How many neurons do we have and why does this matter to education?

Among the many neuromyths circulating in the scientific literature, perhaps the most famous one states that the human brain has a round number of one hundred billion neurons, and ten times more glial cells. New techniques were employed recently to show this is not true.

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Executive summary

Among the many neuromyths circulating in the scientific literature, perhaps the most famous one states that the human brain has a round number of one hundred billion neurons, and ten times more glial cells. New techniques were employed recently to show this is not true. The reason why one should pay attention to the number of cells in the brain is that it may change along life under many different influences, either by accretion of new neurons (neurogenesis), or by loss derived from diseases. Neurogenesis seems to occur in key regions of the nervous system, specifically those involved with memory and learning. So, unraveling the interventions capable of increasing neurogenesis in children and adults may be an important way of improving learning.

About neuromyths and the need to count cells in the brain

Neuromyths have long been recognized as scientific fake news that impact negatively on the beliefs of the population, including on the work of teachers at school, families at home, and citizens in general in many aspects. However, it is noticeable that neuroscientists may also be "victims" of neuromyths. I myself have been one of these victims.

In the late 1990s, I was writing a neuroscience textbook for Brazilian university students and was thinking about an attractive title that could replace the classical, technical titles that are typical of textbooks. My final choice was "One Hundred Billion Neurons"[1], which came accompanied by a "classical" subtitle. After the book was published, a postdoc in the lab questioned me about the evidence available for this round number of neurons attributed by most neuroscientists, at the time, to the adult human brain. I was intrigued about this question, and we started a thorough search in the literature. We found that, although all papers and textbooks referred to the round number as the true amount of neurons in the brain, in fact there was no sound experimental evidence for it, and estimates varied widely between 75 and 125 billion neurons[2]. The reason for this uncertainty was that only coarse estimates could be drawn from counting thin sections of different brain regions through a microscope. Since the heterogeneity of cell layers and nuclei in the brain is very pronounced, to extend the numbers counted within small areas to the whole brain or even to large anatomical regions resulted in highly inaccurate estimates.

The issue appeared to us not a mere question of determining the correct number for the title of a book. It was to be able to precisely count neurons and other cells in the brain of different species and, therefore, arrive at evolutionary rules as well as to count cells in the typical human brain and deviations taking place after developmental and degenerative diseases.

So, Suzana Herculano-Houzel and I decided to investigate the issue and started by inventing a new method[3] to arrive at more reliable counts of cell numbers in the brain. We did it first in rats. Very simply put, the method consisted of grinding and dissolving brain tissue and all cells therein, to finally arrive at a suspension of cell nuclei—a true brain soup. This suspension included all nuclei of the original tissue (the whole brain or its dissected subdivisions), kept in a volume defined by the investigator at will. After all procedures, the highly heterogeneous (anisotropic) nervous tissue had been transformed into a homogeneous (isotropic) suspension of nuclei. Any aliquot of this suspension would then be highly representative of the whole, and we just had to count and multiply it by the volume to arrive at the total number of counted cells. The method was named "isotropic fractionator" and has now been used by different labs in the world, who have confirmed its accuracy and the actual numbers within different brains and conditions.

The next issue to target was to count neurons from adult human brains. The challenge was great because it is not trivial to find brains donated for research available in conditions appropriate for applying the new method. We collaborated with the Brazilian Brain Bank at the University of São Paulo and, after heavy work, we arrived at the correct number of neurons in the adult male human brain[4]: approximately 86 billion, i.e., 15% less than the round number adopted by most authors.

What about the title of my book, now? It was already published, so I opted for adding an interrogation mark to the title of the second edition[5], and tell the whole story in the book's preface. After all, it became a good example of how neuromyths have to be faced by the scientific method to establish what is fact and what is not.

The number of neurons and other cells in animals and humans

Neurons are not the only cell type in the brain. There are other, very important ones called glial cells, besides blood vessel cells and some others, that complete the population of interacting units in the nervous system. Neurons are specialized in generating and propagating signals along multiple circuits that they form by extending their fibers all over the brain. Glial cells modulate the transmission of information between neurons and provide metabolic and protective support to the whole system. Concerning the quantitative distribution of these cell types, another neuromyth held that we would have ten times more glial cells than neurons in the brain. Wrong. We arrived at equal numbers of these two main cell types in the human brain as a whole (see Figure 1), although the ratio varied according to the regions studied. Notice that it is the cerebellum (not the cerebral cortex), despite representing only 10% of the total brain mass, that contains the great majority of neurons in the brain: about 80%, or 70 billion neurons! (See Figure 1.)

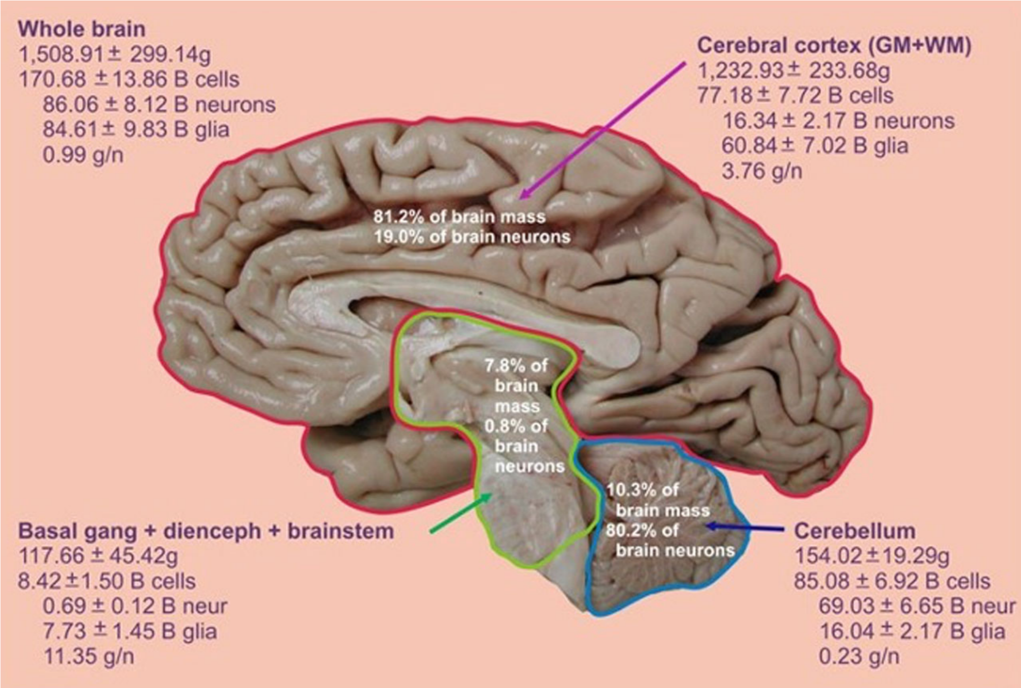

Figure 1. Despite having the largest proportion of brain mass, the cerebral cortex includes only about 19% of brain neurons. The champion is the cerebellum, which holds 80% of brain neurons within only 10% of brain mass. Modified from Azevedo et al. (2009)[4].

These quantitative data challenged another famous dogma of the neurosciences—that the cerebral cortex would be the highest achievement of brain evolution[2]. To give an example, it is worth quoting a sentence from a paper published in a famous article in 2009:

> "The cerebral cortex holds two-thirds of the brain's neurons and thus appears to be a promising candidate for determining the primary neuroanatomical correlates of intelligence"[6]

This concept of great prevalence of the cerebral cortex is still very frequent in the scientific literature and among lay people. Traditionally, the argument of biologists to confirm this dogma was brain size, expressed by its volume or weight (mass). The more sophisticated the functional relevance of a brain region was supposed to be, the bigger its size would become (relative to the total brain size) along evolution. According to this perspective, the cerebral cortex would really be the most complex area of the nervous system, since most studies reveal that this region becomes, proportionally, bigger and bigger along the evolutionary scale. Using the same rationale, the cerebellum, a region of the brain involved in motor control and learning, would remain relatively constant. True or false? False. Taking advantage of our new method, we quantified the number of neurons in the cerebral cortex and the cerebellum of different species of a same order—rodents—from the small mouse to the giant capybara[7]. Later, the same was done for primate species. What we found in rodents, confirmed in primates, was the opposite of the size neuromyth: When considering the number of neurons, the region that grew the most as the brain expanded was the cerebellum, not the cortex (see Figure 2).

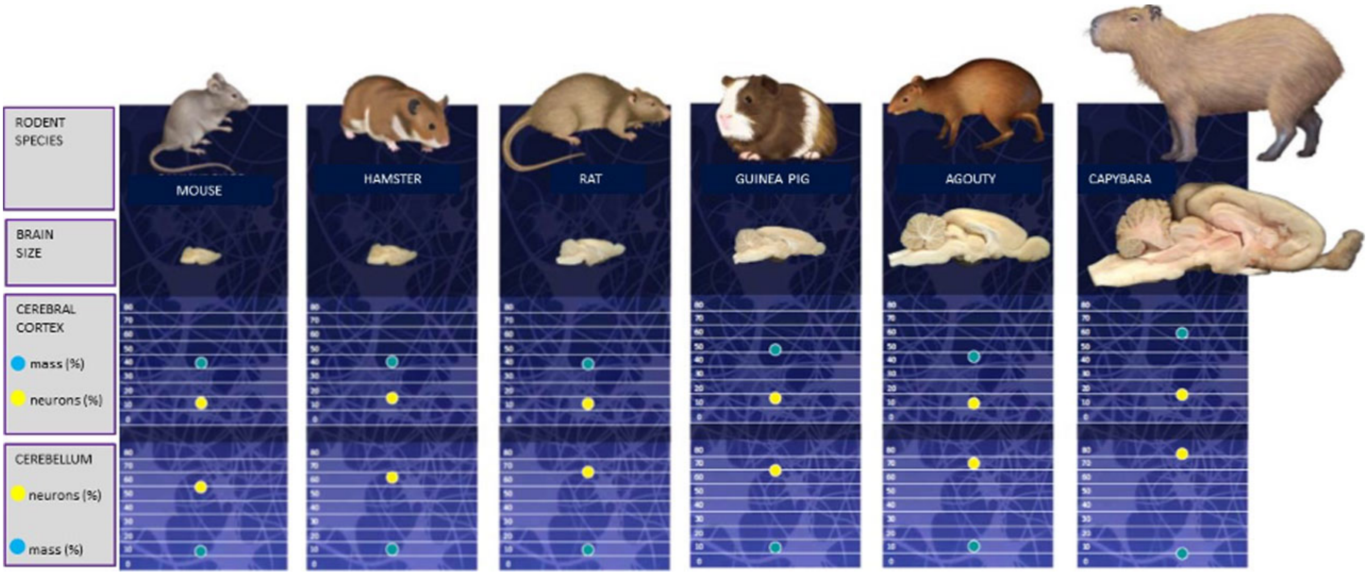

Figure 2. The brain grows as a whole in rodents, as much as body size. Cerebral cortex grows along similar rates, while the cerebellum stays proportionally unchanged. If neurons are considered, however, the number of these cells in the cerebellum grows steeply, while staying relatively stable in the cerebral cortex. Modified from Lent et al. (2010)[8].

More recently, it has been possible to extend our studies to glial cell subtypes. A nuclear marker has been developed for astrocytes[9], and another for oligodendrocytes[10]. The former are very important in modulating the transmission of information between neurons, controlling the flow of substances between the blood and the brain, and regulating the amount of neurotransmitter substances. The latter are responsible for an insulating sheath that covers nerve fibers and contribute to accelerating the propagation of electric signals from one region to another in the brain. We are working hard to establish the accurate number of these glial cell subtypes in different brain regions under diverse conditions.

How the number of neurons vary and why this is important

By knowing the accurate composition of cell types in the brain of animals, especially in the human brain, one may also determine, for example, how these numbers vary between men and women (sexual dimorphism), and what happens with these numbers under different environmental situations (ageing, for instance). This can be related to functional and cognitive parameters, and therefore can help explain the deficits and functional specializations of the owners of these neurons.

With this aim, we wanted to know whether the number of neurons in some key brain regions would show differences when comparing women with men. We first studied the olfactory bulb[11], a tiny blob of tissue situated above the nose inside the cranium, that receives the inflow of olfactory information coming from the nasal mucosa. Counts revealed that females have almost 50% more neurons than males in this region, and almost 40% more glial cells. It is difficult to be sure about what exactly these differences mean in functional terms, although one may be tempted to relate them to some olfactory abilities of women which are well-known to be superior to men's[12]. The second region we targeted was the medial temporal lobe, where lies the hippocampus, a brain region involved in memory consolidation and spatial memory[13]. Results were now the opposite from those of the olfactory bulb: men showed 34% more neurons in this region, as compared with women. Again, it is very difficult at present to arrive at consistent functional correlations. But the take-home message in this case is that the number of neurons may vary differently according to gender, in the different sectors of the brain, and this may reveal functional specializations.

Brain cellularity also changes with ageing, with a slight reduction of about 10% between 50 and 90 years old. But the difference gets much higher, especially in the hippocampus and in the cerebral cortex, when the person shows symptoms of dementia due to advanced Alzheimer's disease[14]. Findings here are important because some people show signs of Alzheimer's disease in their brains, but no memory loss or dementia: In this case, their neuronal numbers were typical for their age as compared to other individuals without Alzheimer's. However, when memory losses and dementia take place, the number of neurons drop significantly in the temporal lobe where the hippocampus is located, accompanied by an increase in the number of glial cells. This finding contributed to eliminating another neuromyth, prevalent among clinicians: that the protein plaques and tangles that are deposited in the brain of elderly persons are the cause of dementia. Wrong. According to our data, it is the loss of neurons, independent of plaques and tangles, that correlates with Alzheimer's symptoms.

Influences on the number of neurons along development

If your reading has survived up to this point of my text, you should be asking yourself what at all this issue of cell numbers has to do with education.

It is well established that some regions of the brain of adult animals conserve a very important feature of development: neurogenesis. This has been strongly demonstrated in rodents and other species in the olfactory bulb[15] and the hippocampus[16]: New neurons continue to be generated throughout adulthood in those regions. Our work using the isotropic fractionator for the brain of developing rats has contributed insight into the controversial existence of neurogenesis in the adult cerebral cortex[17]: Our findings were positive, but contrary to other authors who have reported negative results (see Figure 3).

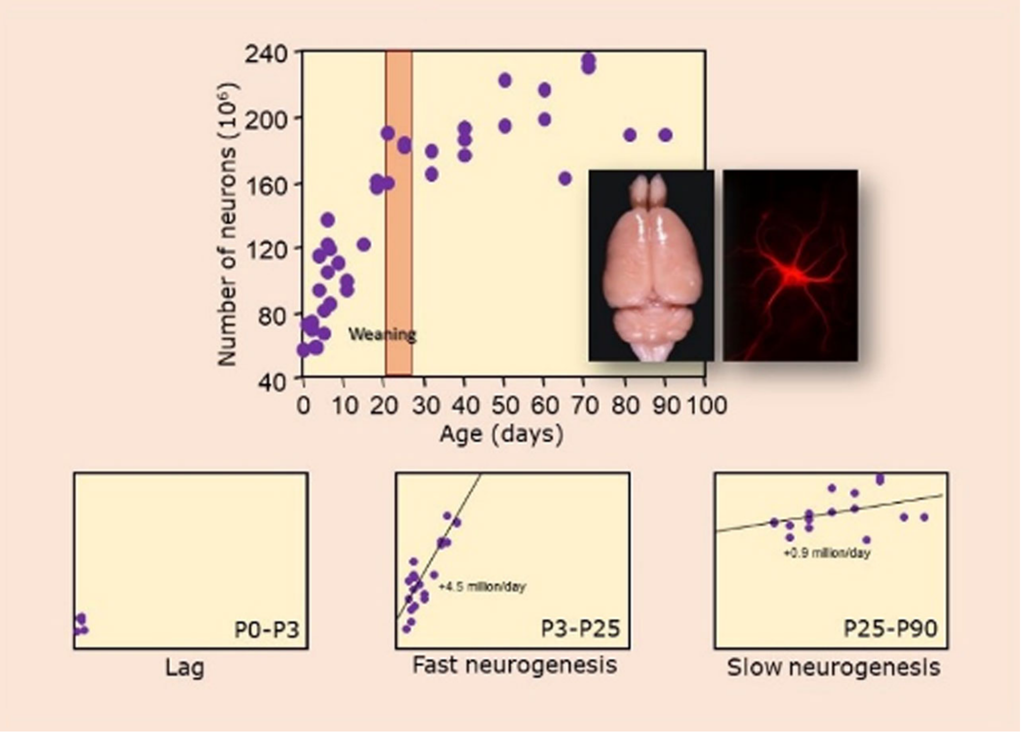

Figure 3. Postnatal neurogenesis in the brain of the rat, as detected by counting the absolute number of neurons.

The issue of adult neurogenesis has become even more controversial for the human brain. A study by a Swedish group of researchers used the clever method of measuring [14]C radioactivity in the brains of humans born during the Cold War years when atomic bomb tests were made by different countries. They confirmed the existence of adult neurogenesis in the human hippocampus and corpus striatum (a deep region in close connection with the cortex), but not in the cortex itself, or in the olfactory bulb[18]. The controversy has heated up in recent years, with results for and against the existence of adult neurogenesis in humans.

The most important issue derived from the existence of adult neurogenesis in the hippocampus is that a number of studies have established that, when newly generated neurons are stimulated after different interventions, better memory and learning take place. One good example is that of physical exercise. Hippocampal (and cortical) neurogenesis is largely increased in rats after a period of moderate aerobic exercise. New neurons were assessed both by using the isotropic fractionator, and by measuring the concentration of chemical factors which indicate the presence of neuronal precursors and cell division[19]. Behavioral tests for memory were also performed, detecting that exercised animals performed better than sedentary ones.

Most surprisingly, aerobic exercise is beneficial—both in terms of neurogenesis and behavioral performance—to the pups of mice mums who underwent daily sessions of aerobic exercise during pregnancy[20]! Adult neurogenesis, therefore, can be seen as a mechanism that favors learning and memory. So, one obvious consequence of these findings for education is that physical exercise should not be considered any longer as just a procedure to benefit pupils' body health, but also an activity that contributes to learning.

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