4.09 Remarkable, But Not Special: What Human Brains Are Made of

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Abstract

Most textbooks at this point still consider that the human brain is "larger than expected," has "the most developed cerebral cortex," and "costs an extraordinary amount of energy," encouraging the view that the human brain has escaped the evolutionary rules that apply to all other animals. This chapter reviews new evidence on the numbers of neurons that compose the human brain and how they compare to numbers in other primates. A new understanding of our place in nature is proposed as a species whose brain is not extraordinary in evolutionary terms—but is indeed capable of remarkable feats, thanks to its unique biological capabilities and the development and cultural transmission of technology that those capabilities make possible, leading to human brains of amazing cognitive abilities.

4.09.1 The Former View: The Human Brain Is Special

Humans are formidable creatures, capable of transforming their food to refined "molecular" gastronomy, building skyscrapers, modifying their own bodies, and inquiring about themselves. Once the brain became recognized as the seat of mental functions, in the 19th century, it became clear that all those abilities must come from the brain. Yet the human brain appears nowhere as formidable as its feats: at best, it ranks 14th in size, after 2 species of elephants and 11 cetaceans, whose brains can weigh as much as 9 kg, six times larger than the human brain.

Cortical folds were once considered an indication of expansion of the cortical sheet and its number of neurons, and therefore the degree of gyrification was presumably an indication of intelligence (Jerison, 1973). Yet, the human cerebral cortex is not the most folded; larger cortices, such as those of the elephant and various cetaceans, have much larger folding indices (Hofman, 1985). The human cerebral cortex, although not the largest (the honor, again, goes to cetaceans), is the largest relative to the brain as a whole, in terms of the percentage of brain volume that it occupies—but, at 76–84% (Stephan et al., 1981; Hofman, 1988), it ranks first by very little, followed closely by the cerebral cortex of the chimpanzee, horse, and short-finned pilot whale, at 73–74% of brain volume (Hofman, 1988). It is unlikely that such a small difference accounts for the distance that we like to put between our cognitive feats and those of all other animals. The cerebral brain does cost a seemingly extraordinary 25% of all the energy that runs the body, when its mass represents but 2% of the body (Kety, 1957), and it has often been proposed that the extraordinary cost of the human brain reflects its extraordinary prowess and would have resulted from human-specific changes in genes related to metabolism (Cáceres et al., 2003; Uddin et al., 2004; Somel et al., 2013). But that is at odds with the very low specific cost of the human brain, when expressed as glucose use per gram of tissue: gram per gram, the human brain costs less than the mouse brain (Karbowski, 2007).

How could the human brain be so remarkable when it did not rank an obvious first in any category that could reasonably explain its outstanding cognition? The paradox seemed to be resolved when Harry Jerison introduced the use of the encephalization quotient: a unitless measure of how much larger or smaller a brain is compared to how large it is expected to be, given the relationship between brain mass and body mass that applies across mammals as a whole (Jerison, 1973). The human brain finally ranked first: in comparison to all other mammals, it was over seven times larger than it "should" be. The outstanding encephalization quotient, which finally matched the outstanding cognitive powers of humans, is often illustrated by comparing humans and the largest great apes. Gorillas can weigh up to 200 kg, and because larger species tend to have larger brains, gorillas, who are obviously larger than humans, should also have larger brains to go with those bodies—and yet, their brains weigh about only one-third as much as human brains (Marino, 1998). That large encephalization quotient supposedly meant that humans had over seven times as many neurons as necessary to operate the body—an excess that would then be available for cognitive functions, thus accounting for the formidable capabilities of human brains (Jerison, 1973). Moreover, human encephalization quotients stood a distant first from quotients for the species ranked next: at best, they reached values of around 3, against 7 for humans (Jerison, 1973; Marino, 1998).

For almost 40 years, the view that the human brain is special, an outlier in its relative size compared to the body, remained the standard view, disseminated not only in the scientific literature but also in popular books for the lay public (for example, Gazzaniga, 2008). At the very least, the rules that relate brain and body size in all other mammals did not seem to apply to humans. Round numbers accompanied that tag: the human brain contained 100 billion neurons and 10 times as many glial cells. Along the same vein, a search for genes that set the human brain apart from all other primates soon ensued, and sure enough, there appear to be human-specific genes related to brain size (Evans et al., 2004; Dumas et al., 2012), synapse formation (Dennis et al., 2012; Charrier et al., 2012), speech and language development (Enard et al., 2009), cell metabolism (Somel et al., 2013), and the shape of the human wrist and thumb (Prabhakar et al., 2008).

The reign of the highly encephalized human species lasted about four decades. Recently, novel data on the numbers of neurons that compose different brains and how they relate to body mass and the energetic cost of the brain forced a reexamination of the view of the human brain as an outlier, the sole brain that escapes the scaling rules that apply to bodies in evolution. As it turns out, humans are no rebels or mavericks: the same rules of evolution that apply to every other species also apply to them. Our species does seem, however, to have come up with a neat trick that led them to escape one of the natural limitations that curb the number of brain neurons that other species can afford: the sole species to modify its food before it is ingested, humans can afford the largest number of neurons in any cerebral cortex. The findings that led to this new view of what makes the human brain remarkable were reviewed in depth recently (Herculano-Houzel, 2016) and are summarized in this chapter.

4.09.2 The Human Brain as a Scaled-Up Primate Brain

Prompted by the realization that the often cited "100 billion neurons and 10 times as many glial cells" in the human brain was at best an order of magnitude estimate (reviewed in von Bartheld et al., 2016), rather than an estimate based on actual measurements, and armed with a new method as reliable as stereology that allowed the rapid and precise estimation of numbers of cells in whole brains (Herculano-Houzel and Lent, 2005; Herculano-Houzel et al., 2015a), we recently determined the numbers of cells that compose human brains (Azevedo et al., 2009). We found that the (male) human brain has on average 86 billion neurons, 16 billion of which located in the cerebral cortex and 69 billion in the cerebellum, leaving fewer than 1 billion neurons in the "rest of brain": the ensemble of brain stem, diencephalon, and striatum (**Fig. 1**; Azevedo et al., 2009). While this number falls in the 10^{11} order of magnitude, it is more than a baboon brain's worth short of the mythical 100 billion neurons so widespread in the literature (von Bartheld et al., 2016). Not a single human brain examined so far came close to that round mark; individual brains varied around 80 and 90 billion neurons—and interestingly, the largest number was found in the oldest brain examined, of 71 years of age (Azevedo et al., 2009).

The most important aspect of finally knowing the number of neurons that compose the human brain and their distribution is that we are now able to compare it to other primates and determine whether the human brain is out of the ordinary—an exception to the rules that apply to other primates—or just a scaled-up primate brain. That comparison is possible because we have by now examined the cellular composition of the brains of enough primate species to be able to determine the mathematical pattern that describes the relationship between the number of neurons that compose each structure, their density (the inverse of average cell size; Mota and Herculano-Houzel, 2014), and the resulting mass of the brain structure (reviewed in Herculano-Houzel et al., 2014a, and Chapter 2.07, What Modern Mammals Teach About the Cellular Composition of Early Brains and Mechanisms of Brain Evolution). These mathematical patterns are power laws, in which the mass of a brain structure (or its neuronal density) varies with the number of neurons in the structure raised to a certain exponent. These exponents are significantly larger than 1 for nonprimate species, indicating that brain structure mass scales up rapidly as numbers of neurons increase across species, but close to 1 for primates, indicating that brain structure mass in these animals scales close to linearly as numbers of neurons increase. As a result, primate brain structures are composed of many more neurons than nonprimate structures of similar mass—and the larger the structure, the larger the difference in numbers of neurons favoring primates (Herculano-Houzel et al., 2014a; see Chapter 3.02, "What Primate Brains Are Made of" in Volume II of this series for a more recent review).

Given these relationships between number of neurons, neuronal density, and brain structure mass, to which we refer collectively as the "neuronal scaling rules" that apply to a part of the brain across primates and nonprimates, we could determine how the human brain compared to other species. Did the different brain structures in the human brain have the mass predicted for a primate, given their number of neurons? If they had a significantly larger or smaller mass than predicted that would indicate that the human brain was indeed extraordinary, unique in its cellular makeup—special, indeed. But if their brain structures had the mass predicted for their number of neurons, that would be evidence that the human brain was built according to the same rules that apply to other primates.

We found that the latter was the case: the mass of each major brain structure in the human brain is very close to the predicted value for a generic primate with that many neurons, falling well within the 95% confidence interval (**Fig. 1**). In contrast, when compared to a nonprimate, the human brain and its structures would indeed appear to be special, with 7.4, 9.1, 6, and 3.1 times more neurons in the whole brain, cerebral cortex (gray and white matter combined), cerebellum, and rest of brain than predicted for a nonprimate of similar mass in each structure. When the cortical gray matter and white matter are considered separately, the human brain still obeys the same relationship between structure volume and number of neurons that applies to other primates (**Fig. 2**). That is, the volume of the gray matter of the human cerebral cortex is not significantly larger than expected for a primate with its number of cortical neurons, and neither is the volume of the human cortical white matter. Altogether, these findings indicate that the human brain is just a scaled-up primate brain in its number of neurons.

The 86 billion neurons in the human brain are accompanied not by 10 times more glial cells, as legend had it (reviewed in von Bartheld et al., 2016), but rather by only as many nonneuronal cells (84.6, to be exact; Azevedo et al., 2009). Of the 84.6 billion nonneuronal cells in the human brain, 60.8 billion are found in the cerebral cortex, 16.0 billion are located in the cerebellum,

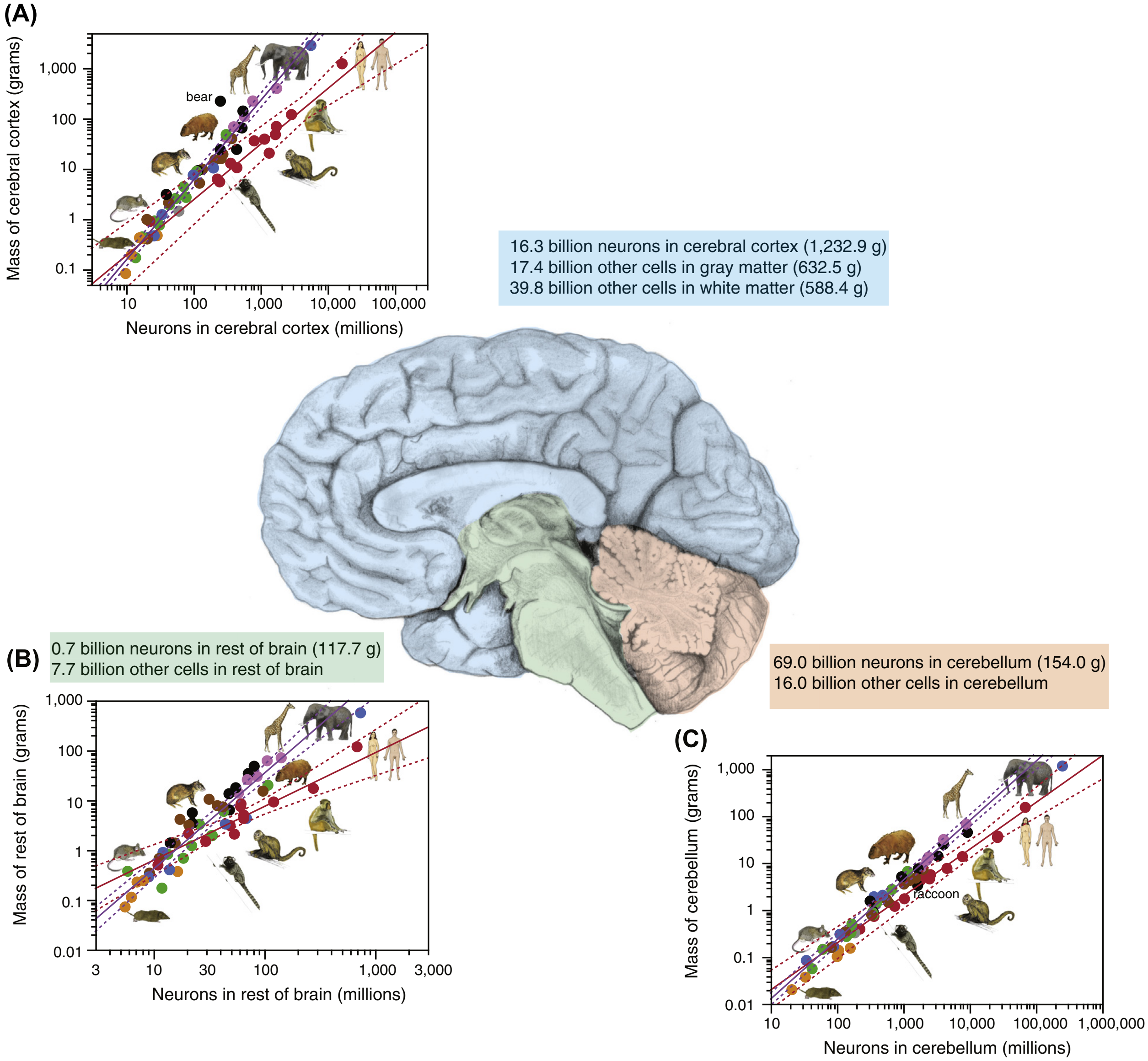

Figure 1 Numbers of neurons in the human brain make it a generic scaled-up primate brain. Numbers of neurons that compose each major brain structure are shown in colored boxes for the cerebral cortex (*blue*), cerebellum (*red*), and rest of brain (the ensemble of brain stem, diencephalon, and striatum, not including the olfactory bulbs; *red*). (A) The mass of the cerebral cortex (including the white matter) varies as a power function of the number of neurons in the structure that is shared across all nonprimate mammalian species examined so far (*purple*; exponent, 1.582 ± 0.039, $r^2 = 0.978$, $p < .0001$; primates, *red*; exponent, 1.087 ± 0.074, $r^2 = 0.956$, $p < .0001$). The human cerebral cortex has a total mass that falls within the 95% confidence interval of the mass predicted for its number of neurons. (B) The mass of the rest of brain varies as a power function of the number of neurons in each structure across all nonprimate species (plotted in *purple*; exponent, 1.921 ± 0.120, $r^2 = 0.867$, $p < .0001$) and as a different function across primates (plotted in *red*; exponent, 1.198 ± 0.116, $r^2 = 0.915$, $p < .0001$). The human rest of brain conforms to the scaling relationship that applies to other primates. (C) The mass of the cerebellum (including the white matter and deep nuclei) varies as a power function of the number of neurons in the structure that is shared across afrotherians (with the exception of the elephant; Herculano-Houzel et al., 2014b), glires, carnivorans, and artiodactyls (plotted in *purple*; exponent: 1.267 ± 0.036, $r^2 = 0.982$, $p < .0001$). Marsupials, primates, and eulipotyphlans deviate from this relationship, each in a different manner (marsupials, exponent 1.186 ± 0.037, $r^2 = 0.992$, $p < .0001$; primates, plotted in *red*, exponent 0.976 ± 0.036, $r^2 = 0.985$, $p < .0001$; eulipotyphla, exponent 1.028 ± 0.084, $r^2 = 0.980$, $p = .0012$), with more neurons than predicted for cerebellar mass in other clades. The human cerebellum conforms to the scaling relationship that applies to primates. Illustrations by Lorena Kaz.

and 7.7 billion in the rest of brain (Fig. 1; Azevedo et al., 2009). Importantly, these numbers match the universal relationship between numbers of nonneuronal cells and the mass of each of the major brain structures that we observed for any mammal, primate or not (Fig. 3A; Herculano-Houzel, 2014). Thus, the human brain has the number of nonneuronal cells in each major brain structure expected for the mass of those structures.

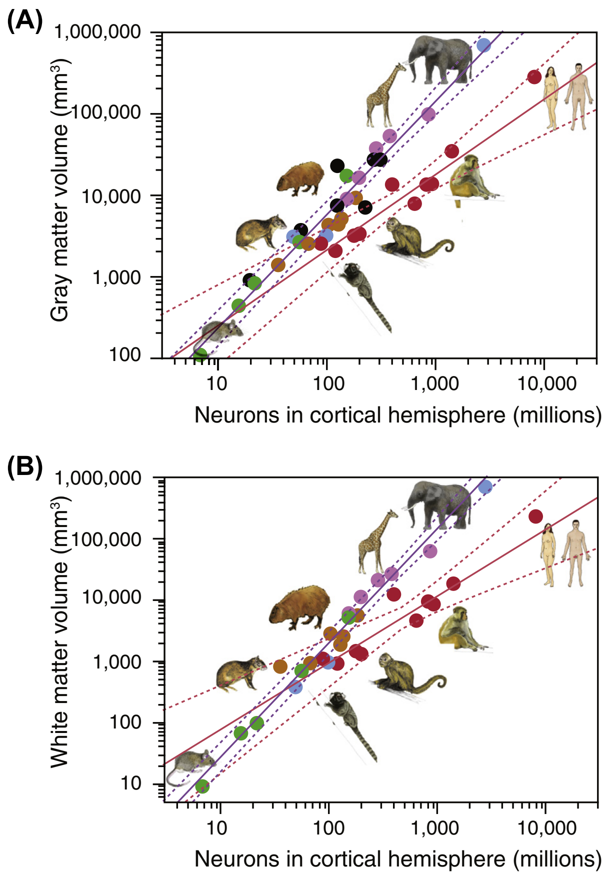

Figure 2 The human cerebral cortex conforms to the relationships between numbers of neurons and volumes of the gray and white matter. The volume of the gray matter scales as a different function of the number of neurons in the cortex in each mammalian clade analyzed, in such a way that for similar numbers of neurons, primates have the smallest volume of gray (A) and white matter (B). Importantly, humans do not depart significantly from the expected gray and white matter volumes given the number of cortical neurons in a primate. Exponents in (A): artiodactyls, 1.992 ± 0.180, $r^2 = 0.984$, $p = .0081$; rodents, 1.587 ± 0.064, $r^2 = 0.995$, $p = .0001$; marsupials, 1.076 ± 0.104, $r^2 = 0.964$, $p = .0005$; primates, 0.918 ± 0.083, $r^2 = 0.938$, $p < .0001$. Exponents in (B): rodents, 2.009 ± 0.065, $r^2 = 0.997$, $p < .0001$; artiodactyls, 1.637 ± 0.225, $r^2 = 0.964$, $p = .0183$; marsupials, 1.101 ± 0.271, $r^2 = 0.805$, $p = .0005$; primates, 1.080 ± 0.120, $r^2 = 0.909$, $p < .0001$. Data from Ventura-Antunes, L., Mota, B., Herculano-Houzel, S., 2013. Different scaling of white matter volume, cortical connectivity, and gyrification across rodent and primate brains. Front. Neuroanat. 7, 3 and Herculano-Houzel et al. (unpublished observations). All values are for a single cortical hemisphere.

Because only a small minority of nonneuronal cells can be expected to be endothelial cells (about 1–6%; Buchweitz and Weiss, 1986; Lauwers et al., 2008; Tsai et al., 2009), most of these nonneuronal cells must be glial cells. That means that at best, the glia/neuron ratio for the human brain as a whole is 1.0. That number, however, hides the fact that the glia/neuron ratio is widely different across brain structures. Within the human brain, the average glia/neuron ratio (that is, the nonneuronal/neuronal cell ratio) is 1.48 in the cortical gray matter, a much larger 11.35 in the rest of brain (the ensemble of brain stem, diencephalon, and striatum), but only 0.23 in the cerebellum (Azevedo et al., 2009). As different as they are, these ratios are still just the expected for the neuronal density in each structure of the human brain, given the universal relationship that we have found to apply between the glia/neuron ratio and neuronal density across brain structures and mammalian species alike (**Fig. 3B**; Herculano-Houzel, 2014).

There is variation in the G/N ratio within the human cerebral cortex, as reported by other authors (Sherwood et al., 2006), but again we found that local G/N ratios within the human cerebral cortical gray matter are predicted by local variations in neuronal density (Ribeiro et al., 2013). Glia/neuron ratios, which once were considered an indicator of "progressive cognitive development" (Friede, 1954), are now known to simply reflect the average size of neuronal cells in the tissue (Herculano-Houzel, 2014; Mota and Herculano-Houzel, 2014).

4.09.3 The Energetic Cost of the Human Brain

Well before our group showed that the glia/neuron ratio was inversely proportional to neuronal density across structures and species, and thus directly proportional to the average size of neurons in the tissue (Herculano-Houzel, 2014; Mota and Herculano-Houzel, 2014), it was widely held that this was the case due to the expected larger metabolic cost of larger neurons (Hawkins and Olzewski,

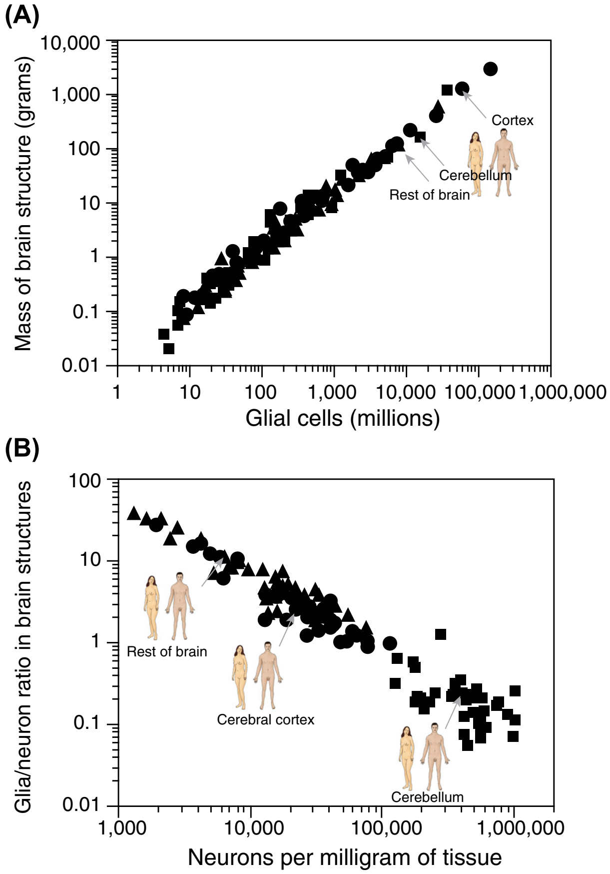

Figure 3 Human brains have expected numbers of glial cells and glia/neuron ratios. (A) The mass of major brain structures (cerebral cortex, *circles*; cerebellum, *squares*; rest of brain, *triangles*) varies as a power function of the number of nonneuronal cells in each structure that is shared across all mammalian species examined so far. Numbers of nonneuronal cells in the human cerebral cortex, cerebellum, and rest of brain (*arrows*) conform to the predicted for a generic mammalian species. (B) The glia/neuron ratio in each major brain structure (symbols as in A) varies universally across brain structures and species, increasing with decreasing neuronal density (which indicates larger average neuronal cell size). The glia/neuron ratios in human cerebral cortex, cerebellum, and rest of brain conform to the scaling relationship that applies across mammalian species as a whole. Original data on 5 species of eulipotyphlans, 6 species of afrotherians, 10 species of glires, 12 species of primates, and 5 species of artiodactyls are available in Herculano-Houzel, S., Catania, K., Manger, P.R., Kaas, J.H., 2015b. Mammalian brains are made of these: a dataset of the numbers and densities of neuronal and nonneuronal cells in the brain of glires, primates, scandentia, eulipotyphlans, afrotherians and artiodactyls, and their relationship with body mass. Brain Behav. Evol. 86, 145–163.

1957). However, once data on the numbers of neurons that compose the brains of enough species that also had their metabolic cost measured directly, we found that the average metabolic cost per neuron did not vary significantly with neuronal density in the cerebral cortex or cerebellum of different species (Herculano-Houzel, 2011). In the human cerebral cortex, the average cost per neuron was 1.32×10^{-8} μmol of glucose per minute, as much as the 1.39×10^{-8} μmol of glucose per minute per neuron in the mouse cerebral cortex (Herculano-Houzel, 2011). Per gram of tissue, the mouse cerebral cortex costs about three times more glucose than the human cerebral cortex because the density of neurons is about three times higher in mouse than in human cerebral cortex.

Without a significant variation in average glucose cost per neuron across species, the total glucose use of a cerebral cortex, or of the brain as a whole, turned out to be a simple linear function of the number of neurons in the cortex or whole brain across rodents and primates alike (Herculano-Houzel, 2011)—species that we then knew to have different relationships between numbers of neurons and brain mass (Herculano-Houzel et al., 2006, 2007). It thus became evident that the previously reported hypometric power function describing the scaling of the metabolic cost of brains with increasing brain mass (Karbowski, 2007) was a result of the particular combination of neuronal densities in the data set. Most importantly, the data showed that, given an average cost of 6 kcal per billion neurons per day, the human brain cost just as much energy as expected for a rodent or primate with its number of neurons: about 516 kcal day^{-1} (Herculano-Houzel, 2011).

The reason why the human brain is so expensive in proportion to the body then turned out to be simply that a different relationship between body mass and number of brain neurons applies to primates: compared to other mammals of similar body mass, primates of increasing body mass have larger and larger numbers of brain neurons (reviewed in Herculano-Houzel et al., 2015b). The human brain does not cost a relatively enormous amount of energy because it is "special," but simply because it is the largest primate brain, with the largest number of neurons among primates (Herculano-Houzel, 2016).

It became apparent then that the question regarding the human encephalization quotient could be reframed: given that the energetic cost of a brain depending on its number of neurons was so large, what if instead of humans having larger brains than expected for their bodies, it was great apes who could not afford the large brains that would be expected for their very large bodies? Once we learned that also the brains of great apes conformed to the relationship between number of neurons and brain mass that applied to primates as a whole (Herculano-Houzel and Kaas, 2011) and that humans conformed to the relationship between body mass and number of brain neurons that applied to nongreat ape primates (Azevedo et al., 2009), it appeared that great apes, not humans, were the outliers. Actually, it was the inclusion of great apes to the brain versus body comparison that made humans appear as outliers (Herculano-Houzel, 2016).

The mathematical consideration of the increasing energetic costs of bodies of increasing mass and of brains of increasing numbers of neurons, which must be balanced by energetic intake that depends on body mass and number of hours of feeding per day, showed that great apes indeed could not afford a brain any larger than it is (Fonseca-Azevedo and Herculano-Houzel, 2012). Because of the energetic limitation imposed by the primate diet, there is a trade-off between body mass and number of brain neurons: past the optimal combination, where numbers of neurons are maximal, larger bodies can only be sustained at the expense of decreasing numbers of brain neurons. According to our calculations, for gorillas to have the number of brain neurons that would be expected for their body masses, in a brain that corresponded to 2% of body mass as in humans and other primates, they would need to afford an additional 122 billion neurons—and that would require ingesting an extra 733 kcal, which would take over two more hours of feeding per day (Fonseca-Azevedo and Herculano-Houzel, 2012). For a primate that already averages almost 8 h of eating per day, that seems to be unviable. Orangutans, which similarly feed for about 8 h day^{-1}, do not seem capable of eating for longer periods during periods of low food availability and lose body mass (Knott, 1998). Feeding 8 h day^{-1} seems to be the practical limit for primates.

According to the same calculations, and considering the raw diet of extant nonhuman primates, *Homo habilis* would have required daily feeding times close to 7.5 h day^{-1}, close to the 8 h day^{-1} limit, and late *Homo erectus* individuals, such as modern *Homo sapiens*, would be required to feed consistently more than 9 h day^{-1} to afford their estimated body mass and number of neurons (Fonseca-Azevedo and Herculano-Houzel, 2012). Modern humans, therefore, would not be viable on the raw diet typical of other primates. Given that both body and brain in humans cost the expected amount of energy for their mass and number of neurons, respectively, and eating longer hours is not an option, there remains but one alternative to explain how human brains attained their modern numbers of neurons: with a change in diet that significantly increased caloric intake, preferably while decreasing feeding time.

Cooking does just that. The controlled use of fire to break down foods prior to ingestion increases the caloric yield of foodstuffs to 100% of their theoretical nutritional value, while also decreasing the time required to consume them (reviewed in Wrangham, 2009). Evidence of habitual use of fire to cook exists about 1–1.5 million years ago (Gwolett et al., 1981; Berna et al., 2012), a time that coincides with the steep increase in brain size in human ancestors—but, as Wrangham's critics like to point, might be too late to explain the earlier beginning of the ascent, about 2 million years ago.

In a looser definition, however, "cooking" has been around for much longer than 2 million years. Cutting, bashing, crushing, and otherwise tenderizing foods prior to chewing are forms of predigestion that also increase caloric yield significantly (Zink and Lieberman, 2016) and were available to early *Homo* and their hunter-gatherer ancestors at least 3.3 million years ago (Harmand et al., 2015). Between cold and hot versions of cooking, early *H. habilis*, with modernlike hands capable of precision grips by 2 million years ago (Susman, 1998; Alba et al., 2003), and certainly *H. erectus* of 1 million years ago must have enjoyed a luxury that no modern primate, or mammal, for that matter, seems to enjoy: having enough calories to feed an increased number of neurons as well as the free time to do more interesting things with them than looking for food and eating. Such "optional" activities, such as socializing and organizing hunts, which rely on memory, planning, reasoning, self-control, and awareness of the mental state of others, probably exerted selective pressure for even more brain neurons. Once over the energetic constrain that a raw diet imposes to other animals, the brain of *Homo* was then free to keep scaling as primate brains do. At this moment, this is the best narrative that we know to account for how *H. sapiens* came to have the largest primate brain, with the largest number of neurons in any cerebral cortex, without ever deviating from the biological rules of evolution. We never stopped being primates (Herculano-Houzel, 2016).

4.09.4 The Expanded Human Cerebral Cortex Does Not Have Relatively More Neurons

The expansion of the cerebral cortex relative to the remaining brain structures is probably the feature that is most equated with "brain evolution" in mammals, and in primates in particular (Stephan and Andy, 1969; Jerison, 1973; Frahm et al., 1982). A cerebral cortex that expands in relative size within the brain, coming to represent over 80% of brain volume in humans, would be expected to also expand in relative number of brain neurons. That is, the relatively larger cortex of humans would be expected to contain a relatively larger proportion of all brain neurons than in other primate species.

Contrary to that expectation, however, we found that the human cerebral cortex, which represents 82% of brain mass, has only 19% of all neurons in the human brain—a proportion that is similar to that found in the guinea pig, although the cerebral cortex of the latter represents a much smaller 53% of the brain (Azevedo et al., 2009; Herculano-Houzel et al., 2006). This similarity is not particular to these two species: across mammalian species, we find that although the cerebral cortex represents between 50% and 80% of brain mass, it typically holds 15–25% of brain neurons, while the cerebellum, at only 10–20% of brain mass, holds 70–85% of all brain neurons (Herculano-Houzel, 2010; Herculano-Houzel et al., 2014a). As illustrated in **Fig. 4A**, relatively larger cerebral cortices do not hold significantly larger percentages of all brain neurons. The expansion of the human cerebral cortex in evolution thus represented a gain in absolute numbers of neurons without a gain in relative numbers of neurons within the brain.

The reason is that the cerebellum, which alone holds the majority of all brain neurons, gains neurons together with the cerebral cortex, keeping a fairly steady average proportion of four neurons in the cerebellum to every neuron in the cerebral cortex across extant species (**Fig. 4B**; Herculano-Houzel, 2010; Herculano-Houzel et al., 2014a). This joint scaling of the two structures agrees with the modern view that they work in tandem (Leiner et al., 1989; Ramnani, 2006; Ito, 2008) and is in line with the concerted increase of the volume of connected cerebral cortical and cerebellar regions in primates (Ramnani et al., 2006; Balsters et al., 2010). Together, however, they do gain neurons significantly faster than the rest of brain across primate species, which means that larger primate brains have increasing ratios of numbers of cortical (and cerebellar) neurons over numbers of neurons in the rest of brain (Herculano-Houzel et al., 2014a). Across primate species, for example, the ratio between numbers of cortical motor neurons and neurons in the spinal cord increases from less than 1 in the mouse lemur to 4 in the macaque and 20 in the chimpanzee and human (Herculano-Houzel et al., 2016). We have proposed that this faster scaling of numbers of cortical versus brain stem and also spinal cord neurons in primates explains the corticalization of motor control in humans (Herculano-Houzel et al., 2016), that is, the dependence of motor control on the corticospinal tract in humans.

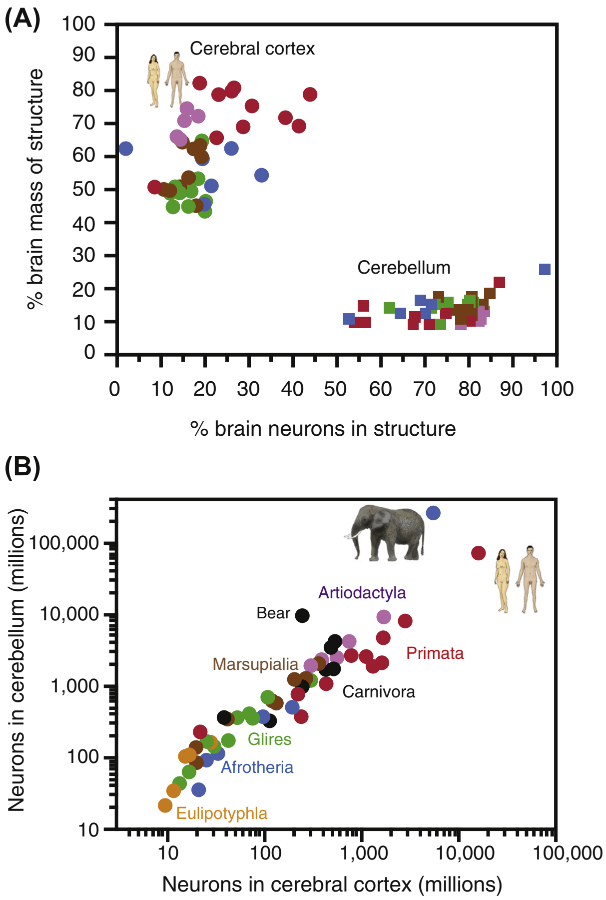

Figure 4 Relatively larger cerebral cortices do not have relatively larger proportions of brain neurons. (A) Although the cerebral cortex (*circles*) represents between 40% and 82% of brain mass in the species we have analyzed so far, it typically contains only between 15% and 25% of all brain neurons—and those animals that have relatively larger cortices do not have relatively more brain neurons in it (Herculano-Houzel, 2010; Herculano-Houzel et al., 2014a). The human cerebral cortex, in particular, represents 82% of brain mass, but holds only 19% of all brain neurons (Azevedo et al., 2009). Likewise, although the cerebellum (*squares*) usually represents only between 10% and 20% of brain mass, it holds typically between 70% and 80% of all brain neurons—but relative cerebellar mass and relative number of cerebellar neurons are not correlated. The human cerebellum, in particular, represents only 10% of brain mass, but holds 69% of all brain neurons (Azevedo et al., 2009). (B) The cerebral cortex and cerebellum gain neurons coordinately across mammalian species. With the sole exceptions of the African elephant and the brown bear, there is a relatively steady average of four neurons in the cerebellum for every neuron in the cerebral cortex across species, regardless of the relative size of the cerebral cortex as a percentage of brain mass. The human brain, in particular, conforms to the same proportionality that applies to other primates and to mammals as a whole. Original data on 5 species of eulipotyphlans, 6 species of afrotherians, 10 species of glires, 12 species of primates, and 4 species of artiodactyls are available in Herculano-Houzel, S., Manger, P.R., Kaas, J.H., 2014. Brain scaling in mammalian evolution as a consequence of concerted and mosaic changes in numbers of neurons and average neuronal cell size. Front. Neuroanat. 8, 77. Data on carnivorans from Messeder et al. (unpublished observations). Data on marsupials from Dos Santos et al. (unpublished observations).

We find a similar expansion of numbers of cortical neurons over numbers of thalamic neurons across primate species. Although the primary visual cortex represents a relatively constant 36% of all cortical neurons across nonhuman primate species, the ratio between numbers of neurons in the primary visual cortex and in the lateral geniculate nucleus (LGN) (the visual nucleus of the thalamus) increases together with brain size, from 50 times more neurons in the visual cortex compared to the LGN in the marmoset to 133 in the baboon (Collins et al., 2013). Thus, it appears that larger primates have more cortical motor neurons to control each downstream effector neuron that operates the body, and also more cortical sensory neurons to elaborate on sensory input received, adding complexity and flexibility to behavior. In that vein, the human brain seems to benefit from being the most extreme case of faster addition of neurons to the cerebral cortex over the rest of brain across primates (Herculano-Houzel et al., 2016).

Interestingly, while the expansion of the cerebral cortex over other brain structures has been considered evidence of increased cortical functioning, it should not be taken as evidenced of diminished processing abilities by other structures. A case in point is the olfactory bulb. The residual volume of the primate olfactory bulb has long been known to decrease with increasing brain size across primate species, in contrast to the increasing residual volume of the primate cerebral cortex (Stephan and Andy, 1969)—meaning that given the relationship between structure volume and body mass, the primate cerebral cortex becomes larger and larger than predicted, while the olfactory bulb becomes smaller and smaller. It was based on these findings, confirmed by later repeated analyses (Baron et al., 1983; Finlay et al., 2001), that primates—and humans in particular—came to be considered microsmatic.

However, once absolute numbers of neurons in the olfactory bulb were determined directly in a number of mammalian species, it became clear that the supposedly microsmatic primates had olfactory bulbs composed of as many neurons as species highly reliant on olfaction, such as shrews: both groups have a similar range of number of neurons in the olfactory bulb, between 2 and 30 million (Ribeiro et al., 2014). Humans, in particular, have an estimated 15–16 million neurons in the olfactory bulb, which is more than the 10 million found in the highly olfactory star-nosed mole, an animal that relies on olfaction to catch its prey. The information processing capabilities of a sensory system should depend on the number of neurons available for that system, regardless of how many neurons are available to other sensory modalities. Thus, decreased reliance on one sensory modality because another came to be favored, such as vision in primates, by no means is synonymous of decreased abilities of the first modality; given the new information on numbers of olfactory bulb neurons, it seems that the increased reliance of primates on vision over olfaction did not occur at the expense of olfaction, but in addition to it. Indeed, recent behavioral studies showed that primate olfaction is far better than presumed, both in squirrel monkeys (Laska et al., 2000) and humans (Porter et al., 2006): When blindfolded humans were invited to go down on all fours and track a chocolate scent on the grass using only their noses, most were perfectly capable of doing so. Given the similar numbers of neurons in the olfactory bulbs of highly visual humans and highly olfactory shrews, humans, like other primates, should no longer be considered microsmatic. Perhaps the difference is simply that, contrary to small mammals, we live with our noses over 5 feet above the ground.

4.09.5 The Expanded Human Cerebral Cortex Does Not Have Relatively More Neurons in the Prefrontal Region

As reviewed previously, our quantitative analyses showed that while cortical expansion in primate evolution did not amount to significantly increased percentages of total brain neurons, larger cortices do gain neurons significantly faster than the rest of brain (ie, brain stem, diencephalon, and striatum; Herculano-Houzel et al., 2014a). In the literature on brain evolution, a pervasive notion has been that the expansion of the primate cerebral cortex has been accompanied by a relative expansion of the prefrontal region within it—associative cortex required for so-called higher cognitive functions such as planning and logical reasoning. This view dates back to German neurologist Korbinian Brodmann, who estimated that the frontal cortex (prefrontal plus motor cortex) occupied 29% of the cerebral cortex in humans, but only 17% in the chimpanzee and 11% in macaque monkey (Brodmann, 1912).

However, using modern imaging techniques, Katerina Semendeferi and colleagues showed in 2002 that the frontal cortex of humans, bonobos, chimpanzees, gorillas, and orangutans occupies the same 35–37% of the cortical volume—percentages that, while higher than the 30% in macaques, did not single out humans. The studies that followed alternately argued that the human prefrontal white matter (although not the prefrontal gray matter) was larger in humans than expected (Schoenemann et al., 2005; Smaers et al., 2011), or simply that both human prefrontal gray and white matter had the volumes expected for a primate of human brain mass (Barton and Venditti, 2013).

Our own recent study comparing numbers of cells rather than volumes support Barton and Venditti's view that the prefrontal region of the cerebral cortex is not disproportionately expanded in humans (Gabi et al., 2016). Actually, we found no expansion at all of the percentage of cortical neurons located in prefrontal regions, anterior to the callosum (the same criterion used by Schoenemann et al., in 2005): almost all primate species analyzed, including humans, had a similar 8% of all cortical neurons located anterior to the callosum. Humans also fell well within the expected values of numbers of other cells in the prefrontal white matter compared to numbers of neurons in prefrontal gray matter or nonprefrontal white matter, indicating that the prefrontal white matter is also not preferentially expanded in the human brain (Gabi et al., 2016).

What does distinguish the human brain from others seems to be simply its absolute number of neurons in the cerebral cortex, the largest found so far (**Fig. 5**). The human cerebral cortex has about three times as many neurons as the twice larger cerebral cortex of the African elephant (Herculano-Houzel et al., 2014b). This "human advantage" lies simply in the fact that the human brain is built in the image of other primate brains, with more neurons per mass compared to other brains of similar brain mass (Herculano-Houzel, 2012). Across primates, even though humans share with other species the same 8% of all cortical neurons in prefrontal,

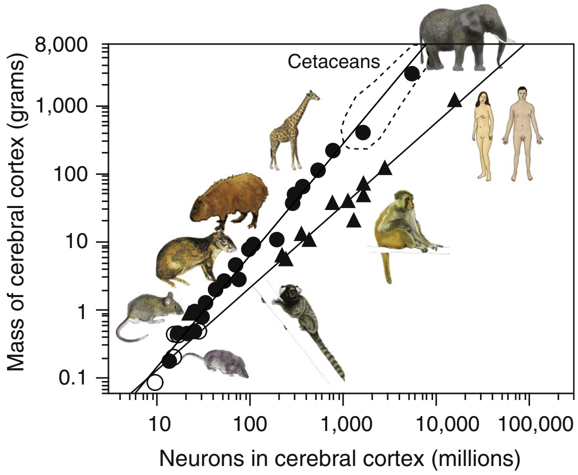

Figure 5 Because it conforms to the primate neuronal scaling rules, the human cerebral cortex has more neurons than any other mammalian cortex. The graph illustrates how the mass of the cerebral cortex varies across primate and nonprimate species, including our prediction for numbers of neurons in cetacean cortices (*dashed area*), around 1–5 billion neurons, given the neuronal scaling rules that apply to artiodactyls, with which cetaceans share the order Cetartiodactyla (Kazu et al., 2014). Although stereological studies have estimated that the cortex of the minke whale and the harbor porpoise are composed of much larger numbers of 13 and 15 billion neurons (Eriksen and Pakkenberg, 2007; Walloe et al., 2010), those studies grossly undersampled the cortices examined (Kazu et al., 2014). Our recent study using the isotropic fractionator estimated a total of fewer than 3 billion neurons in the cerebral cortex of the minke whale (Avelino-de-Souza et al., unpublished observations), in alignment with the prediction made from artiodactyls.

associative regions, that percentage translates into a much larger absolute number of prefrontal neurons in the human cerebral cortex than in other primates: 1.3 billion prefrontal neurons in the human cortex, but only 230 million in the baboon, 137 million in the macaque, and a meager 20 million in the marmoset (Gabi et al., 2016). It is not yet clear what percentage of all cortical neurons have associative, prefrontal-like functions in elephant and whale brains, larger than human brains, but it seems that prefrontal areas are but a sliver of the cortical volume of those large brains (Morgane et al., 1980). However, because of the larger number of neurons in the human cerebral cortex even when compared to larger cortices, we can safely expect that our 1.3 billion neurons dedicated to associative, prefrontal functions will be matched by none. Just as more cortical neurons in the human cerebral cortex dedicated to sensory and motor functions can provide the basis for more complex and flexible cognition and motor control (Collins et al., 2013; Herculano-Houzel et al., 2016), more prefrontal neurons may provide the basis for refined integrative functions, planning, and modulation of behavior in the human brain compared to others, especially given that the general pattern of connectivity has been found to be similar across humans and other mammalian species (Shanahan et al., 2013). Although human-specific genes may well exist, their contribution to human cognition is probably in addition to the benefit of the human cerebral cortex having very large numbers of neurons to refine the processing of information relayed by subcortical structures. No exceptionality in regard to evolutionary rules is required, nor does it seem to exist, to account for the remarkable capabilities of the human brain.

4.09.6 Biological Capabilities × Developed Abilities

Having the largest number of neurons in the cerebral cortex certainly makes humans stand out from all other animals, while no longer singling us out as outliers. However, it is important to keep in mind that while having enough cortical neurons seems to be a necessary condition for complex and flexible behaviors, it is not a sufficient condition for such behaviors. There is a crucial distinction to be made here between the cognitive *capabilities* made possible by a large number of cortical neurons and the cognitive *abilities* that an individual cortex may develop. All the popular writing that hails the human brain as a wonder tends to omit the fact that it never starts life like so—although it certainly holds great promise. Even for the cortex with the most neurons, turning biological cognitive capabilities into actual abilities takes a lifetime of learning, practicing, and honing skills—if not generations.

Indeed, a key component of human evolution has been the development of technologies and their cultural transmission to the next generations (Herculano-Houzel, 2016), thus leading to a cumulative increase in abilities not only of individuals, but also populations as a whole (Henrich, 2015). Perhaps the most striking evidence of the divide between cognitive capacities afforded by biology and the abilities that can be fostered with cultural transmission of technologies is the chasm that separates modern humans from their relatives of 100 000–200 000 years ago: judging from brain size, both had similar numbers of neurons in the brain, and in the cerebral cortex in particular—but the feats of the Ice Age version of our species pale in comparison to our modern achievements. Ever since then, humanity has known a history of identifying problems, inventing technologies to deal with them, and passing the knowledge on to the next generations, who can then put their biological capabilities to work on evermore complicating problems and technologies (Herculano-Houzel, 2016). Endowed with a brain that has enough cortical neurons to learn from others, create new knowledge and pass it on, our species stands on the shoulders of all those who came before us. At this point, the achievements of the human species far surpass those of any one individual: humankind has long transcended the individual human brain. That is why science (the knowledge) and engineering (the crafts) must be carefully cultivated, documented, and passed on to the next generations.

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