REVISTA NEUROCIÊNCIAS

Revisão

# Human brain cognition revealed by Suzana Herculano-Houzel's isotropic fractionator studies

## *A cognição do cérebro humano revelada pelos estudos do fracionador isotrópico de Suzana Herculano-Houzel*

## *La cognición del cerebro humano revelada por los estudios del fraccionador isotrópico de Suzana Herculano-Houzel*

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## Resumo

**Introdução.** Durante décadas, a superioridade cognitiva humana foi atribuída ao tamanho relativamente grande do cérebro em relação ao corpo. Mais recentemente, estudos conduzidos por Suzana Herculano-Houzel *et al.* propuseram uma perspectiva diferente, enfatizando o número absoluto de neurônios, particularmente no córtex cerebral, como um dos principais preditores das capacidades cognitivas. **Objetivo.** Discutir a composição celular do cérebro humano e suas implicações para a cognição. **Método.** Trata-se de uma revisão narrativa da literatura. As fontes incluíram artigos científicos originais, artigos de revisão e textos de divulgação científica de autoria de Herculano-Houzel *et al.*, bem como estudos que abordam medidas neuroanatômicas relacionadas à capacidade cognitiva. As buscas foram realizadas nas bases PubMed/MEDLINE, *Scopus* e *Web of Science – Core Collection*, complementadas por informações obtidas em plataformas acadêmicas como o Currículo Lattes. Foram incluídas publicações em inglês ou português no período de 2005 a 2025. **Resultados.** Comparações entre humanos e grandes primatas, como gorilas e orangotangos, indicam que o cérebro humano segue as mesmas regras de escalonamento celular observadas em outros primatas, em contraste com mamíferos de grande encéfalo, como os elefantes. Apesar de possuírem cérebros maiores, os elefantes apresentam menor número de neurônios corticais, reforçando a noção de que a cognição está mais intimamente associada ao número e à organização dos neurônios do que ao tamanho cerebral isoladamente. **Conclusão.** Os achados derivados do trabalho de Herculano-Houzel redefinem a compreensão da singularidade cognitiva humana e oferecem importantes contribuições para a neurociência comparativa e para o estudo da evolução das capacidades cognitivas.
**Unitermos.** Neurônios; Células não neuronais; Capacidades cognitivas; Anatomia comparada; Cérebro humano

## Abstract

**Introduction.** For decades, human cognitive superiority was attributed to the relatively large size of the brain in relation to the body. More recently, studies by Suzana Herculano-Houzel *et al.* have proposed a different perspective, emphasizing the absolute number of neurons, particularly in the cerebral cortex, as a key predictor of cognitive abilities. **Objective.** To discuss the cellular composition of the human brain and its implications for cognition. **Method.** This study consists of a narrative literature review. Sources included original research articles,

review papers, and science communication texts authored by Herculano-Houzel *et al.*, as well as studies addressing neuroanatomical measures related to cognitive capacity. Searches were conducted in PubMed/MEDLINE, Scopus, and Web of Science – Core Collection, complemented by academic platforms such as the Lattes Curriculum. Publications in English or Portuguese from 2005 to 2025 were included. **Results.** Comparisons between humans and great primates, such as gorillas and orangutans, indicate that the human brain follows the same cellular scaling rules observed in other primates, contrasting with large-brained mammals like elephants. Despite their larger brains, elephants have fewer cortical neurons, reinforcing the notion that cognition is more closely associated with neuronal number and organization than with brain size alone. **Conclusion.** The findings derived from Herculano-Houzel's work reshape the understanding of human cognitive uniqueness and provide important insights for comparative neuroscience and the study of cognitive evolution.
**Keywords.** Neurons; Non-neuronal cells; Cognitive abilities; Comparative anatomy; Human brain

## Resumen

**Introducción.** Durante décadas, la superioridad cognitiva humana se atribuyó al tamaño relativamente grande del cerebro en relación con el cuerpo. Más recientemente, estudios realizados por Suzana Herculano-Houzel *et al.* han propuesto una perspectiva diferente, enfatizando el número absoluto de neuronas, en particular en la corteza cerebral, como un predictor clave de las capacidades cognitivas.**Objetivo.** Discutir la composición celular del cerebro humano y sus implicaciones para la cognición. **Método.** Este estudio consiste en una revisión narrativa de la literatura. Las fuentes incluyeron artículos científicos originales, artículos de revisión y textos de divulgación científica elaborados por Herculano-Houzel *et al.*, así como estudios que abordan medidas neuroanatómicas relacionadas con la capacidad cognitiva. Las búsquedas se realizaron en las bases de datos PubMed/MEDLINE, Scopus y Web of Science – Core Collection, complementadas con información obtenida en plataformas académicas como el Currículum Lattes. Se incluyeron publicaciones en inglés o portugués entre 2005 y 2025. **Resultados.** Las comparaciones entre humanos y grandes primates, como gorilas y orangutanes, indican que el cerebro humano sigue las mismas reglas de escalamiento celular observadas en otros primates, en contraste con mamíferos de gran cerebro como los elefantes. A pesar de poseer cerebros más grandes, los elefantes presentan un menor número de neuronas corticales, lo que refuerza la noción de que la cognición está más estrechamente asociada con el número y la organización de las neuronas que con el tamaño cerebral por sí solo. **Conclusiones.** Los hallazgos derivados del trabajo de Herculano-Houzel redefinen la comprensión de la singularidad cognitiva humana y aportan importantes contribuciones a la neurociencia comparativa y al estudio de la evolución de las capacidades cognitivas.
**Palabras clave.** Neuronas; Células no neuronales; Capacidades cognitivas; Anatomía comparada; Cerebro humano

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## INTRODUCTION

If we consider that the basis of cognitive abilities resides in the brain, why are human beings often self-described as the most cognitively capable animals, not those endowed with the largest brain? The idea behind this apparent paradox

is simple: since brains are composed of neurons, it seems reasonable to assume that larger brains contain a greater number of these cells. As neurons are the computational units of the brain, larger brains with more neurons should exhibit greater computational capacity when compared with smaller brains. This question constituted the starting point for the hypothesis proposed by Herculano-Houzel *et al.*[1]. Following this logic, humans should not even occupy a prominent position among animals in terms of cognitive abilities: weighing approximately 1.5kg, the human brain is two to three times smaller than that of an African elephant[2,3] and four to six times smaller than that of several cetaceans[4].

We also do not occupy first place, indeed, we are far from it, when it comes to relative brain size (expressed as a percentage of body mass), absolute cerebral cortex size, or degree of gyrification (cortical folding)[1,5]. At most, we rank first in terms of the relative size of the cerebral cortex in relation to total brain mass, but even this is not a particularly substantial advantage. Although the human cerebral cortex is the largest among mammals in relative terms, accounting for 75.5%, 75.7%, or even 84.0% of total brain mass or volume, other animals, both primates and non-primates, are not far behind: the cerebral cortex represents 73.0% of total brain mass in chimpanzees, 74.5% in horses, and 73.4% in the fin whale[1].

The apparent contradiction between our extraordinary cognitive abilities and the not-so-extraordinary size of our brain has been one of the main factors driving the idea that

the human brain is a special case, an exception to the rules that apply to the evolution of all other animals and brains. A widely accepted explanation for the cognitive superiority of humans relative to other mammals is the extraordinary size of our brain in comparison to body size, that is, our high encephalization quotient (EQ). This index represents the ratio between the observed brain mass and the brain mass expected based on the species' body mass, considering the allometric relationship between these two parameters. Since its definition by Jerison[6], EQ has been regarded as the best indirect indicator of cognitive abilities, as it is the parameter that most strongly highlights humans as exceptional among mammals, with values ranging between 7 and 8[4,6]. Humans stand out as a clear outlier, exhibiting a brain approximately seven times larger than expected based on average mammalian body mass, or about three times larger relative to other primates[1,4,6]. However, how this deviation was achieved still lacks conclusive explanations in the scientific literature.

Several hypotheses attempt to explain why a larger-than-expected brain would be associated with superior cognitive abilities. (A) Encephalization — It has been suggested that species with a higher EQ, such as humans, would be more cognitively capable. However, cases such as capuchin monkeys (high EQ) and gorillas (low EQ), in which the former do not outperform the latter in cognitive performance, call this idea into question. This hypothesis has therefore been challenged in favor of the absolute number of

cortical neurons and connections, or even absolute brain size; (B) Neuron number — The apparent incongruence between our cognitive abilities and brain size may be related to inadequate comparisons between species from different orders. Many studies assume that all brains follow a single structural plan, in which larger brains always contain more neurons, and brains of similar size contain comparable numbers of neurons. However, evidence shows that animals with similarly sized brains, such as cows and chimpanzees (approximately 400g of brain mass), or rhesus monkeys and capybaras (70–80g), can exhibit very different cognitive abilities and behaviors. This suggests either that the idea that larger brains always have more neurons is incorrect, or that neuron number is not the primary determinant of cognitive abilities; (C) Total connectivity — Estimated by the total number of synapses in the brain. Although still poorly investigated, available evidence indicates that synaptic density tends to be constant across species. If this is true, the total number of synapses would be merely proportional to brain size, which would not explain cognitive differences between brains of similar size[1].

Testing the possibility that large brains evolved with different relationships between size and neuron number across distinct mammalian orders became feasible when Suzana Herculano-Houzel *et al.* determined the number of cells composing the brains of more than 30 species belonging to three mammalian orders[1]. These studies were enabled by the development of the isotropic fractionator, a method that

allows accurate counting of neurons and non-neuronal cells based on suspensions of free nuclei obtained from the homogenization of entire brain tissues, divided into anatomically defined regions[1-3,7,8]. Using this method, it became possible to perform quantitative analyses of the cellular composition of developing and adult brains, ranging from mice to humans. Initiated in 2003, this project remains one of the author's main lines of research, providing new insights into several topics, including differences in cognitive abilities across species.

In this context, the contributions of Suzana Herculano-Houzel have been fundamental in reshaping our understanding of what makes the human brain unique. Accordingly, the aim of this narrative review was to critically examine these contributions and their implications for comparative neuroscience, seeking to clarify why the human brain, despite not being the largest, can be considered the most cognitively efficient.

## METHOD

This study consists of a narrative literature review. This method is widely recognized as fundamental to scientific production[9] and is used to describe and discuss the development or the "state of the art" of a given topic from a theoretical or conceptual perspective. Narrative reviews allow the author to interpret and critically analyze the existing literature[10].

The focus of this review is on the contributions of Suzana Herculano-Houzel, particularly with regard to the cellular composition of the human brain and its relationship with cognitive abilities. Special emphasis is given to the development and application of the isotropic fractionator, an innovative method that enabled the accurate counting of neurons and non-neuronal cells, redefining the understanding of how neuron numbers relate to cognition in humans and other species.

Source selection included original scientific articles, review papers, and science communication texts published by Herculano-Houzel *et al.*, as well as seminal studies on neuroanatomical measures considered representative of cognitive abilities, identified through the reference lists of the analyzed articles. Complementary information was also obtained from academic platforms such as the Lattes Curriculum. Texts published in English or Portuguese between 2005 and 2025 were included. The search strategy used to identify original articles and reviews is presented in Table 1.

The selected material was critically analyzed and organized into thematic axes in order to support the discussion and the development of the interpretative synthesis presented in this article.

Table 1. Search strategy by database.

| Databases | Search | Strategy |
|---|---|---|
| **PubMed** | [Author], [tiab] (title/abstract) | (Herculano-Houzel S[Author]) AND ("isotropic fractionator"[tiab] OR ("cellular scaling"[tiab] OR "neuronal scaling"[tiab]) OR (gorilla[tiab] OR orangutan[tiab] OR elephant*[tiab] OR rodent*[tiab]) OR ("equal numbers"[tiab] AND (neuronal OR nonneuronal OR "non-neuronal"))) |
| **Scopus** | AUTH(), TITLE-ABS-KEY(), proximity W/3 | AUTH("Herculano-Houzel, S.") AND TITLE-ABS-KEY( "isotropic fractionator" OR "cellular scaling" OR "neuronal scaling" OR gorilla OR orangutan OR elephant* OR rodent* OR "equal numbers" W/3 (neuronal OR "non-neuronal" OR nonneuronal) ) |
| **Web of Science** | AU= (Author), TS= (Topic: title+abstract+key-words), proximity NEAR/3 | AU=(Herculano-Houzel S) AND TS=("isotropic fractionator" OR "cellular scaling" OR "neuronal scaling" OR gorilla OR orangutan OR elephant* OR rodent* OR ("equal numbers" NEAR/3 (neuronal OR "non-neuronal" OR nonneuronal))) |

## RESULTS AND DISCUSSION

This section will be divided into seven subsections: the first will provide a brief description of Suzana Herculano-Houzel and her contributions; the second will describe the isotropic fractionator method; the third will present differences between the total brain, the cerebral cortex, and the cerebellum in terms of mass and number of neurons across species ranging from rodents to the African elephant; the fourth will describe the human brain in numerical terms; the fifth will compare the human brain with that of the great apes; the sixth will compare the human brain with that of the African elephant; and the seventh will discuss the relationship between the cerebral cortex and the cerebellum.

**Suzana Herculano-Houzel, a biologist, neuroscientist, researcher, writer, and university professor**

Suzana Herculano-Houzel, born in Rio de Janeiro in 1972[11], is a biologist with an emphasis on Genetics, having earned her undergraduate degree from the Federal University of Rio de Janeiro in 1992. In the same year, she began her master's degree in Neuroscience at Case Western Reserve University in the United States, where she defended her dissertation entitled Plasticity of neurotransmitter phenotype of the rat sweat gland innervation, completing it in 1995. She continued her academic training with a PhD in the same field at Université Pierre et Marie Curie (LISE/CNRS) in France, presenting the thesis Modulation of neuronal synchronous oscillations: dynamic variation with level of cortical activation and long-term use-dependent modification in 1999. In that same year, she completed a postdoctoral fellowship at the Max Planck Institute for Brain Research in Germany[12].

She is currently an associate professor at Vanderbilt University in the United States. In addition to her academic career, she is the author of eight popular science books and a columnist for Folha de S.Paulo. Among the recognitions she has received are the Jabuti Literary Prize in the Natural Sciences category and an honorable mention from the José Reis Award for Science Communication[12].

With more than 80 published articles, her research lines encompass topics such as the history of neuroscience, the history of neuroscience communication, science education,

the assessment of neuroscientific illiteracy in the general population (through the project "Você Conhece Seu Cérebro?"), public interest in science, and the use and impact of science communication materials. She also dedicates her research to investigating the cellular composition of the human and animal brain, aiming to estimate the number of neuronal and non-neuronal cells in different brain regions of adult and developing specimens from various species, including humans. These data contribute to the understanding of phylogenetic and ontogenetic rules governing brain construction[12]. These investigations led to the development of one of her most notable contributions to neuroscience: the isotropic fractionator.

**The isotropic fractionator method**

The central idea of the isotropic fractionator is simple: because each cell contains a nucleus, counting all nuclei present in the brain allows an estimate of the total number of cells in the original tissue. To achieve this, the brain (or a portion of it) is fixed and homogenized until a uniform suspension containing only cellular nuclei is obtained. As this suspension has a known volume, small samples are taken for counting the nuclei they contain. In this way, the total number of cells in the brain is calculated. Subsequently, to distinguish neurons from other cell types, a specific marker, the neuronal nuclear antigen (NeuN), is used, which binds exclusively to neuronal nuclei. Counting NeuN-labeled nuclei yields the total number of neurons; the number of non-

neuronal cells (such as glial cells) is obtained by subtraction. This method allows estimation of the total number of cells in approximately two hours and the total number of neurons within up to 24 hours, making a significant contribution to investigations of cellular composition and brain function. For a more detailed description of the method, see Herculano-Houzel and Lent[7]. Table 2 presents a summary of the steps involved in the isotropic fractionator method.

In the following section, studies by Herculano-Houzel *et al*. on the cellular composition of the brain across different species will be presented, all of which were conducted using the isotropic fractionator method[7].

## Quantitative comparison of the human brain and other species

Which neuroanatomical measures are considered representative of cognitive abilities? Total brain mass, cerebral cortex mass, and cortical folding index are among the most frequently cited. However, these values are in fact lower in the human brain when compared to those of several other species[13]. Another commonly mentioned measure is the relative mass of the cerebral cortex, expressed as a percentage of total brain mass. Although this value is indeed the highest in the human brain, the difference relative to other species is only marginal[13], as previously discussed. In this context, this measure has been questioned in favor of other approaches, such as the absolute number of cortical neurons and connections, or even absolute brain size.

Table 2. Main steps, advantages, and critical considerations of the isotropic fractionator for estimating brain cellular composition.

| Stages | Description |
|---|---|
| **Brain collection and preparation** | • Animals: 4 Wistar rats, euthanized by ether;<br>• Perfusion: Saline → 4% paraformaldehyde;<br>• Removal: Brain removed through the foramen magnum;<br>• Post-fixation: Immersion in PFA for 3–30 days;<br>• Dissection: Olfactory bulb, cerebral cortex, cerebellum, and remaining areas, based on anatomical landmarks. |
| **Tissue dissociation, staining, and total cell counting** | 1. Mechanical dissociation: Fixed tissues are mechanically homogenized in a homogenizer with citrate + Triton. The cell membrane is disrupted, while nuclei remain intact → nuclear suspension;<br>2. Collection and centrifugation: Material is transferred to tubes, washed, and centrifuged (10 min, 4000 g). Nuclei form the pellet; the supernatant is separated;<br>3. DAPI staining: The pellet is resuspended in PBS + DAPI. Nuclei fluoresce blue. Density is adjusted (~5–10 million/mL);<br>4. Hemocytometer counting: Aliquots (5 µL) are analyzed under the microscope (400×). Nuclei are counted; variation <10% between samples;<br>5. Quality control: Only intact nuclei are counted. The supernatant is checked. Preparations with excessive debris or free nucleoli are discarded;<br>6. Final estimation: Nuclear density × volume = total number of cells. Subtotals are summed by region. |
| **Neuron identification and calculation of cell types** | 1. Aliquot preparation: 200–500 µL of the nuclear suspension used for neuron identification;<br>2. Epitope retrieval: Centrifugation → resuspension in 0.2 M boric acid (pH 9) → 1 h at 75 °C;<br>3. Primary antibody: Overnight incubation with anti-NeuN (mouse IgG, 1:300);<br>4. Secondary antibody: 2 h incubation with Cy3 anti-IgG + DAPI (40% PBS, 10% goat serum, 50% DAPI);<br>5. Microscopic counting: Fluorescence microscopy: DAPI (nuclei—blue) and NeuN/Cy3 (neurons—red). Counting of ≥500 nuclei;<br>6. Final calculation: % NeuN+ × total nuclei = neurons / Total − NeuN+ = non-neuronal cells. |
| **Total analysis time** | • Total cell estimation: ~2 hours;<br>• Neuron estimation (with NeuN): up to 24 hours. |
| **Advantages** | • Fast, inexpensive, and reliable method;<br>• Does not require complex techniques;<br>• Determines the total number of cells and neurons in multiple contexts (e.g., phylogeny, disease);<br>• Allows visual inspection and distinction between true nuclei and debris;<br>• Identifies cell types based on nuclear morphology;<br>• Accessible to virtually any laboratory. |
| **Critical points** | • The counts depend on intact nuclei; losses may lead to underestimation;<br>• It is not possible to precisely identify non-neuronal nuclei (glial, endothelial, or ependymal);<br>• NeuN-negative nuclei are classified generically until specific markers become available. |

Cy3 – fluorescent dye; DAPI – 4′,6-diamidino-2-phenylindole dihydrochloride; IgG – Immunoglobulin G; PBS – phosphate-buffered saline; PFA – paraformaldehyde; NeuN – neuronal nuclear antigen.

To test the hypothesis that the absolute number of neurons is related to cognitive abilities across different species, including humans, Herculano-Houzel *et al.*[3] analyzed the cellular composition of brains larger than the human brain. In 2009, Azevedo *et al.*[2] had already determined the total cellular composition of the human brain.

According to Herculano-Houzel *et al.*[3], the degree of encephalization is not the best predictor of cognitive abilities; rather, the absolute number of neurons in the cerebral cortex and cerebellum, independently of brain or body size, is a better predictor. It was already known that the human brain contains a significantly greater number of neurons in the cortex and cerebellum compared to other primates and to species with smaller brains, such as rodents[1,8,13]. However, the question remained as to whether the human brain also surpasses even larger brains in terms of neuron number.

Table 3 presents interspecific comparisons, ranging from rodents to the African elephant, regarding the number of neurons in the cerebral cortex and the cerebellum. Figure 1 illustrates brain mass (g), the total number of neurons in the brain, and the distribution of these neurons between the cerebral cortex and the cerebellum across different species, facilitating comparison among these parameters. Table 4 complements this analysis by presenting estimates of the number of neurons in the cerebral cortex and cerebellum of rodents, obtained from the total number of neurons and the proportions indicated in the study by Herculano-Houzel *et al*.[8].

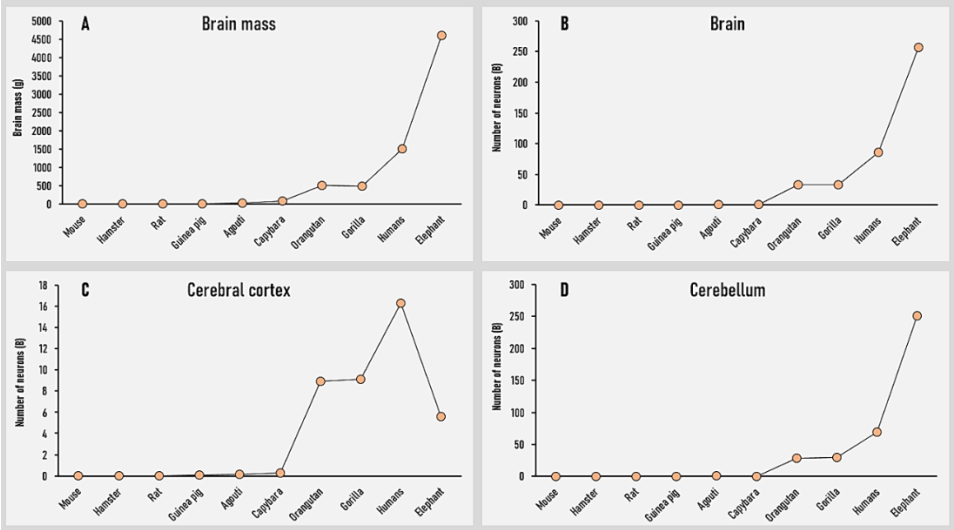
The selection of these articles reflects a methodological trajectory that made it possible to understand the diversity of cellular scaling across species. Studies in rodents marked the beginning of measurements using the isotropic fractionator and established the first scaling rules[8].

Table 3. Comparison of brain mass and number of neurons across different species.

| Species | Brain mass (g) | Total number of neurons | Notes |
|---|---|---|---|
| **Adult male Swiss mouse** (*Mus musculus*, n=4)[8] | 0.416 | **Brain:** 70.89 M<br>**Cerebral cortex:** 12.6 M<br>**Cerebellum:** 41.8 M | **Cerebral cortex:** the mass fraction ↑ from mouse to capybara, while the proportion of neurons remains ≈ stable (~18% in both). Mass ↑↑ as a function of Nn due to strong glial addition, leading to ↓ % neurons and ↑ glia-to-neuron index. Neuronal density ↓ <10× (even though Nn ↑ 23× between mouse and capybara). Contribution to mass derives mainly from neuron number (χN ≈ 0.24), with a smaller contribution from average cell size; in contrast, for non-neuronal cells, growth is driven almost entirely by cell number (Nnn ↑ 86×; density ↓ only ~2×; χNN ≈ 0.89).<br><br>**Cerebellum:** mass ≈ stable, but the fraction of neurons ↑ markedly (mouse ~59% → capybara ~72%). Mass increases more gradually as a function of Nn, with little glial addition, maintaining % neurons ≈ stable and only a slight ↑ in the glia-to-neuron index. Neuronal density is higher than in the cortex or remaining brain regions and ↓ more slowly in larger brains. Neuron number dominates the contribution to mass, although average cell size plays a somewhat greater role than in the cortex (χN ≈ 0.63). For glial cells, growth occurs primarily through cell number, with average size remaining nearly stable (χNN ≈ 0.94).<br><br>**Other structures (brainstem, diencephalon…):** mass fraction ↓ and % neurons also ↓ (mouse ~23% → capybara ~10%). Mass ↑↑ as a function of Nn, accompanied by strong glial addition, resulting in ↓↓ % neurons and ↑↑ glia-to-neuron index. Neuronal density ↓ in parallel with the cortex. The contribution to mass derives mainly from neuron number (χN ≈ 0.23). For non-neuronal cells, growth again occurs almost entirely through cell number, with average size ≈ stable (χNN ≈ 0.82).<br><br>**Overall synthesis (mouse → capybara):** Nn ↑ 23× while neuronal density ↓ <10×; non-neuronal cells ↑ 86×, but density ↓ only ~2×. Brain mass growth results far more from the addition of new cells (neurons and glia) than from increases in cell size, with glial cells being particularly conserved in size and the main contributors to mass increase. |
| **Golden hamster** (*Mesocricetus auratus*, n=2)[8] | 1.020 | **Brain:** 89.97 M<br>**Cerebral cortex:** 15.9 M<br>**Cerebellum:** 54.0 M | |
| **Adult male Wistar rat** (*Rattus norvegicus*, n=4)[8] | 1.802 | **Brain:** 200.13 M<br>**Cerebral cortex:** 31.6 M<br>**Cerebellum:** 120.1 M | |
| **Young adult male guinea pig** (*Cavia porcellus*, n=2)[8] | 3.759 | **Brain:** 239.62 M<br>**Cerebral cortex:** 42.7 M<br>**Cerebellum:** 146.2 M | |
| **Adult agouti** (*Dasyprocta primnolopha*, n=3; 1 female)[8] | 18.365 | **Brain:** 856.74 M<br>**Cerebral cortex:** 148.2 M<br>**Cerebellum:** 565.4 M | |
| **Adult female capybara** (*Hydrochoerus hydrochaeris*, n=2)[8] | 76.036 | **Brain:** 1.6 B<br>**Cerebral cortex:** 285.0 B<br>**Cerebellum:** 1,159.2 M | |
| **Adult orangutan** (*Pongo pygmaeus*, n=3; 1 female, 2 of unknown sex)[13] | 511.8 | **Brain:** 32.6 B<br>**Cerebral cortex:** 8.9 B<br>**Cerebellum:** 28.5 B | Predicted (mass/neurons) by scaling equations based on cerebellar cell numbers. Observed: brain/cortex measured by MRI; in the cerebellum, "observed (neurons)" refers to granule cells (Purkinje cells in millions; interneurons not included). Fixation >10 years → reduced mass without affecting cell counts. |
| **Gorilla** (*Gorilla gorilla*, n=1; sex unknown)[13] | 486.1 | **Brain:** 33.4 B<br>**Cerebral cortex:** 9.1 B<br>**Cerebellum:** 29.3 B | |
| **Adult men** (*Homo sapiens*, n=4)[2] | 1508.91 | **Brain:** 86.06 B<br>**Cerebral cortex:** 16.34 B<br>**Cerebellum:** 69.03 B | The majority of neurons are located in the cerebellum (~80%), but the cerebral cortex contains 16.34 billion neurons. |
| **Adult male African elephant** (*Loxodonta africana*, n=1)[3] | 4618.62 | **Brain:** 257.04 B<br>**Cerebral cortex:** 5.59 B<br>**Cerebellum:** 250.71 B | The majority of neurons are located in the cerebellum (~98%), whereas the cerebral cortex contains only 5.59 billion neurons. |

↑ = proportional increase; ↑↑ = marked/abrupt increase; ↓ = proportional decrease; ↓↓ = marked decrease; ≈ stable = virtually constant; Nn = number of neurons; Nnn = number of non-neuronal (glial) cells; % neurons = relative percentage of neurons in a given structure; glia-to-neuron index = ratio between the number of glial cells and neurons; density = number of cells per unit of tissue mass; χN = relative contribution of neuron number to the mass of the structure; χNN = relative contribution of non-neuronal cell number to the mass of the structure.

Figure 1. Brain mass and distribution of neurons across species. The panels show (A) brain mass (g), (B) the total number of neurons in the brain, (C) the number of neurons in the cerebral cortex, and (D) the number of neurons in the cerebellum for different mammalian species. Although brain mass and total neuron number increase markedly across species, the cerebral cortex contains a relatively smaller and more stable proportion of neurons when compared with the cerebellum.




The panels show (A) brain mass (g), (B) the total number of neurons in the brain, (C) the number of neurons in the cerebral cortex, and (D) the number of neurons in the cerebellum for different mammalian species. Although brain mass and total neuron number increase markedly across species, the cerebral cortex contains a relatively smaller and more stable proportion of neurons when compared with the cerebellum.

Table 4. Number of neurons in the cerebral cortex and cerebellum of rodents.

| Species | Total number of neurons | Cerebral cortex (≈18%) | Cerebellum (≈60–72%) | Calculation used |
|---|---|---|---|---|
| **Mouse** (*Mus musculus*) | 70.89 M | 12.6 M | 41.8 M | 70.89 multiplied by 17.8% (cortex), 70.89 multiplied by 59.0% (cerebellum) |
| **Golden hamster** (*Mesocricetus auratus*) | 89.97 M | 15.9 M | 54.0 M | 89.97 × 17.7% (cortex), 89.97 × 60.0% (cerebellum) |
| **Wistar rat** (*Rattus norvegicus*) | 200.13 M | 31.6 M | 120.1 M | 200.13 × 15.8% (cortex), 200.13 × 60.0% (cerebellum) |
| **Guinea pig** (*Cavia porcellus*) | 239.62 M | 42.7 M | 146.2 M | 239.62 × 17.8% (cortex), 239.62 × 61.0% (cerebellum) |
| **Black-rumped agouti** (*Dasyprocta prymnolopha*) | 856.74 M | 148.2 M | 565.4 M | 856.74 × 17.3% (cortex), 856.74 × 66.0% (cerebellum) |
| **Capybara** (*Hydrochoerus hydrochaeris*) | 1601.12 M | 285.0 M | 1159.2 M | 1601.12 × 17.8% (cortex), 1601.12 × 72.4% (cerebellum) |

Cerebral cortex and cerebellum values were obtained from the total number of neurons (Table 3) multiplied by the proportions indicated in the article by Herculano-Houzel *et al.*[8]. The data show that the number of neurons in the cerebral cortex remains around 18% of the total brain across all analyzed species, regardless of brain size. In contrast, the cerebellum contains the majority of neurons, ranging from approximately 59% in the mouse to more than 72% in the capybara. This indicates that, as brain size increases, the cerebellum gains proportionally more neurons than the cerebral cortex. Thus, the results suggest that brain expansion in rodents is strongly associated with an increase in the computational capacity of the cerebellum, rather than solely with the growth of the cerebral cortex.

In primates, data from gorillas and orangutans[13] showed that, despite having larger bodies, they possess relatively smaller brains, challenging the hypothesis that body size predicts brain size. In humans, approximately 86 billion neurons were identified[2], demonstrating that the human brain is an isometrically scaled-up primate brain. In elephants[3], although brain volume is larger, the majority of neurons are concentrated in the cerebellum rather than in the cerebral cortex, demonstrating that cognition is more closely related to the number and distribution of cortical neurons than to absolute brain size.

**Cellular composition of the human brain**

Although the 2014 study was mentioned earlier, its analysis will be addressed later in the chronological sequence. Returning to 2009, Azevedo *et al.*[2] published the article "Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain", aiming to determine the total cellular composition of the human brain using the isotropic fractionator and the same NeuN labeling criterion to distinguish neurons from non-neuronal cells[7]. The objective was to assess whether human brain composition differs from that expected for a primate brain of similar size. Four male brains were analyzed (ages 50, 51, 54, and 71), from individuals who died of non-neurological causes and had no history of cognitive impairment.

The authors estimated that the human brain contains approximately 86 billion neurons (ranging from 78.8 to 95.4 billion), with an overall neuron-to-non-neuron ratio close to 1:1[2]. Neuronal distribution, however, does not follow brain mass proportions: the cerebral cortex accounts for 82% of brain mass but contains only 19% of neurons (~16 billion), whereas the cerebellum, representing just 10% of brain mass, contains about 80% of neurons (~69 billion). Less than 1% of neurons are located in the remaining brain regions (RoB—basal nuclei, diencephalon, and brainstem), a value that may be underestimated due to incomplete NeuN labeling in parts of the brainstem[2].

Non-neuronal cells total approximately 84.6 billion, yielding an overall non-neuronal to neuronal ratio of 0.99. This ratio varies markedly across brain regions: 11.35 in the RoB, 1.48 in the cortical gray matter, and 0.23 in the cerebellum. Unlike neurons, non-neuronal cells are distributed more proportionally to brain mass, with 72% in the cerebral cortex (~60.8 billion), 19% in the cerebellum (~16.0 billion), and 9% in the RoB (~7.7 billion)[2].

Based on these findings, the authors proposed that the human brain is essentially a proportionally enlarged primate brain, maintaining the same structural and cellular organization observed in other primates. This interpretation challenges the traditional view that the human brain is seven times larger than expected for a generic mammal[6] or three times larger than that of a primate with similar body mass[4]. Such estimates arise from methodological choices that either

apply non-primate brain–body scaling rules or include great apes, whose large body size is disproportionate to their brain mass. Consequently, the authors suggest that humans may not possess an unusually large brain; rather, great apes may have disproportionately large bodies relative to their brains.

When great apes are included in these comparisons, the predicted body mass for a human with a 1509g brain would be 216kg, far exceeding the actual average of ~77kg. Conversely, for a 70kg human body, the predicted brain mass would be only 557g, substantially smaller than the real human brain. This issue is explored further in the following section.

When body mass is disregarded, the human brain, with approximately 86 billion neurons and 85 billion non-neuronal cells, matches the cellular composition expected for a generic primate brain of equivalent volume[2]. Given the linear neuronal scaling rules that apply to the cerebral cortex, cerebellum, and other brain structures in primates[14], the human brain can be understood as a primate brain expanded linearly in cell number. Moreover, comparisons of brain and body mass across six New and Old-World primate species indicate that the human brain exhibits the mass and cellular composition expected for a primate weighing approximately[2] 70kg[2].

This sharply contrasts with earlier claims that the human brain represents an outlier in brain–body scaling[4,6]. Such discrepancies likely stem from the strong dependence of brain–body scaling exponents on species selection,

whereas neuronal scaling rules remain more consistent and sampling-independent[15]. Thus, body mass emerges as a poor predictor of brain mass in primates.

This also suggests that body mass may not be a relevant parameter for assessing cognitive abilities[2]. Consistent with more recent evidence[16], absolute brain size, rather than brain-to-body proportionality, appears to correlate more strongly with cognitive performance. From this perspective, human cognitive superiority relative to other primates may be explained simply by the fact that humans possess the largest brain, constructed with an isometrically expanded number of neurons, independent of body weight.

**Comparisons with great apes**

At the time the 2009 article was published[2], Herculano-Houzel was investigating whether the brains of gorillas and orangutans also followed the cellular scaling rules observed in other primates, including humans, an investigation that would culminate in the publication of a paper in 2011[13]. This line of research is particularly relevant because the literature indicates that gorillas and orangutans are primates that match or even exceed humans in body size, yet their brains correspond to only about one third of the size of the human brain[4,13]. If this hypothesis were confirmed, it would reinforce the idea that, rather than humans possessing brains that are too large for their bodies, it is in fact the great apes that have disproportionately large bodies relative to their brain size,

even though in both cases the brains are built according to the same scaling rules that apply to primates.

In the 2011 study, the authors analyzed the numbers of neurons and other cells composing the cerebellum of three orangutans and one gorilla (entire cerebella from three adult orangutans—Pongo sp., one female and two of unknown sex—and one gorilla—*Gorilla gorilla*, sex unknown)[13]. The aim was to determine whether these numbers matched the predictions for primates, in comparison with hypothetical rodents with cerebella of similar size, used as an outgroup reference. Based on the number of cells found in the cerebella of the great primates, the authors also estimated the expected size of the brain as a whole and of the cerebral cortex in primates, comparing these values with those previously reported in scientific literature.

The results indicated that the cerebella of the gorilla and the orangutan have similar sizes and cellular compositions, with masses of 37.56g and 35.06±4.34g, respectively, and containing 29.3 billion and 28.5±3.78 billion cells. The observed cellular composition differs by 30% to 40% from what would be expected based on primate scaling rules, a variation slightly greater than that found in other primates, including humans. However, the authors attribute this difference to tissue shrinkage caused by more than ten years of fixation in paraformaldehyde, which reduces organ mass without significantly altering cell number. Specifically, the number of cells observed in the gorilla cerebellum was 24.7% lower than expected for a mass of 64.5g, whereas in

the orangutan the difference was only 5.2% relative to the predicted value for a 48.5g cerebellum. Conversely, the cerebella of these species contain nearly five times more cells than would be expected for rodent cerebella of similar size, reinforcing that, unlike rodents, great primates follow the cellular scaling rules typical of primates[13].

In addition to analyzing the cellular composition of the cerebellum in these apes, the authors also used the number of cells present in the cerebella to estimate the expected size of the cerebral cortex, based on primate cellular scaling rules. The results indicated that the number of cells in the cerebellum is a good predictor of cerebral cortex mass and cellular composition in primates, with a typical accuracy of approximately 20%. Based on the 28.5 to 29.3 billion cells found in the cerebella of these species, the authors estimated that their cerebral cortices (including white matter) should weigh between 394 and 406g. These estimates showed less than a 10% deviation from values reported in the literature, which indicate cortical masses of 415g for the orangutan and 377g for the gorilla. In contrast, rodents with the same number of cerebellar cells would have cerebral cortices weighing more than 2200g, highlighting that primates follow distinct cellular scaling rules. Thus, even without direct analysis of the cortices, the data strongly suggests that the brains of gorillas and orangutans follow the same linear cellular scaling rules observed in other primates, including humans[13].

Finally, the authors estimated the number of neurons and other cells in the whole brain of these animals and in their respective structures, using the human brain as a reference and applying equations derived from data available in the study by Herculano-Houzel *et al.*[14]. Based on the number of cells recently identified in the human cerebellum[2], it was estimated that the human brain weighs 1433g and contains 93 billion neurons, distributed across different structures in a manner very close to the values obtained using the isotropic fractionator. This correspondence validates the approach of estimating primate brain mass and cellular composition from the number of cells present in the cerebellum.

The findings indicate that the brains of orangutans and gorillas consistently follow primate cellular scaling rules. The orangutan brain was estimated to weigh 470g and to contain approximately 32 billion neurons and 35 billion non-neuronal cells, whereas the gorilla brain was estimated to weigh about 483g, with 33 billion neurons and 36 billion non-neuronal cells, values very close to those reported in the literature and with cellular proportions similar to those of other primates, including humans. In contrast, rodent brains with the same number of cerebellar cells would have much greater masses, exceeding 2800g, which further supports the conformity of great apes to primate-specific scaling rules. However, despite the conformity of brain scaling, the body mass of gorillas and orangutans deviates substantially from the relationship observed in other primate species, exceeding

expected values by more than 100%, suggesting a dissociation between brain and body scaling in these species.

The analysis of the cellular composition of the cerebellum in these apes shows that this structure follows the cellular scaling rules that apply to other primate species, including humans. Moreover, the number of cells in the cerebellum is a good predictor of cortical and whole-brain mass, making it likely that the complete brains of these great apes also follow the same scaling rules applicable to other primates. Thus, the authors infer that the brains of these animals, like the human brain, are built according to the same linear cellular scaling rules observed in other primates.

Because brain size has been shown to increase linearly with neuron number in non-human primates[14], as well as in humans[2], the authors postulated that neuron number in hominin taxa should also relate to brain mass in a similar manner, although such data were not reported in this review. The authors expect that estimates of the number of neurons composing the brains of these hominin species will make a significant contribution to future studies on the evolution of cognitive abilities across species, as well as to comparative investigations among taxa with large brains, such as dolphins, whales, and elephants (a topic addressed below). This is particularly relevant in light of the proposal that the absolute number of neurons in the brain, regardless of its size, constitutes a limiting factor for cognition and therefore a more accurate predictor of cognitive abilities than relative or absolute brain size or degree of encephalization, as

previously suggested by Herculano-Houzel *et al.* in other studies.

Given that the cognitive abilities of non-human primates are directly related to absolute brain size and, consequently, to the total number of neurons in the brain, it is reasonable to consider that an increase in brain size, resulting from an increase in neuron number, may have played an important role in reducing dependence on body size for competition over resources and mates. Moreover, this increase may have contributed, through superior cognitive abilities, to the evolutionary success of our species[17].

**The elephant brain case**

If cognition is dictated by the number of neurons, how can the elephant be explained? This was the central question that Herculano-Houzel *et al*.[3] set out to address with the publication of "The elephant brain in numbers". The aim of the study was to investigate the cellular composition of the African elephant brain, a giant with a brain substantially larger than the human brain, in order to determine whether, despite its greater volume, it possesses an absolute number of neurons capable of rivaling or surpassing that of the human brain.

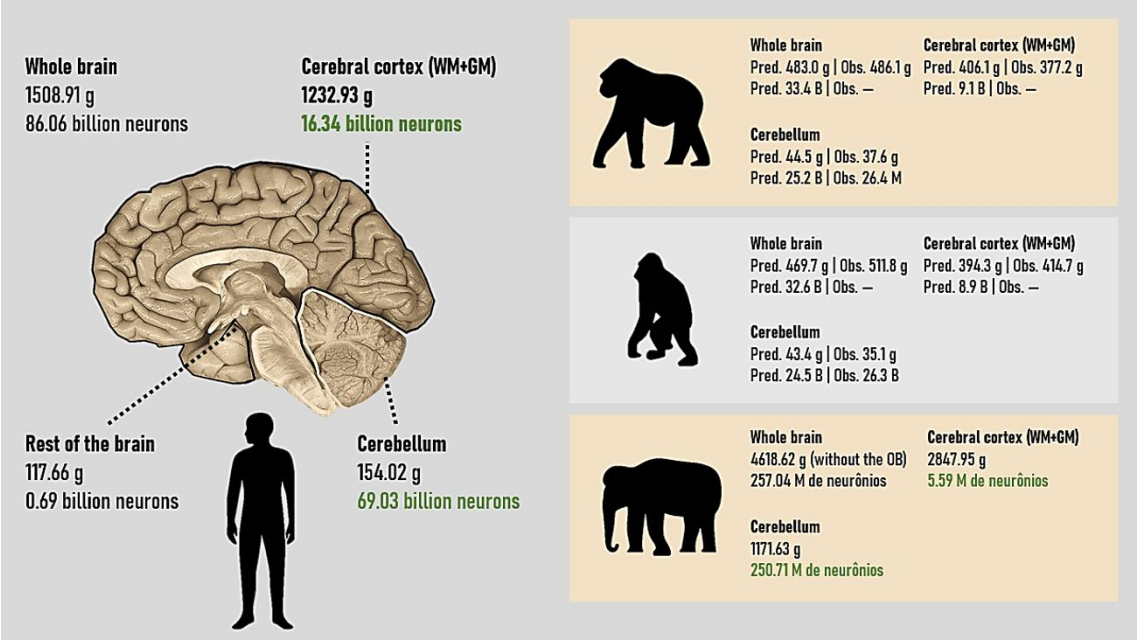
Relevant results were obtained regarding the cellular composition of the African elephant brain (*Loxodonta africana*). Weighing 4618.6g (excluding the olfactory bulb), the brain of this animal is approximately three times heavier

than the human brain and contains a total of 257 billion neurons[3], also about three times the average of 86 billion neurons observed in the human brain[2]. However, despite this large total number of neurons, the African elephant cerebral cortex contains only 5.6 billion neurons[3], which corresponds to approximately one third of the average 16.3 billion neurons found in the human cerebral cortex[2]. This occurs even though the elephant cortex has a mass of 2848g (considering gray and white matter combined), more than twice the mass of the human cerebral cortex[3].

The African elephant cerebral cortex contains significantly fewer neurons than the human cerebral cortex[2,3], as well as fewer than estimated for great apes, such as approximately 9 billion neurons in gorillas and orangutans and about 8 billion in chimpanzees[13] (Figure 2). Nevertheless, the number of cortical neurons in the elephant exceeds that observed in macaques of the genus Macaca and in baboons, which possess between 1 and 3 billion neurons[15].

The authors speculate that cognitive abilities shared by great apes and elephants, such as cooperation and mirror self-recognition, may be related to cortical neuron numbers that, although lower than those found in the human cerebral cortex, are still higher than those of many other mammals, including monkeys and large artiodactyls.

Figure 2. Brain mass and neuronal distribution in the cerebral cortex and cerebellum across different species.




They emphasize, however, that further investigation is needed to determine how neuron numbers in prefrontal (tertiary associative) cortical areas compare across these species, as well as to examine synapse numbers and connectivity patterns. To date, the available evidence supports the hypothesis that the most plausible explanation for the extraordinary cognitive abilities of the human brain lies in the high number of neurons concentrated in the cerebral cortex[3], a number consistent with that expected for a primate brain with human proportions[1]. Thus, the absolute number of neurons in the human cerebral cortex, rather than in the brain as a whole, appears to be more directly related to superior human cognitive abilities when compared with elephants and other mammals with larger brains.

## Relationship between the cerebral cortex and the cerebellum

Here, we will focus on the relationship between the cerebral cortex and the cerebellum in humans, although some aspects will also be illustrated by studies conducted in other animals.

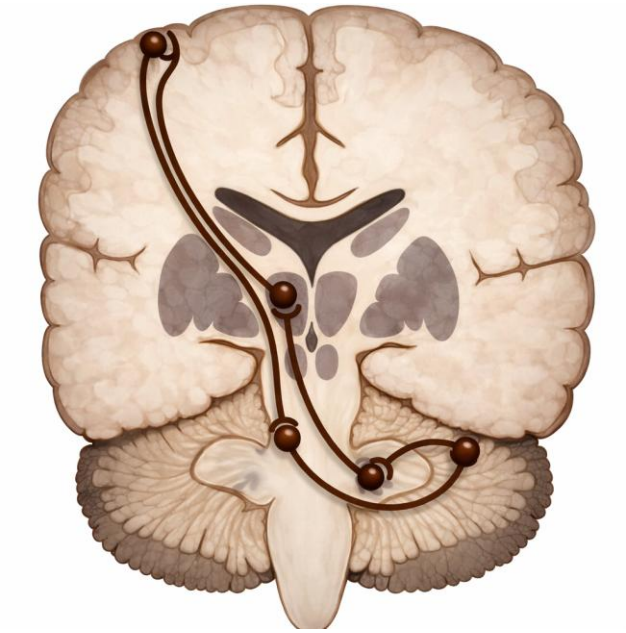
What about the relationship between the cerebral cortex and the cerebellum? Compared with other primates and with species that have smaller brains, such as rodents, the human brain stands out by presenting a significantly higher number of neurons in both the cerebral cortex and the cerebellum[1-3,8,13].

We will highlight this relationship, which has changed over the years. With advances in research, there has been a shift in the understanding of the cerebellum. It is now known that the cerebellum does not act exclusively in somatomotor processing, but rather participates in circuits distributed throughout the cerebral cortex, including a particularly extensive processing of information originating from the prefrontal cortex, which supports its contribution to cognitive functions[18,19]. In this context, primate evolution was marked by a coordinated increase in the volume of the prefrontal cortex, prefrontal projections to the corticopontine pathway, and cerebellar lobules projecting to the prefrontal cortex[3]. The cerebellum is interconnected with the contralateral cerebrum primarily through two polysynaptic circuits: an afferent pathway, which synapses in the pons and crosses to the cerebellum, and an efferent pathway, which projects first

to the deep cerebellar nuclei, then to the thalamus, and finally to the cerebral cortex[19] (Figure 3).

In an extensive review conducted by Diamond[18], the author presents multiple lines of evidence supporting this functional coupling. In summary: functional neuroimaging studies and investigations of patients with brain lesions point to a close association between the dorsolateral prefrontal cortex and the cerebellum.

Figure 3. Functional coupling between the cerebral cortex and the cerebellum.



With respect to functional neuroimaging, these studies consistently demonstrate that when a cognitive task increases activation in the dorsolateral prefrontal cortex, there is also an increase in activation in the contralateral cerebellum. Likewise, when a decrease in dorsolateral

prefrontal cortex activation is observed, for example, when a task has been practiced and requires less concentration, a concomitant reduction in cerebellar activation is also observed. Activation in these two regions is remarkably correlated and closely coupled[18] (Figure 4).

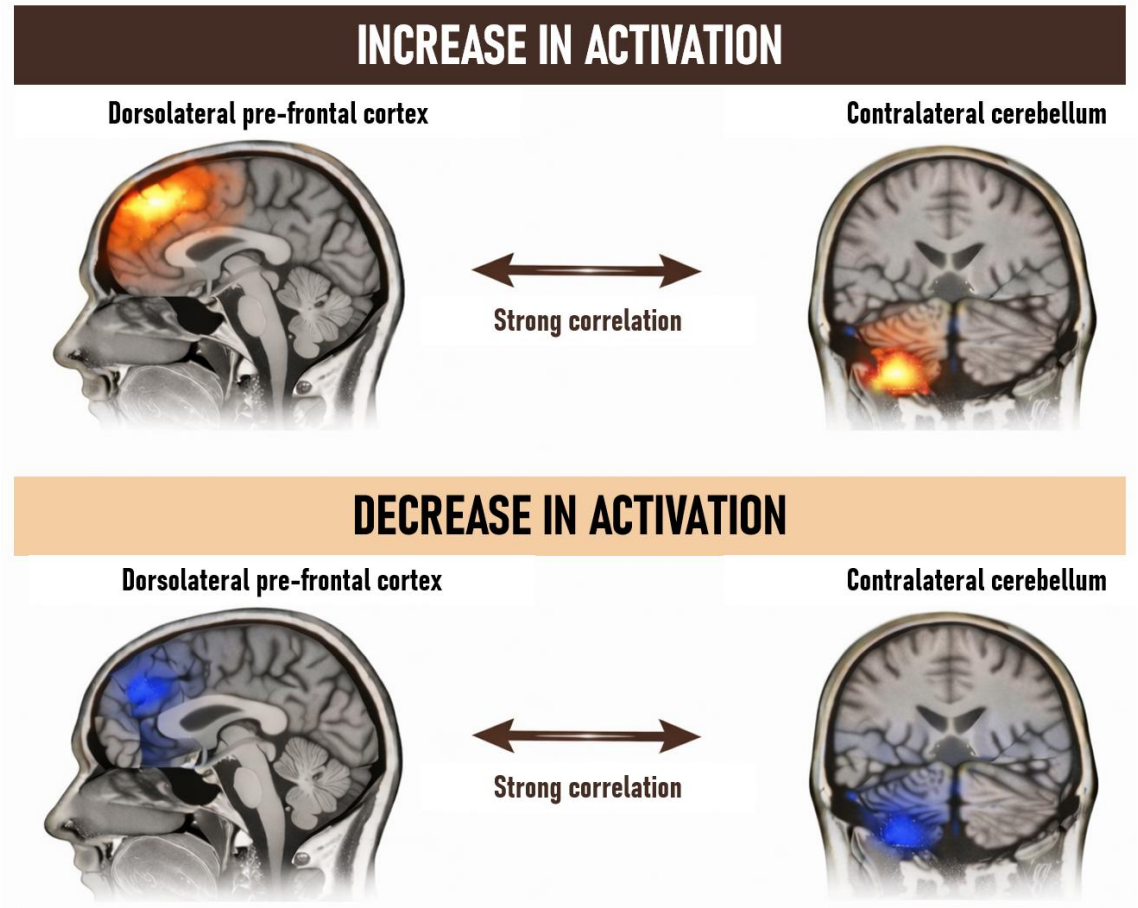
Regarding studies of patients with brain lesions, the findings indicate that lesions in the prefrontal cortex can cause hypometabolism in the contralateral cerebellum. Similarly, cerebellar damage can lead to frontal hypometabolism[18].

Thus, the cerebellum and the prefrontal cortex form an essential neural circuit, particularly recruited during more difficult or novel cognitive tasks that require adaptation to changing conditions, rapid responses, and increased attentional demands, in contrast to simpler, familiar, predictable, or automated situations[18].

Another relevant point is the discrepancy observed when comparing the number of neurons in the cerebral cortex and the cerebellum. As examples, humans and African elephants can be considered: in the cerebral cortex, they exhibit approximately 16 billion and 5.6 billion neurons, respectively, whereas in the cerebellum the values are about 69 billion in humans and 251 billion in elephants, as discussed in previous sections. The evolution of brain structures is largely constrained by embryonic developmental limitations, the sequence of neuronal birth, and scaling relationships among different brain regions[19]. In this context, the literature has proposed multiple

interpretations for the large size of the cerebellum in primates and humans, including explanations based on adaptive pressures related to motor and cognitive functions, as well as the hypothesis that such expansion represents a byproduct of selection for an overall increase in brain size rather than the result of direct, cerebellum-specific selection.

Figure 4. Functional coupling between the dorsolateral prefrontal cortex and the contralateral cerebellum.




Functional coupling between the dorsolateral prefrontal cortex and the contralateral cerebellum during conditions of increased (upper panel) and decreased (lower panel) neural activation, demonstrating a strong functional correlation between these regions.

The differential growth of brain structures throughout evolution appears to follow general scaling rules imposed by embryonic development, rather than being driven exclusively by region-specific adaptive pressures. As total brain size increases across mammalian species, different structures scale in a predictable manner but at distinct rates, with the cerebral cortex exhibiting the highest rate of expansion and the cerebellum the second highest[19]. Comparative evidence from rodents indicates that, although the cortex increases more rapidly in mass and volume, it maintains a relatively stable fraction of neurons, whereas the cerebellum preserves a constant fractional volume but accumulates neurons disproportionately as the brain grows[8]. This pattern reinforces the interpretation that cerebellar expansion in primates and humans may reflect, at least in part, a byproduct of global brain expansion, with relevant implications for understanding its functional role in cognition.

## CONCLUSION

Based on the analysis of Suzana Herculano-Houzel's contributions, particularly through the development and application of the isotropic fractionator, this review highlights the relevance of the absolute number of neurons, especially in the cerebral cortex, as the primary predictor of cognitive abilities in primates, including humans. In contrast to traditional perspectives based on the encephalization quotient or absolute brain mass, the evidence presented demonstrates that the human brain is not an outlier but

rather a primate brain scaled up in an isometric manner at the cellular level. Comparisons with great apes, such as gorillas and orangutans, as well as with species possessing even larger brains, such as elephants, further reinforce the notion that cognitive efficiency is more closely associated with neuronal density and distribution than with gross brain size.

The findings discussed throughout this review also challenge the idea that body mass is a reliable predictor of cognitive abilities, suggesting instead that the total number of cortical neurons constitutes a more robust and evolutionarily meaningful indicator. This framework not only repositions the human brain within the primate evolutionary spectrum but also offers a novel perspective for investigating the evolution of cognitive abilities in both extinct and extant species.

In this sense, Herculano-Houzel's contributions not only reshape our understanding of the human position on the evolutionary scale but also pave the way for more precise and comparative investigations into the relationship between brain structure, neuronal number, and cognition. Such advances provide a solid foundation for future research in comparative neuroscience, brain evolution and development, and may further impact fields such as education, artificial intelligence, and applied neuroscience in health.

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