

Brain Development: The Generation of Large Brains

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What Larger Brains Are Made Of

More Neurons

One century of comparative studies has led to the notion that larger mammalian brains are built with larger numbers of neurons whose average size increases only modestly as brain size increases. Although technical difficulties preclude precise estimates of average neuronal size, changes in this parameter can be inferred from changes in neuronal density. Compared to the large volumetric expansion of structures such as the cerebral cortex, the relatively small decrease in neuronal density (presumably a result of larger neuronal size) in the structure across species indicates that increasing neuronal size is a factor in the generation of large brains, but one that is less important than increasing numbers of neurons. For example, the brain of the capybara, a giant Amazonian rodent, is 180× larger than the mouse brain, contains 22× more neurons, but its density of neurons per unit of tissue is only 8× smaller than in the mouse. The discrepancy may be even greater in primates: although the human brain weighs 175× more than a marmoset brain and has a 162× heavier cerebral cortex, the neuronal density in this structure is only about 3× smaller in humans. This indicates that the increase in average neuronal size contributes to increasing cortical size, but is a minor factor compared to increased number of neurons, in making the human cortex much larger than the marmoset cortex. Therefore, the generation of larger brains, at least within mammalian orders, requires the generation of larger numbers of neurons during development.

More Surface

The larger cerebral and cerebellar cortices of larger brains are increased mostly in their surface area, rather than in thickness. For example, the gray matter of the human cerebral cortex is roughly 1000× larger in surface area than the gray matter of the mouse cortex, but only about 2× thicker than the latter. The addition of larger numbers of neurons to cortical structures during brain development must thus proceed in a way that privileges surface expansion rather than greater thickness of the cortical wall.

More Glia

In contrast to the decreasing neuronal density, and therefore presumably increasing average neuronal size, large brains have densities of nonneuronal cells that are fairly similar to those found in smaller brains. This suggests that the average size of nonneuronal cells does not vary much with brain size, although their total number must increase rapidly in larger brains. In rodents, the total nonneuronal cell density in the brain is only 2× smaller in the capybara than in the mouse, even though the 180× larger brain of the former species has 85× more nonneuronal cells than the latter, suggesting that nonneuronal cells are not much larger in larger brains. Thus, besides the generation of larger numbers of neurons of moderately larger neurons, the development of larger brains requires the formation of an even larger number of glial cells whose size is presumed to vary little.

Neurons First, Glia Later

Brain development follows a series of well-documented steps. Early in development, the progenitor cells that compose the proliferative zones that line the ventricles undergo a series of symmetrical divisions, which expand exponentially the number of progenitors that will eventually give rise to neurons and glial cells in the brain. These symmetrical divisions establish the size of the founder population of progenitor cells that will build the brain.

Asymmetrical divisions ensue, in which one progenitor gives rise, for instance, to one self-renewing progenitor and one proliferating cell, which will give rise to the neurons that migrate outward to form the cortical plate and the parenchyma of other brain structures. Regressive events also occur in development, and may drastically reduce the neuronal population. According to some estimates, the total number of cortical neurons may be cut in half during development due to cell death.

The glial population of the brain is formed only once the neuronal population is already in place, as cell-intrinsic mechanisms eventually promote a switch from neuronal to glial production by progenitor cells. Neurogenesis is mostly prenatal; gliogenesis extends into postnatal life.

How to Add More Neurons

If large brains have an increased number of neurons, their generation must involve the production of larger

numbers of neurons during development. This may be achieved in at least three ways: by increasing the number of progenitors, by increasing the number of neurons generated by each progenitor, and by decreasing the number of neurons lost to cell death. These processes necessarily take time, so it seems logical that large brains take longer to develop than small brains. Indeed, the neuronal population of the mouse cortex is generated over about 6 days, while it takes about 55 and 100 days to generate all neurons in the macaque and human cortex, respectively. Gestation time increases coordinately with brain size at birth, among various mammalian orders.

More Progenitors Expand the Cortical Surface

Clonal analysis has shown that the neurons generated from one single progenitor are often clustered radially in the cerebral cortex. Since larger cerebral cortices are increased mostly in surface rather than in thickness, they should be generated by a larger number of radial clusters of neurons. If each radial cluster is derived from one progenitor cell, it follows that, all other things being equal, a larger number of progenitor cells should give rise to a larger surface of cerebral cortex of an unchanged thickness, containing a larger number of radial clusters of neurons. This is the essence of the 'radial-unit hypothesis,' proposed by Pasko Rakic in 1985.

Since the population of progenitor cells is expanded exponentially by symmetric cell division, small increments in the number of divisions will give rise to much larger numbers of progenitors. With only $3\times$ extra rounds of cell division, for instance, a $2^3 = 8\times$ larger number of progenitors would be generated. If all other factors remain unchanged, these three extra rounds will generate a brain with $8\times$ more neurons. In this scenario, the $22\times$ larger number of neurons in the capybara brain could be achieved by an average 45 extra rounds of symmetric division of the early progenitor cells, prior to the generation of neurons.

Experimental data have shown that X-ray irradiation of monkey embryos during the period of symmetric division of progenitors results in a decrease in cortical surface, with little effect on its thickness. Moreover, genetic manipulations that increase the number of progenitors early in development do lead to animals with an abnormally large cortical surface.

However, the expansion of the progenitor symmetrical division is unlikely to be the sole factor that increases the number of neurons in brain structures. The radial-unit hypothesis is based on the proposition by Rockel, Hiorns, and Powell in 1980 that there is a constant number of close to 150 000 neurons underneath 1 mm^2 of cortical surface of any mammalian

species. This proposed uniformity has been contested by several groups, who argue that the number of neurons underneath a given surface may vary by as much as $8\times$ among species. While the expansion of the cortical surface is a major factor in building larger brains, and may be achieved by mechanisms that increase the population of founder progenitor cells, other factors must also contribute.

More Neurons per Progenitor Thicken the Cortical Surface

If increased symmetrical divisions expand the number of radial clones that will compose the cortical surface, increased asymmetrical divisions should expand the number of neurons that compose each clone, and thus increase the thickness of the cortical wall. Accordingly, there is evidence that experimental manipulations that increase the number of neurons generated per neuronal progenitor cell do lead to thickening of the cortical wall within a single species. Comparative studies addressing the number of neurons generated per progenitor across species, however, are lacking in the literature.

Decreased Cell Death Enlarges the Brain

Cell death is a normal mechanism that regulates the number of neurons in the brain. Differentiated neurons are subject to cell death, which is generally expected to cut the neuronal population of the brain in half, but the number of progenitor cells has also been shown to be regulated by cell death. Experimental genetic manipulations that delete genes required for cell death lead to animals with abnormally large brains. However, these mutations are lethal, and it is not known whether more subtle, natural genetic modifications of the cell-death pathway are an actual mechanism in the development of large brains. Interestingly, chemical manipulations that diminish but do not abolish progenitor cell death lead to both, expansion of the cortical surface and thickening of the cortical wall. This shows that the regulation of cell death is a possible mechanism in the generation of brains of different sizes in evolution.

Natural Mechanisms Are Still Unknown

Overall, it is possible that cortical surface and thickness be regulated both independently and coordinately, by developmental mechanisms that seem to apply to other brain structures as well. However, despite the relative wealth of data on experimental manipulations that affect proliferation, differentiation, and cell death and lead to the development of abnormally larger brains, it is still unclear whether

and how these processes vary naturally among species of different brain size.

More Glia Follow

Larger brains tend to have an increased ratio of glial cells to every neuron, or g/n ratio, compared to smaller brains. Fin whales, for example, have a gray matter g/n ratio of 454, while that ratio in humans is 178. Since glial cells appear in development only once the neuronal population is formed, mostly postnatally, mechanisms that adjust the number of glial cells to the number of neurons already present in the cortical wall must be in place in development.

Glial proliferation can be influenced by neuronal activity. Because it has been widely believed that the relative glial expansion has trophic and metabolic meaning for the neuronal population, the increase in the g/n ratio with increasing brain size has often been hypothesized to be regulated directly by neuronal activity. This would take place during gliogenesis, in postnatal development. Accordingly, the neuronal activity-regulated generation of large numbers of glial cells would further expand brain size beyond the enlargement due to the generation of larger numbers of neurons.

However, the numeric expansion of glial cells relative to neurons seems to contradict the observation that the neuronal need for metabolic support remains similar across species. Moreover, the increased g/n ratio of larger brains is not accompanied by any systematic variation in glial density, as large brains have glial cells distributed as densely as in small brains. These discrepancies could be settled if, during development, gliogenesis were regulated not by neuronal activity, but mainly by the overall neuronal mass in structures such as the cortical wall. This is in line with the observation that the proliferation of glial progenitors is controlled by contact inhibition with glial cells. Gliogenesis would thus presumably ensue until the entire cortical wall was occupied by evenly distributed glia. The higher the number of neurons in the cortical wall, the larger the latter would become, and thus the larger would be the volume of tissue to accommodate proliferating glial cells. Since increasing neuronal size also contributes to making brains larger, the cortical volume to be

invaded by newly born glial cells is presumably yet larger in large brains. A larger number of glial cells would thus be generated for every neuron, leading to the increased g/n ratio observed in large brains.

Genetic Regulation of Brain Size

As mentioned above, changes in brain size can be generated experimentally through the manipulation of several genes controlling cell proliferation, differentiation, and death during development. Although it is unclear how these processes vary among species, it is already established that there is variability in genes that regulate brain size across primate species, humans included. For example, cell cycle genes associated with microcephaly (MCPH1, ASPM, CDK5RAP2, CENPJ) and caspase genes controlling cell death have higher evolutionary rates in primates, particularly in great apes and humans, than in rodents or carnivores, and seem to have undergone positive selection. It is unclear, however, how these gene changes are related to brain size.

See also: Allometric Analysis of Brain Size; Brain Connectivity and Brain Size; Brain Evolution: Developmental Constraints and Relative Developmental Growth; Brain Scaling Laws; Neurogenesis in the Intact Adult Brain; Programmed Cell Death.

Further Reading

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