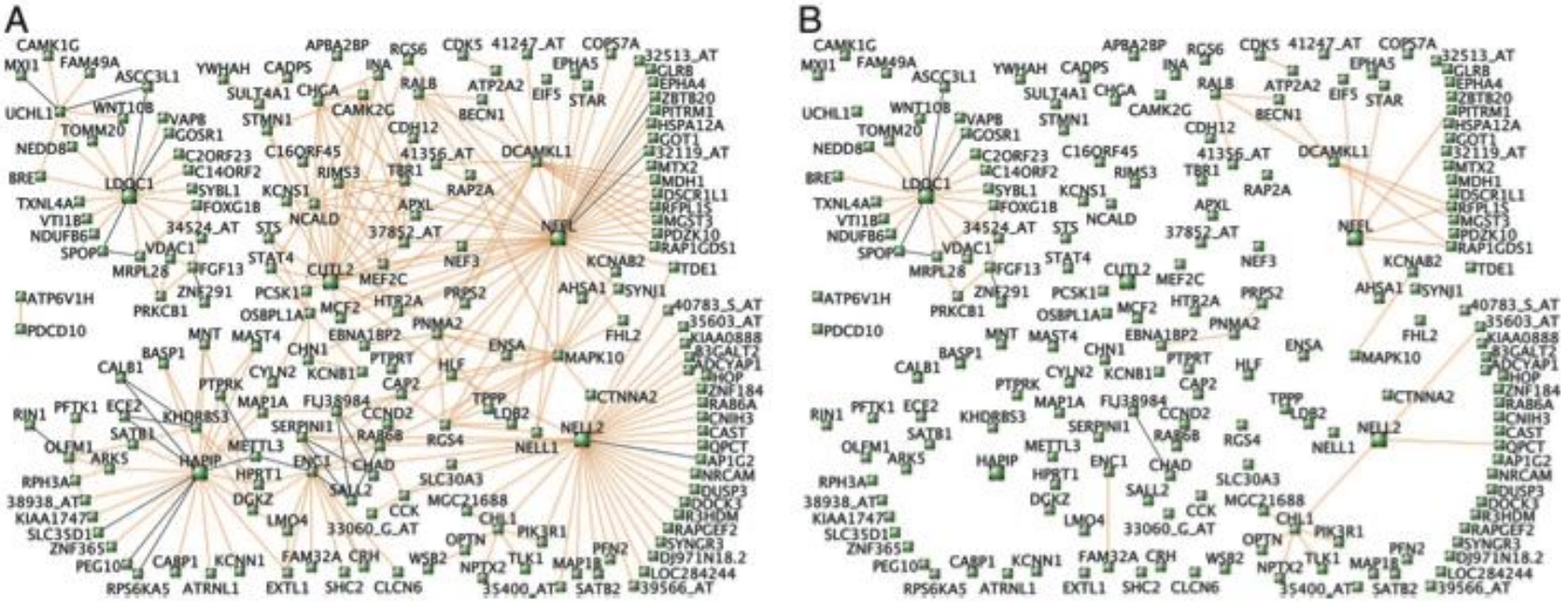


Fig. 3. Module visualization identifies hub genes and human-specific connections. (*A*) Three hundred pairs of genes with the greatest TO in humans are depicted for cortex (brown module). Genes with expression levels that are negatively correlated are connected by black lines. Where gene symbols are unknown, Affymetrix probe set IDs are shown (e.g., 37158_at). (*B*) Connections from *A* that are present in humans but absent in chimpanzees (see *Materials and Methods*).

Conservation and evolution of gene coexpression networks in human and chimpanzee brains

PNAS | November 21, 2006 | vol. 103 | no. 47 | 17973–17978

Michael C. Oldham*†‡, Steve Horvath§¶, and Daniel H. Geschwind†‡¶

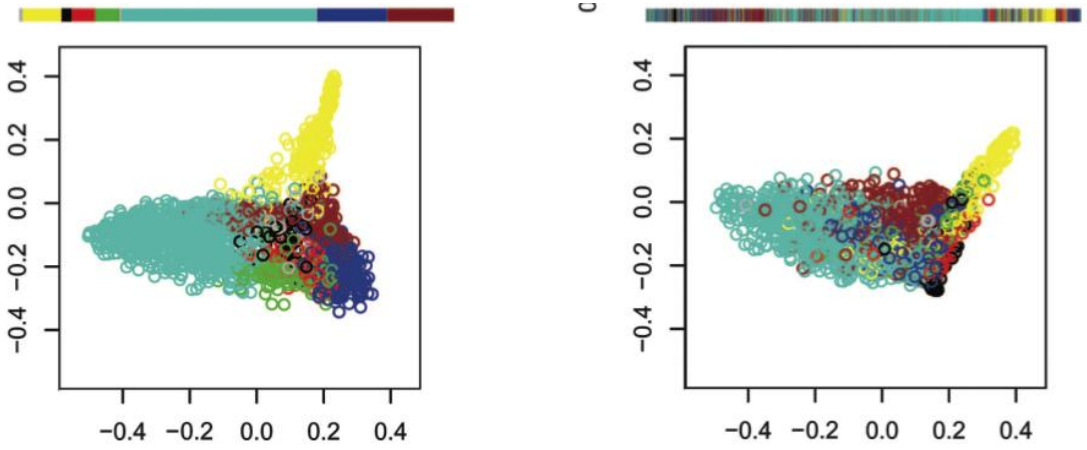


Fig. 1. Network analysis of gene expression in human and chimpanzee brains identifies distinct modules of coexpressed genes in human (*A*) and chimpanzee (*B*). (*A*) Dendrograms produced by average linkage hierarchical clustering of 2,241 genes based on TO (see *Supporting Text*). The red line in the human dendrogram indicates the height at which the tree was cut (0.95) to define modules. Modules were assigned colors as indicated in the horizontal bar beneath the human dendrogram. Genes in the chimpanzee network are depicted by using human module colors to represent the extent of module conservation. (*B*) Classical multidimensional scaling plots in three dimensions (color-coded as in *A*) depict the relative size and cohesion of modules in humans and chimpanzees.

The blue cortical module, which is nearly absent in chimpanzees, contains a number of genes involved in energy metabolism, including 11 members of the ETC. Previous work has shown that several proteins in the ETC, including three members of this module (*COX5A*, *COX6A2*, and *UQCRFS1*), have experienced accelerated evolution in anthropoid primates (24, 29, 30). Categories of genes that have high TO with ETC genes in human cerebral cortex, but not chimpanzee, include mitochondrial distribution and morphology (e.g., *IMMT* and *DNM1L*), synapse formation and vesicle docking (e.g., *DTNAI* and *RAB3A*), and cytoskeletal regulation (e.g., *ABI2*, *CYFIP2*, and *MAP1B*). It is likely that the dramatic increase in parallel processing power engendered by the expansion of the neocortex in humans has made concomitant demands upon energy metabolism; consequently, it is of significant interest to couple this process genetically to hallmarks of cortical activity such as cytoskeletal remodeling and synaptic plasticity. This module also contains several human-specific hub genes of unknown function, such as *FGF12*, *SLC30A9*, *ANKMY2*, and *KIAA1279*, which, given their network centrality, likely play important, yet underappreciated roles in human cortical function.

Energy metabolism
Mitochondrial distribution
Mitochondrial morphology
Synapse formation
Vesicle docking
Cytoskeletal regulation
…

Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution

Ralph Haygood[1,3], Olivier Fedrigo[1–3], Brian Hanson[1], Ken-Daigoro Yokoyama[1] & Gregory A Wray[1,2]

Surveys of protein-coding sequences for evidence of positive selection in humans or chimpanzees have flagged only a few genes known to function in neural or nutritional processes[1–5], despite pronounced differences between humans and chimpanzees in behavior, cognition and diet[6–8]. It may be that most such differences are due to changes in gene regulation rather than protein structure[9]. Here, we present the first survey of promoter (5′-flanking) regions, which are rich in *cis*-regulatory sequences, for evidence of positive selection in humans. Our results indicate that positive selection has targeted the regulation of many genes known to be involved in neural development and function, both in the brain and elsewhere in the nervous system, and in nutrition, particularly in glucose metabolism.

Splice

HUMAN MUTATION 28(10), 978–984, 2007

RESEARCH ARTICLE

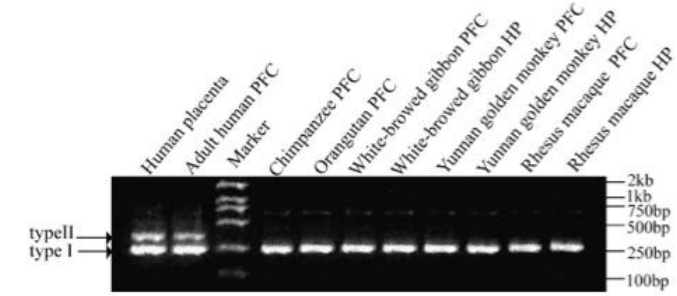
A Human-Specific Mutation Leads to the Origin of a Novel Splice Form of Neuropsin (KLK8), a Gene Involved in Learning and Memory

Zhi-xiang Lu,[1–3] Jia Peng,[1,2] and Bing Su[1,2*]

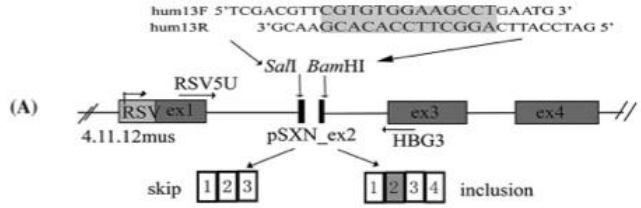
[1]*Key Laboratory of Cellular and Molecular Evolution, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China;* [2]*Kunming Primate Research Center, Chinese Academy of Sciences, Kunming, China;* [3]*Graduate School, Chinese Academy of Sciences, Beijing, China*

Neuropsin (kallikrein 8, KLK8) is a secreted-type serine protease preferentially expressed in the central nervous system and involved in learning and memory. Its splicing pattern is different in human and mouse, with the longer form (type II) only expressed in human. Sequence analysis suggested a recent origin of type II during primate evolution. Here we demonstrate that the type II form is absent in nonhuman primates, and is thus a human-specific splice form. With the use of an in vitro splicing assay, we show that a human-specific T to A mutation (c.71–127T>A) triggers the change of splicing pattern, leading to the origin of a novel splice form in the human brain. Using mutation assay, we prove that this mutation is not only necessary but also sufficient for type II expression. Our results demonstrate a molecular mechanism for the creation of novel proteins through alternative splicing in the central nervous system during human evolution. Hum Mutat 28(10), 978–984, 2007.

KEY WORDS: neuropsin; kallikrein 8; KLK8; alternative splicing; cognition; human evolution



tromorph of the RT-PCR result. The expected products of type I and type II were confirmed by
', prefrontal cortex.



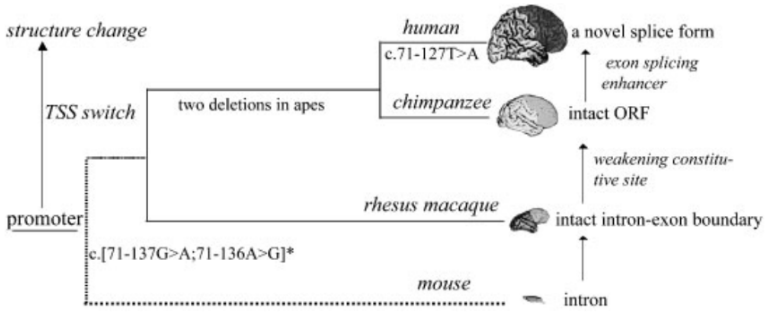


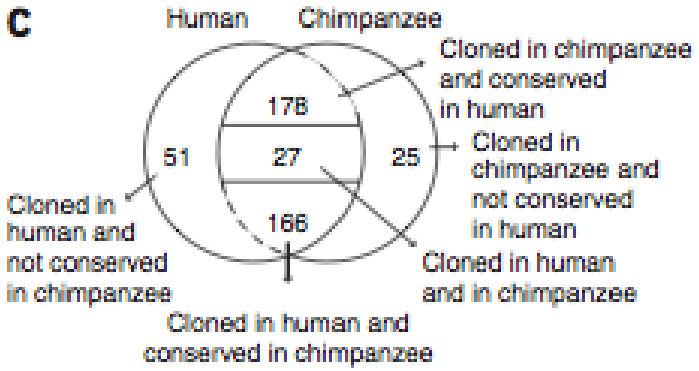
FIGURE 6. **The proposed pathways in creating the novel splicing site in human and expression regulation change of neuropsin during primate evolution. The key mutation events are labeled on the correspondent evolutionary lineages. When compared with mouse, a potential intron–exon boundary occurred due to the GA to AG mutation in primates that created a splicing acceptor site in intron 2–3 [Mitsui et al., 1999]. Two deletions occurred in the ape common ancestor lineage (Site 3 and 4 in Fig. 1), resulting in an intact opening reading frame for type II [Li et al., 2004].**

Diversity of microRNAs in human and chimpanzee brain

NATURE GENETICS VOLUME 38 | NUMBER 12 | DECEMBER 2006

Eugene Berezikov[1], Fritz Thuemmler[2], Linda W van Laake[1,3], Ivanela Kondova[4], Ronald Bontrop[4], Edwin Cuppen[1] & Ronald H A Plasterk[1]

In total, we obtained experimental evidence for 447 new miRNAs (**Fig. 1c**). Although these miRNAs constitute only 1% of the small RNA transcripts in the tissues studied, they more than double the diversity of known miRNAs. Many of the new miRNAs are not conserved beyond primates, indicating their recent origin, and some miRNAs seem to be species-specific, whereas others have been expanded in one of the species through duplication events. These data suggest that evolution of miRNAs is an ongoing process and that along with ancient, highly conserved miRNAs, there is a group of emerging miRNAs, in line with previous observations in plants[11] and animals[4]. The different miRNA repertoire, as well as differences in expression levels of conserved miRNAs, may contribute to gene expression differences observed in human and chimpanzee brain[12]. Although the physiological relevance of miRNAs expressed at low levels remains to be shown, it is tempting to speculate that a pool of such miRNAs may contribute to the diversity of developmental programs and cellular processes and thus provide evolution's playground for the development of new miRNA-containing regulatory pathways. For example, miRNAs recently have been implicated in synaptic development[13] and in memory formation[14]. As the species-specific miRNAs described here are expressed in the brain, which is the most complex tissue in the human body, with an estimated 10,000 different cell types[15], these miRNAs could have a role in establishing or maintaining cellular diversity and could thereby contribute to the differences in human and chimpanzee brain evolution and function.



Genome Analysis

Trends in Genetics Vol.24 No.6

Mutation of miRNA target sequences during human evolution

Paul P. Gardner[1] and Jeppe Vinther[2]

[1] Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton CB10 1SA, UK
[2] Molecular Evolution Group, Department of Biology, University of Copenhagen, Copenhagen Biocenter, DK-2200 Copenhagen N, Denmark

Table 1. miRNA[a] target mutations in the GABA pathway

miRNA target sequence mutated	Gene symbol	Gene name
miR-376c	*GABRA4*	GABA A receptor, α4
miR-128	*GABRA6*	GABA A receptor, α6
miR-27	*GABRA6*	GABA A receptor, α6
miR-183	*GABRB3*	GABA A receptor, β3
miR-326	*GABRB3*	GABA A receptor, β3
miR-22	*GABRE*	GABA A receptor, ε
miR-431	*GABRR1*	GABA receptor, ρ1

[a]miRNA, microRNA.

Escaping repression
At the translation
level

GABA(A) receptor genes have been targeted by mutations in miRNA target sequences

We used Gene Ontology (GO) analysis (http://david.abcc.ncifcrf.gov/home.jsp) to identify functional categories that were enriched within the genes that have had miRNA target sequence mutations [24] (see the full list in Supplementary Table 1b). One of the most significantly enriched GO categories was the GABA signalling pathway ($P = 8.98E^{-04}$), reflecting six miRNA target sequence mutations that have occurred in the genes encoding five different subunits of the GABA(A) receptor [α4, α6, β3 (two mutations), ε, ρ; see Table 1]. The GABA(A) receptor mediates inhibitory neurotransmissions in the central nervous system and are involved in sleep, anxiolysis, associative learning and memory, sensorimotor processing and consciousness [25]. Our results therefore indicate that there has been selection for increased expression of some of the GABA(A) subunits in specific regions of the brain.

Alu elements within human mRNAs are probable microRNA targets

TRENDS in Genetics Vol.22 No.10

Neil R. Smalheiser and Vetle I. Torvik

University of Illinois-Chicago, UIC Psychiatric Institute MC912, 1601 W. Taylor Street, Chicago, IL 606

Recently, we reported that four microRNAs show perfect complementarity with MIR/LINE-2 elements within human mRNAs. This finding raises the question of whether microRNAs might also target other genomic repeats and transposable elements. Here, we demonstrate that almost 30 human microRNAs exhibit typical short-seed complementarity with a specific site within Alu elements that is highly conserved within 3′ untranslated regions of human mRNAs. The results suggest that at least some Alu elements within human mRNAs serve as microRNA targets.

Alu-containing transcripts are not restricted to protein-coding mRNAs. Noncoding Alu transcripts are transcribed by pol III, contain a poly-A region, show a high rate of turnover and are induced during cellular stress [38]. Alu transcription is an essential phase in the retrotransposition of Alu elements in the genome [27]. Although the raison d'être of microRNAs was originally thought to be translational repression of mRNAs, a more fundamental role could be to bind and route RNAs to processing bodies (P-bodies) to be sequestered or degraded [39]. It is currently unknown whether noncoding RNAs can also be routed to P-bodies, but if so, microRNAs that interact with noncoding Alu RNA transcripts might potentially counter retrotransposition in mammalian cells.

Table 2. The number of 3′ UTRs that express one or both 8-mer outlier seed target sites

	Number of hits per 3′ UTR	Number of 3′ UTRs	Length Mean ± SD	Length excluding repeats Mean ± SD
3′ UTRs hit outside repeats	0	23 394	967 (1015)	840 (909)
	1	1090	1,994 (1494)	1,824 (1392)
	2	80	2,890 (1558)	2,744 (1420)
	3+	2	4,400 (274)	4,070 (447)
3′ UTRs hit within Alu	0	23 427	977 (1028)	871 (945)
	1	1017	1,786 (1429)	1,238 (1261)
	2	109	2,684 (1402)	1,620 (1135)
	3+	13	3,645 (1972)	1,910 (1486)

Vol 443|14 September 2006|doi:10.1038/nature05113 nature

ARTICLES

An RNA gene expressed during cortical development evolved rapidly in humans

Katherine S. Pollard[1]*†, Sofie R. Salama[1,2]*, Nelle Lambert[4,5], Marie-Alexandra Lambot[4], Sandra Coppens[4], Jakob S. Pedersen[1], Sol Katzman[1], Bryan King[1,2], Courtney Onodera[1], Adam Siepel[1]†, Andrew D. Kern[1], Colette Dehay[6,7], Haller Igel[3], Manuel Ares Jr[3], Pierre Vanderhaeghen[4] & David Haussler[1,2]

The developmental and evolutionary mechanisms behind the emergence of human-specific brain features remain largely unknown. However, the recent ability to compare our genome to that of our closest relative, the chimpanzee, provides new avenues to link genetic and phenotypic changes in the evolution of the human brain. We devised a ranking of regions in the human genome that show significant evolutionary acceleration. Here we report that the most dramatic of these 'human accelerated regions', HAR1, is part of a novel RNA gene (*HAR1F*) that is expressed specifically in Cajal–Retzius neurons in the developing human neocortex from 7 to 19 gestational weeks, a crucial period for cortical neuron specification and migration. *HAR1F* is co-expressed with reelin, a product of Cajal–Retzius neurons that is of fundamental importance in specifying the six-layer structure of the human cortex. HAR1 and the other human accelerated regions provide new candidates in the search for uniquely human biology.

An RNA gene expressed during cortical development evolved rapidly in humans

Katherine S. Pollard[1*†], Sofie R. Salama[1,2*], Nelle Lambert[4,5], Marie-Alexandra Lambot[4], Sandra Coppens[4], Jakob S. Pedersen[1], Sol Katzman[1], Bryan King[1,2], Courtney Onodera[1], Adam Siepel[1†], Andrew D. Kern[1], Colette Dehay[6,7], Haller Igel[3], Manuel Ares Jr[3], Pierre Vanderhaeghen[4] & David Haussler[1,2]

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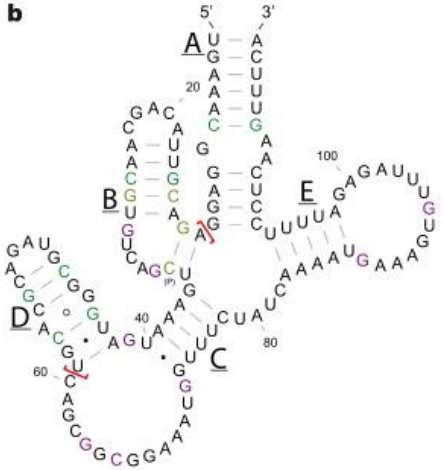
a

Position	20	30	40	50
Human	AGACGTTACAGCAACGTGTCAGCTGAAATGATGGGCGTAGACGCACGT			
Chimpanzee	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Gorilla	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Orang-utan	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Macaque	AGAAATTACAGCAATTTATCAGCTGAAATTATAGGTGTAGACACATGT			
Mouse	AGAAATTACAGCAATTTATCAGCTGAAATTATAGGTGTAGACACATGT			
Dog	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Cow	AGAAATTACAGCAATTCATCAGCTGAAATTATAGGTGTAGACACATGT			
Platypus	ATAAATTACAGCAATTTATCAAATGAAATTATAGGTGTAGACACATGT			
Opossum	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Chicken	AGAAATTACAGCAATTTATCAACTGAAATTATAGGTGTAGACACATGT			
Fold	(((((((.....)))))).....))[[[[[.(((.(((....))))).)))			
Pair symbol	lmnopqr rqpon ml rstuvwx xwvutsr			

b



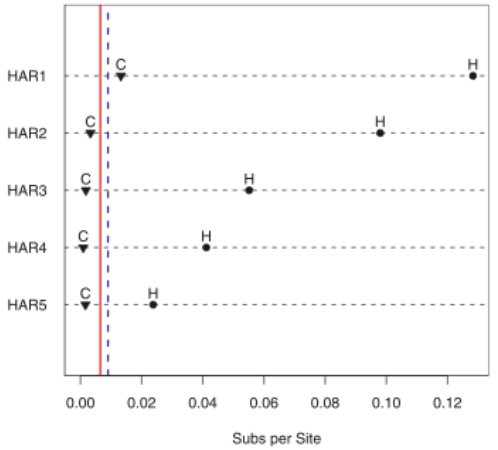


Figure 1. Comparison of Substitution Rates in HAR1–HAR5

For each HAR element, the estimated substitution rate is indicated by a circle for the human lineage and by a triangle for the chimp lineage. As a benchmark, background human-chimp substitution rates estimated from 4d sites in ENCODE regions [39] are marked with vertical lines, solid red for the genome-wide neutral rate, and dotted blue for the neutral rate in final chromosome bands. The chimp rates in all five elements fall well below the human rates, which exceed the background rates by as much as an order of magnitude. H, human; C, chimp.

DOI: 10.1371/journal.pgen.0020168.g001

HAR1 lies in a pair of novel non-coding RNA genes

Brain Evolution and Uniqueness in the Human Genome

Jordan P. Amadio[1,2] and Christopher A. Walsh[1,*]

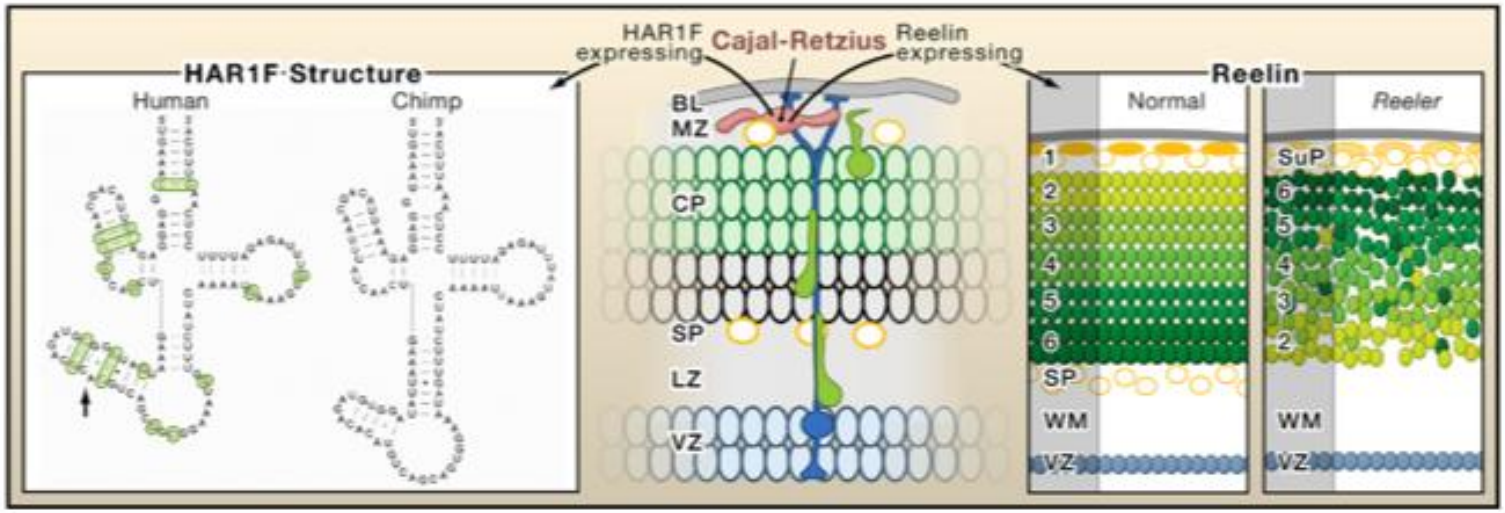


Figure 1. *HAR1F* and Cortical Development

(Left) The *HAR1* region, which lies within a putative noncoding RNA gene, has incorporated 18 human-specific fixed nucleotide substitutions (highlighted) since the divergence of humans and chimpanzees from their common ancestor less than 7 million years ago. The predicted secondary structure of this region of the forward RNA transcript (*HAR1F*) is shown for both human and chimpanzee. In the human structure, which appears to be unique among mammals, one RNA helix is selectively elongated.

(Middle) A representation of the developing neocortex is shown. Neurons (solid green) migrate along the radial glia (solid blue) that span the entire cortical wall from the ventricular zone (VZ) to the basal lamina (BL). Neurons migrate from the ventricular zone through the fiber rich-intermediate zone (IZ) into the developing cortical plate (CP). Cajal-Retzius cells (solid red), which are found in the marginal zone (MZ), express both *HAR1F* and reelin. Although the function of *HAR1* in neuronal development is not known, reelin has been implicated in orchestrating the correct layering of neurons in the cortical plate.

(Right) In wild-type mice, neurons migrate into the cortical plate and form six well-defined layers (green), which overly the subplate (SP) and a band of white matter (WM). In mice lacking reelin, this layering appears disorganized or inverted. In such "reeler" mice, the cortical plate develops beneath the subplate (here called the superplate [SuP] because of its altered position). Future work may establish whether *HAR1* contributes to patterning or migration of cortical neurons.

Opinion TRENDS in Genetics Vol.23 No.1

Feng-Jie Sun[1], Sophie Fleurdépine[2], Cécile Bousquet-Antonelli[2], Gustavo Caetano-Anollés[1] and Jean-Marc Deragon[2,3]

Common evolutionary trends for SINE RNA structures

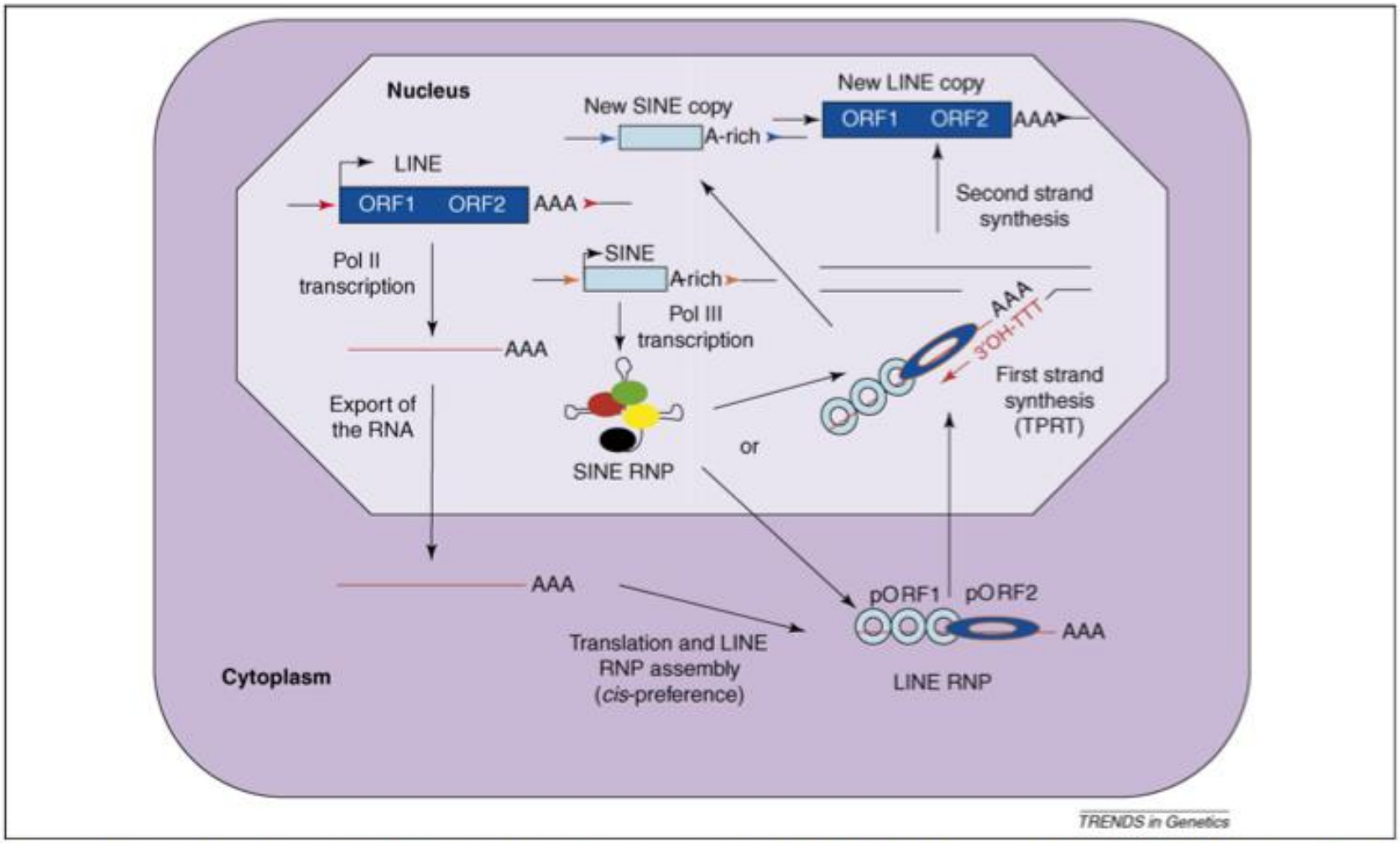


Figure 1. A general model of SINE and LINE retroposition (for a general review, see Ref. [33]). LINE elements are transcribed from an internal RNA polymerase II (Pol II) promoter to generate full-length sense-strand LINE RNAs that subsequently are exported to the cytoplasm. Following translation, pORF1 and pORF2 co-assemble with their encoding RNA (by a process named *cis*-preference) to form the LINE RNP. This complex is imported into the nucleus (or enters during mitosis) and engages in the TPRT process that leads to the first-strand cDNA synthesis. Subsequent steps such as second-strand cleavage, second-strand cDNA synthesis and ligation of the resultant cDNA to genomic DNA have yet to be explained. SINE elements are transcribed from an internal Pol III promoter to generate a full-length SINE RNA that is probably guided through several post-transcriptional modifications [49] before or during RNP assembly. We suggest that, to engage in TPRT and to retropose, the SINE and LINE RNPs must first interact, either in the cytoplasm or in the nucleus ('or'). In addition, a common 3′ region or poly(A) tail between SINE and LINE RNAs is needed for the SINE RNA to capture the LINE machinery [7,50]. As for LINEs, the subsequent steps leading to SINE integration are unknown.

DEVELOPMENTAL BIOLOGY

Jumping-gene roulette

NATURE|Vol 460|27 August 2009

Sandra L. Martin

Jumping genes, which make DNA copies of themselves through an RNA middleman, provide a stochastic process for generating brain diversity among humans. The effect of their random insertion, however, is a bit of a gamble.

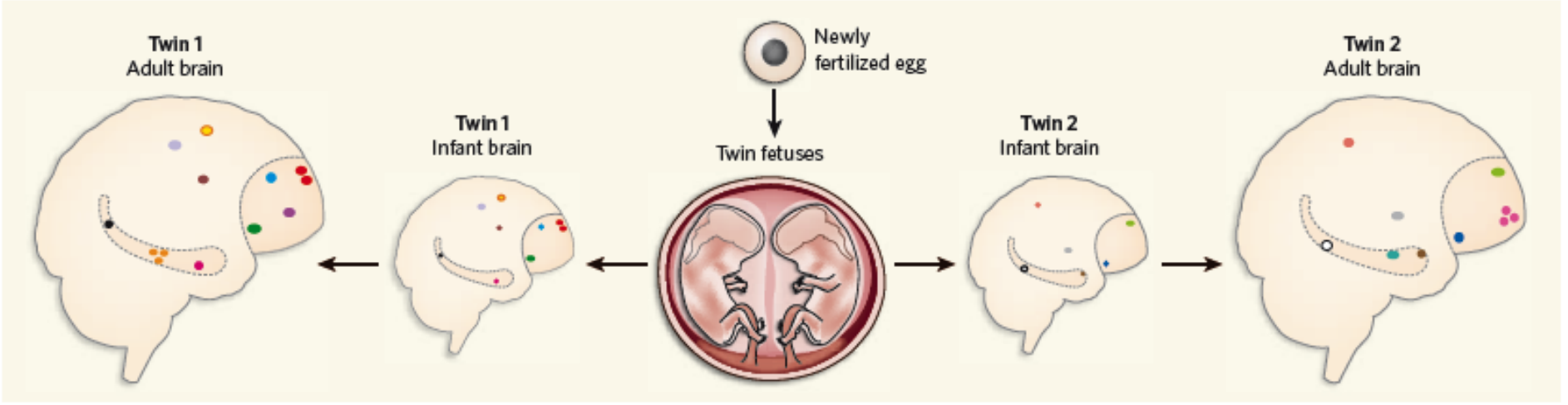


Figure 1 | Human brain variation by retrotransposition. These twins are genetically identical at conception, but at birth their brains differ because of new L1 insertions that take place during the development of the nervous system in the fetus. Ongoing retrotransposition in neural progenitor cells as shown to occur by Coufal *et al.*[1] will further diversify the genetic make-up of their brains in adulthood. Depending on the target genes and the neurons affected by L1 insertions, the twins may differ in brain function or dysfunction. Each unique insertion is represented by a different colour. Darker-shaded areas highlight regions of the brain where L1 retrotransposition may be more likely to occur after birth.

Figure 3 | **Children at the Oneida Community in the 1870s.** Probably most of the children in this photograph were 'stirpiculs', the products of the selective breeding programme. Reproduced with permission from the Collection of the Oneida Community Mansion House, Oneida, New York, USA.

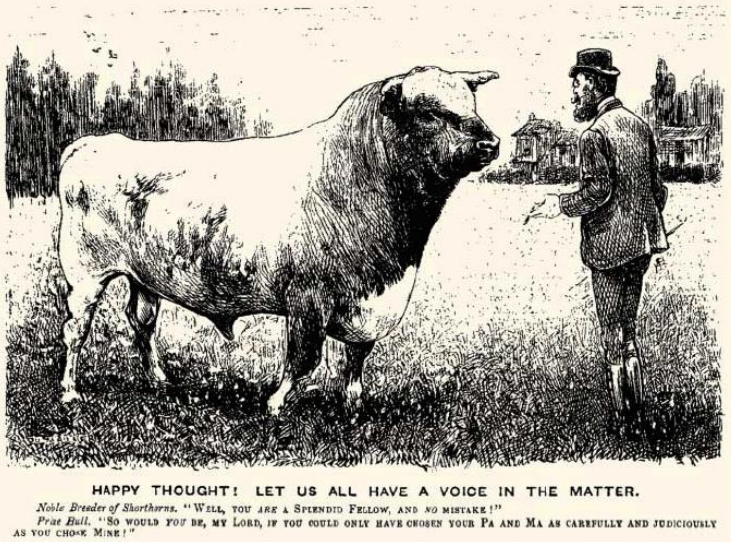


Figure 2 | **A *Punch* cartoon commenting on the connection between animal and human selective breeding.** Reproduced from *Punch* p.126 (20 Mar 1880).

Figure 4 | **"Yea I have a goodly heritage".** A medal awarded to winners of 'Fitter Family' contests. Image courtesy of the American Philosophical Society, Philadelphia, USA.

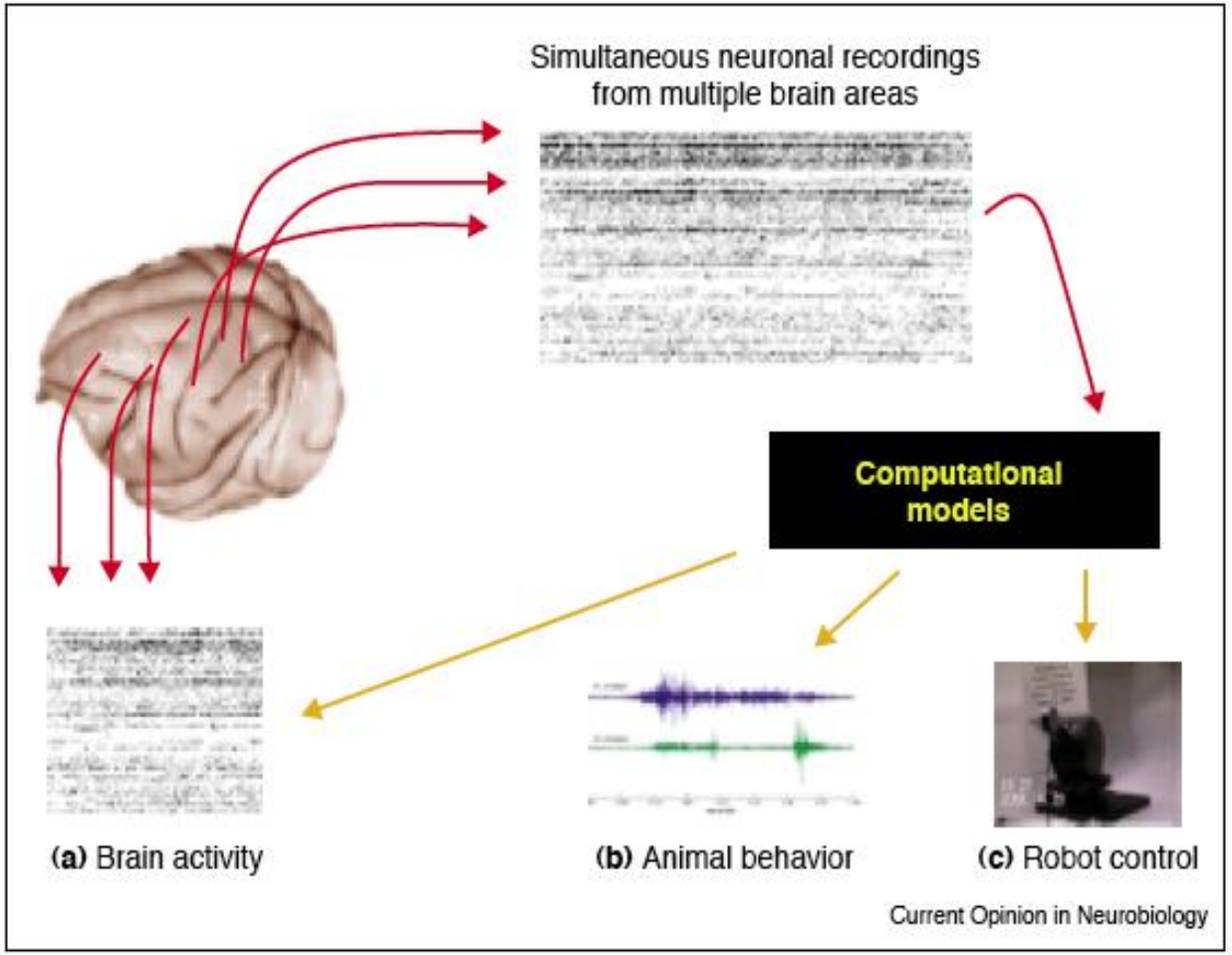
Multielectrode recordings: the next steps

Miguel AL Nicolelis*†‡§ and Sidarta Ribeiro*

Current Opinion in Neurobiology 2002, 12:602–606

Figure 1

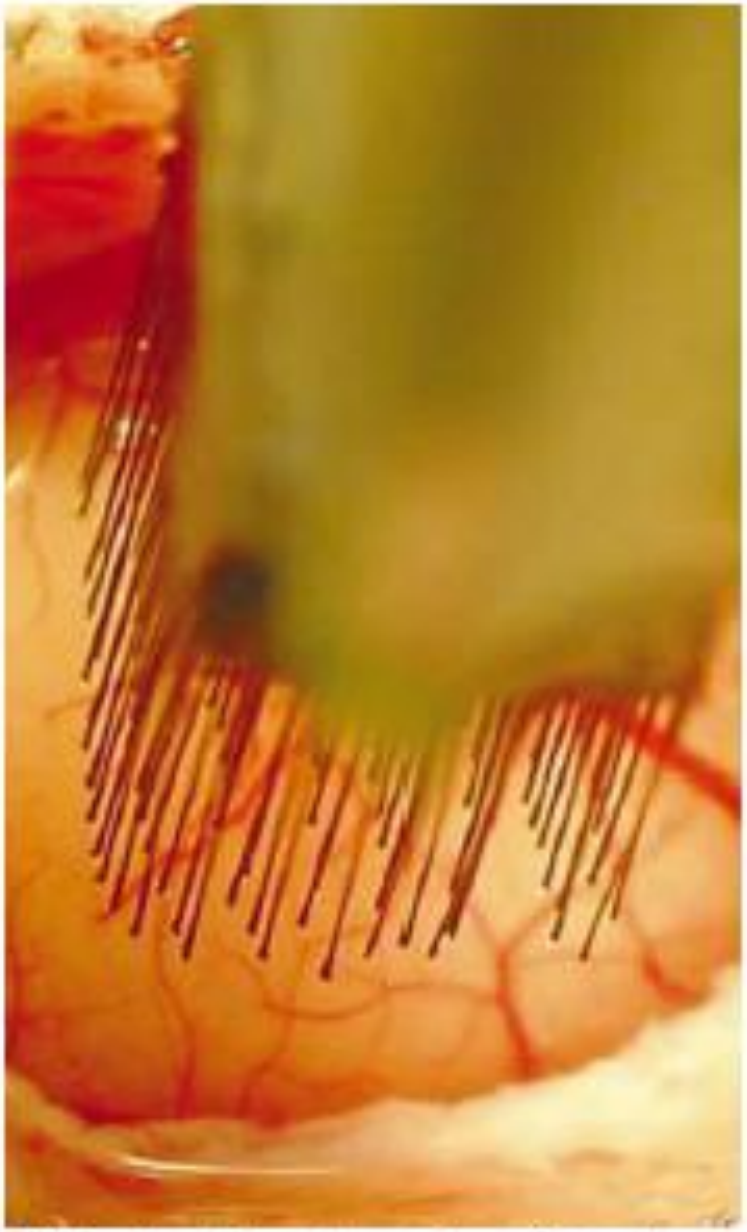
Real-time neurophysiology. Simultaneous neuronal recordings from multiple brain areas are fed to a computational model, which yields real-time predictions of **(a)** the activity of other interconnected brain areas, and **(b)** motor behavior. A similar approach **(c)** allows for the neural control of a robotic device.



Remote control

Could wiring up soldiers' brains to the fighting machines they control be the future face of warfare? Hannah Hoag investigates the US military's futuristic neuroengineering research programme.

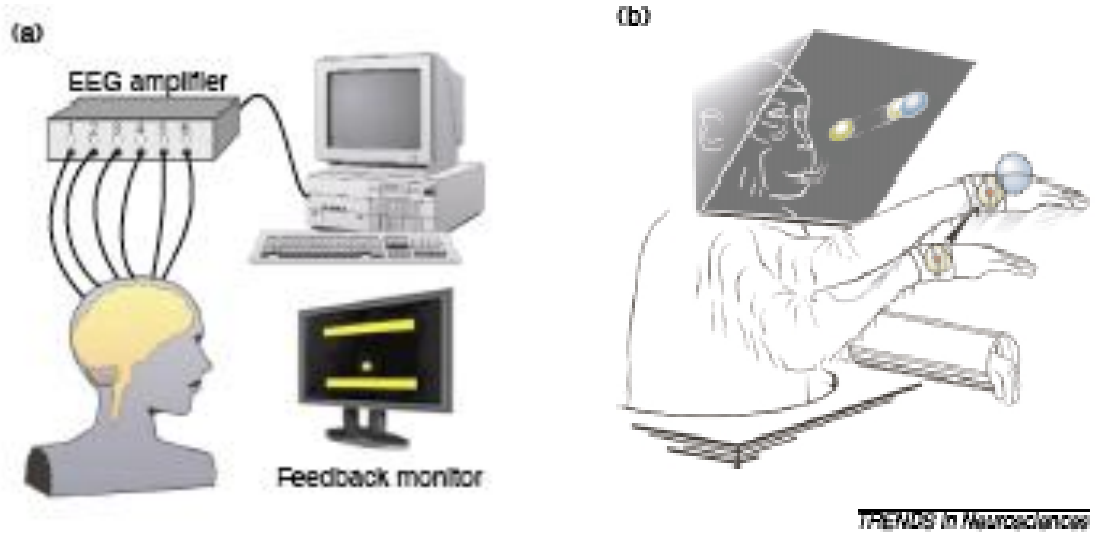
The military has always been visionary when funding neuroscience.



Mind reader: electrodes are inserted into the cortex of a macaque to monitor neural activity.

Ferdinando A. Mussa-Ivaldi and Lee E. Miller

TRENDS in Neurosciences Vol.26 No.6 June 2003



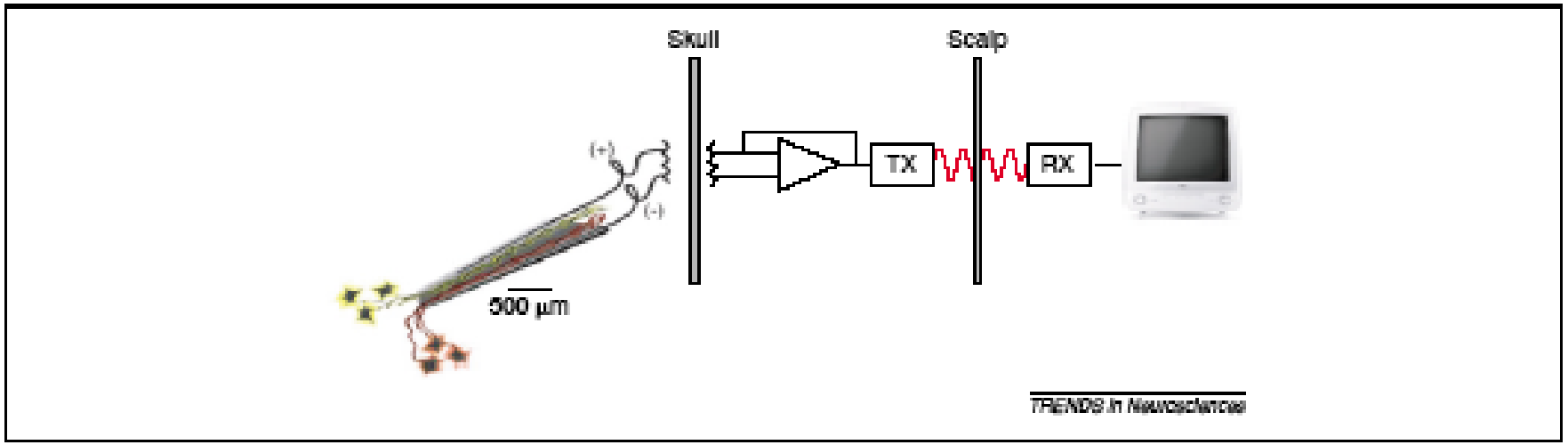


Fig. 2. Block diagram of the neurotrophic electrodes used by Kennedy and colleagues for implantation in human patients [31–33]. Neurites that are induced to grow into the glass cone make highly stable contacts with recording wires. Signal conditioning and telemetric electronics are fully implanted under the skin of the scalp. An implanted transmitter (TX) sends signals to an external receiver (RX), which is connected to a computer. Figure courtesy of Phillip R. Kennedy.

OPINION

Brain–machine interfaces to restore motor function and probe neural circuits

NATURE REVIEWS | NEUROSCIENCE

Miguel A. L. Nicolelis

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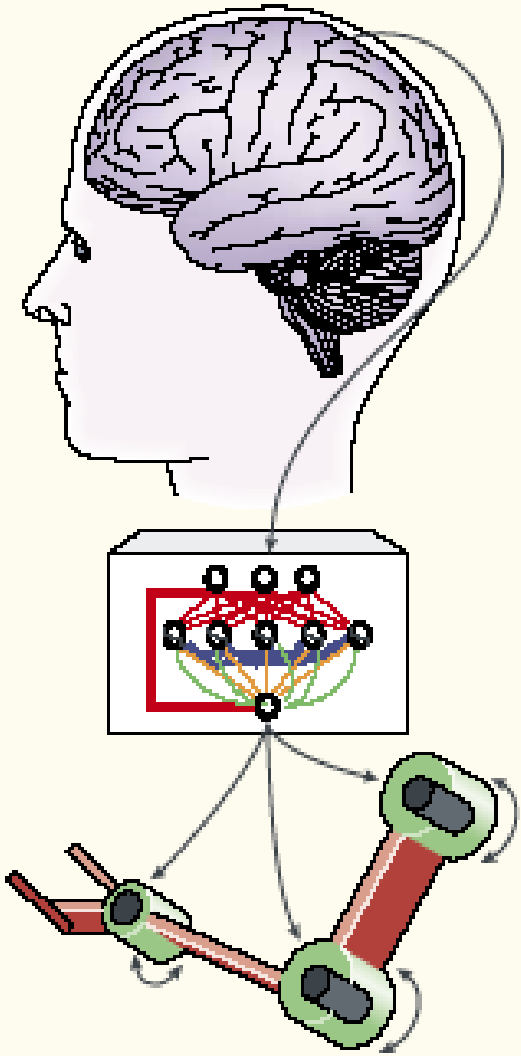
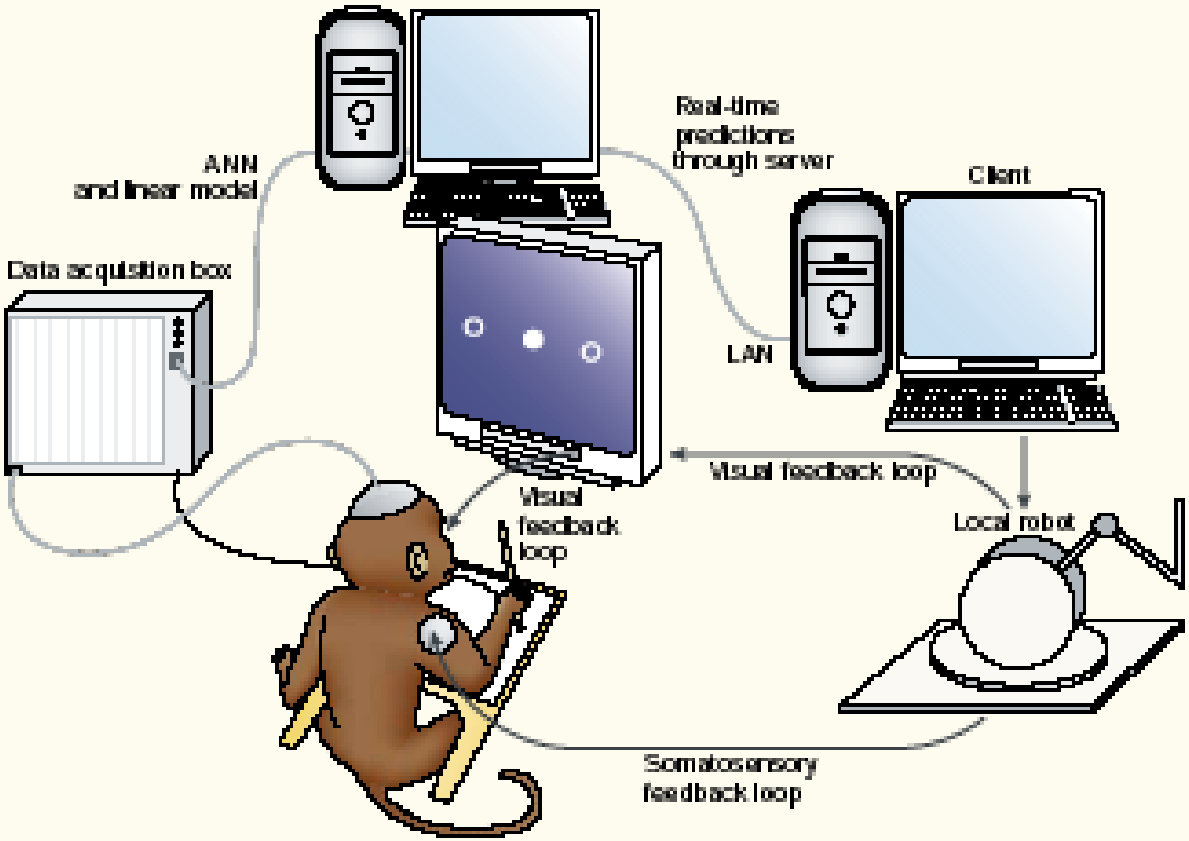
"Ultimately, I believe that the design of a successful BMI for restoring control of upper limb movements will have to take into account general physiological principles of how motor signals underlying these movements are encoded in the primate brain."





Brain–machine interfaces: past, present and future

Mikhail A. Lebedev[1] and Miguel A.L. Nicolelis[2]

TRENDS in Neurosciences Vol.29 No.9

2006

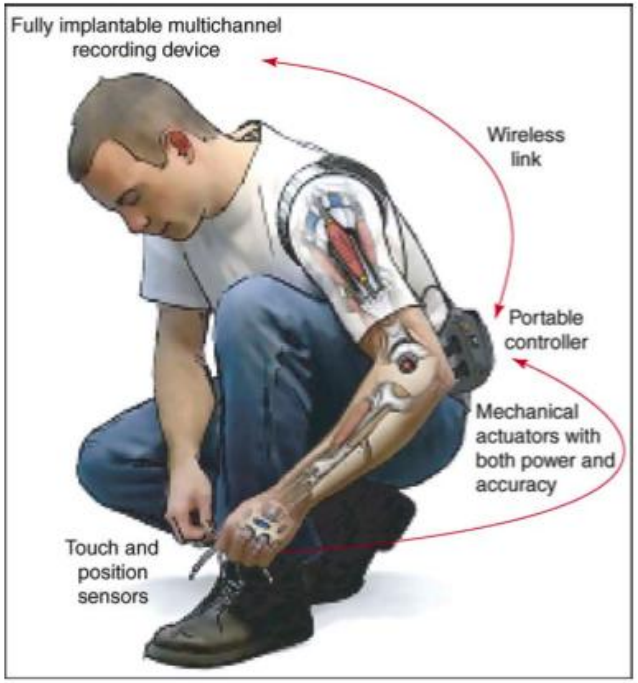


Figure 3. How a fully-implantable BMI could restore limb mobility in paralyzed subjects or amputees. Although the details of this system have to be worked out through future research, it is clear that the BMI for human clinical applications should be encased in the patient's body as much as possible. Wireless telemetry offers a viable solution for this purpose. The prosthesis not only should have the functionality of the human arm in terms of power and accuracy of the actuators, but also should be equipped with the sensors of touch and position from which signals can be transmitted back to the subject's brain.

Cognitive functions?