3

A Matter of Size

A feature early neurologists rapidly became aware of was that humans are endowed with unusually large brains compared to those of many other animals. This fact tempted many people to associate brain size with intelligence, not only across species but also among humans. Darwin claimed that the large size of the human brain, compared to that of the gorilla or orangutan, was closely related to the higher mental powers of humans, and noted that the effect of brain size was also found in insects, where social ants and bees had much larger cerebral ganglia than beetles (Darwin 1871). Darwin also asserted that one of the requisites to achieve language was to be endowed with higher mental capacity. As we will see throughout this book, it may have been the other way around, communication skills being a strong selective force for the increase in both brain size and cognitive capacity. In this chapter, I will review some aspects of the intense research agenda involved in determining the functional, developmental and evolutionary aspects of brain size differences. Not surprisingly, this continues to be a contentious topic as it is the most evident difference in brain anatomy between us and other primates.

F. Aboitiz, *A Brain for Speech*,
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Brain and Body

Animals like elephants and whales have brains much larger than ours. In fact, the brain is simply another organ of the body, subject to similar growth rules as other organs. Thus, larger animals tend to have larger brains than smaller animals, but are they smarter? Supporting the notion that brain size is a determinant of intelligence and learning capacity, in the early twentieth century Karl Lashley proposed the "principle of mass action", stating that the amount of damaged neural tissue is proportional to the amount of memory impairment produced, a concept that challenged the localizationist hypotheses at the time (Lashley 1929). Later on, Harry Jerison interpreted Lashley's concept in an evolutionary context and proposed the "principle of proper mass", which relates overall brain size to processing capacity across species (Jerison 1973). Jerison claimed that brain weight correlated best with the number of neurons in the brain, and that the amount of information processing per unit of volume was constant across species, implying that increased brain volume is directly associated with increased information capacity. Jerison statistically analyzed brain and body sizes of many species of vertebrates and found a consistent correlation between brain and body size among species, but little correlation in these variables within a species. In sexually dimorphic species (like humans), each sex was treated as a separate species. He graphically showed his results in standard allometric diagrams called log-log graphs in which both variables are displayed exponentially in each axis. With this method, exponential relations are displayed linearly and one can apply standard statistical methods to the data. If two variables (brain and body) have a linear relationship (a twofold increase in one implies a twofold increase in the other), the relationship is isometric and the slope of the graph is 1. If the slope is other than 1 in either direction, the relationship is allometric. In isometric growth, overall size increases result in scaled versions of the smaller versions, but in allometric growth, components (say body and brain) increase in size at different rates. Note that in an allometric relationship growth among different components still correlates, only some increase in size faster than others. A third possibility is that

structures grow independently, that is, there is no correlated variability in size among distinct components of the body. The latter suggests little genetic correlation among the components, at least in relation to the determination of size. It is important to be clear about this, as some controversies have been caused by a lack of precision in describing comparative data.

In the case of body and brain, twofold increases in body size result in less than twofold increases in brain size, implying that smaller animals have larger brains for their body size than bigger animals. Jerison considered the strong body size dependency of brain size as the amount of neural tissue that was necessary for controlling bodily functions, and called it the "somatic factor", which was variable across vertebrate groups. Jerison's body-brain slope in mammals was about two-thirds, which fits the geometrical ratio between body size and body surface area. Therefore, he speculated that brain size scaled not with body weight but with the animals skin surface, as it needed to match the sensory receptors distributed in the skin. New analyses have revealed that the brain-body slope is not two thirds, but actually three-fourths, that is, if the body doubles in size, the brain increases 1.5 times in size (Martin 1981). According to this, a new interpretation for brain-body scaling is that brain size is determined by basal metabolic rate, which Max Kleiber showed to scale at three fourths with body size (Fig. 3.1) (Kleiber 1975). Since the brain is one of the most expensive organs in terms of energy needs (in humans it uses about 20% of total body energy), a lower metabolism in larger animals put limits to brain growth during gestation. However, no relationship was found between metabolic rate and brain size in a statistical analysis that eliminated body size (Pagel and Harvey 1988). In effect, metabolic rate and brain size only correlate because they both depend on body weight.

More detailed studies in the 1980s revealed that the variable that best fits the mammalian brain body slope is the period of prenatal body growth (Riska and Atchley 1985). During development, brain growth follows an exponential curve that can be subdivided into three distinct phases. There is an initial rapid growth phase in which the brain increases in size concomitant with body size and roughly corresponds to the period of prenatal growth. There is then a second

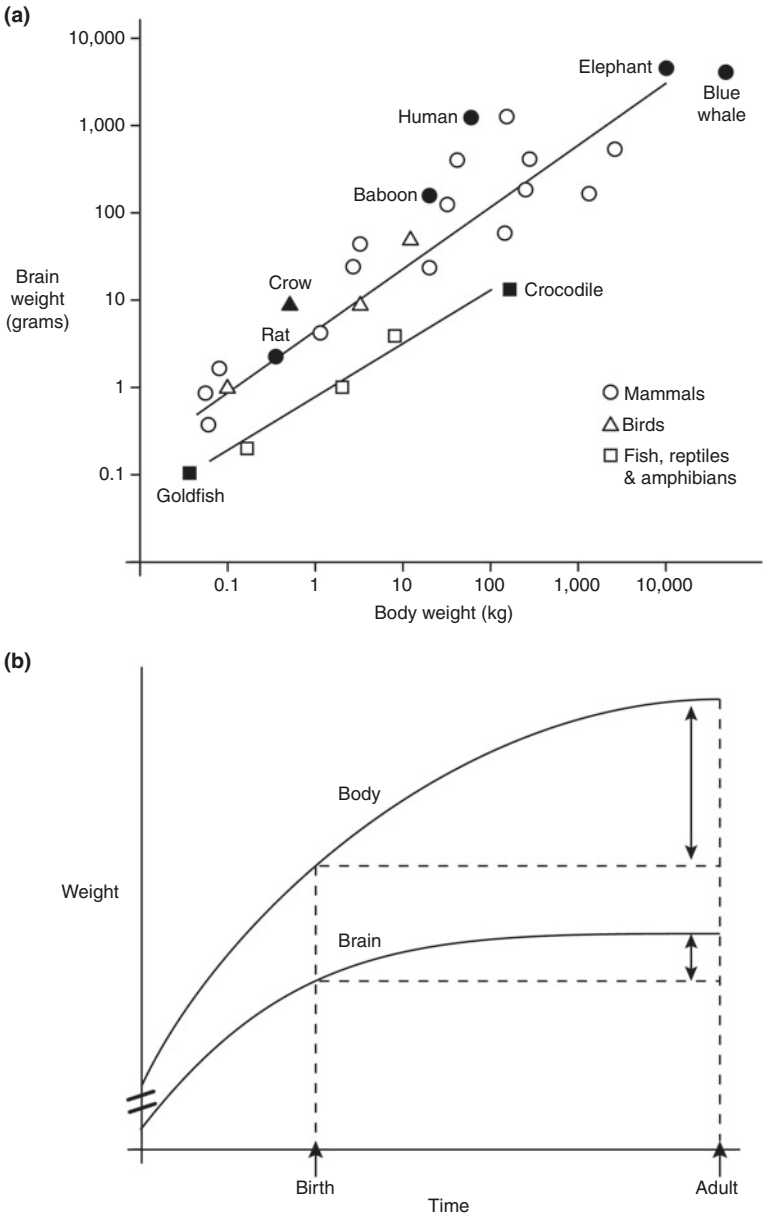

Fig. 3.1 Brain and body growth. (**a**) Brain weight depends on body weight across species. Birds and mammals tend to have larger brains for a given body

phase in which brain growth slows down with respect to body size and more or less fits the period around birth, and finally there is a postnatal period of slow brain growth in which the brain decouples from body growth, which maintains a high rate of growth. As species increase in body size, the period of postnatal body growth increases disproportionately to prenatal growth, which largely determines adult brain size. In evolution, this makes neonatal body size and adult brain size grow more slowly than adult body growth. This is important, as neurogenesis (the production of neurons during development) in mammals is largely restricted to the embryonic and fetal periods, with the notable exception of regions like the dentate gyrus, the olfactory bulbs and other brain regions where adult neurogenesis is, however, very limited. The brain keeps growing after birth by increasing neural ramifications (dendrites), increasing glial cells, myelination and glial cell production, but the neuronal population is largely determined by prenatal and early postnatal growth.

The length of the gestation period varies considerably among species, as altricial species like humans deliver their young prematurely and the period of rapid brain growth continues beyond birth. This makes the period of postnatal brain growth more important in determining adult brain size in these animals than it is in other species. Notwithstanding the variability of gestation period among mammals, brain development follows more or less the same schedule in all species. Barbara Finlay and colleagues (Workman et al. 2013, Finlay and Workman 2013)

Fig.3.1 (Continued)
size than other vertebrates, and primates and birds like crows have brains twice the size of those of other mammals or birds, respectively. Finally, although there is a statistical correlation between brain and body size, brain size grows more slowly than body size, so that larger animals tend to have smaller brains relative to their body size than smaller animals (humans are an exception). (**b**) The lifetime curve of body and brain growth of an average mammalian species. Most brain growth occurs prenatally, but the rest of the body keeps growing at a rapid rate long after birth. The postnatal period is increasingly important for the body growth of large-bodied species (double arrows) while postnatal brain growth is slower. Primates are unique in that their brains are larger at all ages, and grow more rapidly in the initial stages than the brains of other mammals of the same body size.

developed an extensive cross-species developmental timetable, showing that the ordering of many critical events like the initiation and end of neurogenesis, the appearance of important neural connections, and differentiation of cell types and nuclei all follow an extremely conserved sequence that scales logarithmically with post-conception time. Furthermore, the slope and the intercept of these curves increase steeply in species that end up with larger cerebral cortices, like humans. More recently, Andrew Halley showed that the rate of rapid brain growth in early development is somewhat conserved among mammals, although primates show a faster rate of growth, and even start their development with a larger fetal brain size relative to fetal body size than other species (Halley 2016). Notably, this is not due to more rapid brain growth, but to slower prenatal body growth in relation to other mammals.

The Anatomy of Intelligence

In the late nineteenth century, Francis Galton quantified the relationship between brain size and intelligence, by multiplying head length by width, and comparing this with the academic performance of about 1,000 Cambridge students (Galton 1907). He reported that the best students had a brain size around 4% larger than the rest. After that, speculation about differences in brain size among ethnic groups became widespread, Europeans supposedly having the largest brains and Africans the smallest. The idea that brain size correlates with intelligence was pervasive but still controversial during most of last century. In the early eighties, Stephen Jay Gould published his popular and highly influential book *The Mismeasure of Man*, where he strongly refuted the idea of racially based differences in brains and intelligence, showing categorically that there was no evidence for ethnic differences in intellectual ability (Gould 1981). He did recognize that there might be differences in brain size across human groups, but these were mostly related to differences in body height. Since then, sporadic reports suggesting racial differences in brain size or capacity have appeared, although these have produced more controversy than consensus. For example, Philippe

Rushton has been one of the main defenders of an association between brain size and intelligence, arguing for significant racial differences in both parameters, which has brought him under intense criticism, as would be expected (Rushton and Ankney 2009). In any case, should racial differences in IQ or brain size exist, these would be explained largely by cultural, socioeconomic or even alimentary differences rather than by genetic load.

Searching for differences in cognitive capacity among species, Jerison and others also showed that the brain-body relationship was not the same for all vertebrate groups. For any given body size, an average mammal has a larger brain than a reptile, and reptiles have larger brains than amphibians or fish (Jerison 1973). Birds have a brain-to-body ratio much like that of mammals. Furthermore, both are homeotherms, or warm-blooded, which points again to some relation between brain size and metabolism. Among mammals, primates have brains that are about twice as big as the brain of non-primate mammals of the same size. Transitional species like *Archaeopteryx* (the earliest bird) or *Triconodon* (an early mammal) have relative brain sizes intermediate between those of reptiles and birds or mammals, respectively. In addition, birds and mammals display more complex behaviors than small-brained, cold-blooded reptiles, and among mammals, primates are characterized by elaborate social lives. Thus, there seems to be at least some phylogenetic relationship between (absolute or relative) brain size and whatever we may call intelligence or cognitive abilities. Within each vertebrate group (birds, mammals or reptiles), a proportion of the brain-body data lies outside the best-fitting curve, yielding species with higher or lower than expected brain sizes for their given body size. The coefficient between the expected and actual body size has been defined as the encephalization quotient (EQ). An EQ greater than 1 indicates that a species has a larger brain than the average mammal with the same body size. This difference is interpreted as excess brain mass attributable to higher cognitive capacities (Jerison 1973). Humans are the most encephalized species of all, followed by dolphins and elephants. Whales have enormous brains, particularly the blue whale with a 7 kg brain, but their gigantic body size renders their EQ on the mammalian average. Among birds, crows and parrots have very large EQs.

Although it is a controversial measure, the encephalization quotient has shown a statistical relationship to certain behavioral capacities. For example, it varies with the predictability of food resources, such that extant carnivores tend to have higher EQs than herbivores and other animals that feed on abundant food (Aboitiz 1996). Among bats, echolocating insectivore species tend to have the lowest EQs, which increase in fruit-eating and nectarivorous bats, reaching a maximum in the hematophagous vampire (Pirlot and Pottier 1977). Among rodents, fossorial and folivorous species tend to have smaller EQs than terrestrial and granivorous species; and among primates, folivorous species usually have smaller brains for their body size than frugivorous species (Frahm et al. 1997). However, in many cases, it is not clear if these differences are due to the cognitive challenges involved in finding food, or to the quality of the food source, as abundant food is usually poor in nutrients. Social animals also tend to have larger EQs than non-social animals (Shultz and Dunbar 2010). Other studies have found that absolute brain mass, regardless of body weight, is indeed a relevant trait. Evan MacLean and collaborators compared performance in self-control tasks in about 36 species of mammals and found that absolute brain mass correlates better with behavior than brain mass corrected for body size (MacLean et al. 2014). Likewise, Jeffrey Stevens reported that absolute brain size was the best predictor of self-control, measured as the capacity to wait for the delivery of reward (Stevens 2014).

As noted, the quality of food has repeatedly been proposed as a limiting factor for brain growth, animals that feed on less nutritional food having smaller encephalization quotients. Humans stand out for their high encephalization quotient, and the evolutionary explanations range from selective pressure to compete in social environments to the increasing availability of energy rich nutrients provided by the invention of cooking over fire. A modern variant of the energy hypothesis of brain growth mentioned above was put forward as the "expensive tissue" hypothesis, which postulates a trade-off between the size of the brain and that of the digestive tract, both tissues requiring large amounts of energy. More specifically, Robert Foley and Leslie Aiello proposed that in human evolution, increasing brain size only became possible when humans acquired an energy rich carnivorous diet, allowing for a

reduction of the gastrointestinal tract and the release of energy constraints to build a large brain (Foley and Lee 1991; Aiello and Wheeler 1995). In a similar line, Suzana Herculano-Houzel points out that apes, which spend much of the day eating large amounts of low calorie leaves, are limited in their energy intake by the duration of the active period of the sleep-wake cycle (Fonseca-Azevedo and Herculano-Houzel 2012; Herculano-Houzel 2015). Accordingly, cross-species increases in neuronal numbers are adaptively associated with decreasing sleep requirements. The shift by our recent ancestor to high-calorie meat liberated them from this limitation, contributing to the rapid increase in brain size. The anthropologist Richard Wrangham has further hypothesized that the advent of fire-based cooking, which made nutrients more accessible for digestion, was a critical event that permitted the increase in brain size and neuron numbers in early humans (Wrangham 2009). Likewise, among apes, humans exceed by far the other species in total energy expenditure, which is largely explained by an increase in basal metabolic rate (Pontzer et al. 2016). Still, the energy hypothesis remains controversial, and there are arguments for and against it. For example, Alianda Cornélio and collaborators made an extensive analysis of hominin brain volumes over time and found no relation between brain size increases and archeological evidence for the use of fire (Cornélio et al. 2016). Another energy variable that has been related to brain size is adipose tissue, which some authors have found to correlate negatively with brain size among mammals (Navarrete et al. 2011), although humans have been reported to have the highest percentage of body fat among apes (Pontzer et al. 2016).

Wrinkled Brains

Because brain size is largely determined by cortical surface, larger brains soon reach a point at which further cortical growth is limited by the volume of the cranium in which the brain is contained. Species with relatively small cortices tend to have smooth brains and are called lissencephalic, while species with larger cortices display convoluted, or

gyrencephalic brains characterized by inward sulci and outward gyri that develop in the embryo as the brain increases in size. In larger brains, the cortex seen on the brain's surface is a very minor fraction of the total cortical area, as most of the cortex lies buried within highly intricate sulci. The anatomical pattern of sulci and gyri is specific for different mammalian orders, such that the brain of an elephant folds somewhat differently from that of a carnivore or a primate brain. Our brain folds follow a general primate pattern. This indicates a strong within-group genetic determinant of cortical folding mechanics, of which we still know little.

While gyrification does not necessarily reflect the development of neuronal networks in the brain, the developmental and mechanical factors involved in their generation have attracted the attention of many researchers, including myself. Explanations of gyrification have been proposed over the years, but we still have no real way of determining which of these, if any, is correct. The models fall into three main categories, one emphasizing the role of the deep ventricular surface of the brain, where neurons and the radial glia are produced, as proposed by Pasko Rakic, and Robert Hevner and Tao Sun (Rash and Rakic 2014; Sun and Hevner 2014). The radial glia is a critical cell type for brain development, whose cell body is located in the depth of the hemisphere and has a process that reaches the external surface of the brain (the pia mater), spanning the entire thickness of the developing hemisphere. We will come to other functions of this cell type below, but for now it is suffice to say that it is like a chord attached to the external (pia mater) and internal (ventricular epithelium) brain surfaces that produces mechanical tensions, for example, in the depth of sulci, as the cerebral cortex expands in development. Regions where radial glia are for some reason more elastic and can increase in length will grow and fold outwardly, while regions in which radial glia are "stiffer" will remain buried, close to the ventricular surface, forming the depth of sulci.

Other models emphasize a role of cortical expansion *per se*, implying the differential growth of the superficial layers of the cortex as opposed to the slower expansion of the deep layers, producing an intracortical mechanical pressure that leads to folding (Sun and Hevner 2014, Striedter et al. 2015). Another possibility is that cortical expansion

generates mechanical pressure on the cranial cavity that leads to folding. Georg Striedter and collaborators recently proposed a mechanism by which newly arriving neurons to the developing cortex must intercalate in the horizontal plane between older neurons that arrived there earlier (Striedter et al. 2015). This produces a mechanical tension in the tangential direction, particularly in the superior cortical layers, that leads to the differential expansion of the cortex relative to deeper structures. According to Eric Lewitus, the onset of gyrification in a mammalian group depends on a critical neuron-number threshold, which is about 10^9 neurons (Lewitus et al. 2014). David Van Essen, and more recently Helen Barbas, proposed a different model, in which short-range cortico-cortical axonal connections exert mechanical tension between the connected areas such that as the cortex grows, these two areas tend to fold against each other, forming a gyrus. Long cortico-cortical connections, on the other hand, exert less tension and are allowed to grow underneath the depth of the sulci formed by adjacent gyri (van Essen 1997; Hilgetag and Barbas 2009).

Suzana Herculano-Houzel proposed a mixed model to account for connectivity and cortical expansion processes, and considers gyrification a strategy to optimize connectivity in a large brain, an idea that goes back to Georg Striedter (Striedter 2005). Herculano-Houzel found that the surface area of white matter increases less rapidly than the number of cortical neurons (Herculano-Houzel et al. 2010). In primates, whose cerebral cortex is particularly large, the scaling of white matter relative to neuron number is actually slower than that of other species like rodents, which means that primates have relatively less white matter. This implies a general decrease in connectivity in larger brains, presumably reflecting a strategy to minimize redundancy in connectivity. Furthermore, Herculano-Houzel claims that cortical folding in large brains contributes to solving the connectivity problem by minimizing the length of cortical connections with critical regions deeper in the brain. Moreover, Herculano-Houzel recently published a mathematical model for cortical folding in which the degree of folding depends on the product between surface of cortical area and the square root of average cortical thickness (Mota and Herculano-Houzel 2015). Notably, the model

closely fits to what is found when folding paper sheets of different thicknesses: folding capacity is much higher with thinner than thicker sheets. In fact, human mutations in which the cortex is particularly thick have low folding indexes, and species with large brains but thin cortices like dolphins and whales have highly convoluted cortices, much more than that of humans. Georg Striedter contended that these models assume that the cerebral cortex folds once it has already grown (like a sheet of paper), but in fact the cortex folds as it develops and the model does not make any assumptions about the embryological mechanisms involved, apart from the general hypothesis of a tension-based mechanism from the underlying white matter (Striedter and Srinivasan 2015). Nonetheless, the model may well reflect the physical constraints involved in gyrification, to which the developmental mechanism must in last instance be subordinate.

Perhaps the most elegant physical model for cortical folding was recently published by Tuomas Tallinen, Jun Young Chung and collaborators, who developed a 3D printed gel model of a 22-week-old fetal human brain, coated with a layer of a different gel that absorbs liquid and progressively swells over time (Tallinen et al. 2014). Under these conditions, the surface gel expands tangentially and develops a complex pattern of gyri and sulci that strikingly resembles the normal fissural development in the human brain, closely reproducing the orientation of the major and secondary sulci. Note, however, that the 3D printed template already shows an incipient temporal lobe, an exposed insula and the superior operculum of the Sylvian fissure. Therefore, this model does not account for the initial formation of the most fundamental fissural components of the human brain, namely the Sylvian fissure and the insular lobe. Nevertheless, this and Herculano-Houzel's studies strongly imply that purely physical parameters are at the very least significant determinants of fissurization. However, this does not account for differences among individuals and species in cortical folding, or for hemispheric asymmetries. This variability may depend on the differential expansion of distinct cortical regions, or on other aforementioned factors like the mechanical influences of radial glia and subcortical white matter, which may be under genetic control.

Cell Counts

Following Harry Jerison's principle of proper mass, many of the above studies have assumed that in larger brains there will be more processing neurons, more connectivity among them and more information capacity. This is in line with the micro-modular organization of the neocortex that we discussed in the previous chapter, where the building block of the cerebral cortex is the cortical column. Thus, in larger brains there will be more columns, neurons, and processing capacity. As we will see now, this may be correct but only to some extent. Despite a general conservation of the basic module, the comparative evidence indicates that there are areal and species differences in some details of the canonical microcircuit, based on the variability of neuron number in each column, and the proportions of neuronal types.

After the classic study of Andrew Rockel and collaborators, who reported that the number of neurons underneath a unit of cortical area was constant throughout the cerebral cortex, the latter was considered by many as an extended sheet of tissue that increases mostly in surface and very little in depth (Rockel et al. 1980). However, some findings appeared not much later that partly challenged this notion. Some years after Rockel's study, Herbert Haug published an extensive account of neuronal densities across brain regions and species using a technique called stereology (Haug 1987). This is a standardized method to make a three-dimensional representation of a series of two-dimensional microscopic cross sections of neural tissue, yielding accurate information about the total number of neurons in a given volume. Haug found that neuronal density varies both across regions and across species. In addition, Haug reported that gray matter neuronal density was lower in species with larger brains than in species with smaller brains. Comparing most species, neuron numbers tend to increase with brain size, but at a lower rate than the increase in brain size. As a result, neuronal density tends to decrease with increased brain size, providing more space for neuronal connections for each neuron. This notion is consistent with many developmental studies that indicate that training induces lower neuronal density and higher dendritic growth in specific brain regions,

which may be associated with increasing connectivity and processing capacity (Diamond et al. 1993, Diaz et al. 1994, Scheibel 1988).

In 2005, Suzana Herculano-Houzel presented a new methodology to count cells in brain tissue, called the isotropic fractionator, which has challenged some of the ideas discussed earlier in this chapter (Herculano-Houzel 2005, Herculano-Houzel et al. 2015c). The isotropic fractionator consists of dissociating cell nuclei in a given volume of tissue, suspending the nuclei in a chemical solution and then staining them for neuronal or non-neuronal markers with specific antibodies. This allows for discerning and accurately counting the number of neurons and glial cells. Herculano-Houzel and collaborators confirmed and extended Haug's earlier finding that in most mammals, there is an increase in neuron numbers with increasing brain size, but the rate of additional neurons is slower than the increase in brain size, resulting in lower neuronal density in larger brains (Herculano-Houzel et al. 2015a, b; Mota and Herculano-Houzel2014). Furthermore, she and colleagues have observed that the rate of neuronal increase in relation to brain size differs across mammalian orders, such that distant species with similar brain sizes can have very different neuron numbers. On the other hand, glial cells maintain a constant density across species and their number accurately reflects differences in brain size. Herculano-Houzel has therefore proposed that for comparative studies, an estimator of the total neurons per brain should be used, called the Neuronal Index. This measure, she argues, may be a better predictor of cognitive ability than the EQ or brain size.

According to Herculano-Houzel, primate brains are unique in their neuronal composition (Wong et al. 2013; Ventura-Antunes et al. 2013). This group is characterized by a very rapid rate of neuronal addition, in which an 11-fold larger brain contains 10 times more neurons (and about 12 times non-neuronal cells, mostly glial), which results in a nearly constant and very high neuronal density despite brain size increases. As a result, primate brains have many more neurons than non-primate brains of the same size, and humans are no exception to this. This may relate to the more rapid fetal brain growth relative to body size in primates than in other species as I mentioned above (Halley 2016). With their very large brain, humans

have the highest absolute neuron number (regardless of body size), some 86 billion neurons (and an equal number of glial cells), of which about 16 billion are in the cerebral cortex (these numbers are at odds with the classical estimates of 100 billion total neurons and 1,000 billion glial cells). Contrary to claims of a disproportionate increase in cortical neurons in large-brained species, Herculano-Houzel argues that cortical neurons represent about 20% of the total neurons in the brain across many species, including humans (Herculano-Houzel et al. 2014). The elephant brain is three times as large as the human brain, but has only 5.6 billion neurons in the cerebral cortex. Likewise, dolphins and whales, despite having large brains, have characteristically fewer neurons in their cerebral cortex. Even the smaller-brained gorillas, with a brain size one-third that of humans, also have more brain neurons than elephants and false orcas! Importantly, Herculano-Houzel, working with Tecumseh Fitch and other researchers, showed that parrots and songbirds have on average twice the number of neurons as primates of the same size (Olkowicz et al. 2016). Furthermore, most of these neurons are located in the pallium, a region involved in higher cognitive processing, comparable in functions to the mammalian cerebral cortex (see Chapter 9).

How do we reconcile Herculano-Houzel's findings with the earlier literature on the EQ? The model of prenatal neuronal addition may hold some cues. If most neurons are added in the prenatal and early postnatal periods (depending on the species), neuronal number should be a better proxy for immature brain size than adult brain size. In fact, during early development most cell division results in neurogenesis, but in postnatal development cell division is produced mostly by glial cells, and neuronal density and size may vary significantly during postnatal life. Thus, the prenatal/early postnatal period of growth is the main determinant of neuron number. But why would primates and some birds achieve such high neuronal densities? Perhaps it has to do with the inherent physical costs of having a brain volume (and head) that becomes too large in relation to body size, plus computational difficulties due to longer nerve paths. If we had the same neuronal density as the average mammal, in order to keep the same number of neurons, our brains (and heads) would have to about twice the size they are now! The same constraints

may hold for birds, especially as these animals have the additional constraint of minimizing head weight in order to be able to fly.

Nonetheless, Diarmuid Cahalane, Chistine Charvet, and Barbara Finlay have been particularly critical of the isotropic fractionator method, claiming that this technique has strong limitations in anatomical resolution (Cahalane et al. 2012). They compared different histological cell counting methods for the primary visual cortex and the entire cortex of rodents and primates and found significant outlier effects for the isotropic fractionator that resulted in differences of 50% or more from the counts obtained by other methods. Although determining the number and size of neuronal cells (as well as neuronal types) may be a much better way to estimate processing capacity than brain size or the EQ, we still need to do many more comparative and developmental studies and assess the different techniques against each other to get a consensual estimate of these critical variables.

How to Build a Big Brain

How are larger brains produced? We have seen that there is an increasing number of neurons and glia in larger brains, but we haven't yet addressed the mechanisms by which the brain increases in size, for which we will need to briefly review cellular processes involved in cortical development. In the 1970s, Pasko Rakic proposed the radial model of cortical development, in which neurons are produced in the deep surface of the brain and migrate outward to reach the cerebral cortex (Rakic 1978). In the early embryo, there are self-renewing progenitor cells, called radial glia because they have a long process that connects the internal or ventricular surface, with the external surface or pia mater of the brain. The cell bodies of radial glia are located deep in the ventricular zone, and undergo symmetric divisions (that is, each progenitor gives rise to two identical radial progenitors). Thus, their numbers grow exponentially as development proceeds. In later stages, these progenitors divide asymmetrically, where one daughter cell is an immature neuron that stays some time in the ventricular zone and then

migrates toward the brain surface attached to the radial glia's process (Tamamaki et al. 2001; Noctor et al. 2002). Migration is arrested in the cortical plate by a stop signal, and the cell differentiates as a mature neuron. The stop signal is a molecule called reelin, which is secreted by a special kind of cell called the Cajal-Retzius cell. Once stopped, neurons arrange themselves into a laminar and columnar scaffolding (Rakic 2009; Geschwind and Rakic 2013). Neurons that migrate along the same glial cell are likely to derive from the same radial glia, and arrange themselves in columns in the cortical surface (Fig. 3.2) (Noctor et al. 2001; Kriegstein and Noctor 2004; Yu et al. 2009).

Although successful, Rakic's model has required important modifications. In the late 1990s, John Rubenstein and collaborators showed that while excitatory neurons use radial migration to reach the cortex, inhibitory neurons do not arise from the cortical ventricular zone, but are born in the ventral hemisphere, in the region where the basal ganglia develop (Fig. 3.3) (Anderson et al. 1997). Rubenstein and his group performed minute surgery on the brains of fetal mice, separating the basal ganglia primordium from the cortical primordium. Impressively, in these animals, no inhibitory neurons were observed in the developing cortex, although the number of excitatory neurons was normal. The embryonic basal ganglia were then recognized as the major site for production of inhibitory neurons in the cerebral hemisphere, while most excitatory neurons are generated in the cortical ventricular zone. Once born in the ventral hemisphere, inhibitory neurons migrate following a tangential route, that is, perpendicular to the orientation of radial glia and parallel to the brain surface, and end in the different cortical layers as the cortex develops.

Several developmental studies in the 2000s revealed that in late cortical development, a layer of cells called the subventricular zone (located just above the ventricular zone) contains highly active neural progenitors (Rakic 2009) called intermediate progenitors, which derive from radial glia but have not yet differentiated as neurons. Instead, they continue proliferating for two or three cell divisions, and then migrate outwardly to the developing cerebral cortex. Studies by Zoltán Molnár (Cheung et al. 2007, 2010), Christine Charvet, Arnold Kriegstein and others established that the subventricular zone is absent or barely discernible in reptiles and

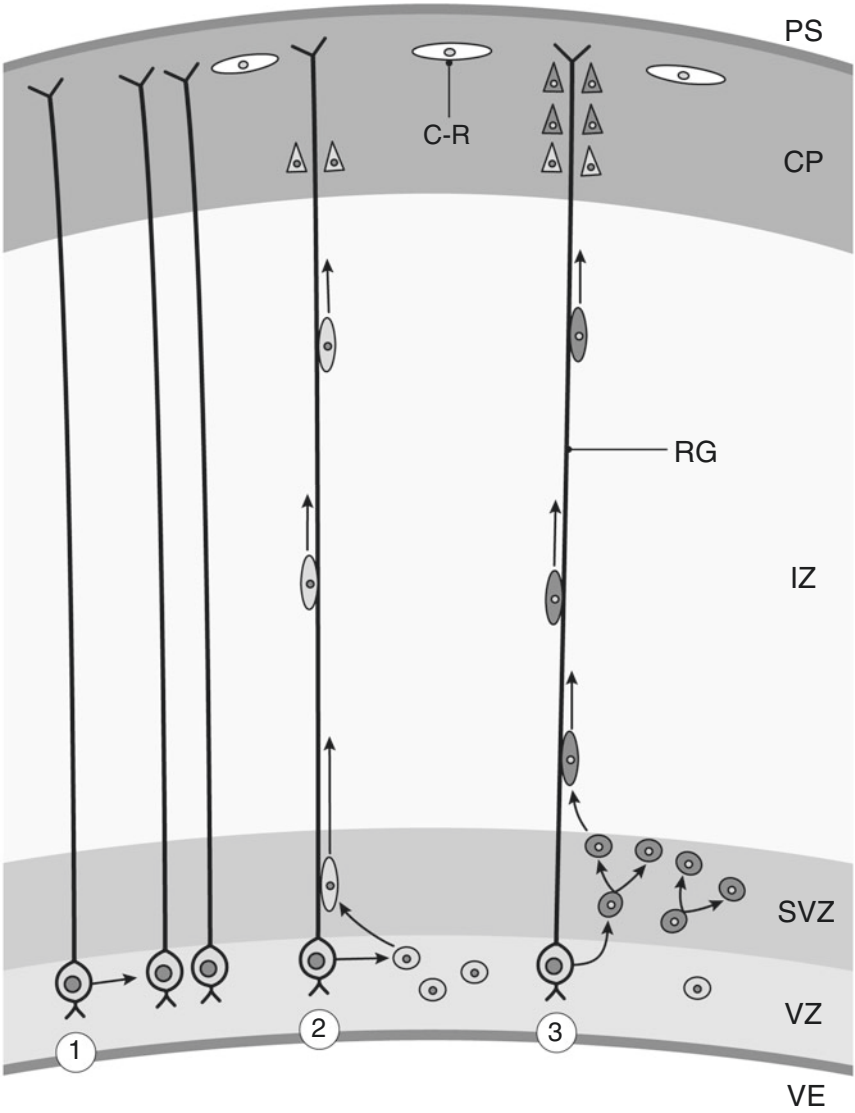

Fig. 3.2 Development of the cerebral cortex. In this region, radial glia (RG) extend a process that crosses the ventricular wall from the ventricular epithelium (VE) to the pial surface (PS). In early stages (1), radial glia divide symmetrically, their numbers increasing exponentially. In later development (2),

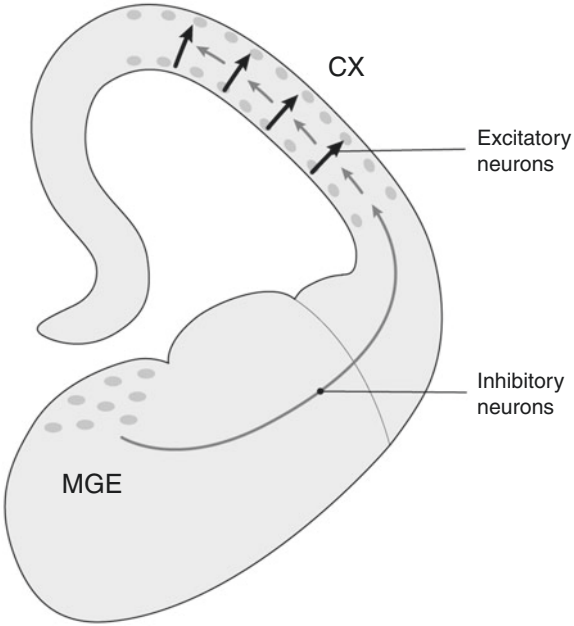

Fig. 3.3 Radial and tangential migration in brain development. A cross-section of the embryonic mammalian brain (one hemisphere), in which the cerebral cortex (CX) develops. Excitatory neurons migrate from the deep ventricular zone of the cortical primordium (black arrows). Inhibitory interneurons originate in a deep brain region, the medial ganglionic eminence (MGE), and arrive to the cortex by a process of tangential or horizontal migration (gray arrows)

Fig.3.2 (Continued)
these neurons divide asymmetrically, producing one radial glia and a daughter neuron (circles). These neurons migrate from the deep ventricular zone (VZ) (ovals) to the cortical plate (CP), attached to the glial process (RG) across the intermediate zone (IZ), to make up the deep cortical layers. In a third stage (3), radial glia produce daughter progenitors that proliferate in the subventricular zone (SVZ) and then migrate outwardly to form superficial cortical layers (but they also contribute to deep layers; not shown). Cajal-Retzius neurons (C-R) are located in the most superficial layer (called the marginal zone), and secrete the protein reelin, which controls the laminar arrangement of the cerebral cortex (see Chapter 9)

some marsupials, modest in rodents and highly developed in large-brained primates, including humans (birds have also developed a subventricular zone, likely independently of mammals but reflecting similar mechanisms of brain growth; see Chapter 9) (Charvet and Striedter 2011; Lui et al. 2011). Furthermore, a cell type called outer radial glia, which is present in the subventricular zone (as opposed to the canonical radial glia, located in the ventricular zone), is abundant in species with large brains, especially humans, producing further intermediate progenitors (Hansen 2010; Shitamukai et al. 2011; Florio and Huttner 2014).

The genetic cascade involved in this amplification process seems to be highly conserved across species, including birds. Pax6, a regulator gene originally found in the fruit fly and critical for eye development in most animals studied, from insects to vertebrates (see Chapter 10), is also a key promoter of radial glia self-renewal (Georgala et al. 2011). Increasing Pax6 activity results in more rapid production of neural progenitors, which at some point start invading the subventricular zone to keep dividing before migrating to the cortex. Thus, Pax6 is a key regulator of overall progenitor numbers, and together with downstream and related genes, has been proposed as an essential element of cortical expansion in mammalian brains. My students, particularly Juan Montiel and Francisco Zamorano (Aboitiz and Montiel 2007a, b; Aboitiz and Zamorano 2013) and I have further argued that amplification of a Pax6 cascade, or of related genes, was a key event in the origin of the mammalian cerebral cortex, as well as in the expansion of the avian brain, indicating a strongly conserved genetic cascade that underlies brain development and evolution, possibly in all vertebrates (see Chapter 9).

Pax6 is a key candidate for increasing neuronal numbers in mammalian and human brains, but there are also many other related genes that participate in this process, whose mutation could lead to smaller or larger brains (Georgala et al. 2011). One example is the genes involved in the regulation of neuronal death, such as Notch1 and CASP, which are also important in regulating neuronal cell numbers during development (Ables et al. 2011). Recently, Lei Wang and collaborators reported a role of a developmental regulatory gene called Hedgehog in the regulation of progenitor division and expansion of the cerebral cortex (Wang et al. 2016). Other evidence points to so-called microRNAs,

small RNA pieces that do not code for a protein structure but regulate the activity of other genes. These tiny molecules can depress or enhance the activity of genes involved in progenitor division, finally affecting neuronal numbers (Somel and Khaitovich 2013).

Another source of evidence is genetic disorders that result in cortical malformations, particularly microcephaly, a condition well known now because of the Zika virus (Geschwind and Rakic 2013). Genes associated with this condition are MCPH and ASPM, both involved in the proliferation of neural progenitors (Pulvers et al. 2015). In contrast, macrocephaly is a condition in which there is an excessively large head, usually concomitant with a larger than normal brain. A larger brain can be the result of hydrocephalous or other conditions that affect the volume of the ventricular cavities, but can also be produced by megalencephaly (an abnormally large brain wall and cerebral cortex). Notably, over 20% of autism cases display macrocephaly to some degree. For example, overactivation of the gene AKT3 can result in megalencephaly, and its inhibition can result in microcephaly (Gai et al. 2015). Another interesting gene associated with macrocephaly is PTEN, which is also linked to autistic traits (Garcia-Junco-Clemente and Golshani 2014). Determining which of these and other genes have been involved in the evolution of our uniquely large brain is a matter of intense research today, with new and interesting candidates appearing every day. Still, there is a long way to go to provide a coherent picture of the genetics and evolution of human brain size.

The Brain Hangs Together

In 1995, Barbara Finlay and Richard Darlington published an influential paper showing that the evolution of brain size proceeds according to a highly conserved developmental schedule shared by most mammalian species (Finlay and Darlington 1995). They analyzed the sizes of major brain components in a huge sample of 131 species of primates, bats and insectivores, observing an extremely well-conserved correspondence between the volume of major brain components and the overall size of

the brain. The only components that deviated from this relationship were limbic and olfactory-related components, which varied independently of brain size, and presumably in relation to ecological demands. Interestingly, the cerebral cortex scales disproportionately to other brain structures, so that species with larger brains tend to have relatively larger cerebral cortices. However, this explosive brain growth fits a clear allometric trend across species, which indicates that the cerebral cortex does not increase in size independently of other brain structures. In other words, all brain components (except olfactory/limbic) tend to grow together, although they do so at different rates. Considering this allometric growth, humans have the expected cortical size and proportions of a hypothetical primate of the same overall brain size. Finlay and Darlington concluded that there is only one way to increase the size of brain structures, which is by growing an overall larger brain. This conserved pattern has more recently been extended to all vertebrate groups, from sharks to mammals (Yopak et al. 2010). According to Finlay and Darlington, the independent development of brain components is not impossible, but very unlikely.

Subsequently, Finlay, Darlington, and collaborators expanded on their findings, presenting evidence for a conserved developmental schedule in mammalian brains, excepting limbic, and olfactory structures (Finlay et al. 1998; Workman et al. 2013). There is a neurogenetic gradient from back to front and from ventral to dorsal, such that anterior, late-generated brain components are disproportionately larger than posterior, early generated structures; and ventral (motor) structures tend to grow less than dorsal (sensory) structures. This meets Georg Striedter's dictum of "late equals large equals well-connected", meaning that late-developing structures tend to grow more and establish more interconnected networks (Striedter 2005), but adds the antero-posterior and dorso-ventral time gradients. According to Finlay and collaborators, this imposed gradient specifies a priori which structures will grow larger. Thus, it is not common to find species with a large brainstem component but very small cerebral hemispheres (with the exception of some rare species like mormyrid fish that have an hypertrophied cerebellum). In this line, the cerebral cortex is located exactly in the most expansive brain region, not because this is a functionally strategic region but

because this is where it will grow faster. In other words, cognitive networks allocate in the most expanding regions, rather than cognitive functions specifying the brain regions that will expand. This line of thought is akin to Stephen Jay Gould and Richard Lewontin's notion that developmental mechanisms and constraints may be more important than the selective processes in shaping morphology in evolution (Gould and Lewontin 1979). In my opinion, this does not necessarily mean that development determines everything. The neurogenetic gradient is not a given, but responds to a basic functional constraint that has been the target of natural selection. The position of the brain subordinates to the oral end of the animal to regulate food intake. Likewise, sense organs are also localized near the oral end, making up the head. The postero-anterior neurogenetic gradient probably responds to this requirement, facilitating the formation of neural networks that regulate the most basic behaviors like orientation for food sources and other signals near the mouth and sense organs. In this sense, the disproportionate growth of anterior brain structures like the cerebral cortex may be the result of an ancient developmental mechanism that has been selected to favor the establishment of neural networks in the anterior end of the animal. Sensorimotor and cognitive networks, including those involved in language, are an extension of purposeful orientation behavior and develop atop this ancestral scaffolding. This perspective agrees with Robert Barton and colleagues' recent conclusion that allometric relations may ultimately result from functional rather than developmental constraints (Montgomery et al. 2016).

Specialist Brains

Finlay and Darlington acknowledge that the brain divisions they used are rather gross, and that there may be space for reallocation of functions within each division (Finlay and Darlington 1995). Furthermore, despite the observed correlations, Finlay and Darlington's data allow for two to threefold variation in the size of individual parts, which leaves space for independent variation of the different components. In this line,

many authors have focused on the adaptation of specific brain systems to ecological conditions, considering their growth to be somewhat independent of that of other networks. A good example of this particulated strategy is food-storing birds, which have a larger hippocampus (a brain structure critical for the acquisition of memory, which we will discuss in Chapter 9) than that of non-foodstoring birds (Clayton 1998). This increase in size has been associated with postnatal addition of neurons, but there have been contesting reports. Likewise, in the brood parasitic cowbird, which lays its eggs on the nests other species, females have to remember the location of several nests of other species and wait until eggs are laid in one of these to deposit their own eggs there. Consequently, the hippocampus is larger in females than in males of this species (Sherry et al. 1993). However, part of this may be due to acquired increases in size, as in the famous study showing that London taxi drivers and bus drivers have larger hippocampi than control subjects (nowadays, with the help of satellite-directed navigators this character may be lost) (Maguire et al. 2006). In addition, migratory birds tend to have smaller encephalization quotients than all-year resident birds, presumably because they need more cognitive capacity to find food in the harsh winter. However, a recent report by Orsloya Vincze et al. 2015 and collaborators has shown that, despite having a smaller brain, migratory birds tend to have larger than expected relative sizes of the optic tectum in the brainstem, which is the main visual processing area in the bird brain. This character may be of benefit for visual orientation during migration.

Beginning in 1995, Robert Barton and collaborators published a series of extensive studies of visual and olfactory structures in primates, bats and insectivores and their evolutionary relationships (Barton et al. 1995; Harvey 2000; Barton 2004). After removing the effect of overall brain size, they found correlated changes in size among functionally related structures (visual with visual, and olfactory with olfactory structures), while correlations between visual and olfactory structures were negative in primates, nonsignificant in insectivores and positive in bats. In primates and insectivores, nocturnal habits are associated with larger olfactory systems and smaller visual systems, but there are also associations of visual structures with frugivory (color vision helps detect ripe

fruit) in primates and insectivores, and between frugivory and olfaction, but only in bats.

Barton and Chris Venditti recently reported an important correlation between cerebellar and cerebral cortex growth (Barton 2012, Venditti 2014). Furthermore in apes and humans, the cerebellum increased in size more than would be expected based on cortical expansion. Barton proposed cerebellar growth was associated with extractive foraging, which consists of locating and processing food that is either underground (roots or ants, for example), or embedded in hard shells, which can require tool making, as has been shown in chimpanzees in the wild. This implies that cerebellar function has been an important achievement in ape and human evolution and may have been involved in social behavior, cognition and motor dexterity, possibly associated with making and throwing tools, and other behaviors relevant to early hominids. Supporting Barton and Venditti's claims, Herculano-Houzel also determined that the cerebral cortex does not grow alone, but as extra cells are added to this structure, there is a coordinated increase in neuronal numbers in the cerebellum (Herculano-Houzel 2010). Although the cerebellum only increases modestly in size with growing body size, the number of cerebellar neurons are added in tight correlation with increased body mass. Furthermore, the rate of addition of neurons is uneven; there being about 8 new cerebellar neurons and 2 cortical neurons for each neuron added to the rest of the brain. This results in a tremendous increase in neuronal density in the cerebellum of larger animals. Finally, a note on the developmental and evolutionary aspect of this correlation, while the correlation between the cerebral cortex and cerebellum probably results from the fact that both are late-generated structures (as argued by Finlay; see above), natural selection may have benefited lineages in which the neurogenetic schedules of these two structures synchronize.

The Cortical Mosaic

There is conserved developmental and architectural scaffolding in the regions of the cerebral cortex. Barbara Finlay and Ryutaro Uchiyama recently subdivided the cortex into an exteroceptive zone including

visual, somatosensory and motor areas, and an interoceptive zone including temporal, insular and ventral frontal areas (oddly, auditory regions are labeled in the interoceptive zone) (Finlay and Uchiyama 2015). In this organization, sensory and motor areas are "seeds" shared by all mammals, while higher order and association areas appear and expand between them, concomitant with increasing brain size in mammalian evolution. A neurogenetic gradient is added to this in which neurogenesis continues in posterior cortical regions until later stages, and consequently neuron numbers and density are greater than in frontal regions where neurogenesis ends earlier (Charvet 2014; Cahalane et al. 2012). Cortical connections tend to arrange themselves in this same direction, preferentially aligning antero-posteriorly. According to Finlay, this conserved organization represents a compromise between network redundancy, providing robustness against perturbations, and evolvability by permitting genetic and environmental variability (Anderson and Finlay 2014). In this line, the group led by Henry Kennedy has made a thorough analysis of connectivity in the macaque and mouse, showing a conserved pattern of connectivity among cortical areas, where the density of interareal connections decreases exponentially with areal distance. Nonetheless, this decay is much more pronounced in the larger brain of the macaque than in the smaller mouse brain, indicating that there is a constraint for long-range connectivity as brains increase in size (Ercsey-Ravasz et al. 2013; Horvát et al. 2016). Even so, primates show a tendency to have more dense cortico-cortical connectivity than other mammals (Charvet et al. 2017).

In addition to this conserved scaffolding, there is evidence that cortical regions can vary in size in different directions among species. Using modern anatomical and electrophysiological mapping methods, Jon Kaas and others have exhaustively analyzed the areal composition of the cerebral cortex in different mammals, obtaining large species differences in the number and relative extent of these areas (Kaas 2011, 2013). Based on the presence of distinct cortical areas in all the studied mammal species, Kaas proposed that the ancestral mammal had only a few cortical regions, with four visual areas, four somatosensory areas, a gustatory and viscerosensitive (insular) area, and an auditory area. There was also a small frontal cortex with medial (cingulate cortex) and orbitofrontal components, and a small, multimodal parietal area. In the course of

mammalian brain evolution, different areas have been added as the cerebral cortex has increased in size. A general process of areal separation and input segregation was first noted by Sven Ebbesson, who postulated the "parcellation theory" for brain development and evolution (Ebbesson 1980). Basically, Ebbesson argued that there are initially heterogeneous projections in both neural development and brain evolution that converge in specific brain regions. As the brain increases in size, there is a pervasive tendency of these projections to segregate into different areas that end up receiving more specific inputs, thus parcellating an ancestral multi-targeted convergence center, and favoring parallel processing. The idea sparked intense debate at the time, but eventually gained support, not as the exclusive mechanism for the evolution of brain projections, but as a common phenomenon. Parcellation is likely to occur especially as the convergence zone increases in size and allows for the spatial segregation of different inputs. This is in fact what happens in the cerebral cortex, because as the cortex grows in size disproportionately to the thalamic nuclei that relay information to it, the numbers of neurons receiving input from a specific source keep increasing, which favors the segregation of axons and the eventual separation of different brain areas.

Leah Krubitzer has proposed an updated version of Ebbesson's theory, in which small-scale mechanisms of afferent segregation also contribute to increasing input specificity and processing efficiency (Krubitzer 2009; Seelke 2012). The addition of new areas is considered a result of a process that includes increased size of a given area, subsequent within-area microscopic segregation of different inputs into distinct laminae or stripes, and eventually the separation of these areas in two regions. For example, the primary visual cortex is microscopically segregated into a laminar distribution of neurons according to responsiveness to specific kinds of visual stimuli, each of which then projects to distinct areas of the temporal and parietal lobes (see Chapter 7). This pattern of spatial amplification of microscopically segregated inputs may also take place during evolution, generating the observed diversification of cortical areas in the large brains of many species.

The main exception to the parcellation process is the well-known invasion of inputs to a region that up to then received few if any afferents

from a given brain component. Examples of this are the connections between both cerebral hemispheres, and the corticospinal tract that sends axons from the cortex to the spinal cord, both tracts appearing only in mammals. Suzana Herculano-Houzel and collaborators have clarified that the disproportionate increase in descending axons from the cerebral cortex in primates, and especially in humans, is explained simply by the fact that the number of descending cortical projections invading the brainstem and spinal cord nuclei increases as the cortex grows in size (Herculano-Houzel et al. 2016). On the other hand, the number of cells in the brainstem and spinal cord nuclei does not increase as rapidly as does the cerebral cortex, and they are invaded by descending axons. To what extent is cortical control of human speech a consequence of this allometric scaling? I will discuss this question in Chapters 8 and 10.

The relative size of individual cortical areas can also change according to behavioral adaptations. For example, the somatosensory representation of the tactile vibrissae of rodents occupies a large extent of the cortex and is organized into a series of "barrels", each representing one whisker (Kaas 2011, 2013). Likewise, the star-nosed mole, a subterranean animal that has developed many tentacle-like protuberations in its nose to maximize tactile sensitivity, has a very enlarged representation of each of these tentacles in the cerebral cortex (Catania 1995). And the platypus, the only mammal known to have electrosensory capacities (located in its beak, which it uses to find prey in mud underwater), also has a hypertrophied beak representation in the somatosensory cortex (Krubitzer et al. 1995). Bats also have an enlarged auditory cortex, which I will describe in more detail in Chapter 10.

Evidence gathered in recent years shows that both plasticity-driven and genetically modulated mechanisms operate in concert to determine the differentiation of cortical regions. To show the effects of neural plasticity, Migranka Sur, Sarah Pallas, and collaborators have taken advantage of a common phenomenon in early brain development, namely transient exuberance of incoming cortical connections such that nuclei from one sensory modality (say visual) initially send axons to cortical areas destined to another modality (say auditory or somatosensory) (Sur et al. 1990). However, these connections soon retract

during normal development. By surgically eliminating the natural auditory or somatosensory input to the presumptive auditory and somatosensory areas, researchers have found that the originally transient visual projections to the remaining areas stabilize, establishing functional synapses. Neurons in these areas become visually sensitive, having similar visual responses to those in the original visual cortex. Altogether, the evidence of transient exuberance of cortical projections and the subsequent retraction or segregation of these projections is in accord with Ebbesson's parcellation hypothesis, and also indicates a period of intense plasticity of projections that can be remodeled according to differential patterns of activity (recall the critical period of development, see Chapter 1). In normal circumstances, circuits processing different inputs (like visual or auditory) become largely separated and can perform their computations relatively independently of each other. However, if there is an imbalance in this process in early development caused by a lesion or deprivation, it is possible that circuits from a different modality take over. This occurs in people blind from birth, whose visual areas become auditory or somatosensory sensitive.

However, plasticity does not account for everything. There are also genetic mechanisms, perhaps not imposing a fixed mosaic pattern of cortical areas, but establishing continuous developmental gradients across the cortical surface, which serve as scaffolding for the differentiation of cortical areas. Three such gradients have been found at this point, the Pax6 gradient (the same gene involved in progenitor proliferation we saw above) distributed from lateral to medial cortex; a gradient including genes called Wnts and Emx2 among others, from posterior to anterior regions; and finally a gradient of a gene called FGF8 and related ones, from anterior to posterior. Dennis O'Leary and colleagues first observed that in mutant mice in which Pax6 is inactive, lateral structures (olfactory cortex, amygdala) and frontal areas, where Pax6 should be active, become strongly regressive (O'Leary and Sahara 2008; Bishop et al. 2002). Conversely, posterior (visual) areas where the Emx2 gene is normally active become regressive at the expense of amplification of frontal regions when this gene is mutated. Other experiments by Elizabeth Grove and collaborators showed that injecting the anterior signal FGF8 in the posterior cortex of the mouse produced a duplicate somatosensory area in the posterior cortex (Grove and Fukuchi-Shimogori 2003). Thus, differential modulations of these gradients may

expand presumptive territories destined to different cortical areas, and furthermore, as the cortex increases in size, these gradients may also extend, providing more space for areal differentiation.

The current consensus about areal specification in the cerebral cortex is that gene patterning mechanisms play a role in establishing what is called a protomap or blueprint of the topographic arrangement of cortical areas, which is refined in later development by neuronal activity and plastic processes. Projecting this to evolution, both factors may play a role. Studies indicate that there may be more variability in the arrangement of sensory areas within each species than the variability seen among related species, indicating either that genetic variability is very high or that plastic mechanisms are relevant in establishing the final configuration of cortical areas. It is likely that both mechanisms were important in human evolution. Furthermore, considering that language must have arisen quite rapidly in evolutionary time, it is very likely that the advent of culture-induced plastic reorganizations of the brain, and at the same time, generated a selective pressure for mutations favoring these reorganizations.

Primates Are Different (Again)

Besides having a large brain, primates have privileged visual systems among mammals. While reptiles and birds have a rich color perception, in mammalian origins some of the genes involved in color vision were lost, presumably due to early adaptations to nocturnal life (see Chapter 9). As a consequence, most mammals have only two visual pigments, one detecting blue light and the other detecting a sort of green light. Another common adaptation to nocturnal life is frontal vision, which increases light and contrast sensitivity. Early primates are thought to have been both nocturnal and arboreal, a lifestyle that strongly selects for frontal vision (Aboitiz and Montiel 2015). When primates invaded the diurnal niches, they redeveloped color vision by duplicating the gene for the green pigment, and mutating one of these copies into a close-to-red light detecting pigment. Thus, primates are usually trichromats (have three color pigments) as opposed to most other mammals that are dichromats. In 2004, Robert Barton elegantly showed that the degree of optical convergence

in primates is associated with the expansion of several visual brain components, which ends up increasing overall brain size (Barton 2004). This was shown by a tight correlation across species between optical convergence and the volume of thalamic visual nuclei, the visual cortex, and overall brain size, which were independent of increases in body size.

Another factor that has been invoked to explain the large brains of primates is social behavior. Robin Dunbar and his colleagues collected evidence for an increase in relative volume of the cerebral cortex (this time compared to total brain size) and social group size in different primates including humans (Schultz and Dunbar 2010). Likewise, Simon Reader and Kevin Laland made an exhaustive analysis of documented instances of behavioral innovation, social learning and tool use among primates (which tend to correlate among themselves) and found that these variables strongly correlate with both absolute and relative brain volumes (Reader and Laland 2002). However, a very recent study reports that a main determinant of brain size among primates is frugivorous diet rather than social complexity (DeCasien et al. 2017). The most likely possibility is that there are many factors influencing brain size, and determining the relative weight of each may depend on several variables.

One possibility to integrate these hypotheses is that with the development of a complex visual system and the regression of olfactory structures, the social life of primates underwent important modifications, increasingly based on visual and gestural cues rather than olfactory or pheromonal signals. There is a report that loss of olfactory receptor genes is concomitant with the development of trichromatric vision in primates (Gilad et al. 2004); and Rodrigo Suárez, Jorge Mpodozis and colleagues found that in sexually dimorphic species like primates, that rely more on visual signals for mating, there is a documented reduction of the pheromone-detecting system (Suárez et al. 2011). A visual, gesture-dominated communication system may have propelled the development of cognitive power, which benefited from increasing neuronal numbers and brain size. Gestural communication is also relevant for human speech and language, which would be in line with this possibility.

One of the brain regions that has received more attention in relation to human brain evolution is the frontal cortex, which is in front of the central sulcus that separates the parietal and frontal lobes. On the other hand, the prefrontal cortex covers most of the frontal cortex, but does not include the

premotor and motor cortices, which are located just anterior to the central sulcus (Brodmann's areas 6 and 4). Interest in the prefrontal cortex originates from its involvement in characteristically human abilities like planning behavior, cognition and speech and language. Karl Brodmann was perhaps the first to claim that the frontal lobe represents a larger proportion of cortical surface in humans (28%) than in chimpanzees (17%) and macaques (11%), a concept that became deeply entrenched for most of the past century (Brodmann 1909). However, in the 1940s, Gerhardt von Bonin concluded that the human frontal lobe is the size that would correspond to a primate with that brain size, indicating that the main difference with apes is overall brain size rather than an expanded frontal cortex (von Bonin 1948). Debate about frontal lobe size has continued until now, as studies continue to present contradictory evidence. Many authors have reported different estimates of prefrontal size, including neuroimaging measures of white matter, gray matter, absolute and relative volumes, etc., producing more controversy than consensus (Passingham and Smaers 2014; Smaers et al. 2011; Smaers 2013; Sherwood and Smaers 2013; Barton and Venditti 2013a, 2013b; Smaers et al. 2017). Again, Herculano-Houzel and collaborators have attempted to resolve this issue by the isotropic fractionator method (Ribeiro et al. 2013; Gabi et al. 2016). They found that apart from overall differences in total neuron numbers, humans do not differ from other primates in the proportion of neurons in the prefrontal cortex (about 8% in all species). Furthermore, they claim that new neurons have been added uniformly across cortical areas, and that the main difference between humans and other primates lies in the larger total number of neurons. All in all, at this point it may be safe to say that if there are differences in the size or neuron numbers of the human prefrontal cortex with respect to other primates, they are small enough to strongly depend on the statistics and experimental methodologies used.

Increase Brain Power, Not Cell Numbers

Ursula Dicke and Gerhard Roth have pointed out the inconsistencies of studies attempting to correlate intelligence with general brain properties (Dicke and Roth 2016). They have proposed an estimator of

information processing capacity that depends on the number of cortical neurons, neuronal packing density, interneuronal distance, and axon conduction velocity, to minimize delays because of increasing distances in large brains. Humans have the largest information capacity, followed by apes and monkeys. Despite their large brains, cetaceans and elephants score lower than primates in this estimate. On the other hand, some birds, like crows and parrots, have high neuronal densities that significantly increase their information processing capacity, which may explain their notable learning abilities.

Considering the apparent paradoxes and controversies concerning the relationship between brain size, body size and intelligence, in 1996 I proposed the hypothesis of dual processes of brain growth in evolution (Aboitiz 1996). Most researchers have assumed that as brains get larger or have more neurons, they are automatically better at processing information. But this assumption ignores all the intricate variability in connectivity and plasticity mechanisms that in the end may be more critical than the raw brain cell numbers. Consider, for example, echolocating bats, which, as discussed above, have quite small encephalization quotients. Nevertheless, their auditory cortex is particularly well developed (see Chapter 10). On the other hand, the statistical allometric relationship between body growth and brain growth is undeniable, so that the brain is developmentally coupled to the rest of the body, at least in early developmental stages. In a way, Jerison's "somatic factor" reflects this coupling, although not for the reasons he proposed. Therefore, there is one mechanism of brain growth, which I have called "passive growth" that results from simply following increases in body size. And the specific allometric relationship between body and brain (or number of neurons) depends on the particular developmental coupling between body and brain in each specific lineage, in prenatal and early postnatal stages. In this case, animals whose body size increases also grow a larger brain, but generally to perform the same functions they were doing before at smaller sizes.

There is another way by which brains can grow, which is by selective pressure on behavioral or functional capacities. In this case, it may be of benefit to produce more neurons, as there will be more possibilities of connectional rearrangements and network specialization (even if in some

cases, as in echolocating bats, this can be done with fewer neurons). I call this process "active" brain growth, which is a strategy to facilitate the development of more efficient neural networks and increasing plasticity. Plastic rearrangements that increase processing capacity occur during the lifetime of individuals as a response to immediate environmental demands. Under these conditions, subjects having more neurons in their brains might be at some advantage over those with slightly fewer neurons. I highlighted a role of neural plasticity as a driver for human brain evolution in an early article, proposing that a minimum of genetic changes, mainly (but not exclusively) involved in increasing neural progenitor proliferation in the brain, might account for human brain evolution, while the rearrangement of connectivity would have been largely a byproduct of activity-dependent reorganization of the neural networks in these larger brains (Aboitiz 1988).

More neurons and larger brains may be of benefit for the development of learned social abilities, as Robin Dunbar has observed in primates (Shultz and Dunbar 2010; Gamble et al. 2014). It is conceivable that a sort of "arms race" (to use Richard Dawkins' term; Dawkins 1991) took place among our immediate ancestors, in which every increase in mental capacity resulted in higher fitness relative to the group. Or just to follow Leigh Van Valen's "Red Queen" hypothesis, individuals had to constantly adapt not only to gain fitness relative to others, but also to keep their social status in a rapidly changing social world (changes that were, in turn, produced by the advent of successive cultural innovations) (Liow et al. 2011). Thus, a virtuous circle may have been established in which pressure for increasing plasticity facilitated selection of large brains and more neurons, and in turn these large brains resulted in more intense social pressures and cultural innovations, again putting new selective demands to increase neuron numbers, and so on. Furthermore, increasing brain size may be a relatively simple genetic achievement that can be done in a short time in evolutionary terms.

Subsequently (but certainly not caused by my publication), many authors like Terrence Deacon and others also proposed plastic and epigenetic processes for the rapid evolution of the human brain (Deacon 1997). Very recently, Chet Sherwood and collaborators reported that the heritability of cortical anatomy is much higher in the chimpanzee than in the

human, which firmly supports the concept of a plastic process in brain evolution (Gómez-Robles et al. 2015). They studied a series of human and chimp brains with known kin relationships, and determined variability in brain size and brain shape, measured from a geometric model of cortical anatomy. They then calculated an index of heritability, which is the proportion of variability that cannot be explained by genetics or kinship. Their finding is in line with a strong developmental plasticity of the human brain, which might simply be the result of increasing brain size (larger brains might have more developmental plasticity), an interesting possibility that requires further research.

Finally, I have to point out that things are not so clear-cut regarding the different modalities of evolutionary brain growth. First, in passive growth, brains still need to keep doing what they did before, but in larger networks and with more distance between neurons, which may produce unwanted delays in neuronal communication. As I said above, increasing neuronal density might be a factor contributing to minimizing brain expansion as neuron numbers increase. Furthermore, as mentioned in the previous chapter, oscillatory activity could be especially hampered in large brains. If the transmission delay of nerve impulses is too long, it may take a significant part of an oscillatory cycle, or be even longer than one cycle, which would interfere with the production of synchronized oscillations in large-scale networks, particularly at high frequencies where cycles are much shorter in time. György Buzsáki, Nikos Logothetis and Wolf Singer recently highlighted that the "synaptic path length", or the number of synaptic relays between two connected regions, increases as the distance between these regions expands in larger brains (Buzsáki et al. 2013). Larger brains partly adapt to this situation by growing longer faster conducting axons that are larger in diameter, which serve as shortcuts for long connections (see Chapter 5). Thus, connectivity becomes more complex, with local connections, middle-range connections in different degrees, and long- and very long-range connections that act as shortcuts for different pathways. This pattern corresponds to what is called a "small world" organization, in which the balance among local, intermediate and long-range connections is optimized to maximize processing efficiency. Buzsáki and collaborators have also underlined the fact that the propagation of low frequency oscillations across the cerebral cortex is much faster in the large human brain than in the small brains of rats, pointing

to a relative maintenance of transmission time intervals across the cortex in both species. We will come back to the issue of axonal conduction and brain size in Chapter 5, using the corpus callosum as a model tract for the evolution of brain connectivity.

Thus, there may be compensatory rearrangements during passive growth simply to maintain basic functional requirements. In addition, by increasing neuron number, passive growth provides space for further connectional rearrangements and opens a possibility for increasing behavioral capacity. In fact, in many cases, active growth may make use of general body size increases to increase the overall neuron number. This has happened in human evolution, where there has been a steady increase in body size accompanied with brain size increases, from 30 to 45 kg in Australopithecines and *Homo habilis* to 60 kg in *Homo erectus* and a larger average size in modern humans. However, body size has only doubled, while brain size has tripled from Australopithecines to modern humans, indicating that passive growth is not the only factor involved. Therefore, brain growth, coupled with body growth, may be one of the ways higher processing capacity has been achieved, but selection may also increase brain size (or neuron number) independent of body growth. Moreover, this could also explain why in some cases it is absolute neuron numbers, and in others the number of neurons relative to body size, that best accounts for behavioral capacities in different animal groups. Nonetheless, general brain size, plasticity and epigenetics could not have done it all. We have evolved a specific sensorimotor network, specialized to one hemisphere that enabled our ancestors to engage in complex vocal behavior. In the next chapter, I will refer to another attribute of the human brain, namely brain lateralization, which is an additional innovation that may have required distinct genetic mechanisms.

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