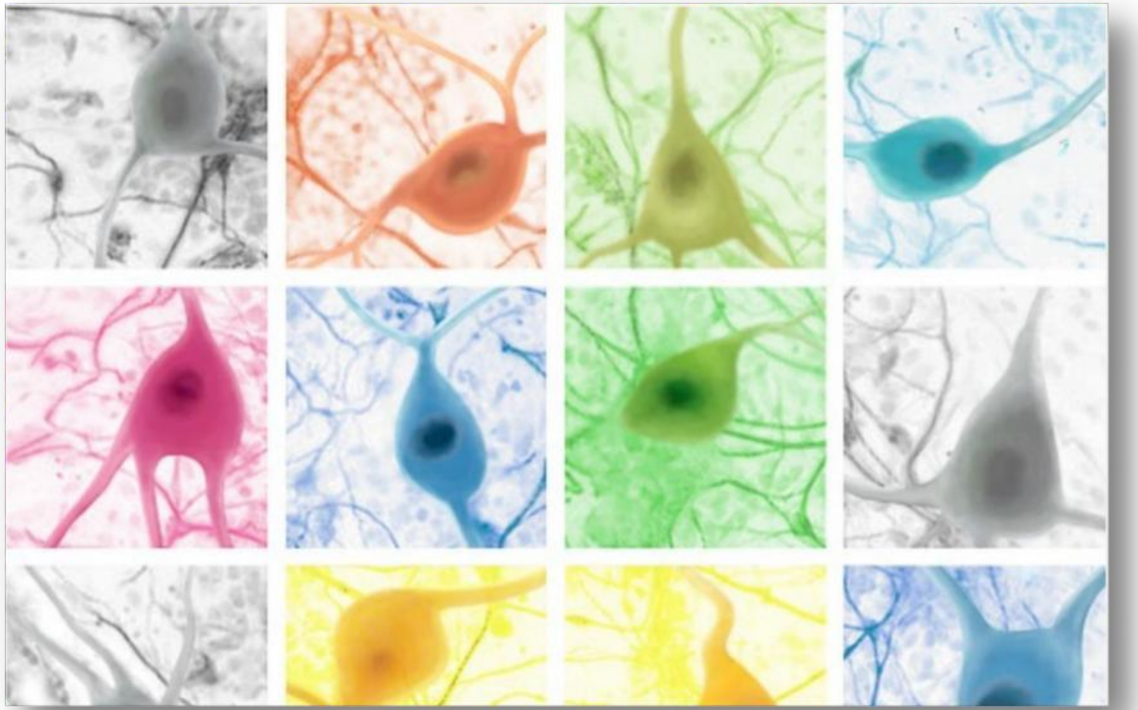


北京师范大学心理学部

Developmental Population Neuroscience

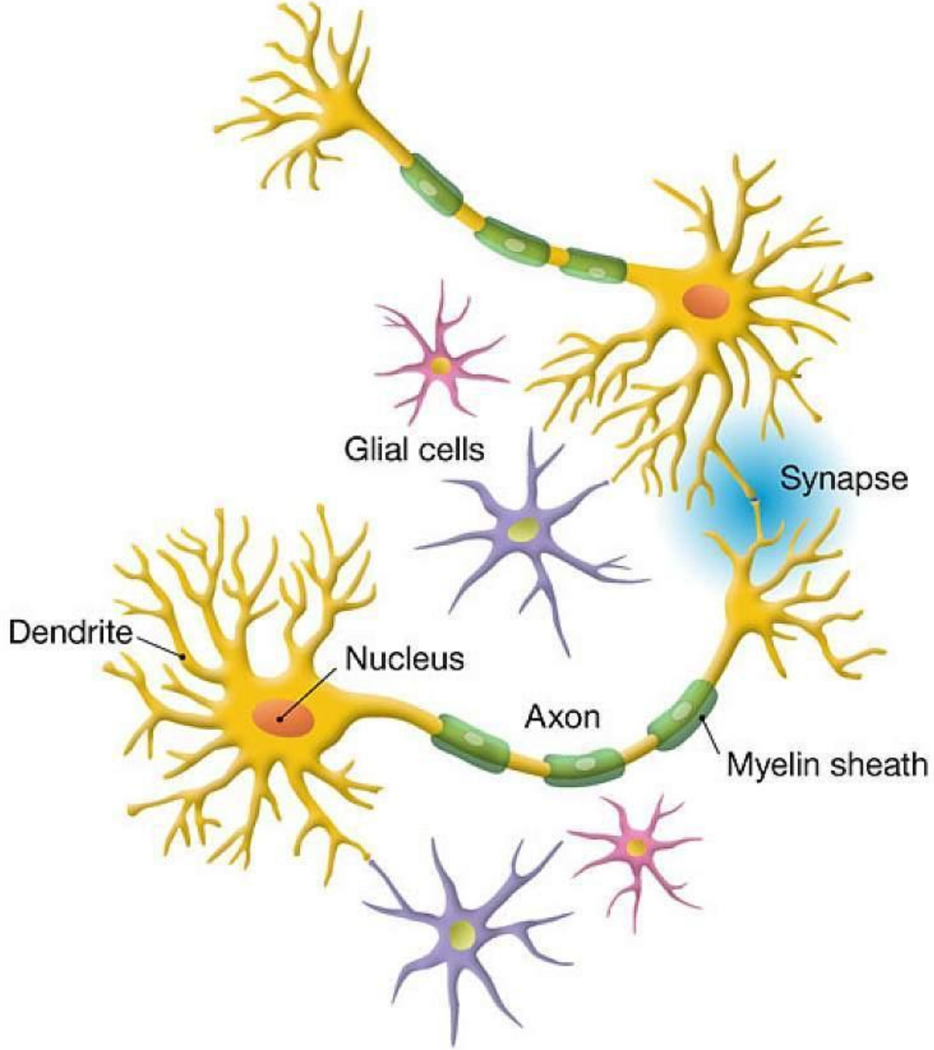
发展人口神经科学（脑细胞）

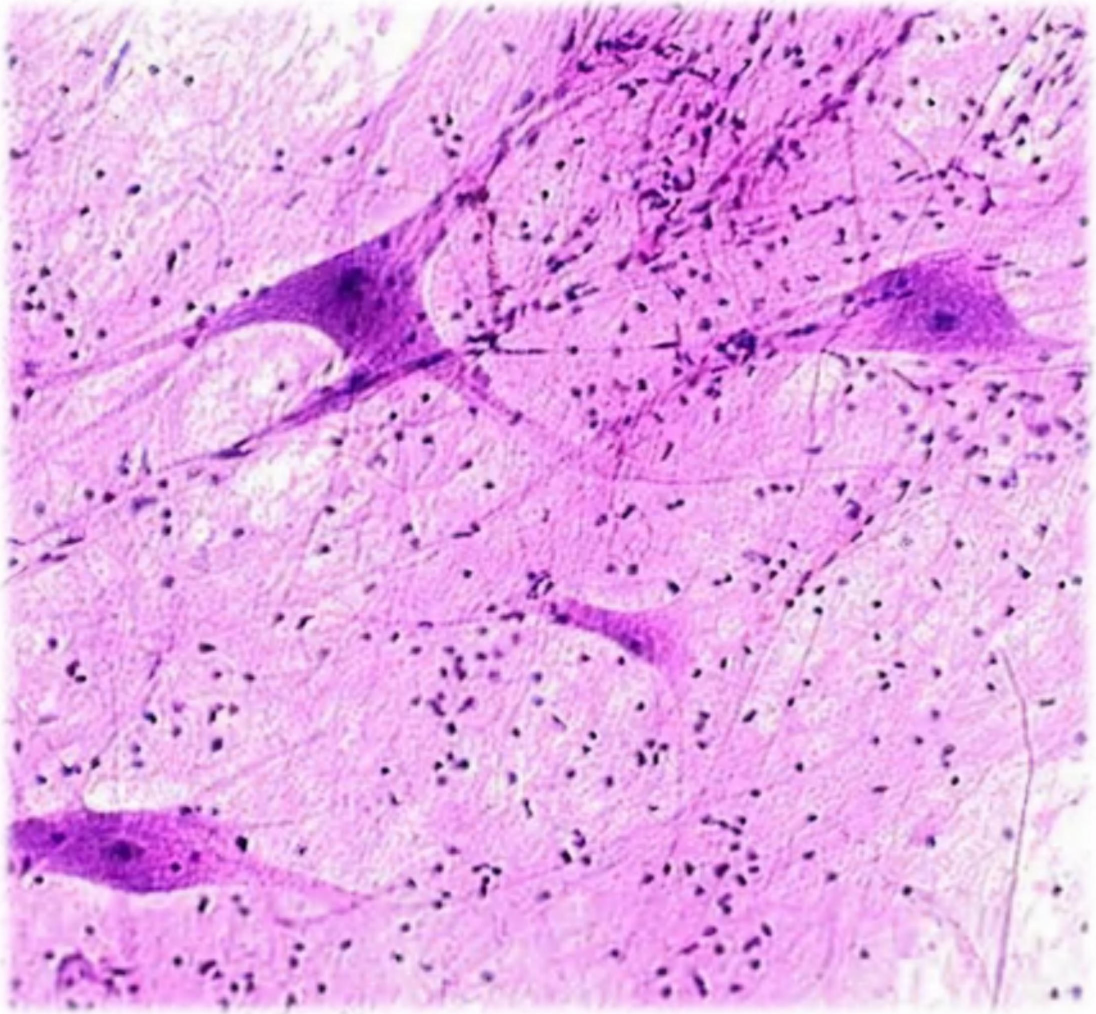
左西年 (Xi-Nian Zuo)

Beijing Normal University
State Key Lab of Cognitive Neuroscience & Learning

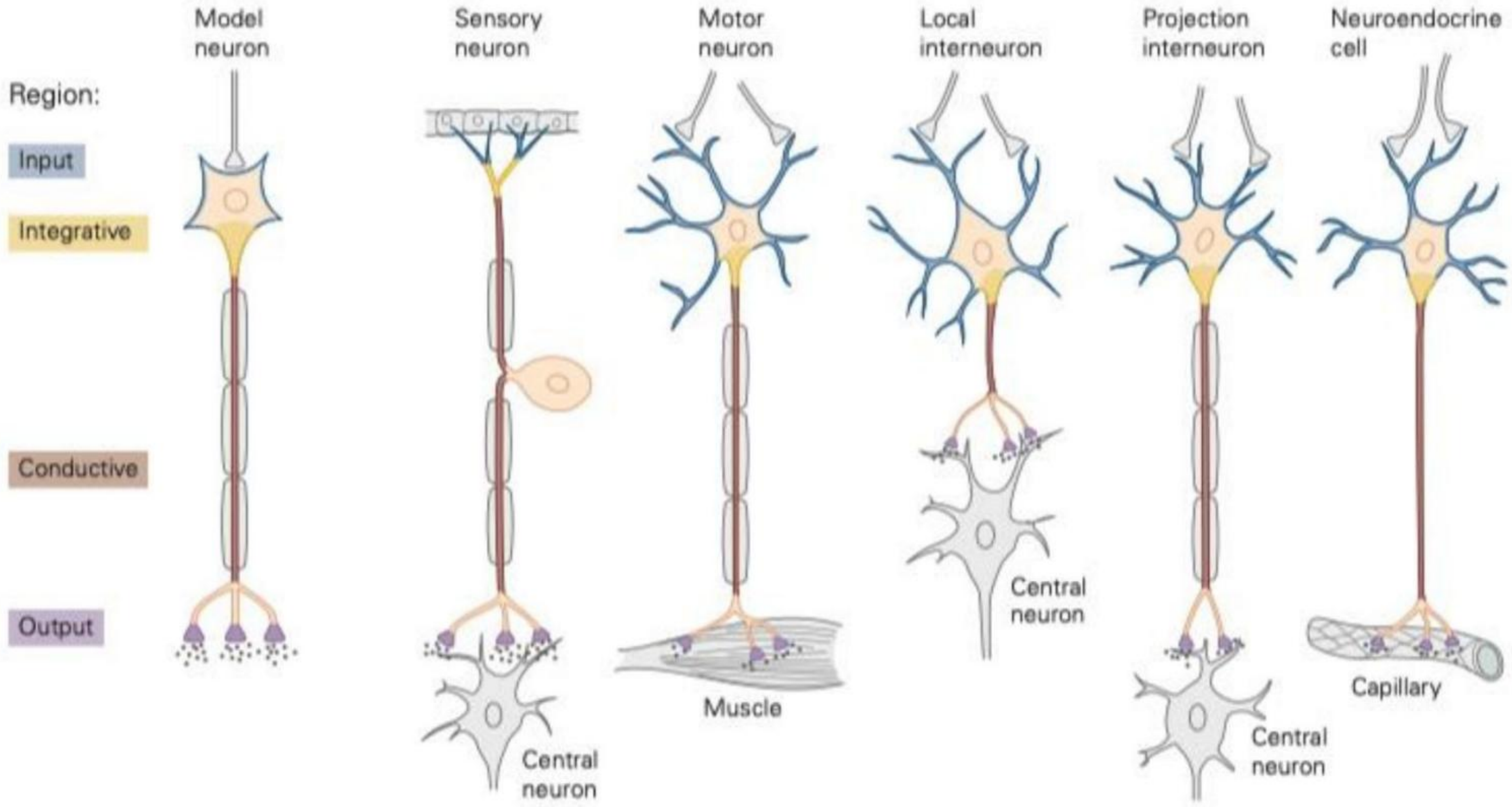
National Basic Science Data Center
Chinese Data-sharing Warehouse for In-vivo Imaging Brain

Cells in The Brain

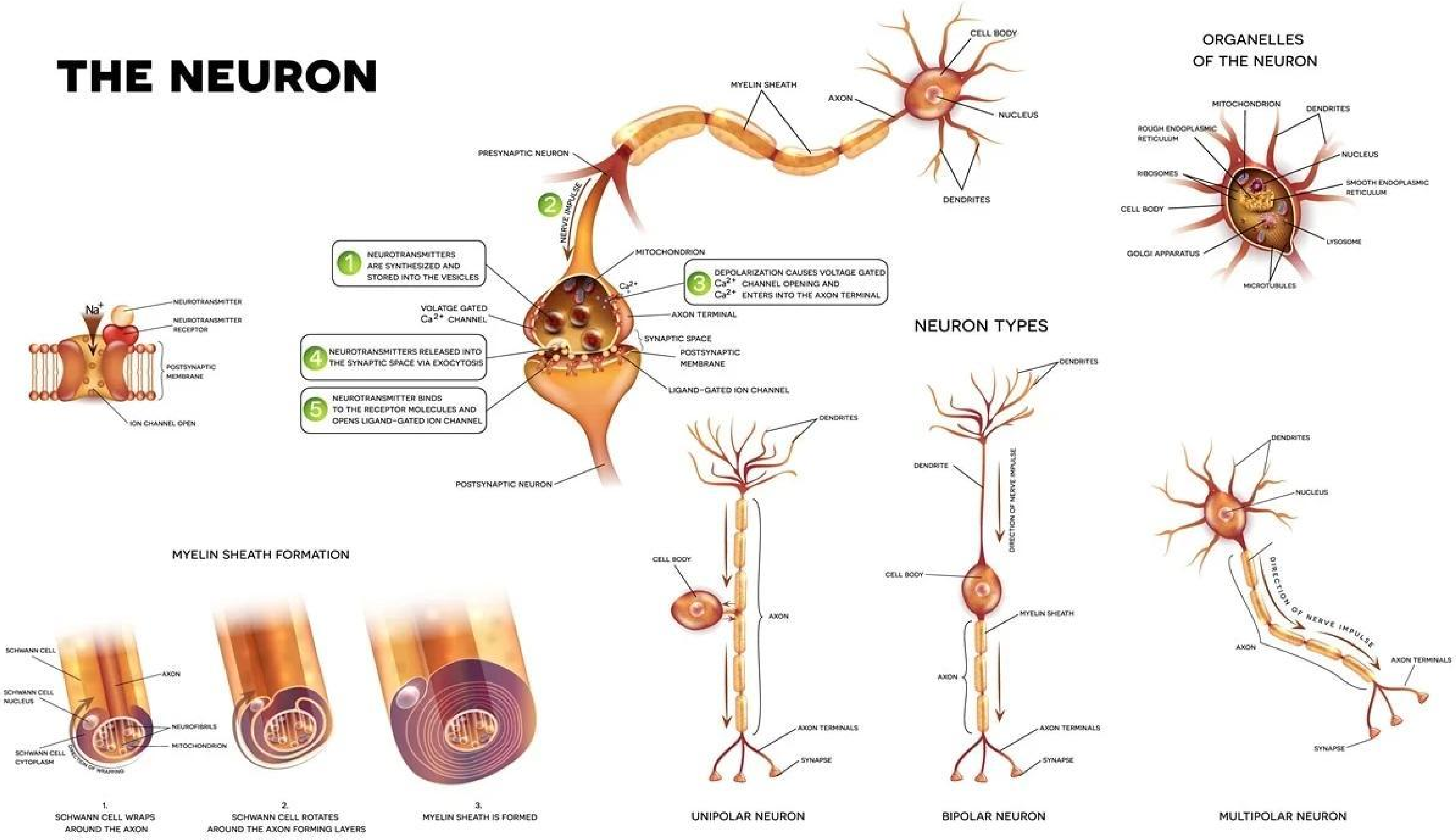




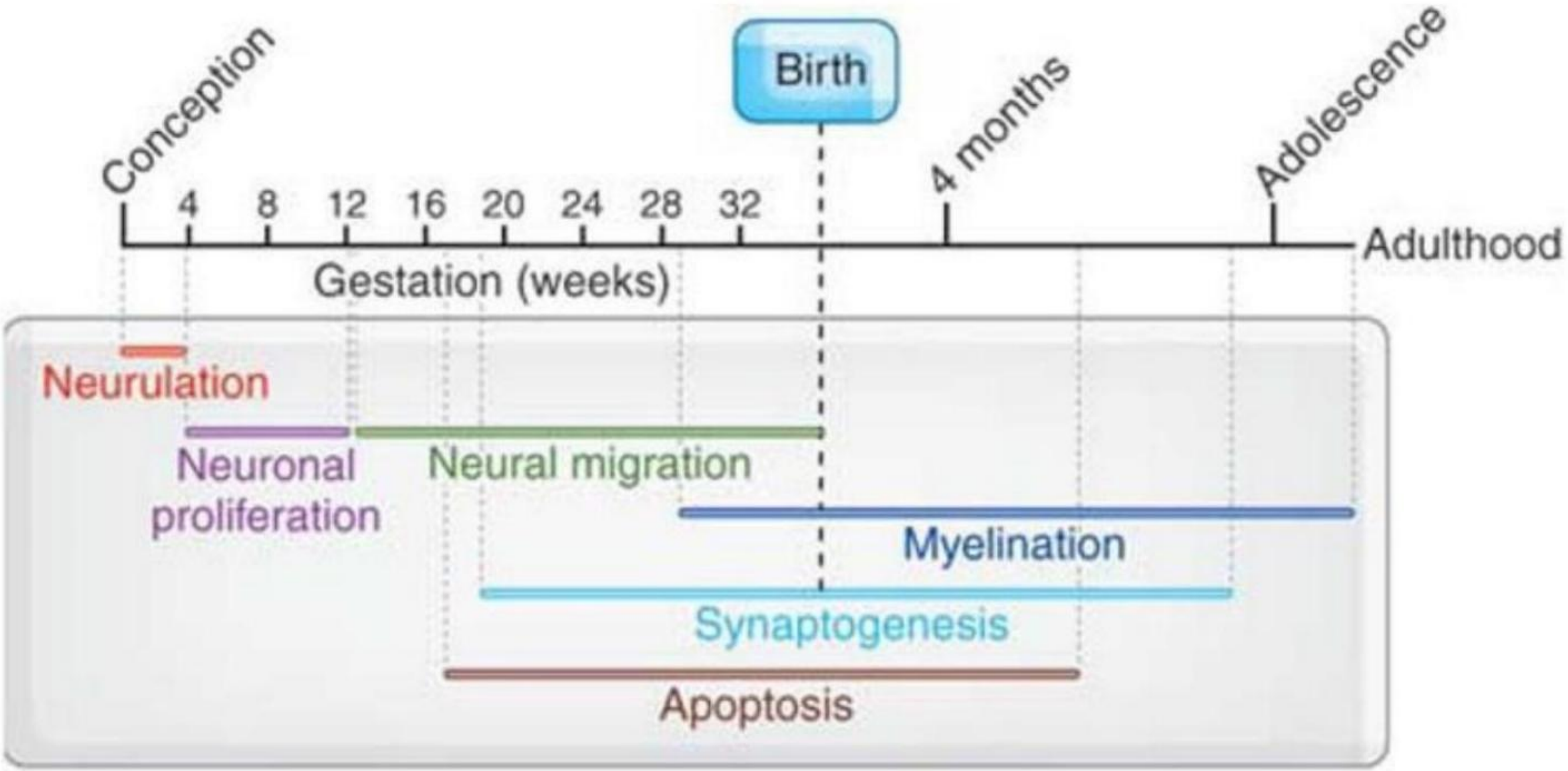
Neurons in The Brain



The Anatomy of A Neuron



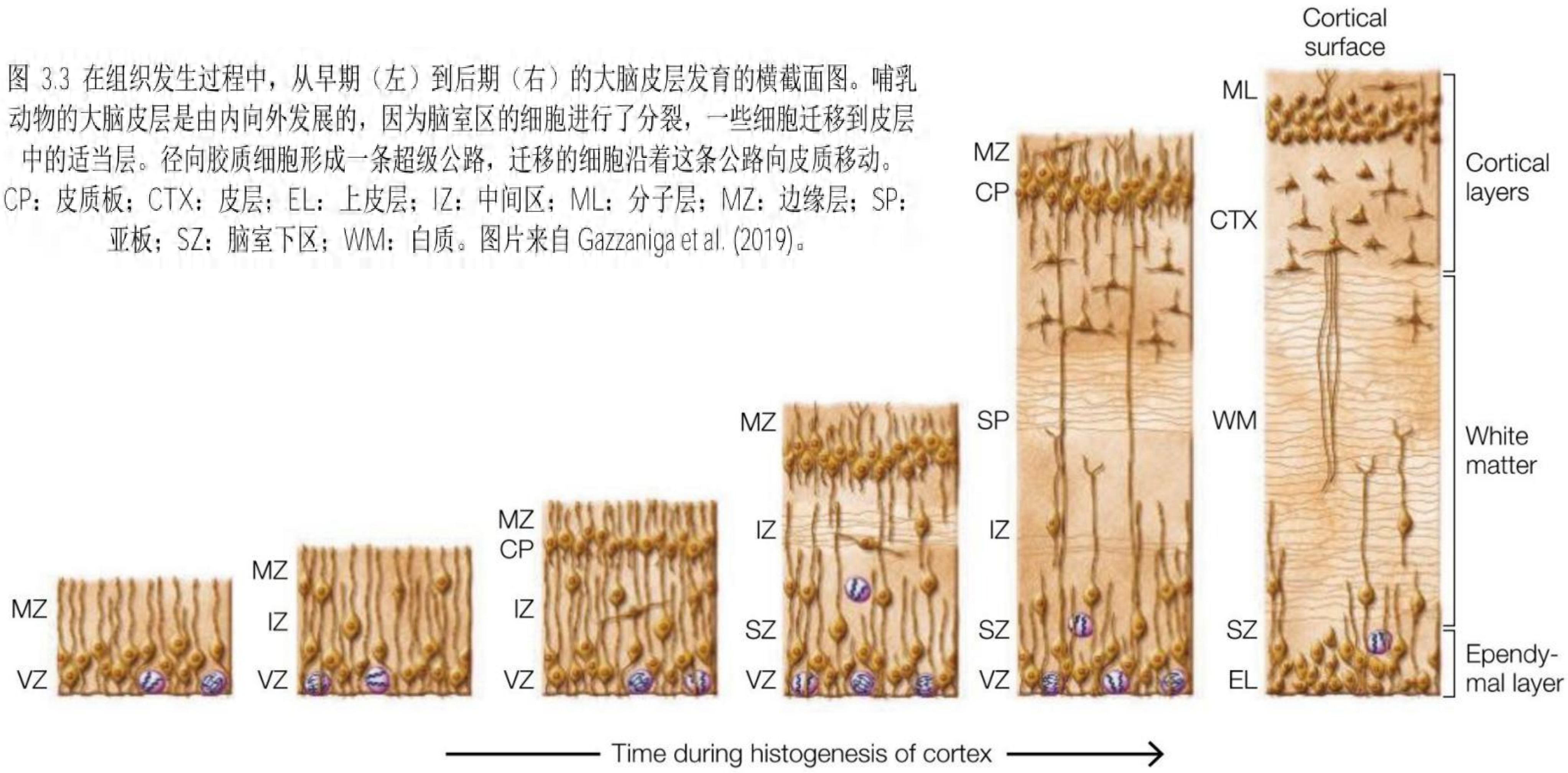
The Development of Neural Circuits



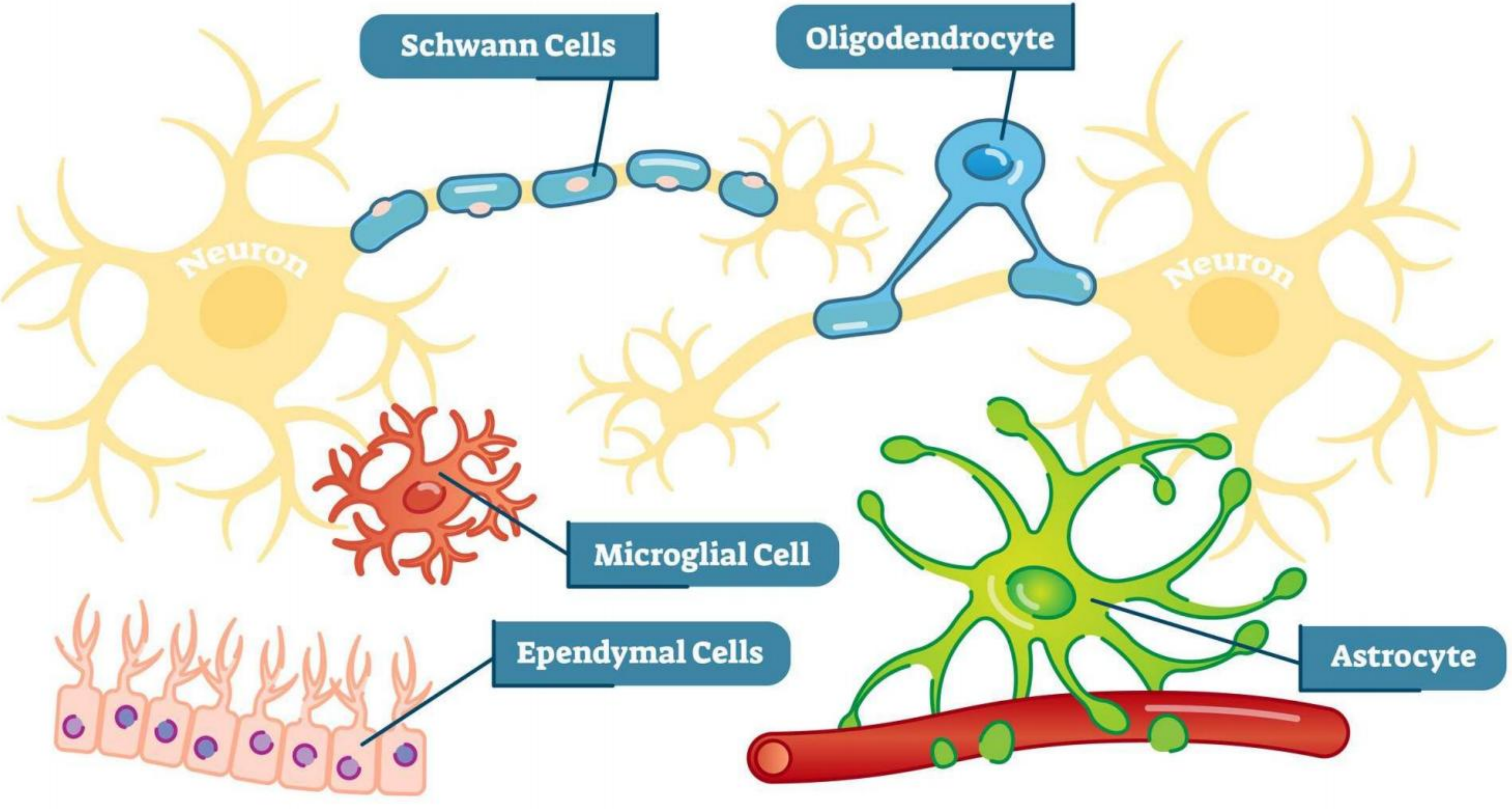
3.2 大脑发育的主要事件时间表。这张图表示大脑发育从神经发育开始，然后是神经元迁移、突触发生、修剪、髓鞘化和皮质变薄。图片来自 Tau and Peterson (2010)。

The Formation of Cortex

图 3.3 在组织发生过程中，从早期（左）到后期（右）的大脑皮层发育的横截面图。哺乳动物的大脑皮层是由内向外发展的，因为脑室区的细胞进行了分裂，一些细胞迁移到皮层中的适当层。径向胶质细胞形成一条超级公路，迁移的细胞沿着这条公路向皮质移动。CP：皮质板；CTX：皮层；EL：上皮层；IZ：中间区；ML：分子层；MZ：边缘层；SP：亚板；SZ：脑室下区；WM：白质。图片来自 Gazzaniga et al. (2019)。

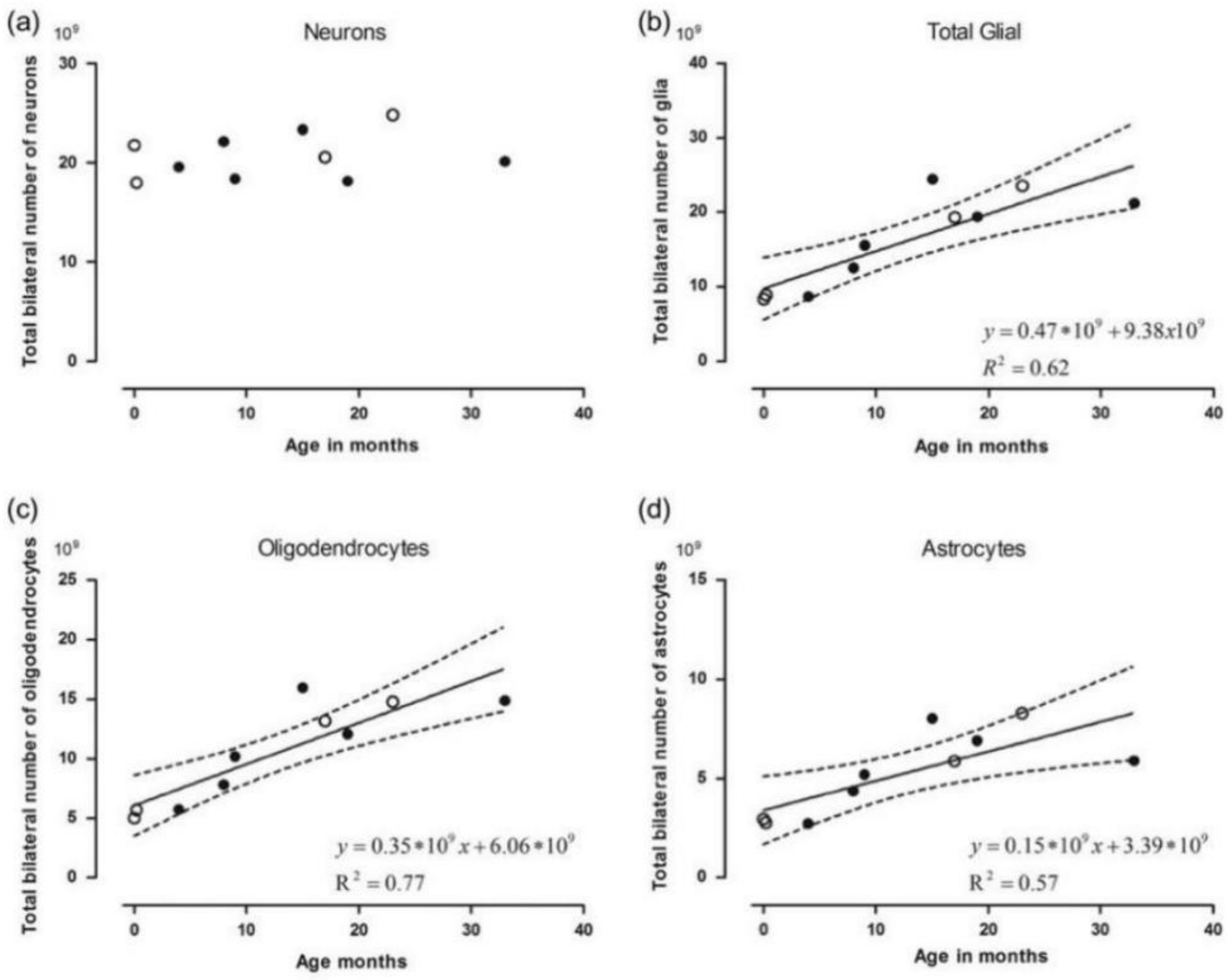


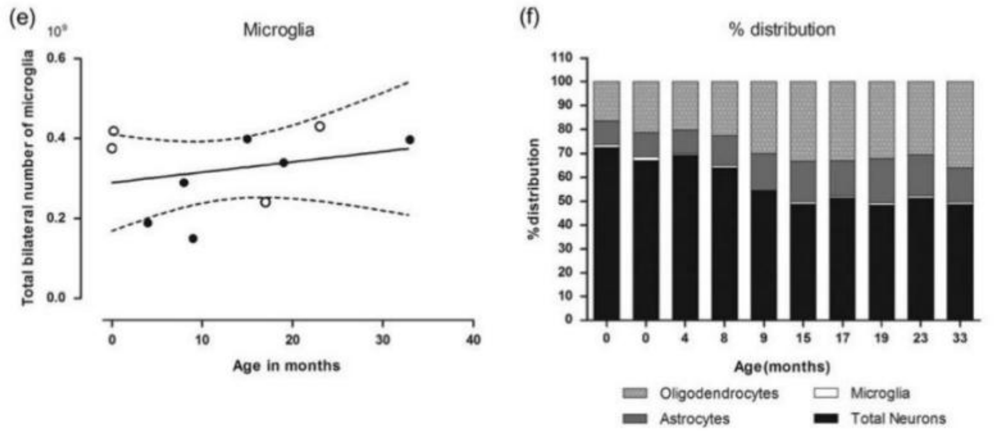
Glial Cells in The Brain

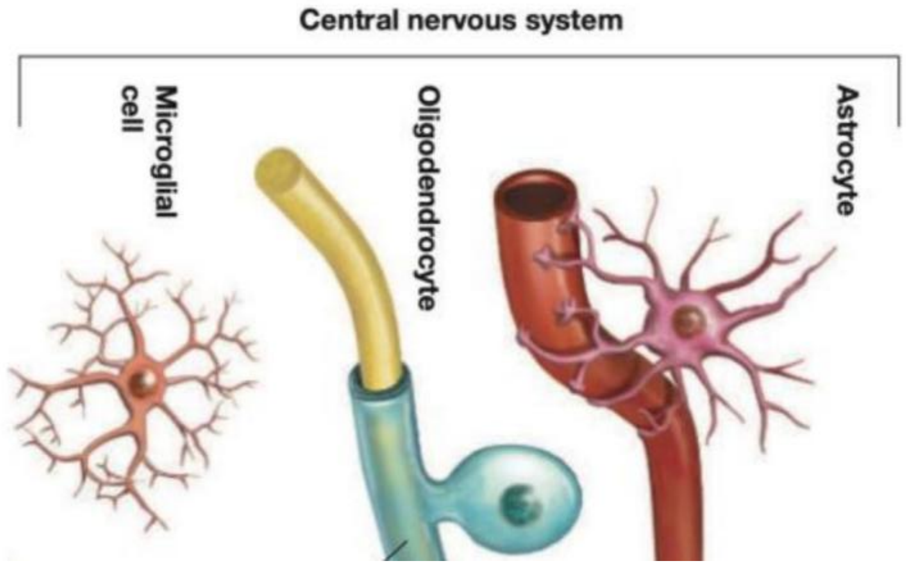


https://www.verywellhealth.com/what-are-glial-cells-and-what-do-they-do-4159734

The Development of Neuroglial Cells







The Synapses of Neurons

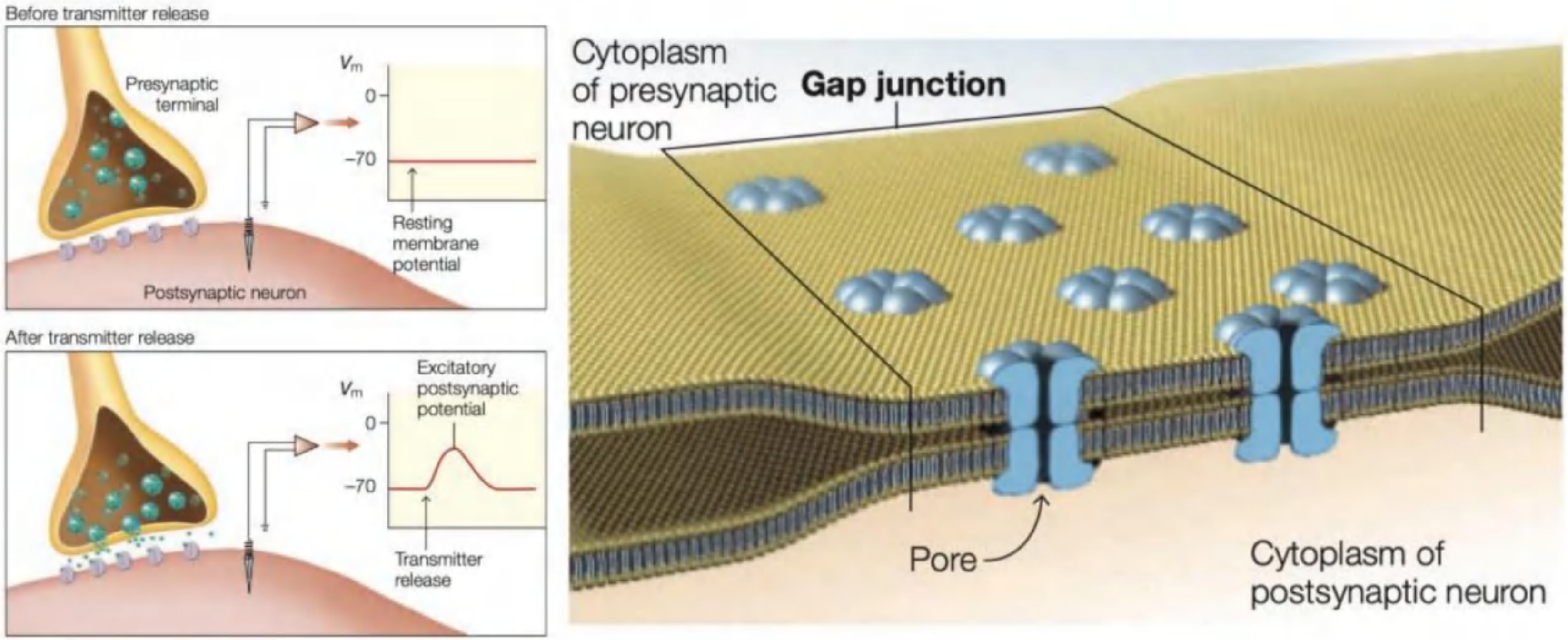
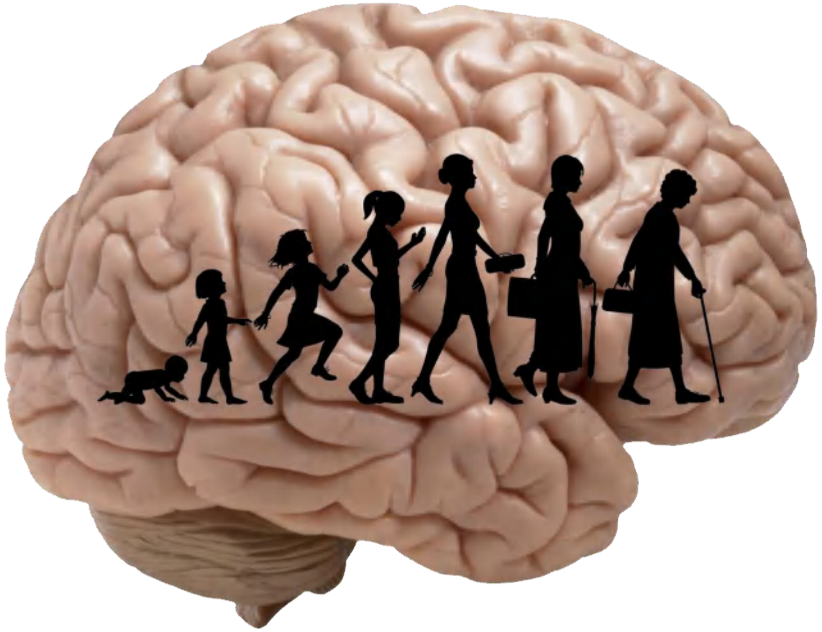


图 3.7 两类突触结构。左图为两个神经元之间的电突触。电突触是由间隙连接形成的，间隙连接是突触前和突触后神经元中的多种跨膜蛋白连接的地方，以创建连接两个神经元的细胞质的通路。右图反映了神经递质导致突触后电位的产生。突触前通过释放神经递质调节突触后神经元的活动，被释放到突触间隙的神经递质与突触后膜受体的结合改变了膜电位。这些突触后电位可以是兴奋性的（使膜去极化），如图所示，也可以是抑制性的（使膜超极化）。图片来自 Gazzaniga et al. (2019)。

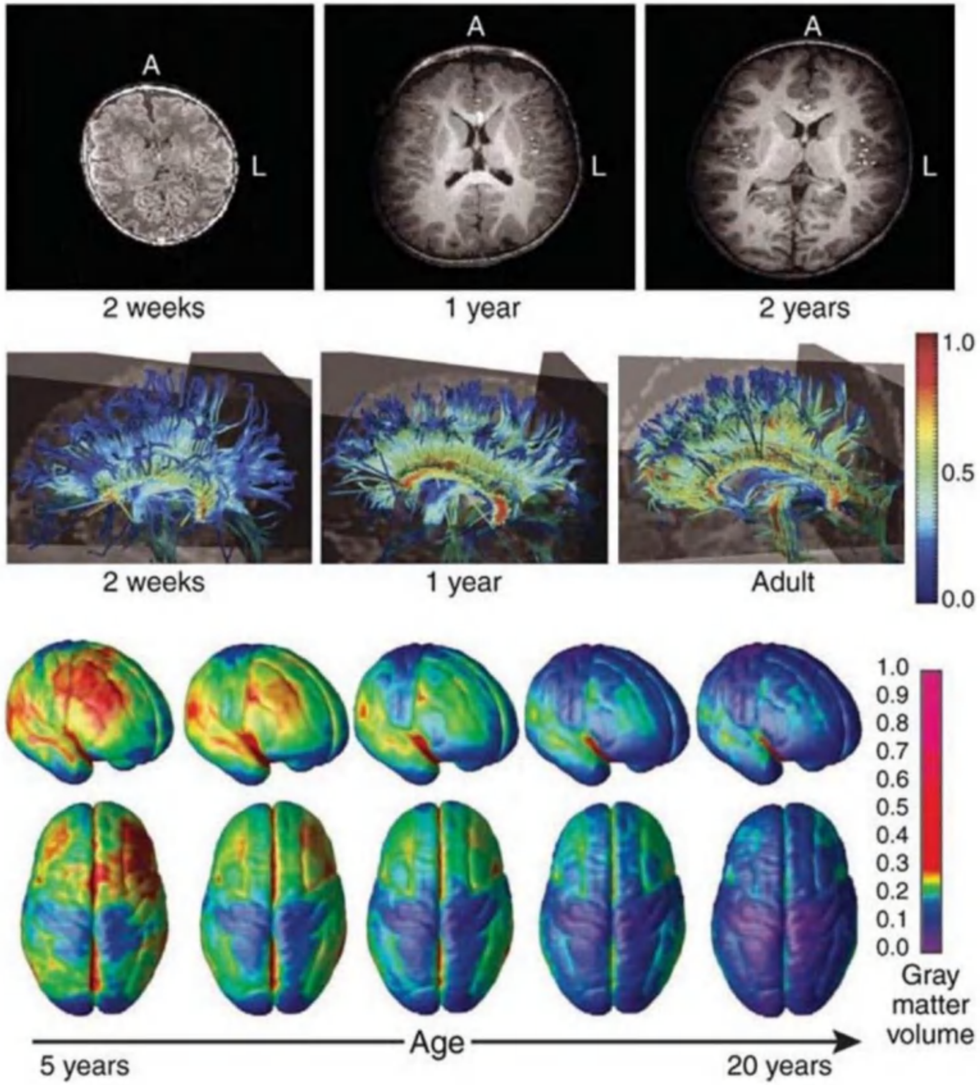
The Lifespan Development of Synapses

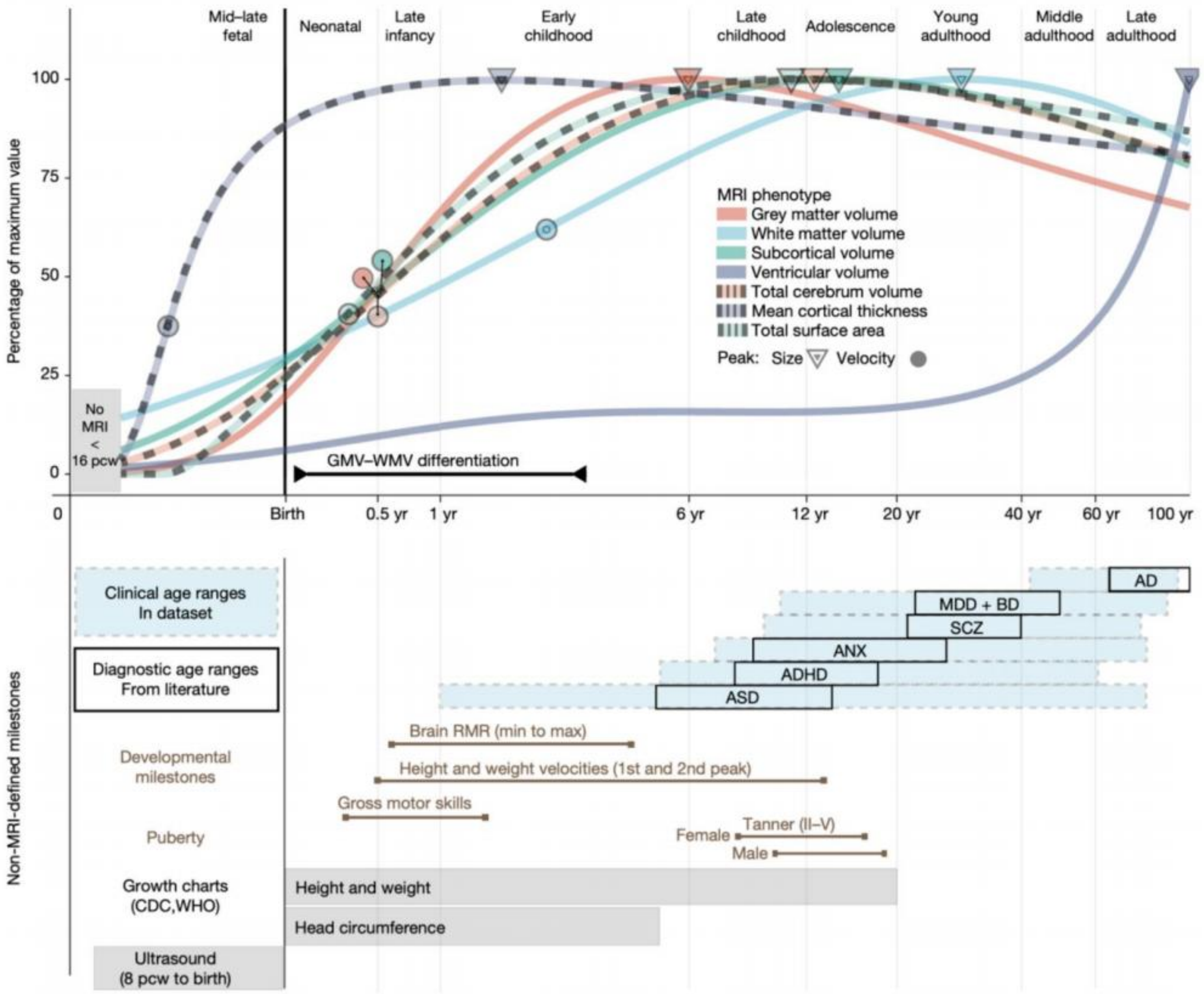
生命周期的突触多样性图谱



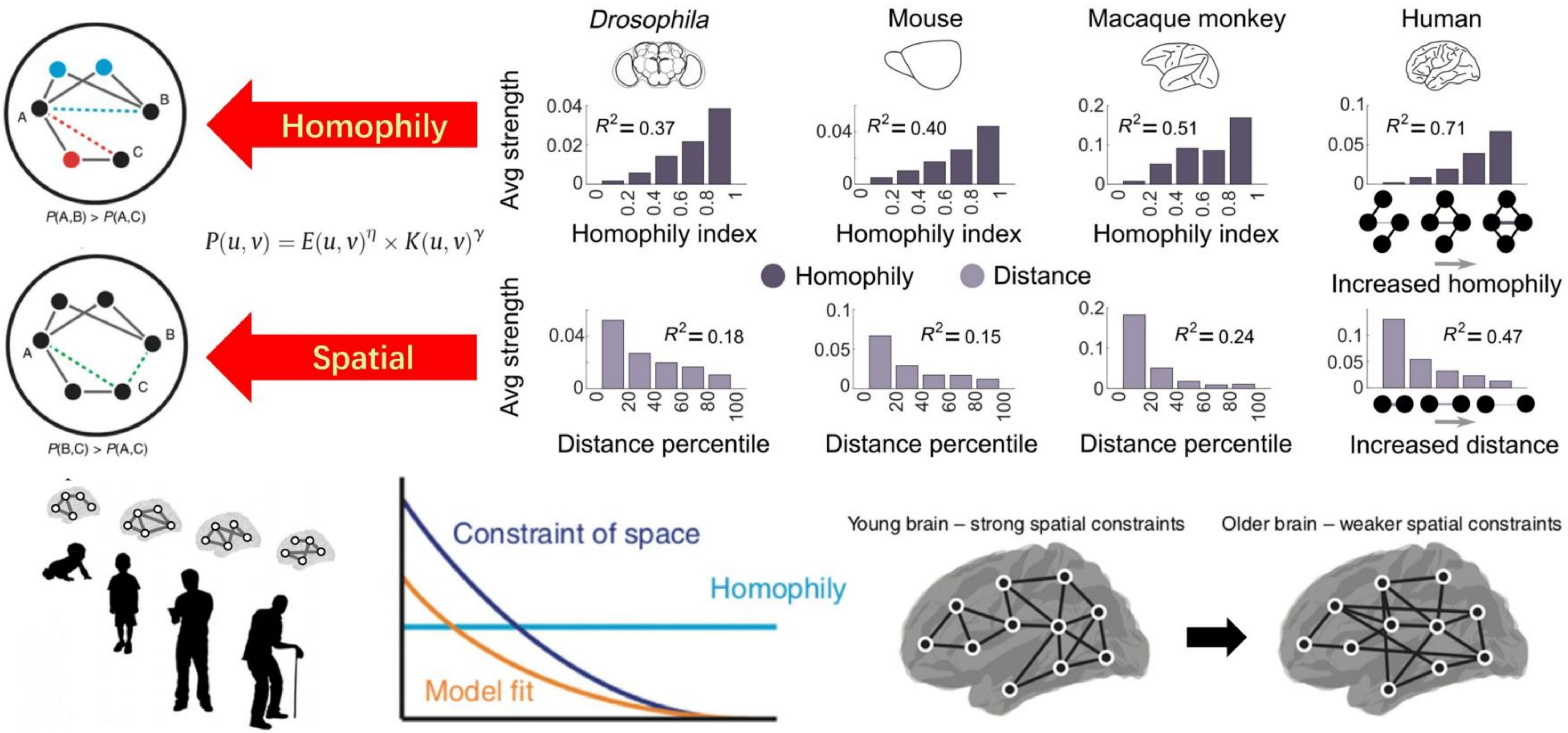
成年人脑中约含一千亿个神经元

The Lifespan Development of Human Brain

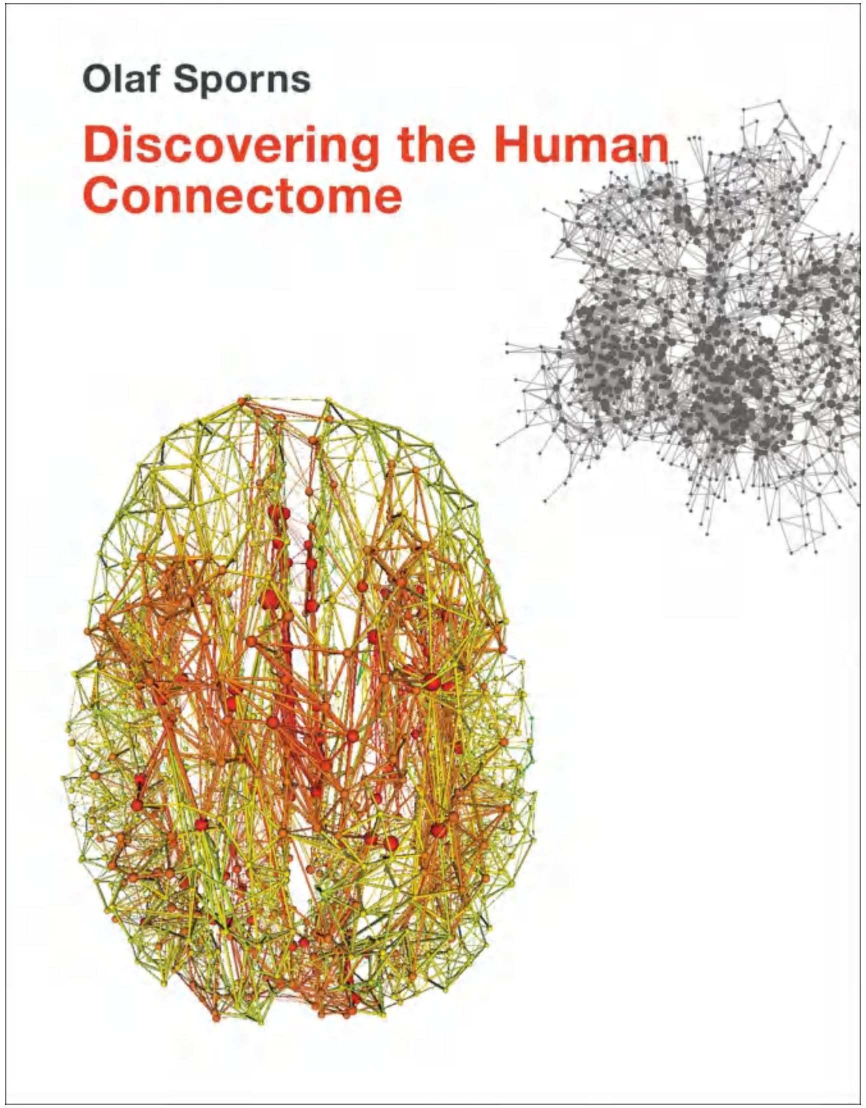


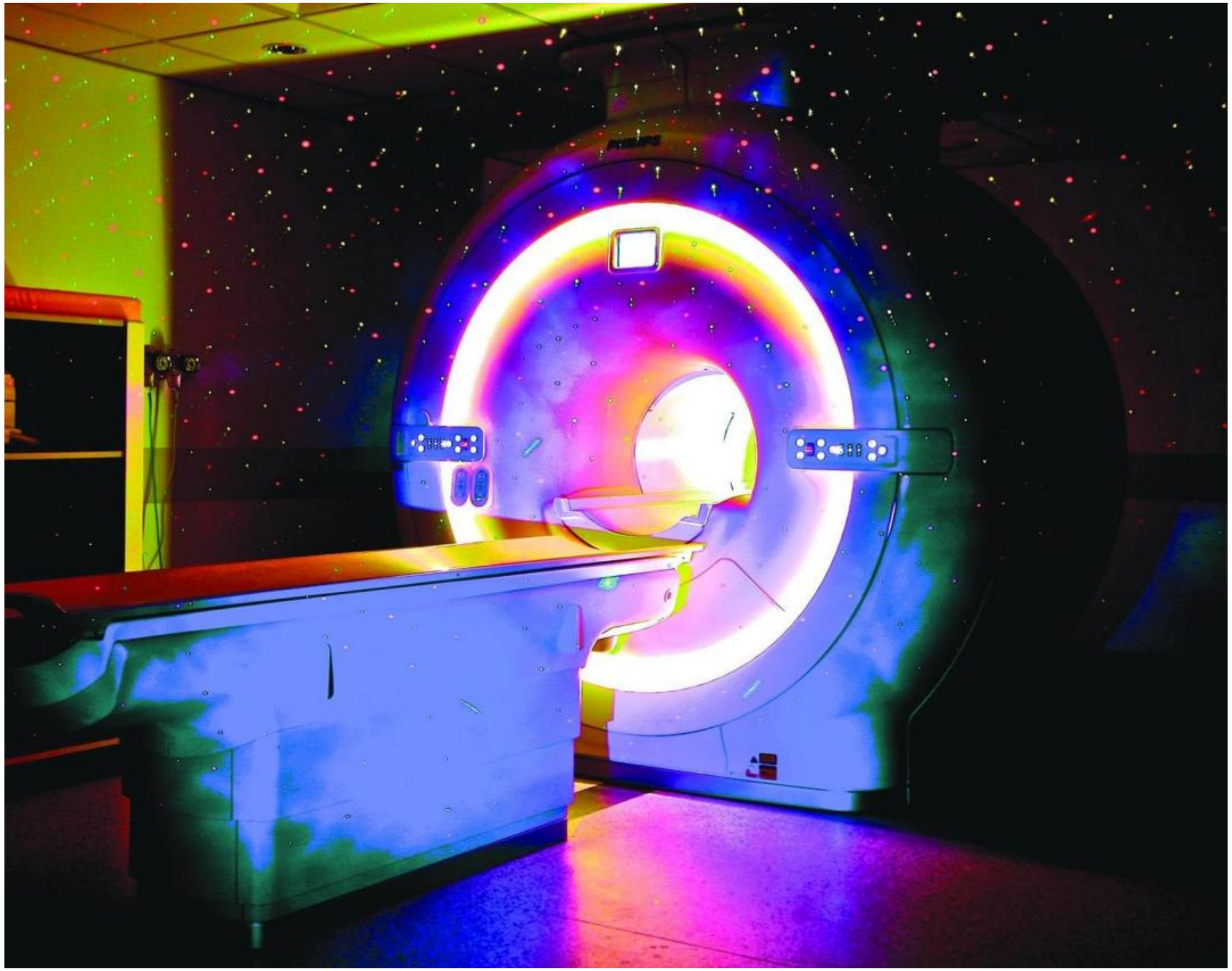


The Lifespan Development of Human Brain



The Human Brain Connectome





Imaging The Development of Human Brain Connectome

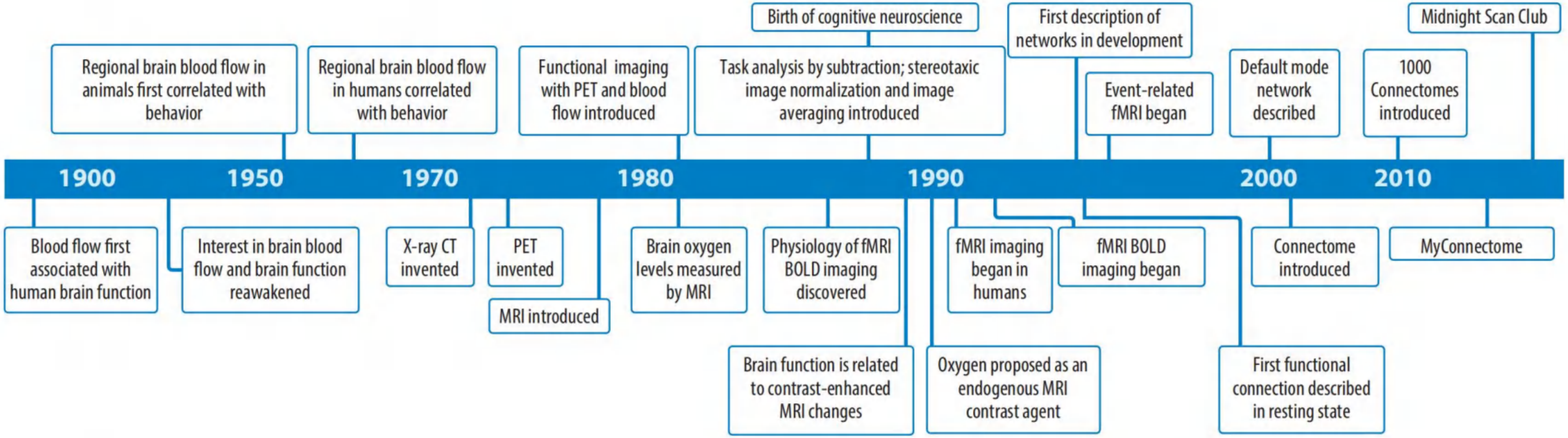
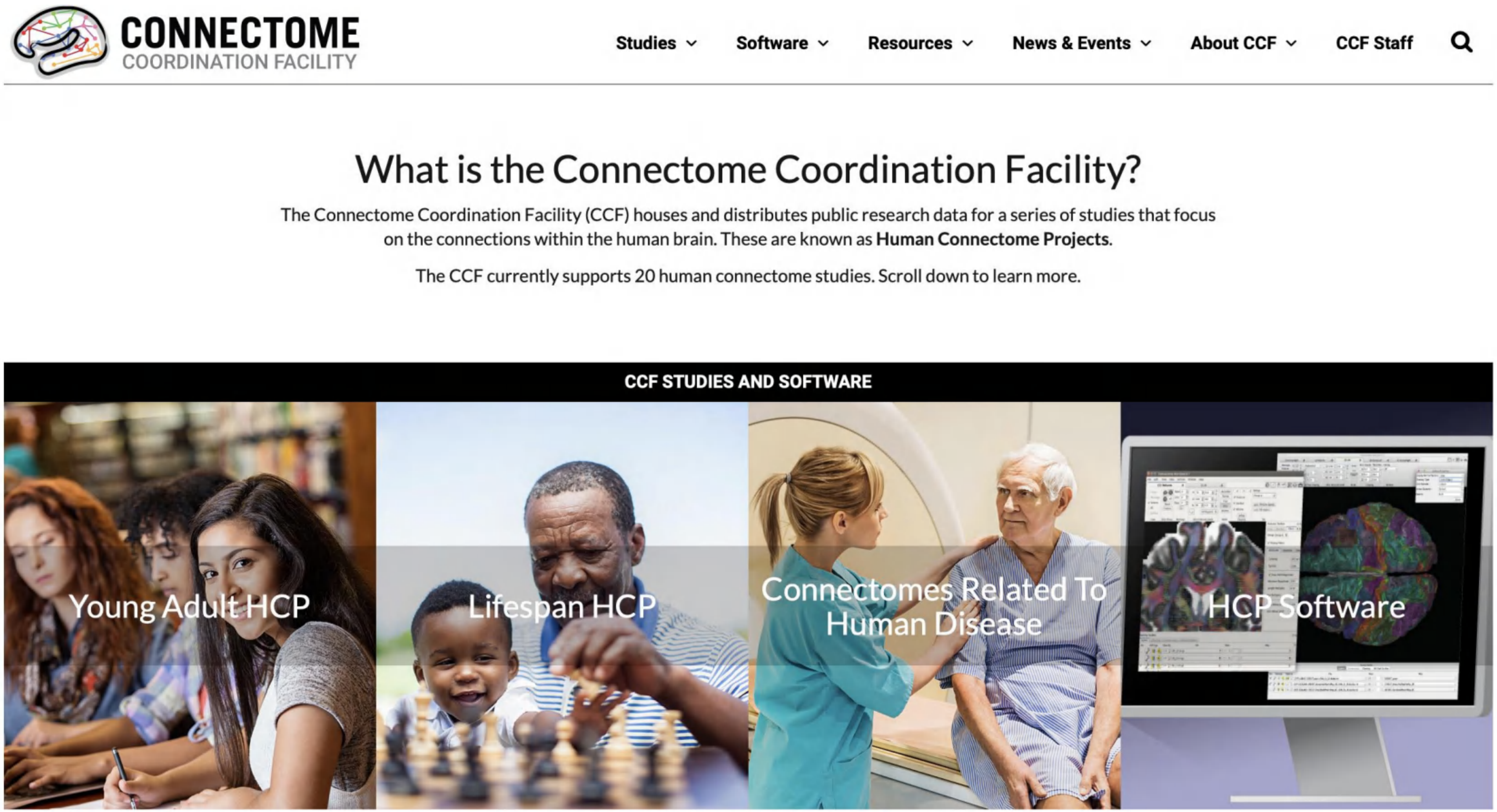


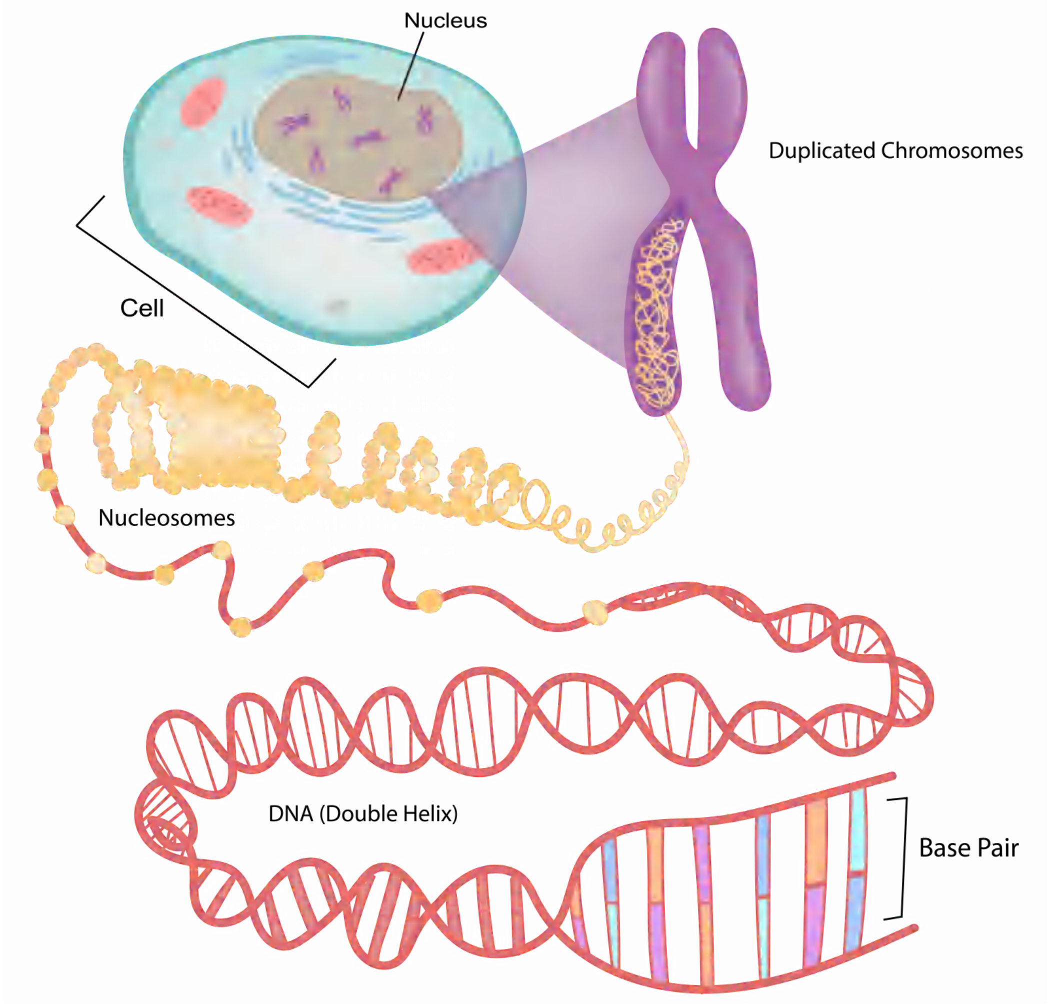
Figure 1

Timeline of developments in brain mapping and network neuroscience. Abbreviations: BOLD, blood oxygenation level–dependent; CT, computerized tomography; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission topography. Figure adapted with permission from Raichle (2009).

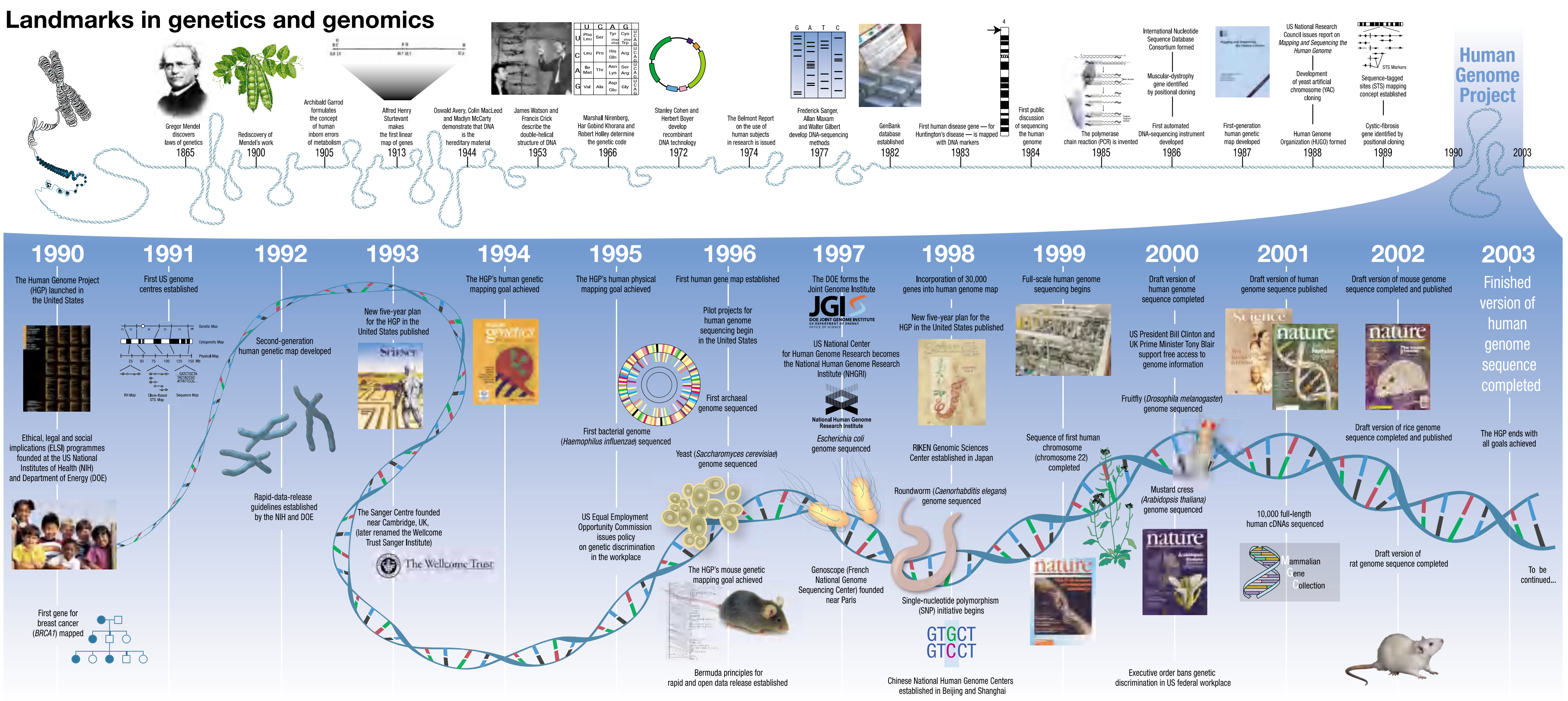
The Human Connectome Project



The Human Genome



The Human Genome Project



PEAS COURTESY J. BLAMIRE, CITY UNIV. NEW YORK; WATSON & CRICK COURTESY A. BARRINGTON BROWN/SPL; *SCIENCE* COVERS COURTESY AAAS

The Human Brain in Numbers: Counting Neurons, Why?

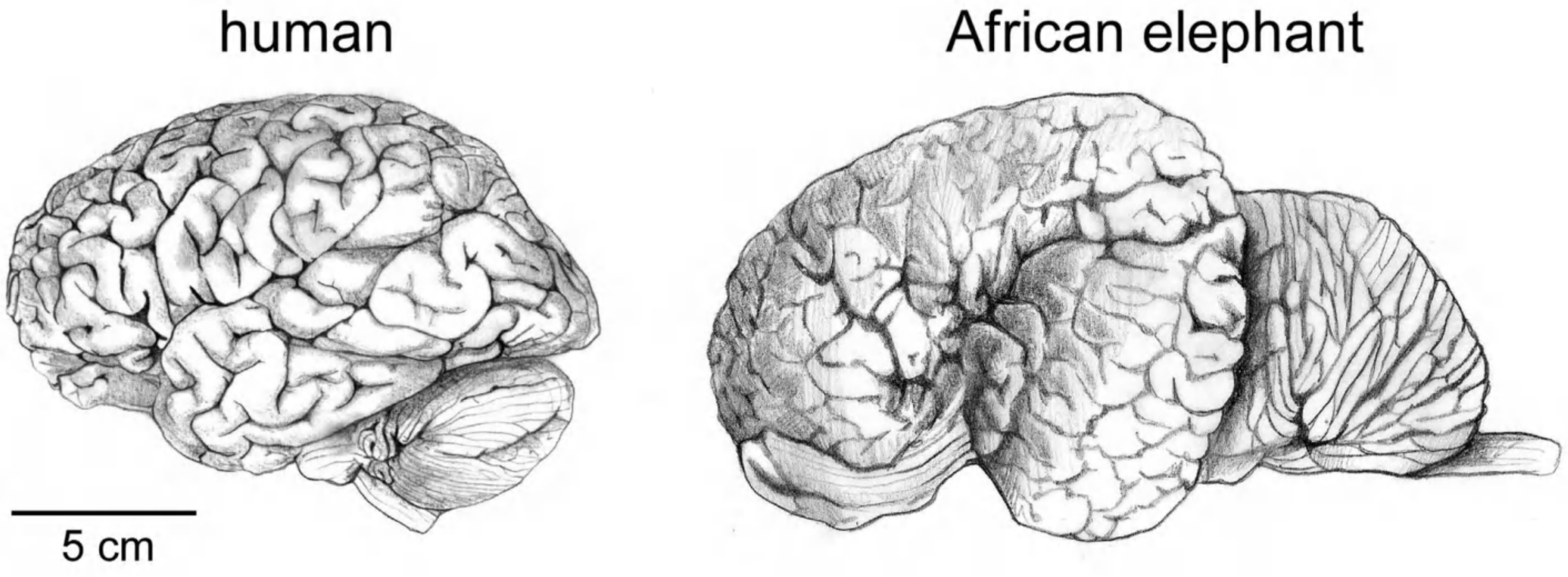
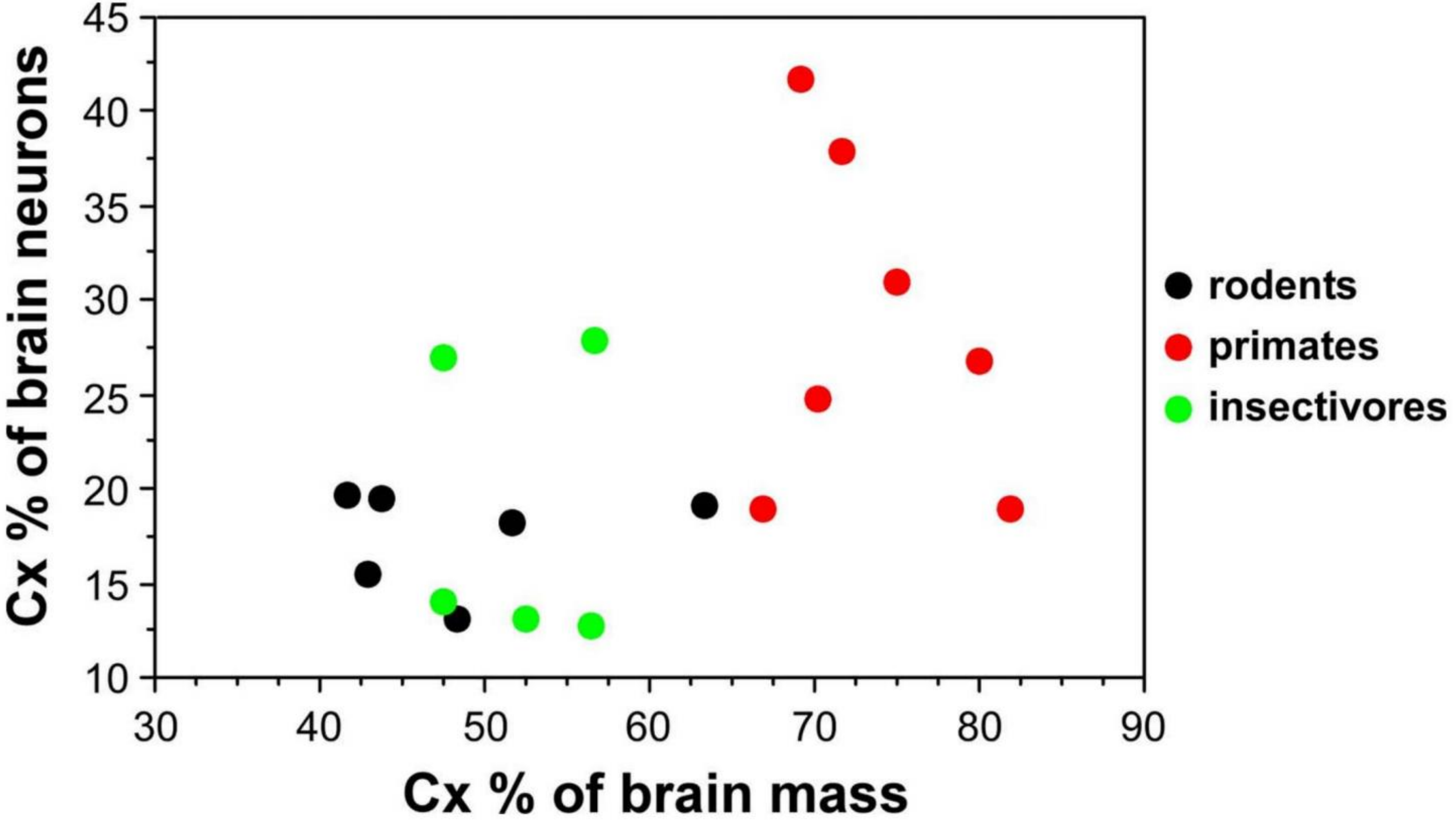
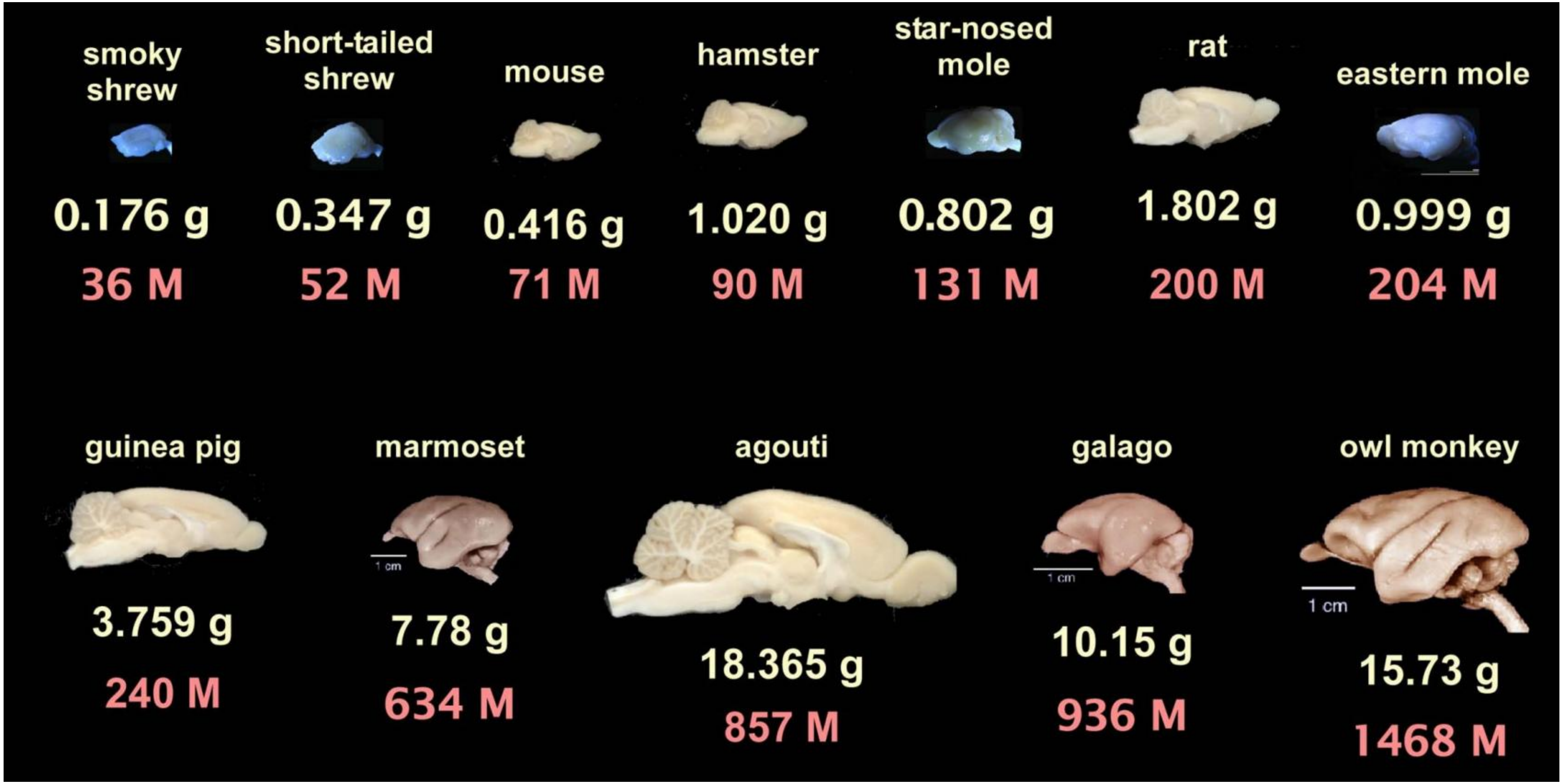


FIGURE 1 | The human brain is not the largest. Brains of a human and of an African elephant are depicted here at the same scale. Drawings by Lorena Kaz based on images freely available from the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections

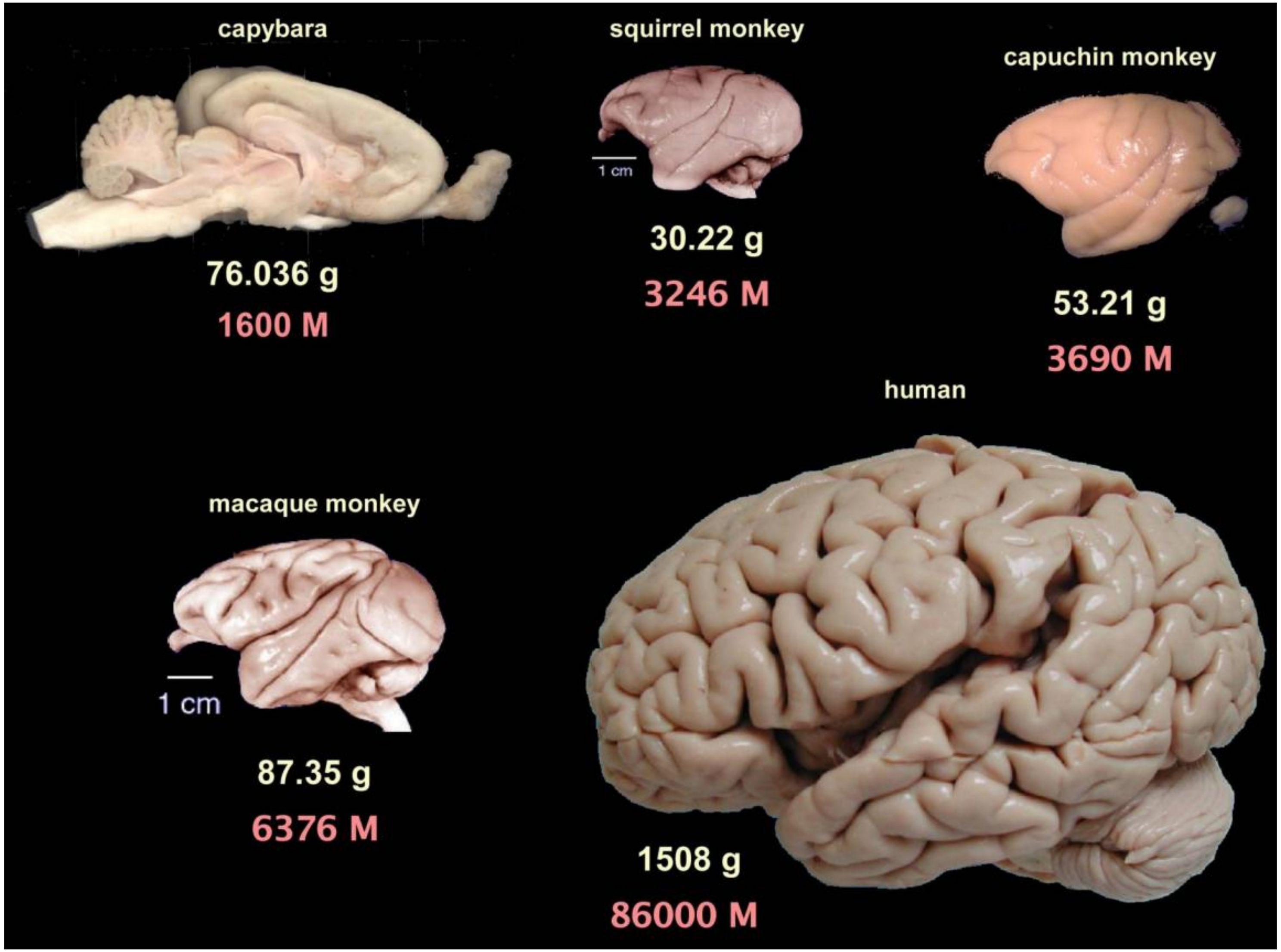
The Human Brain in Numbers: Not Relative Size

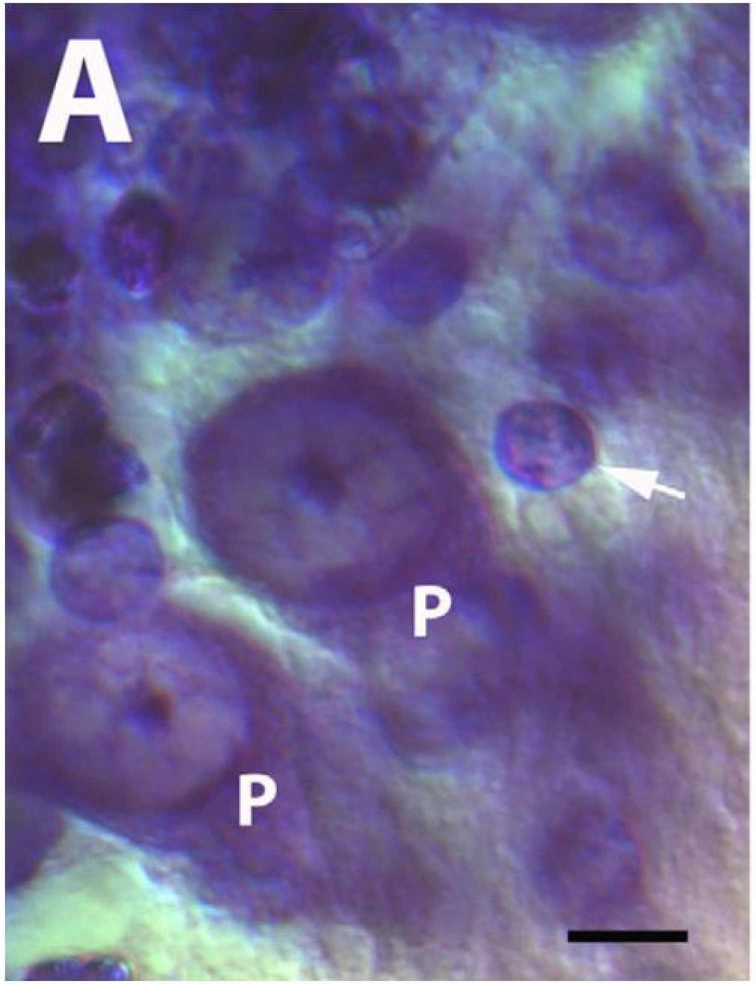


The Human Brain in Numbers: Counting Neurons

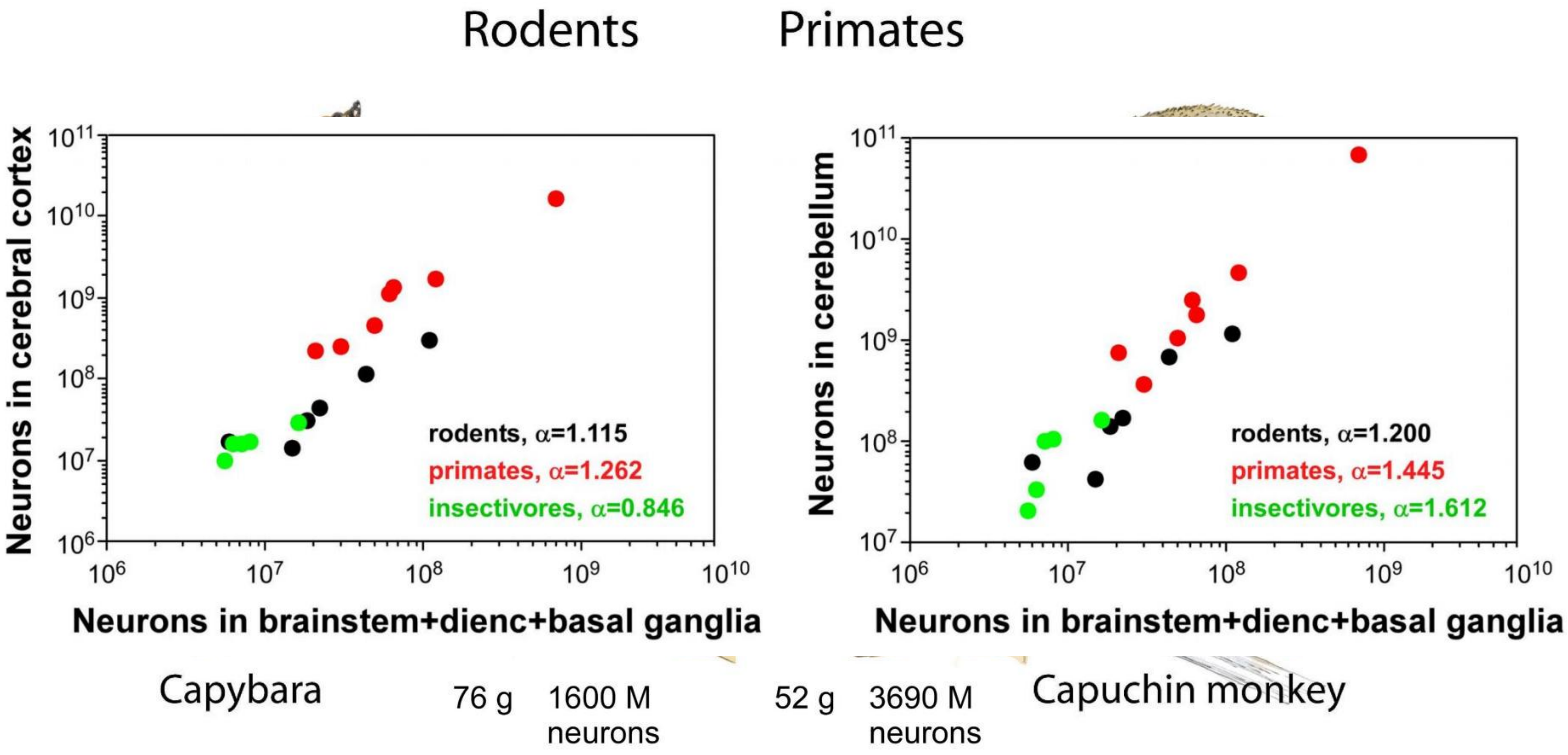


The Human Brain in Numbers: Counting Neurons





The Human Brain in Numbers: Scaling Matters



The Human Brain in Numbers: Reading The History

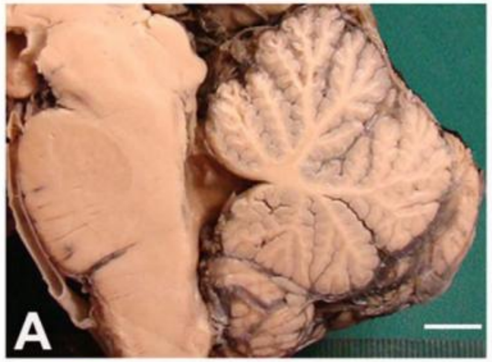
REVIEW

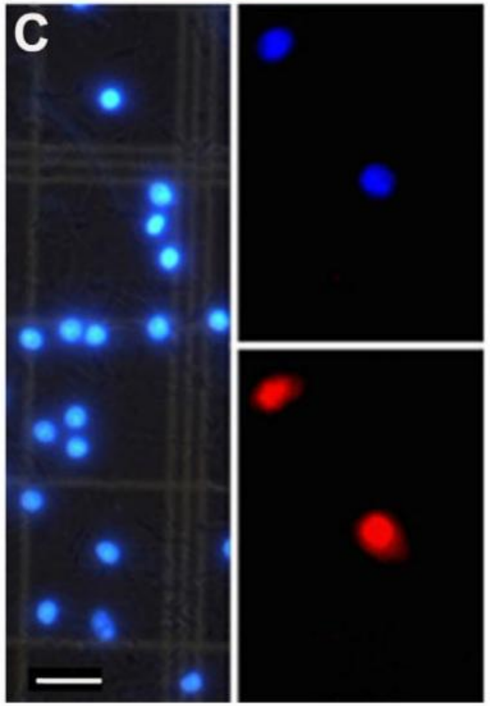
The Search for True Numbers of Neurons and Glial Cells in the Human Brain: A Review of 150 Years of Cell Counting

Reports of Glia-Neuron Ratios (GNRs), Numbers of Total Cells, Glia, and Neurons in Human Brain

GNR	Total cell number	Glia #	Neuron #	Method	Reference
10:1		> "several trillions" (probably)			Verkhratsky & Butt, 2007
1:1	170 bn	<85 bn	86 bn	IF	Azevedo et al., 2009
6:1	[767 bn]	[667 bn](85%)	100 bn (15%)		Fields, 2009
G≫N (glia # "much higher" than neuron #)					Brodal, 2010
3:1 or 4:1			100 bn		Purves, 2010
~1:1 "human brain contains roughly equal numbers of glia and neurons"					Smith, 2010
10:1 ("at least")					Nicholls et al., 2012, 5th ed
2:1-10:1		[200 bn - 1 trn]	100 bn		Kandel et al., 2013, 5th ed
1:1					Verkhratsky & Butt, 2013
~1:1		<78.6 bn	67.3	IF	Andrade-Moraes et al., 2013

The Human Brain in Numbers: Counting Methods





1. Fix brain tissue → 2. Homogenize

↓

3. Collect homogenate → 4. Centrifugate 10’

↓

5. Remove supernatant → 6. Add DAPI: count nuclei in supernatant

↓

7. Suspend nuclei in exact volume (Vol) of DAPI, PBS: **isotropic suspension**

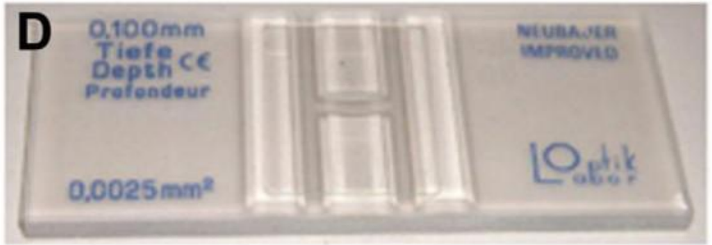
↓

8. Count aliquots: **total cell number = dens nuclei x Vol**

9. Stain sample for NeuN

10. Count aliquots: determine Fr NeuN+

Total neuron number = Fr NeuN+ x Total cell number



The Human Brain in Numbers: History

Estimates of Numbers of Neurons (N), Non-neurons (nN), and Glia (G) in Human Cerebral Cortex (in billion)

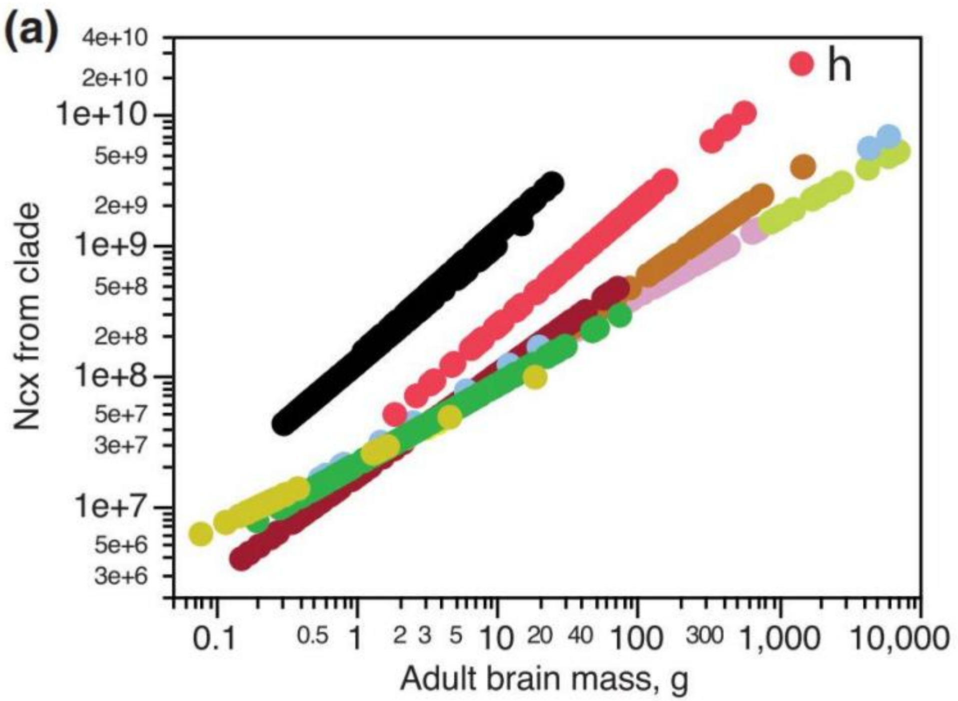
Author	Year	N One side	N Total	nN Total	G Total
Meynert	1868/1872	0.612	1.224		
Donaldson	1895		1.200		
Thompson	1899		9.282		
Berger	1921		5.512		
von Economo & Koskinas	1925		14		
von Economo	1926		13.653		
Agduhr	1941		5.0		
Shariff	1953		6.9		
Sholl	1956	5.000	10.000		
Haug & Rebhan	1956		16.5		
Haug	1959	8.200	16.400		
Pakkenberg	1966		2.6		
Gallatz et al.	1982		10.030		
Haug	1985		13.8 ± 2.4		
Haug	1987		10-19		
Pakkenberg et al.	1989		$\sim$20		
Braendgaard et al.	1990	13.7	[27.4]		
Pakkenberg	1992		25.1		
Jensen & Pakkenberg	1993		23.2		
Pakkenberg	1993		22.1		
Regeur et al.	1994		18.1		
Pakkenberg & Gundersen	1997		19.3-22.8 [range: 14.7 - 32.0]		
Gredal et al.	2000		22.3		
Pakkenberg et al.	2003		19.3-22.8		39
Pelvig et al.	2003		21.2		29.1
Koch	2004		20		
Pedersen et al.	2005		18.8		
Pelvig et al.	2008		21.4-26.3		27.9-38.9
Azevedo et al.	2009	6.18	12.36		
Azevedo et al.	2009		[16.34]	[60.84]	
Lyck et al.	2009		[15-19.7]	[35.4-40.6]	[18.5-20.3]
Karlsen & Pakkenberg	2011		17.9		18.2
Andrade-Moraes et al.	2013		[12.7]	[54.9]	

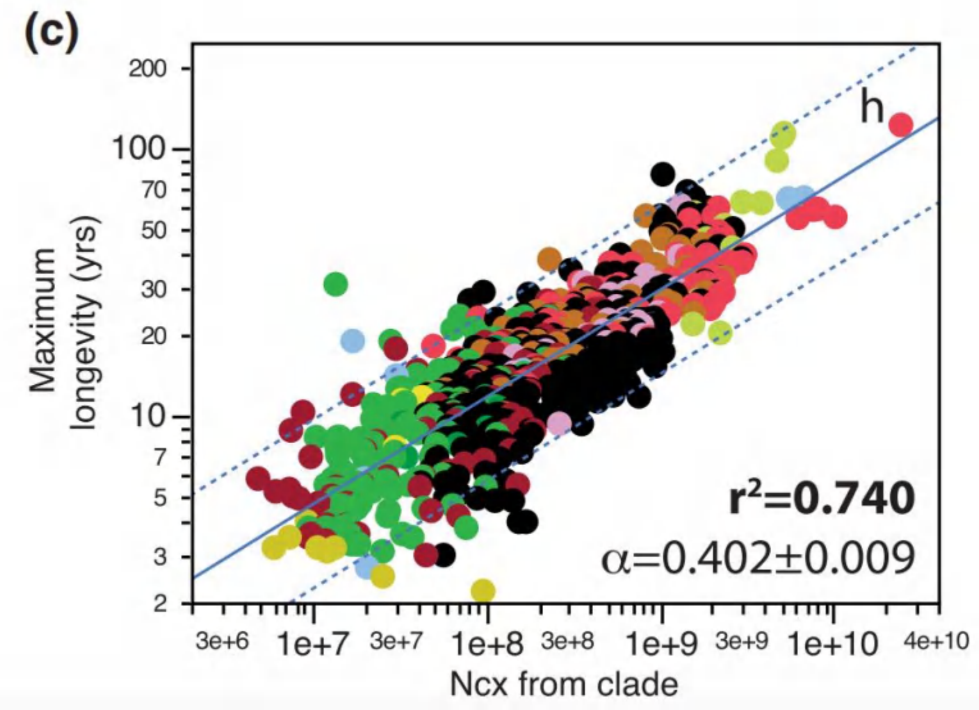
The Human Brain in Numbers: Why?!

RESEARCH ARTICLE

JCN RESEARCH IN SYSTEMS NEUROSCIENCE THE JOURNAL OF COMPARATIVE NEUROLOGY WILEY

Longevity and sexual maturity vary across species with number of cortical neurons, and humans are no exception



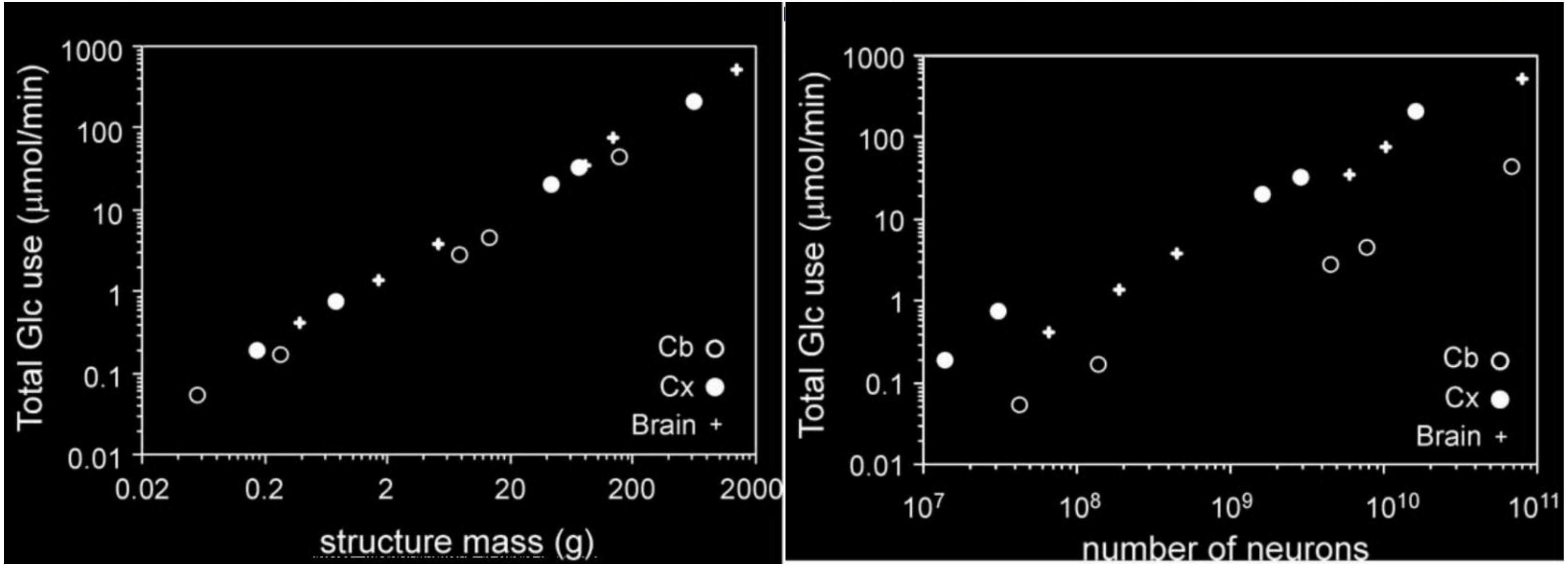


The Human Brain in Numbers: Budgets per Neuron

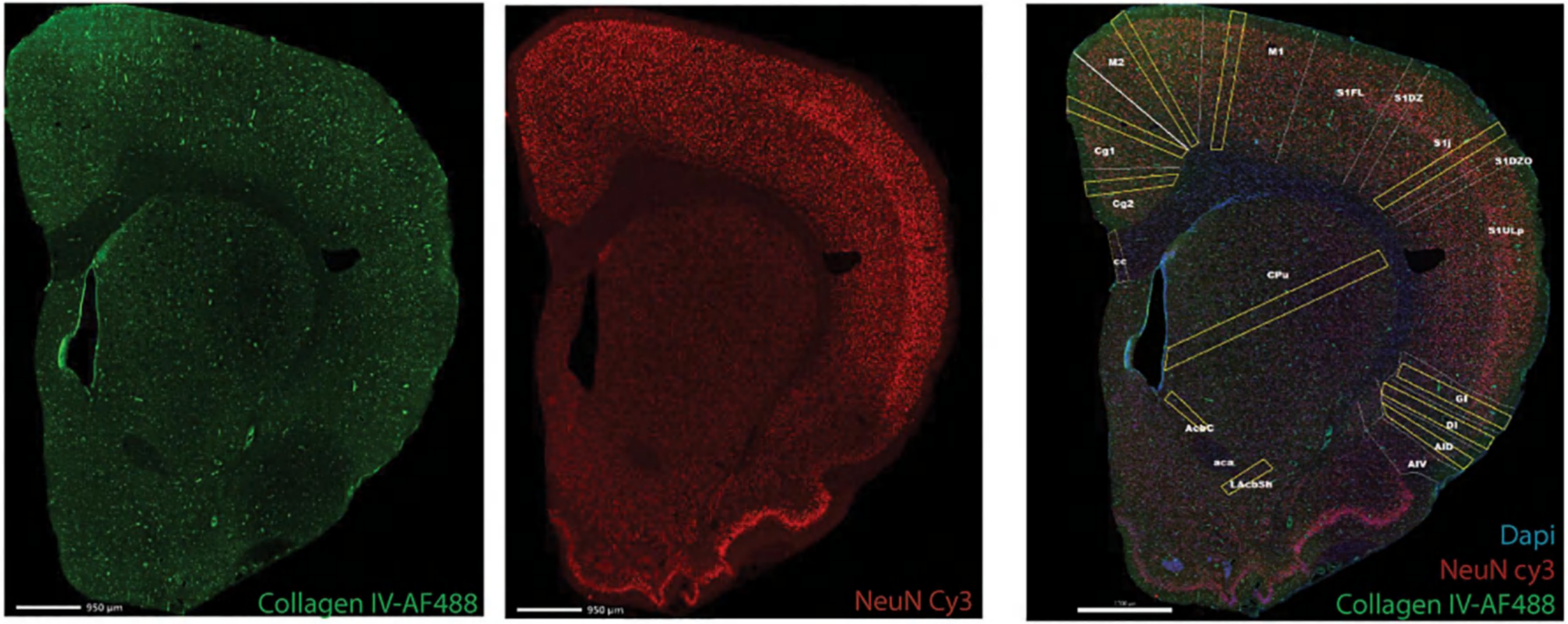
Scaling of Brain Metabolism with a Fixed Energy Budget per Neuron: Implications for Neuronal Activity, Plasticity and Evolution

Hey! brain uses 20% budgets with only 2% weight .

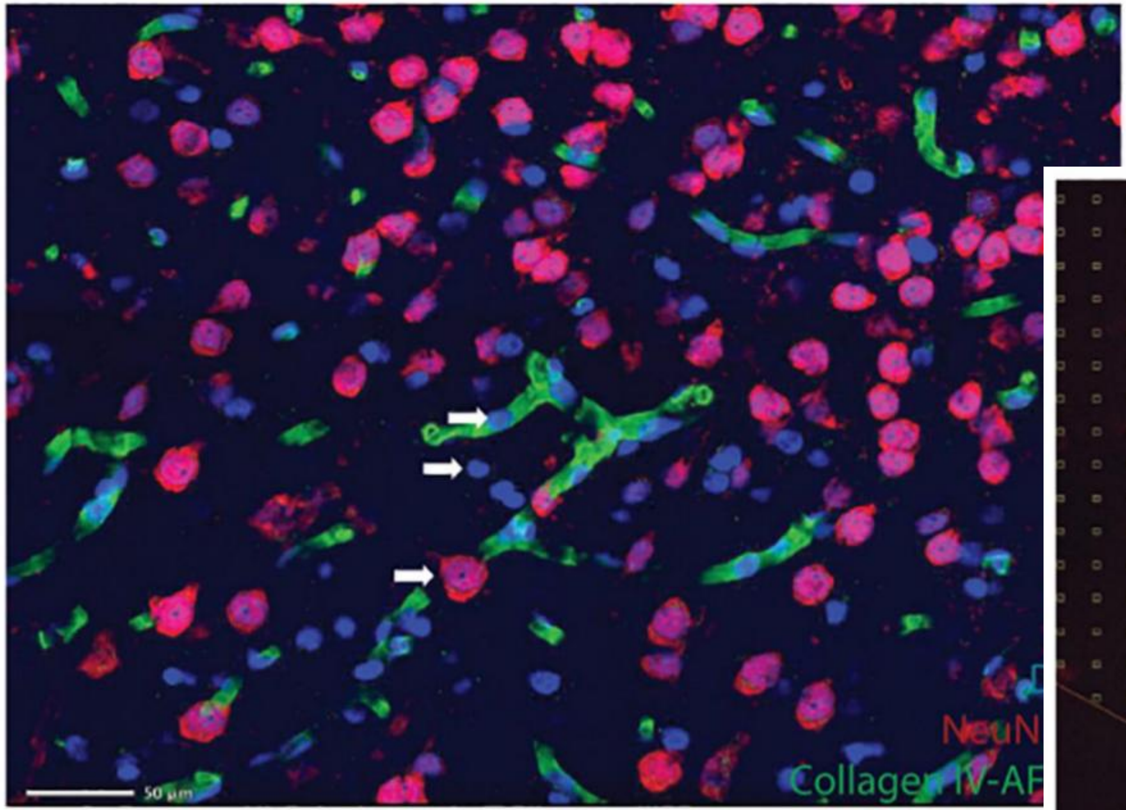
Suzana Herculano-Houzel[1,2*]

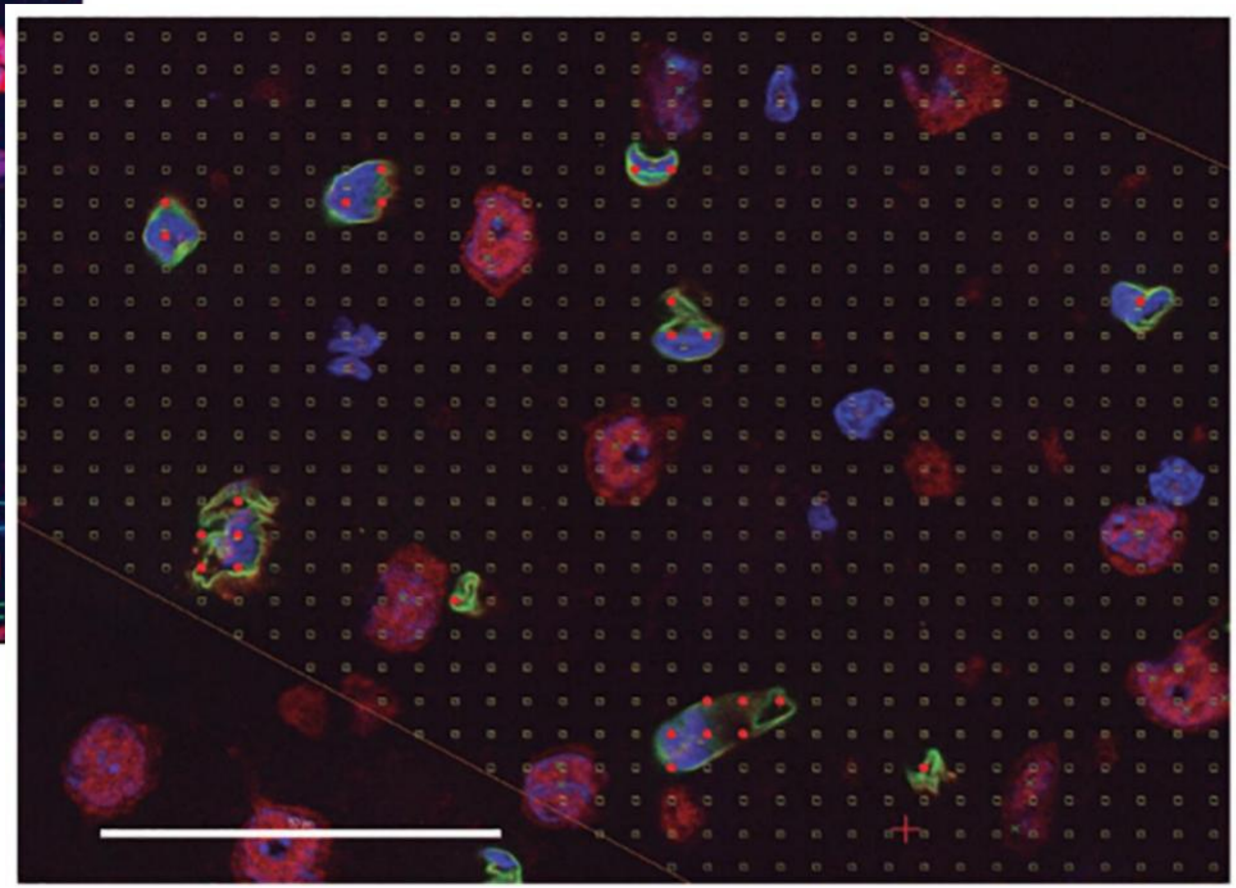


The Human Brain in Numbers: Budgets per Neuron

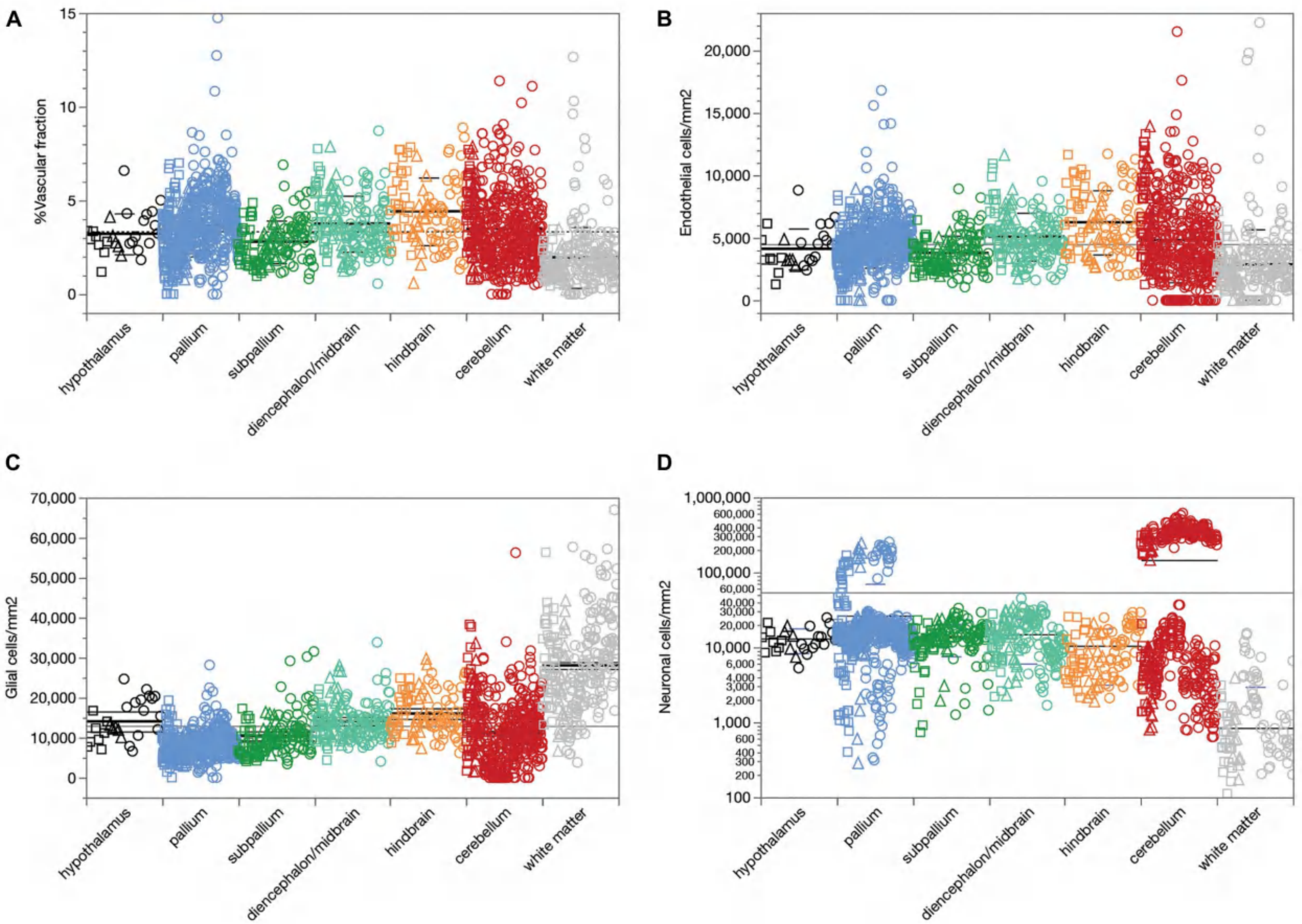


The Human Brain in Numbers: Budgets per Neuron





The Human Brain in Numbers: Budgets per Neuron



The Human Brain in Numbers: Budgets per Neuron

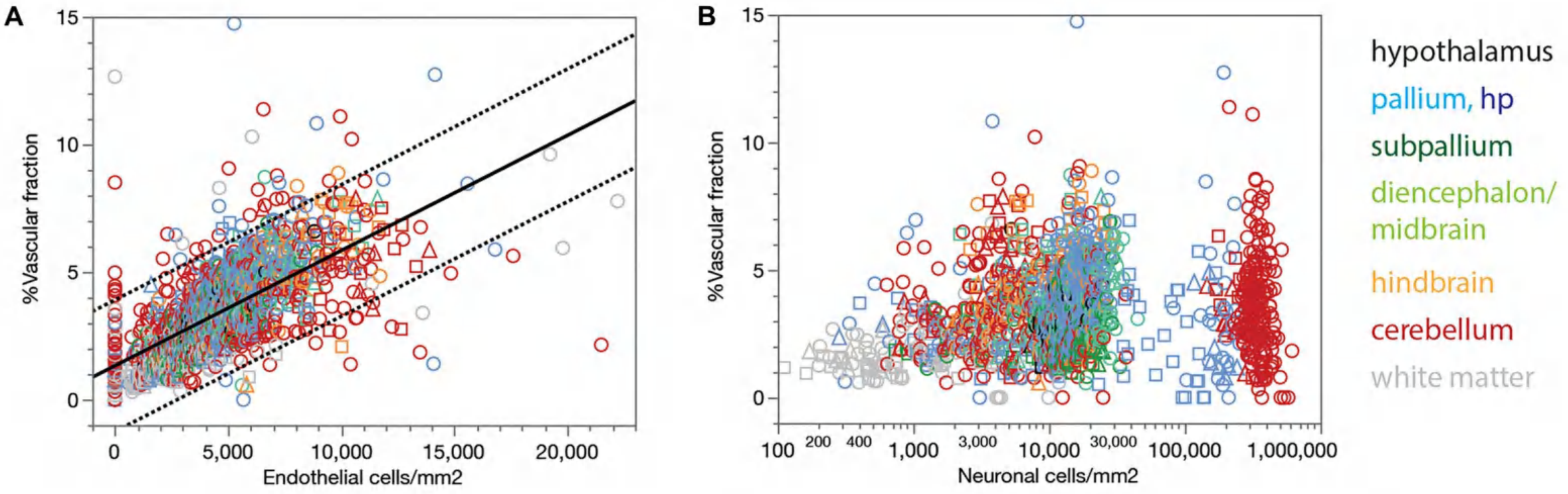
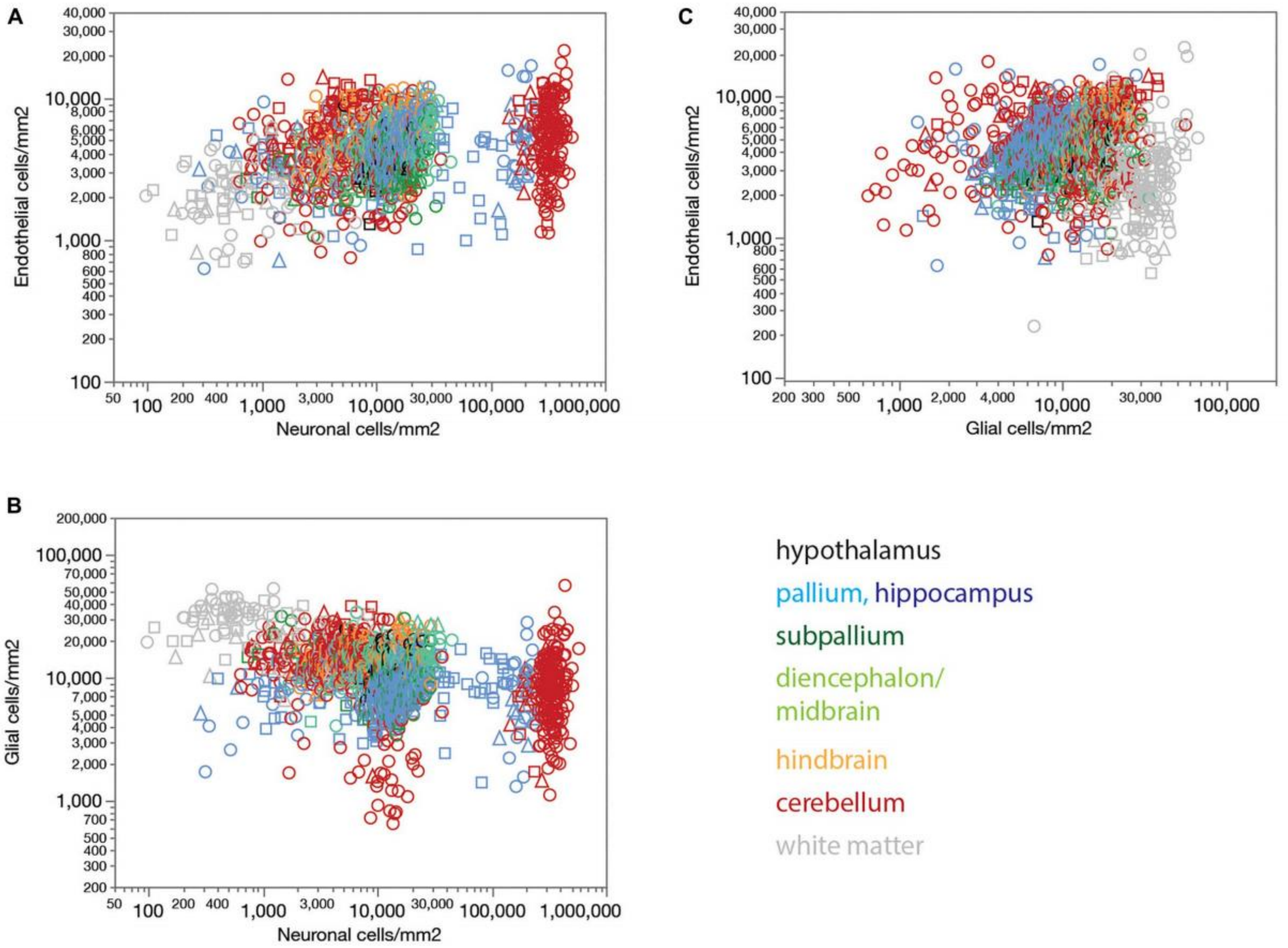
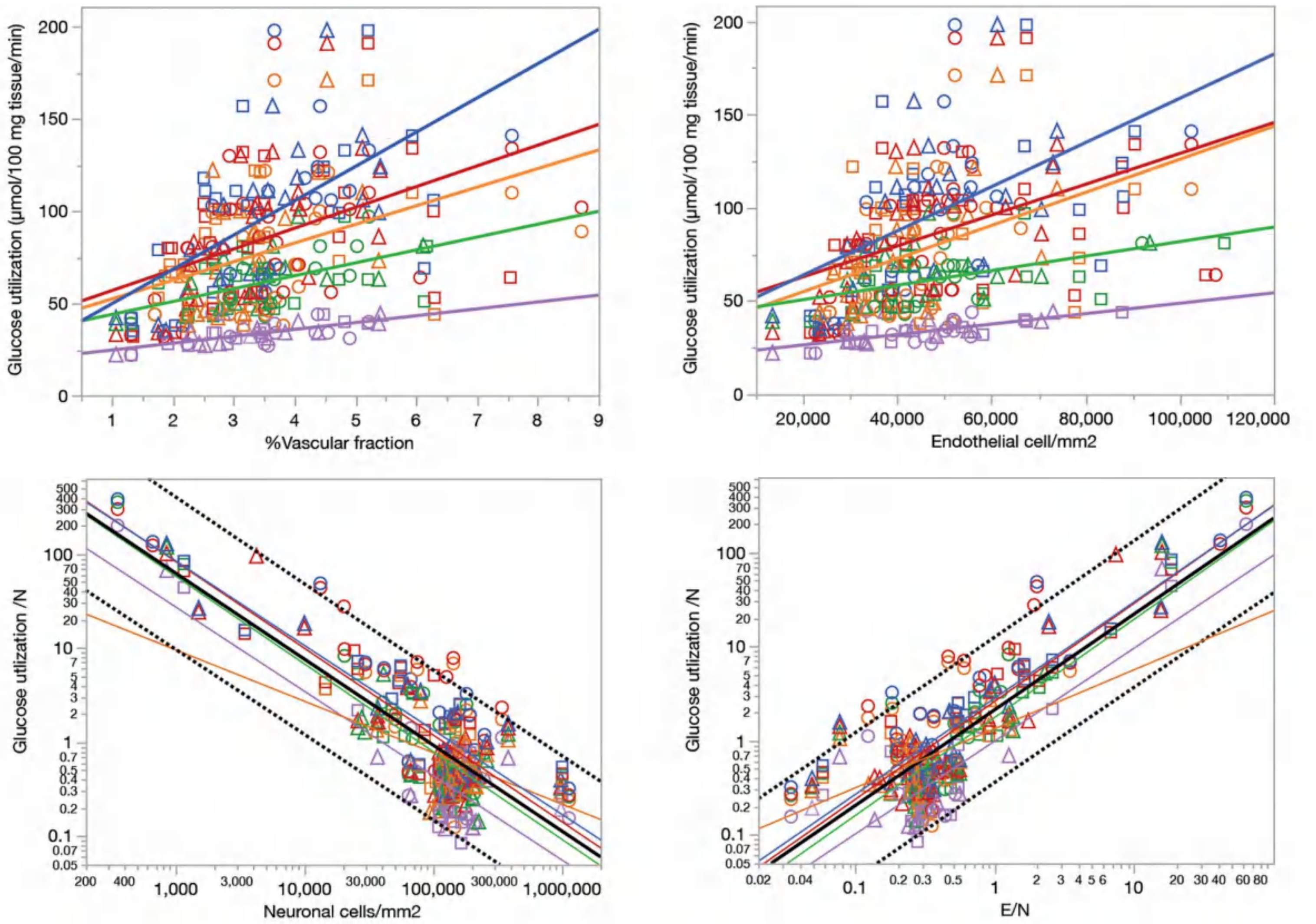


FIGURE 3 | Local vascular fraction increases with endothelial cell density but does not accompany local neuronal density consistently across brain structures. **(A)** Local vascular fraction varies as a linear function of endothelial cell densities across all ROIs of all three animals, and also across sites within each brain subdivision. Spearman correlation across all sites: $\rho = 0.742$, $p < 0.0001$. Spearman correlation within brain subdivisions: Hypothalamus, $\rho = 0.790$, $p < 0.0001$; pallium, $\rho = 0.711$, $p < 0.0001$; subpallium, $\rho = 0.765$, $p < 0.0001$; diencephalon/midbrain, $\rho = 0.801$, $p < 0.0001$; hindbrain, $\rho = 0.806$, $p < 0.0001$; cerebellum, $\rho = 0.654$, $p < 0.0001$; white matter, $\rho = 0.670$, $p < 0.0001$. **(B)** Local vascular fraction correlates significantly with local neuronal density across sites within several brain structures, but not consistently across structures, such that highly disparate neuronal densities occur with similar vascular fractions across structures. Spearman correlation across all sites: $\rho = 0.286$, $p < 0.0001$. Spearman correlation within brain subdivisions: Hypothalamus, $\rho = 0.437$, $p = 0.0226$; non-hippocampal pallium, $\rho = 0.419$, $p < 0.0001$; whole pallium, $\rho = 0.250$, $p < 0.0001$; subpallium, $\rho = 0.099$, $p = 0.2594$; diencephalon/midbrain, $\rho = 0.243$, $p = 0.0017$; hindbrain, $\rho = 0.248$, $p = 0.0005$; cerebellum, $\rho = 0.027$, $p = 0.5511$; white matter, $\rho = -0.002$, $p = 0.9766$.

The Human Brain in Numbers: Budgets per Neuron

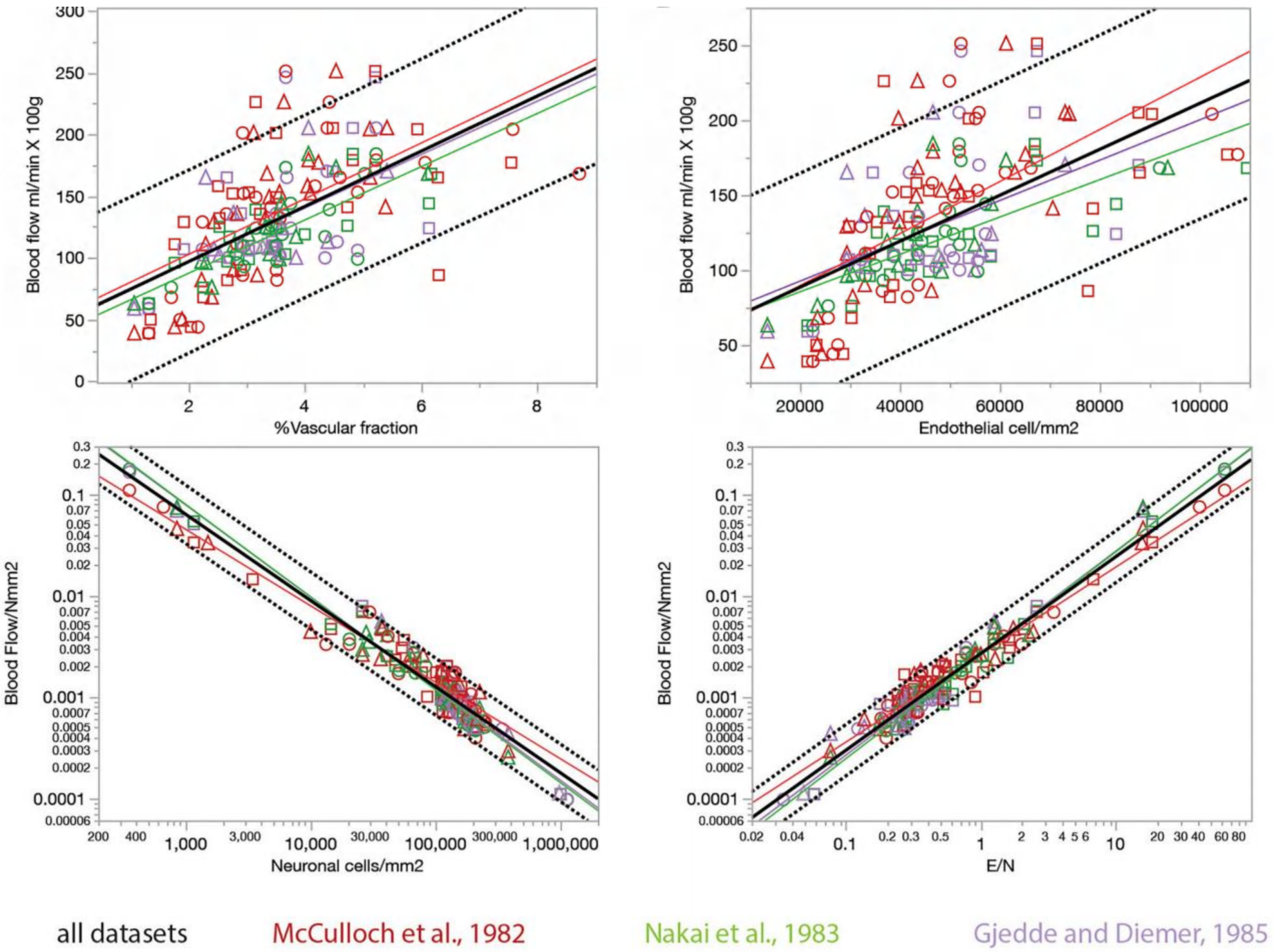


The Human Brain in Numbers: Budgets per Neuron



Sokoloff et al., 1977 McCulloch et al., 1982 Nakai et al., 1983 Gjedde and Diemer, 1985 Levant and Pazdernak, 2004

The Human Brain in Numbers: Budgets per Neuron



The Human Brain in Numbers: Budgets per Neuron

Neuroscientists have become used to a number of "facts" about the human brain: It has 100 billion neurons and 10- to 50-fold more glial cells; it is the largest-than-expected for its body among primates and mammals in general, and therefore the most cognitively able; it consumes an outstanding 20% of the total body energy budget despite representing only 2% of body mass because of an increased metabolic need of its neurons; and it is endowed with an overdeveloped cerebral cortex, the largest compared with brain size. These facts led to the widespread notion that the human brain is literally extraordinary: an outlier among mammalian brains, defying evolutionary rules that apply to other species, with a uniqueness seemingly necessary to justify the superior cognitive abilities of humans over mammals with even larger brains. These facts, with deep implications for neurophysiology and evolutionary biology, are not grounded on solid evidence or sound assumptions, however. Our recent development of a method that allows rapid and reliable quantification of the numbers of cells that compose the whole brain has provided a means to verify these facts. Here, I review this recent evidence and argue that, with 86 billion neurons and just as many nonneuronal cells, the human brain is a scaled-up primate brain in its cellular composition and metabolic cost, with a relatively enlarged cerebral cortex that does not have a relatively larger number of brain neurons yet is remarkable in its cognitive abilities and metabolism simply because of its extremely large number of neurons.

PNAS

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)

Neuroscientists have become used to a number of "facts" about the human brain: It has 100 billion neurons and 10- to 50-fold more glial cells; it is the largest-than-expected for its body among primates and mammals in general, and therefore the most cognitively able; it consumes an outstanding 20% of the total body energy budget despite representing only 2% of body mass because of an increased metabolic need of its neurons; and it is endowed with an overdeveloped cerebral cortex, the largest compared with brain size. These facts led to the widespread notion that the human brain is literally extraordinary: an outlier among mammalian brains, defying evolutionary rules that apply to other species, with a uniqueness seemingly necessary to justify the superior cognitive abilities of humans over mammals with even larger brains. These facts, with deep implications for neurophysiology and evolutionary biology, are not grounded on solid evidence or sound assumptions, however. Our recent development of a method that allows rapid and reliable quantification of the numbers of cells that compose the whole brain has provided a means to verify these facts. Here, I review this recent evidence and argue that, with 86 billion neurons and just as many nonneuronal cells, the human brain is a scaled-up primate brain in its cellular composition and metabolic cost, with a relatively enlarged cerebral cortex that does not have a relatively larger number of brain neurons yet is remarkable in its cognitive abilities and metabolism simply because of its extremely large number of neurons.

glia/neuron ratio | human evolution | encephalization

If the basis for cognition lies in the brain, how can it be that the self-designated most cognitively able of animals—us, of course—is not the one endowed with the largest brain? The logic behind the paradox is simple: Because brains are made of neurons, it seems reasonable to expect larger brains to be made of larger numbers of neurons; if neurons are the computational units of the brain, then larger brains, made of larger numbers of neurons, should have larger computational abilities than smaller brains. By this logic, humans should not rank even an honorable second in cognitive abilities among animals: at about 1.5 kg, the human brain is two- to threefold smaller than the elephant brain and four- to sixfold smaller than the brains of several cetaceans (1, 2). Nevertheless, we are so convinced of our primacy that we carry it explicitly in the name given by Linnaeus to the mammalian order to which we belong—*Primata*, meaning "first rank," and we are seemingly the only animal species concerned with developing entire research programs to study itself.

Humans also do not rank first, or even close to first, in relative brain size (expressed as a percentage of body mass), in absolute size of the cerebral cortex, or in gyrification (3). At best, we rank first in the relative size of the cerebral cortex expressed as a percentage of brain mass, but not by far. Although the human cerebral cortex is the largest among mammals in its relative size, at 75.5% (4), 75.7% (5), or even 84.0% (6) of the entire brain mass or volume, other animals, primate and nonprimate, are not far behind: The cerebral cortex represents 73.0% of the entire brain mass in the chimpanzee (7), 74.5% in the horse, and 73.4% in the short-finned whale (3).

The incongruity between our extraordinary cognitive abilities and our not-that-extraordinary brain size has been the major driving factor behind the idea that the human brain is an outlier, an exception to the rules that have applied to the evolution of all other animals and brains. A largely accepted alternative explanation for our cognitive superiority over other mammals has been our extraordinary brain size compared with our body size, that is, our large encephalization quotient (8). Compared with the trend for brain mass to increase together with body mass across mammalian species in a fashion that can be described mathematically by a power law (9), the human species appears to be an outlier, with a brain that is about sevenfold larger than expected from its body mass compared with mammals as a whole (10), or threefold larger than expected compared with other primates (2), although how we came to be that way has not been well accounted for in the literature.

Why should a larger-than-expected brain bring about larger cognitive abilities? That notion is based on the idea that an "excess brain mass," relative to the brain mass necessary to operate the body, would endow the behavior of more encephalized animals with more complexity and flexibility (11). The most encephalized species should also be the most cognitively able, and that species, finally, was our own.

However, the notion that higher encephalization correlates with improved cognitive abilities has recently been disputed in favor of absolute numbers of cortical neurons and connections (12), or simply absolute brain size (13). If encephalization were the main determinant of cognitive abilities, small-brained animals with very large encephalization quotients, such as capuchin monkeys, should be more cognitively able than large-brained but less encephalized animals, such as the gorilla (2). However, the former animals with a smaller brain are outranked by the latter in cognitive performance (13).

It remains possible that the source of incongruence between our cognitive abilities and brain size is an unwarranted comparison of species across orders. Such comparisons are based on the notion, implicit in most comparative studies to date, that different brains are just scaled-up or scaled-down versions of a common basic plan, such that larger brains always have more neurons than smaller brains and two brains of a similar size always have comparable numbers of neurons. However, this notion is in disagreement with the observation that animals of similar brain size but belonging to different mammalian orders, such as the cow and the chimpanzee (both at about 400 g of brain mass), or the rhesus monkey and the capybara (at 70–80 g of brain mass), may have strikingly different cognitive abilities and behavioral reper-

This paper results from the Arthur M. Sackler Colloquium of the National Academy of Sciences, "In the Light of Evolution VI: Brain and Behavior," held January 19–21, 2012, at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, CA. The complete program and audio files of most presentations are available on the NAS Web site at www.nasonline.org/evolution_vi.

Author contributions: S.H.-H. wrote the paper.

The author declares no conflict of interest.

This article is a PNAS Direct Submission.

[1]E-mail: suzanahh@gmail.com.

The Human Brain in Numbers: Brain Museum

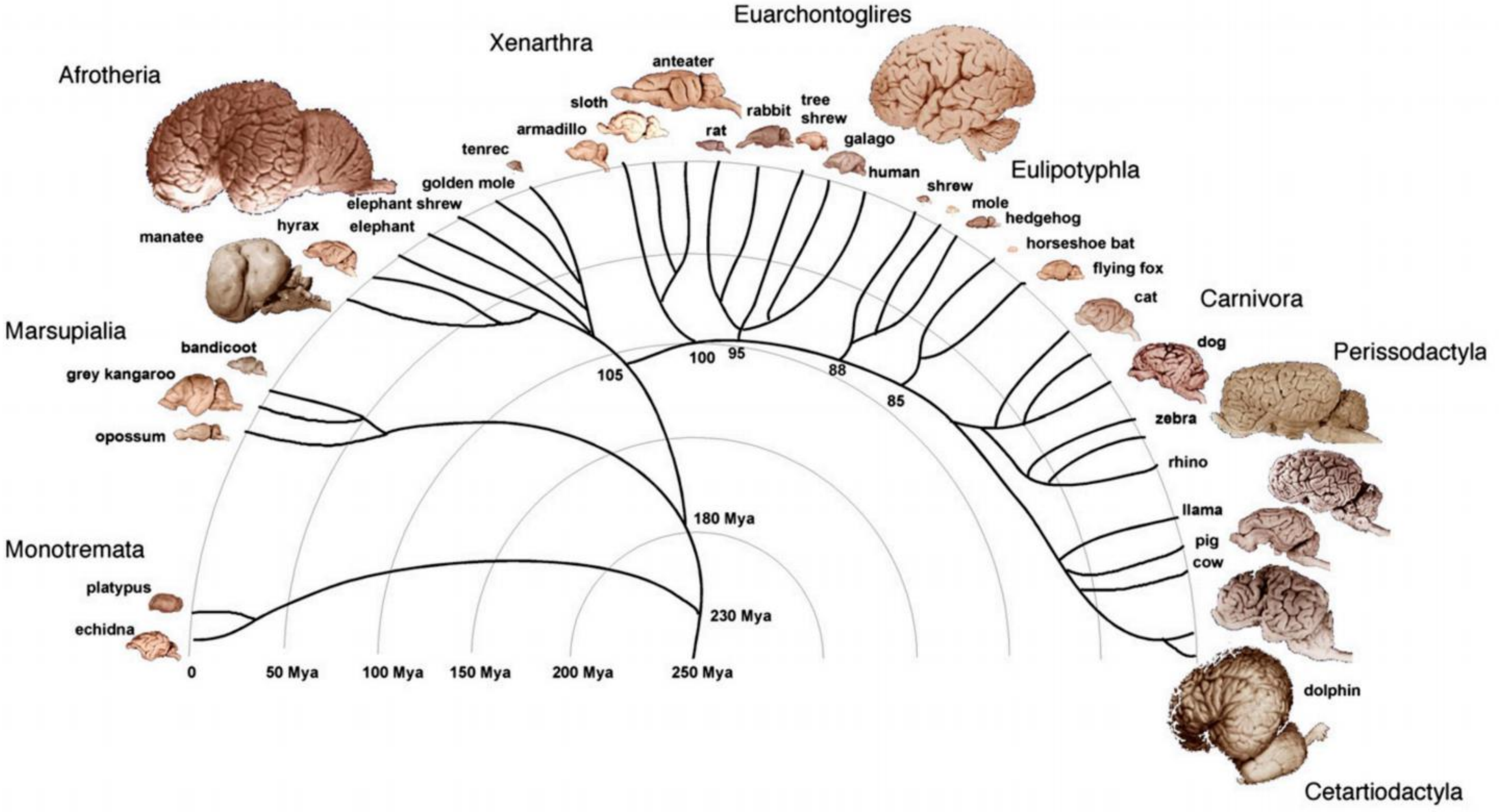


Fig. 1. Large brains appear several times in the mammalian radiation. Example species are illustrated for each major mammalian group. The mammalian radiation is based on the findings of Murphy et al. (18) and Kaas (19). Brain images are from the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections (www.brainmuseum.org).

The Human Brain in Numbers: Brain Museum

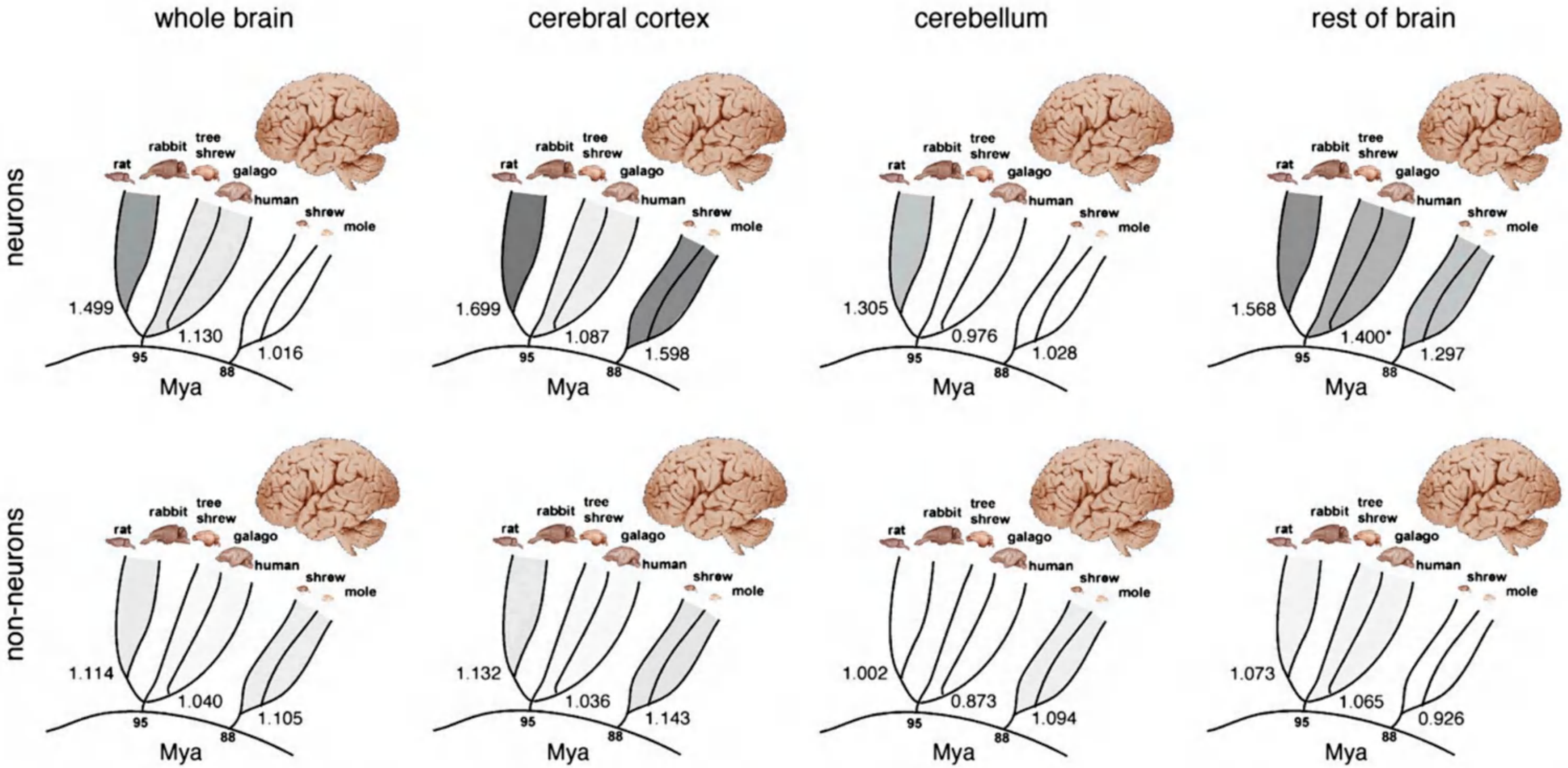


Fig. 2. Comparison of allometric exponents for total brain mass, cerebral cortex mass, cerebellar mass, and the rest of the brain mass as a function of numbers of neurons (*Upper*) or nonneuronal cells (*Lower*). Exponents, given at the base of the radiation of each individual group (Glires, Primata/Scandentia, and Eulipotyphla), are illustrated by the intensity of the shading. Data are from studies by Herculano-Houzel and her colleagues (22–27); exponents are from a study by Herculano-Houzel (20).

The Human Brain in Numbers: Scaling Brain Matters

White matter volume and white/gray matter ratio in mammalian species as a consequence of the universal scaling of cortical folding

Bruno Mota[a], Sandra E. Dos Santos[b], Lissa Ventura-Antunes[b], Débora Jardim-Messeder[c], Kleber Neves[c], Rodrigo S. Kazu[c,d], Stephen Noctor[e], Kelly Lambert[f], Mads F. Bertelsen[g], Paul R. Manger[h], Chet C. Sherwood[i,j], Jon H. Kaas[b,1], and Suzana Herculano-Houzel[b,k,l,1]

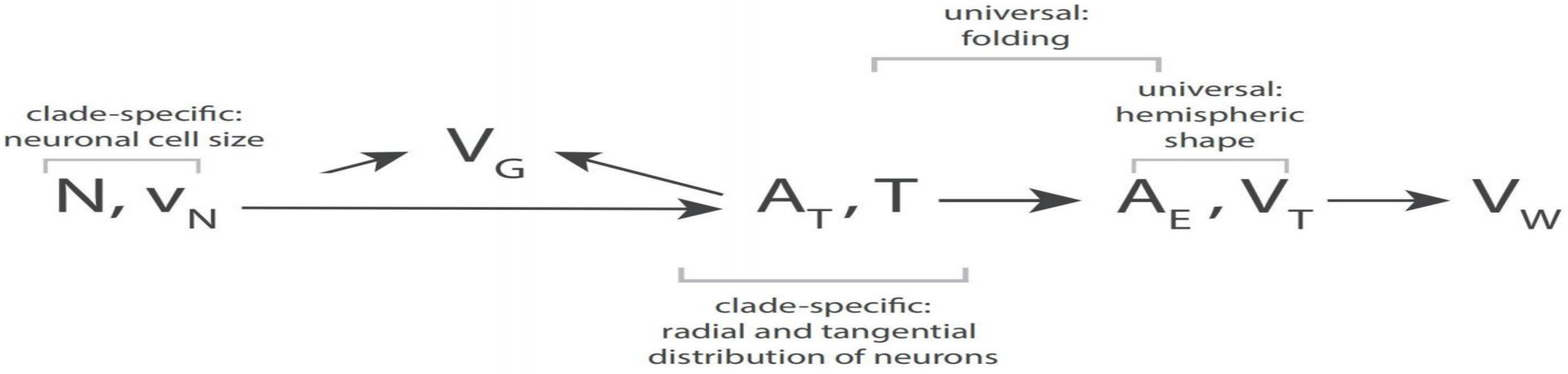
Because the white matter of the cerebral cortex contains axons that connect distant neurons in the cortical gray matter, the relationship between the volumes of the 2 cortical compartments is key for information transmission in the brain. It has been suggested that the volume of the white matter scales universally as a function of the volume of the gray matter across mammalian species, as would be expected if a global principle of wiring minimization applied. Using a systematic analysis across several mammalian clades, here we show that the volume of the white matter does not scale universally with the volume of the gray matter across mammals and is not optimized for wiring minimization. Instead, the ratio between volumes of gray and white matter is universally predicted by the same equation that predicts the degree of folding of the cerebral cortex, given the clade-specific scaling of cortical thickness, such that the volume of the gray matter (or the ratio of gray to total cortical volumes) divided by the square root of cortical thickness is a universal function of total cortical volume, regardless of the number of cortical neurons. Thus, the very mechanism that we propose to generate cortical folding also results in compactness of the white matter to a predictable degree across a wide variety of mammalian species.

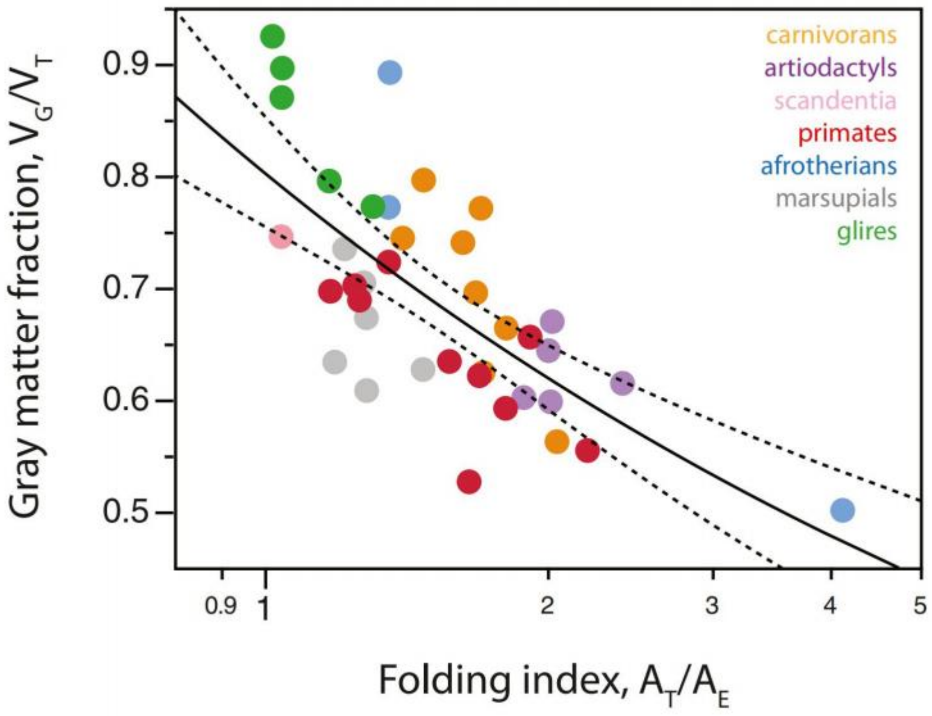
scaling | white matter | cortical folding | brain size | evolution

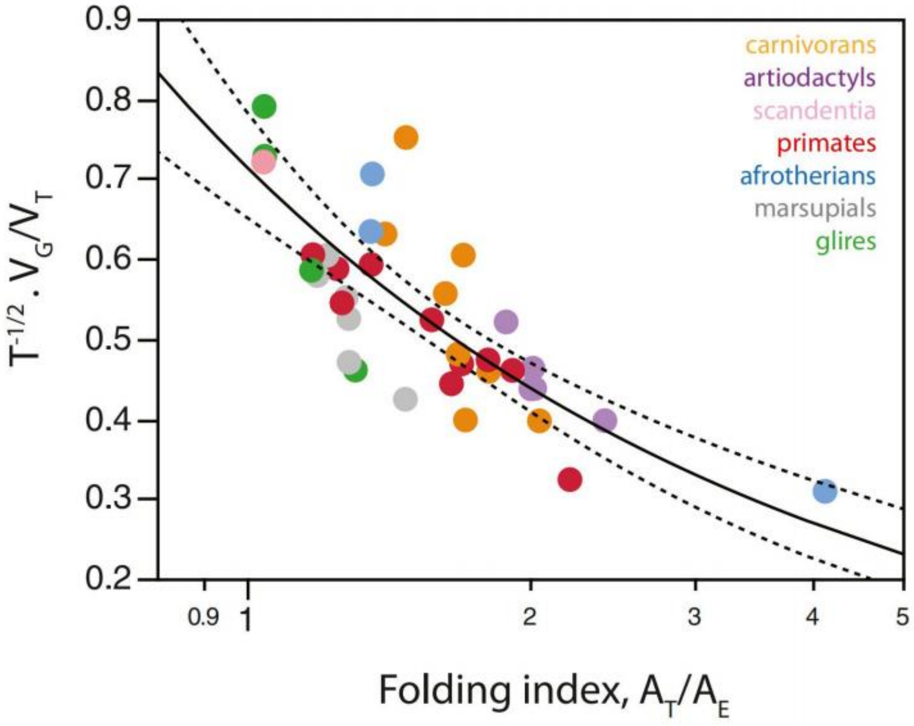
Significance

The white matter of the cerebral cortex contains all axons that support long-range cortical connectivity and increases faster in volume than the gray matter, which contains the connected cortical neuronal cell bodies. We show that the ratio between volumes of white and gray matter scales universally according to the same factors that account for the degree to which the cortex folds, that is, the combination of cortical surface area and thickness. We postulate that the relative white matter volume is determined as the developing cortex settles in the most energetically favorable folded conformation, regardless of its number of neurons.

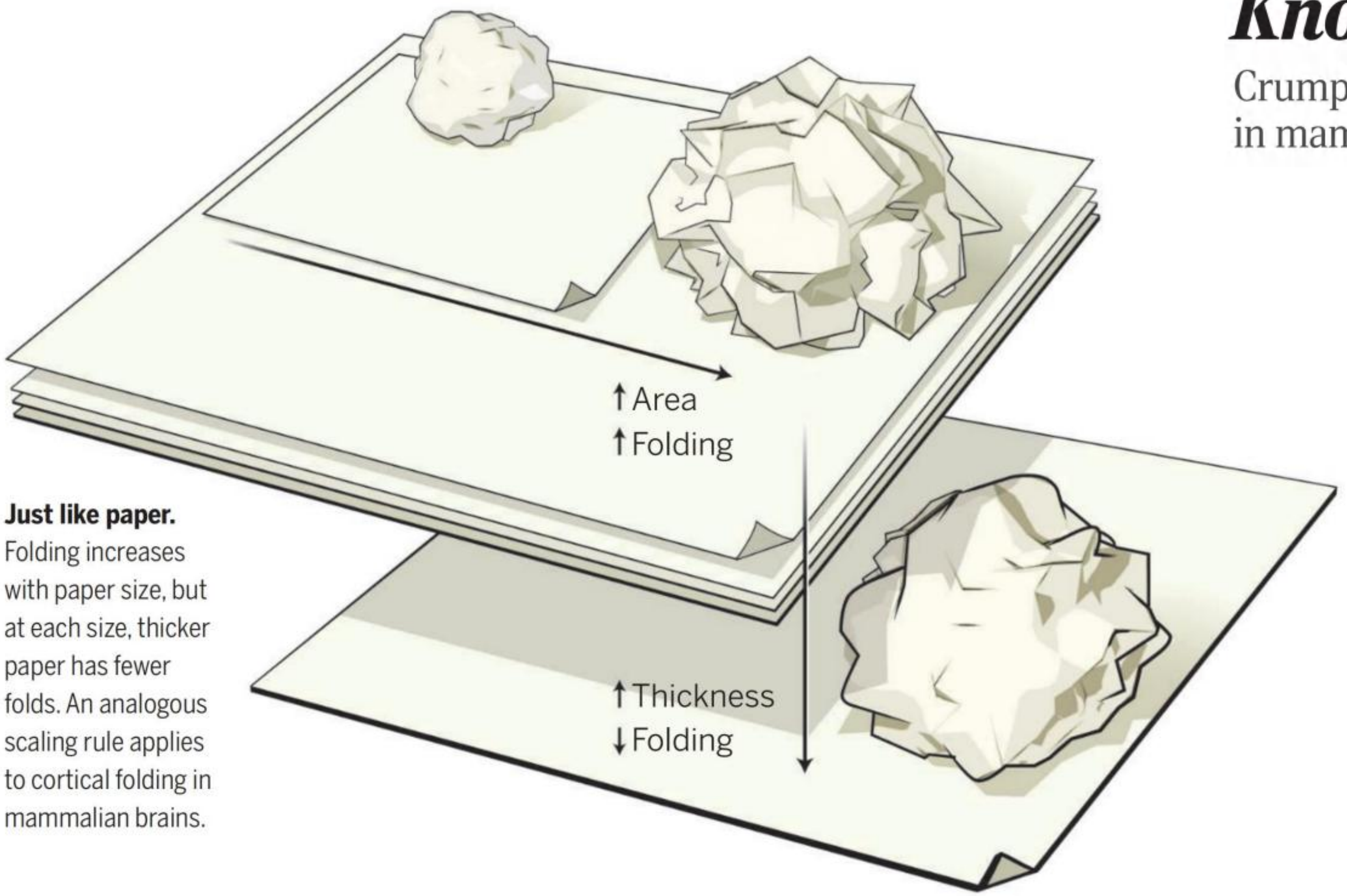
The Human Brain in Numbers: Folding The Brain







The Human Brain in Numbers: Folding The Brain

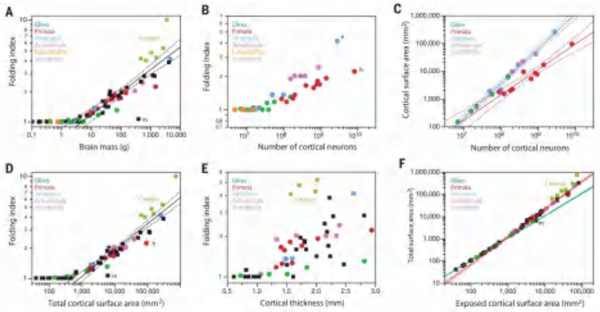


Just like paper. Folding increases with paper size, but at each size, thicker paper has fewer folds. An analogous scaling rule applies to cortical folding in mammalian brains.

BRAIN EVOLUTION

Knowing when to fold them

Crumpled paper is a possible model for cortical folding in mammalian brains



BRAIN STRUCTURE

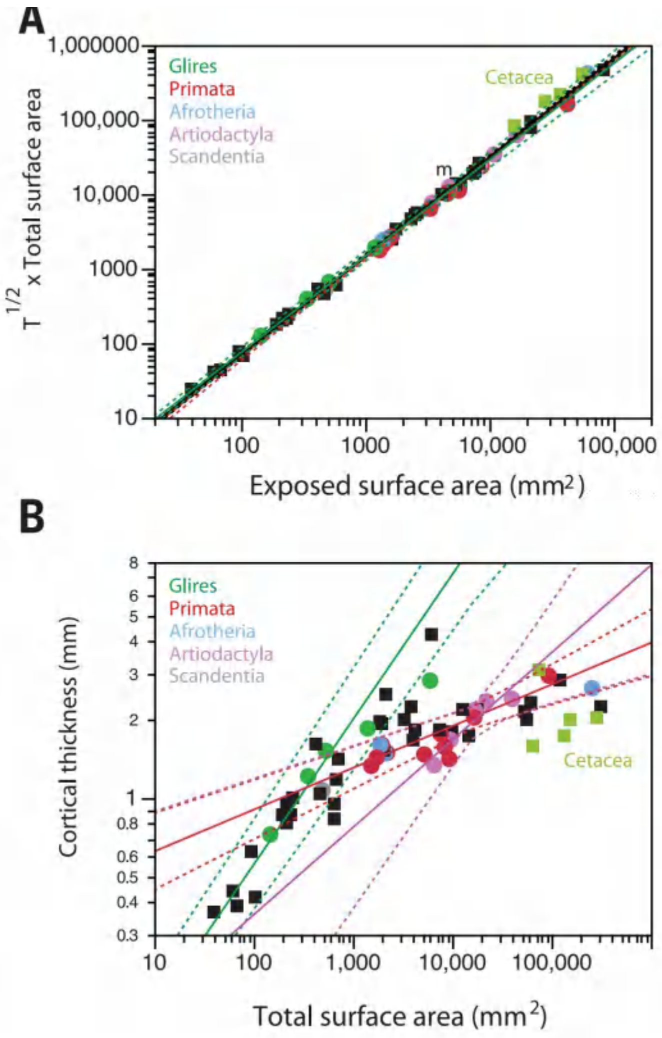
Cortical folding scales universally with surface area and thickness, not number of neurons

Bruno Mota[1] and Suzana Herculano-Houzel[2,3]*

Larger brains tend to have more folded cortices, but what makes the cortex fold has remained unknown. We show that the degree of cortical folding scales uniformly across lissencephalic and gyrencephalic species, across individuals, and within individual cortices as a function of the product of cortical surface area and the square root of cortical thickness. This relation is derived from the minimization of the effective free energy associated with cortical shape according to a simple physical model, based on known mechanisms of axonal elongation. This model also explains the scaling of the folding index of crumpled paper balls. We discuss the implications of this finding for the evolutionary and developmental origin of folding, including the newfound continuum between lissencephaly and gyrencephaly, and for pathologies such as human lissencephaly.

The Human Brain in Numbers: Scale is The Key

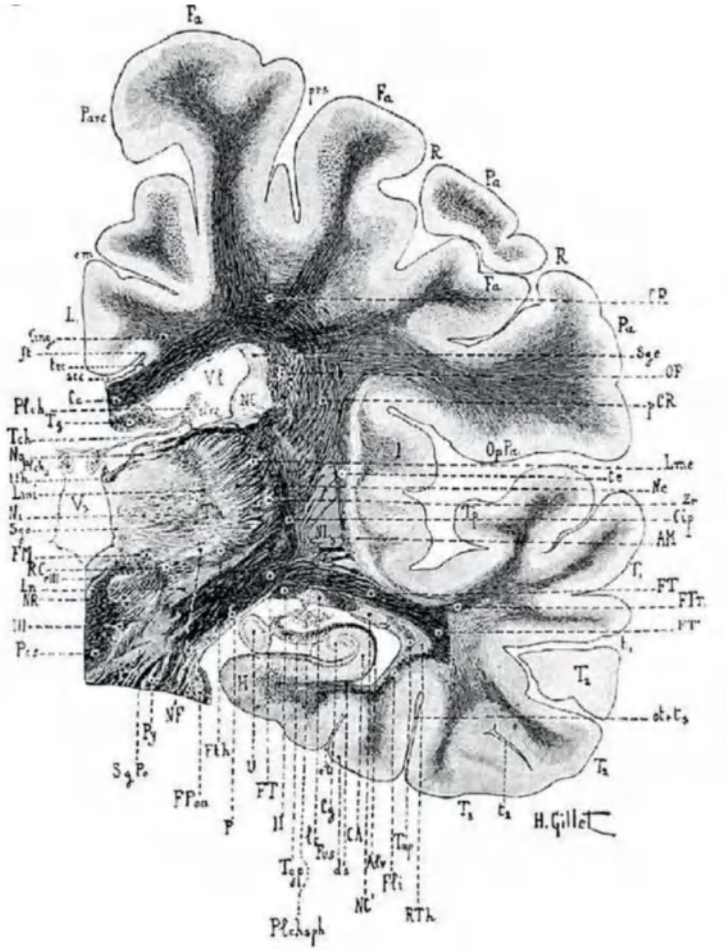
Fig. 3. The degree of folding of the mammalian cerebral cortex is a single function of surface area and thickness across lissencephalic and gyrencephalic species alike, although thickness scales as order-specific functions of cortical surface area. (**A**) The product $T^{1/2}A_G$ varies with $A_E^{1.329\pm0.014}$ ($r^2 = 0.996$, $P < 0.0001$) across noncetacean gyrencephalic species in the combined data set (red line), with $A_E^{1.325\pm0.009}$ ($r^2 = 0.997$, $P < 0.0001$, $k = 0.157 \pm 0.012$) across all species (including cetaceans; black line), and with $A_E^{1.292\pm0.027}$ ($r^2 = 0.994$, $P < 0.0001$) across lissencephalic species alone (green line). Note that the function plotted for lissencephalic species predicts the product $T^{1/2}A_G$ for gyrencephalic species equally well as the functions plotted for gyrencephalic species themselves. (**B**) Cortical thickness varies with cortical surface area $A_G^{0.555\pm0.053}$ ($r^2 = 0.887$, $P < 0.0001$) across lissencephalic species in the combined data set (green line), but with $A_G^{0.160\pm0.025}$ ($r^2 = 0.703$, $P < 0.0001$) across primates (red line), and with $A_G^{0.334\pm0.072}$ ($r^2 = 0.879$, $P = 0.0185$) across artiodactyl species (pink line). All fits exclude cetaceans. Dashed lines indicate the 95% confidence intervals for the fitted functions.



SPECIAL SECTION BRAIN CONNECTIVITY

REVIEW

Scale matters: The nested human connectome



The Human Brain in Numbers: Scale is The Key