Chapter 2: The Convoluted Brain:
Wrinkles and Folds

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In the first lecture we studied the relationship between size and intelligence. This is an example of a *neural correlate*, connecting a brain feature (the size) to its function. We saw that size can be related to some features of the brain but lacks specificity. We also learned that scientists in the 19th Century were disappointed by their results and turned their attention to brain convolutions. Could the *geometry* of the brain and its intricate folds hide some secrets about our mind? How do we characterise these folds? What can they tell us about our brain or the animal brain? And how do they appear in the first place? Let's find out.

2.1 Brain convolutions

2.1.1 Talented people with complex convolutions

When Rudolph Wagner discovered in 1855 that the brain of the mathematical genius, Carl Friedrich Gauss, was large but not humongous and that the largest brains in his collection belonged to mentally disabled individuals, he turned his attention to other features. After fighting so hard to take possession of Gauss's brain, Wagner needed to find something positive to say about it, something that would clearly indicate the supreme morphology of Gauss's supreme intellect. In his description of the brain he noticed that "*the cerebrum is remarkable for the multiplicity of fissures and the great complexity of the convolutions*". This observation was used to compare Gauss to other mathematicians. The brain of the mathematician Johann Peter Gustave Lejeune Dirichlet, a distinguished colleague of Gauss in Göttingen and father of analytic number theory who died in 1859, "*approaches that of Gauss in superiority of development. The frontal lobes are remarkably massive and intricately convoluted*." Others didn't quite measure up: the British Mathematician Augustus De Morgan who died in 1871 had "*an exceptionally large head*" and was found to have *"voluminous frontal lobe convolutions but by no means so intricate as in that of Gauss.*"[23]

Time again, brain convolutions of eminent scientists and artists have been described poetically with some particular flourish. Beethoven's convolution, we are told, *"appeared twice as numerous and the fissures twice as deep as in ordinary brains.*" [31]. The great mathematician Sofya Kovalevskaya who tragically died in 1891 of pneumonia at the young age of 41 was, at the time, a celebrity. The local newspapers reported that the "*brain of the deceased was developed in the highest degree and was rich in convolutions, as might have been predicted, judging by her high intelligence."* [20, p. 35] Similarly, the brain of the great Russian chemist Mendeleev "*had*

a luxurious presentation of convolutions." It was no great surprise that when the researchers of the Moscow Brain Institute were tasked to study the brain of Vladimir Ilyich Lenin, founder of the Russian Communist Party, leader of the Bolshevik Revolution, Grand Architect and First Head of the Soviet State, they found that the *"lower parietal lobe is extremely convoluted and deviates greatly from the average brain"* and that "*the temporal lobes also exhibit a large number of furrows."* [27].

Despite the understanding by many scientists that the study of elite brains is sterile, the mythology of exceptional convolutions still persists in the scientific literature. The most recent example of wishful thinking is the tragicomedy of Einstein's brain saga. Despite his request to be cremated, his brain was collected by Thomas Harvey, the pathologist who conducted the autopsy in 1955. Einstein's brain remained for years in Harvey's home fridge until a journalist tracked him down. The multiple twists and turns in the story of Einstein's brain are recounted in Paterniti's book *Driving Mr. Albert: a trip across America with Einstein's brain* [26] Eventually, it became the object of multiple studies attempting to link morphological traits to superior intellectual abilities, very much in the spirit of Gall and Wagner. Unsurprisingly, it was found, in 2012, that Einstein's cortex *"appears to be highly convoluted around the midfrontal sulcus in both hemispheres"*, that the superior parts of the occipital lobes *"are quite convoluted"* and his *"visual cortex is relatively convoluted in both hemispheres compared with normal brains"* [9].

This form of confirmation bias is not new. It is quite likely that if we were to present the brain of an average person to an enthusiastic neuropathologist and tell them that it is the brain of the greatest mind of all time, they would feel compelled to identify unusual traits, especially if their entire research programme, funding, career, or their life depended on it.

From a modern scientific perspective, we must stay away from vague descriptions of the brain and to make any progress on connecting convolutions to cognitive functions, we must first understand them better and find a way to measure them. But before we step in the 20th Century, we will take a short detour to ancient Egypt more than 3,500 years ago.

2.1.2 Molten copper, roof ripples, and brain wrinkles

The patterns appearing on the surface of the human brain are so characteristic that they were already described in the very first historical description of the brain that appeared on the Edwin Smith Papyrus dating back to 1600 BCE. The Edwin Smith Papyrus is a double-sided scroll 4.68 meters long with 377 lines in 17 columns on one side and 92 lines in five columns on the other side. It is written right-to-left in hieratic, a cursive form of hieroglyphs, in black ink with explanatory glosses in red ink. It has been dated to Dynasties 16–17 of the Second Intermediate Period and named after the American Egyptologist Edwin Smith who purchased it in Luxor, Egypt in 1862. This surgical treatise written in hieratic describes 48 different medical cases of injuries including brain trauma with descriptions of skull structures, meninges, cerebrospinal fluid, and intracranial pulsations. Case 6 describes "*Instructions concerning a gaping wound in the head, rending open the brain*" and includes the first description of convolutions by stating that the surface of the brain looks like the corrugations of molten copper. Now, I don't know about you, but I have no clue what molten copper looks like. If I had to guess, I would say that it looks bubbly, maybe like brain matter!? The description of convolutions also includes the word 'ripple' (or 'wrinkle') as shown, after transliteration to hieroglyphics, in Figure 2.1. Very wisely, the author of the papyrus concludes that if someone has a gap in their skull large enough so that one can see the brain, then it is "*an ailment that shall not to be treated*". It will take thousands of years for medical doctors to exercise the same level of restraint.

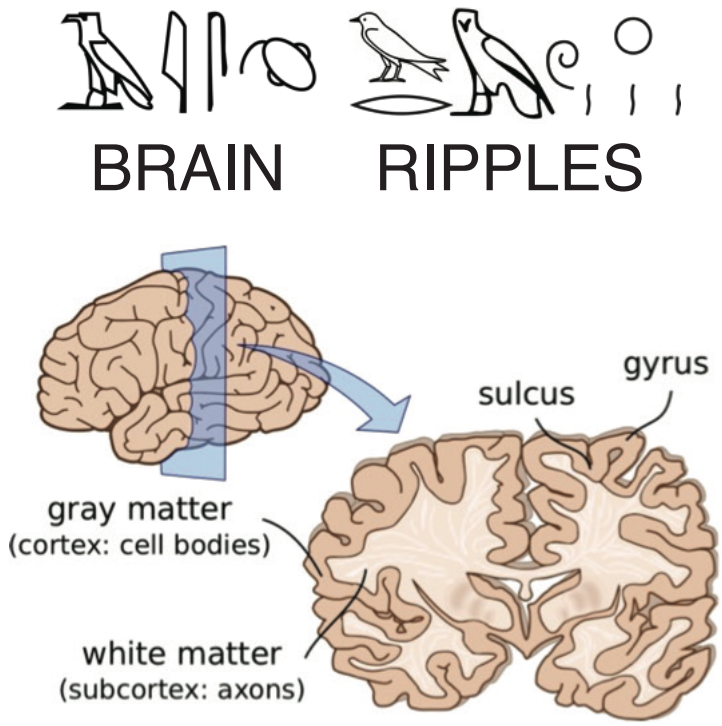

Figure 2.1: The words “brain ripples" first appear in Edwin papyrus in hieratic. Here they are first transliterated to hieroglyphics and transposed to be read sinistrodextrally. These wrinkles appear clearly if we take a coronal cut of the brain. On this slice, we see the valleys (sulci) and summits (gyri) of the brain contour (courtesy of Silvi Budday).

2.2 Measuring wrinkles

These wrinkles are particularly apparent if we look at a brain slice such as the one sketched in Figure 2.1. On this coronal slice, we see the *gyri* (turns) and *sulci* (grooves) that define the brain contour. We also notice two distinct zones, the outer layer, called the *cortex*, made of grey matter, and the inner layer composed of white matter. The brain contains two main types of cells, neuronal and glial. Neurons are electrically excitable cells that communicate with each others and support all our sensory, motor, and cognitive functions. As far as neurosciences go they are the stars of the show. Glial cells, on the other hand, form mostly the logistic team as they provide support, supply, clearance, and protection for neurons. Neurons are elongated cells with long protrusions called ’axons’ that connect to other cells. Neurons are found both in the grey and white matters but grey matter contains many neuronal cell bodies (the *soma*) whereas the white matter contains mostly their axonal projections that are surrounded by a sheath of myelin, known to improve signal transmission. In a freshly cut brain slice, the white matter appears pinkish white because of the high, fat-like, lipid content of myelin and the surrounding capillaries. In the same fresh slice, grey matter will show a light grey-pink-yellow colour which comes from the high concentration of blood vessels and neuronal cell bodies. However, once brain tissue is fixed in formaldehyde, both components turn to their namesake distinct grey and white colours.

The coronal slice shows that the surface of the brain is highly folded into itself. In humans, this folding happens in utero around 7 months as shown in Figure 2.2. More precisely, modern imaging allows to pinpoint the first fold around 25-27 weeks of gestation as shown in Figure 2.3. In Figure 2.4, we see that this *gyrification process* continues through adulthood. Medical resonance imaging gives us a full three-dimensional reconstruction of the brain from which we

can extract both its volume and surface area as it develops. A striking feature of the growth process is that surface area increases faster than the volume. Indeed, if you consider the isometric growth of an object, say a sphere for instance, its area is $4\pi R^2$ which grows like the square of the radius R, whereas the volume is $4/3\pi R^3$ which increases faster, as the cube of the radius. Hence, volume will grow much faster as the sphere expand. For the developing brain, the trend is inverted and we observe the formation of a very large surface for a given volume. The advantage of having a large surface area in a given volume is not disputed. Since most higher cognitive functions take place in the cortex, increasing grey matter cortical area increases the brain processing foetal capabilities for a given volume. Since the total volume of a human head is constrained by the initial requirement that a newborn should be able to squeeze through the birth canal among other factors, the main way to increase the number of cells in the cortex is by folding it onto itself.

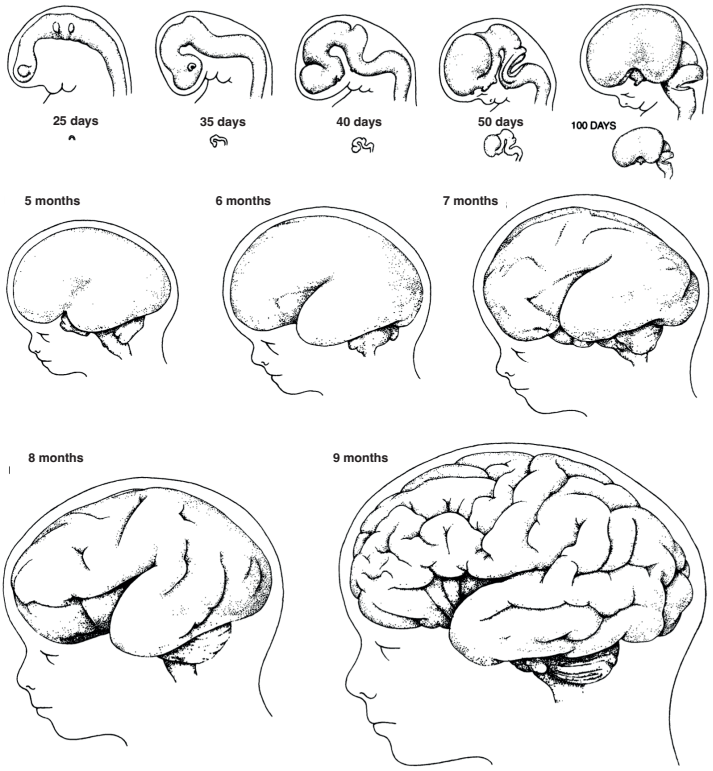

Figure 2.2: Development of the human brain viewed from the left side at successive embryonic and foetal stages. The top row of drawings at embryonic stages are enlarged to an arbitrary common size to show structural details (actual relative sizes are also shown). We see progressive gyrification appearing from 7-9 months (Reproduced from [7]; illustrated by Tom Prentiss.)

Of course, there could be many different ways to do so, and understanding the particular human architecture and how it is related to other mammalian brains is particularly interesting.

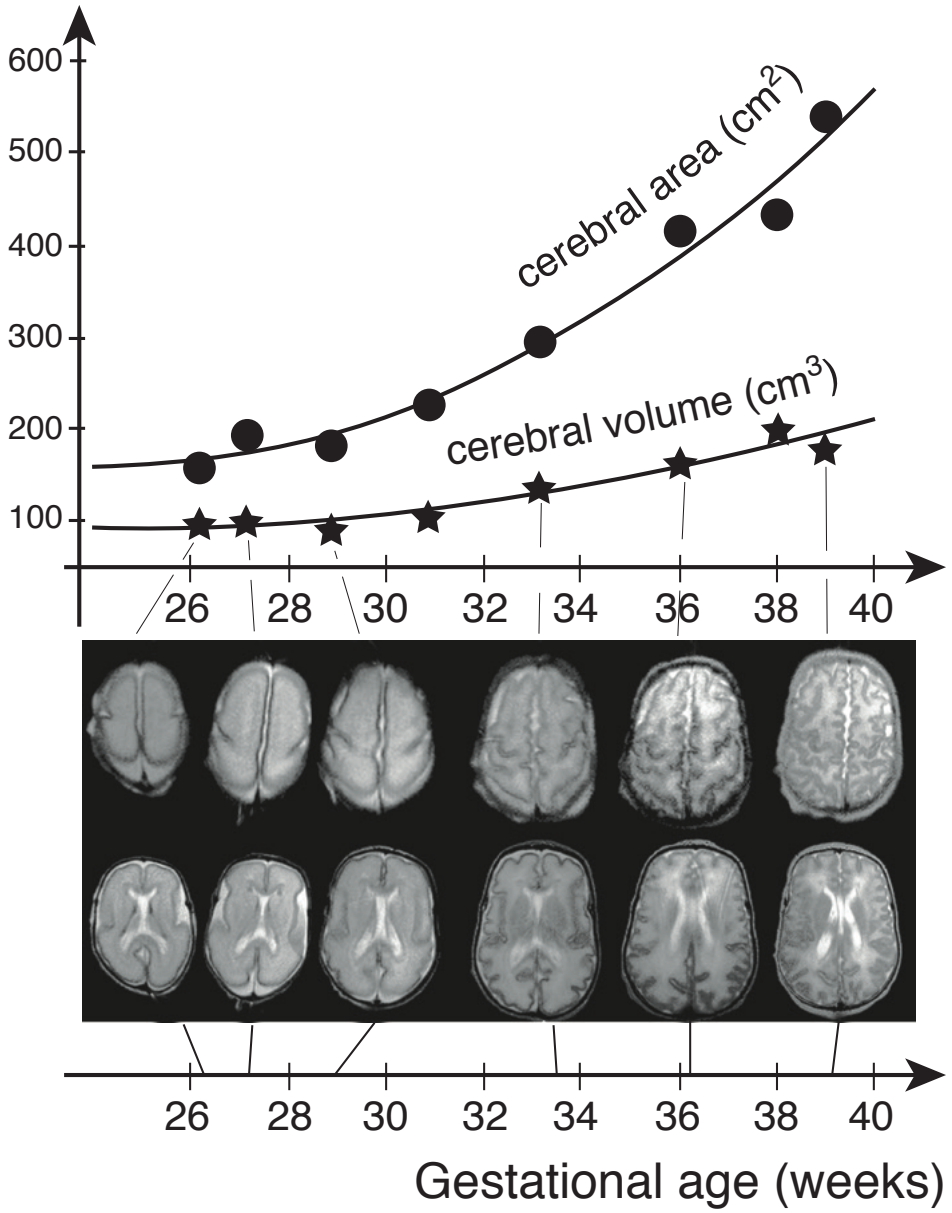

Figure 2.3: Serial MR imaging of brain growth in a normal female preterm infant born at 25 weeks. The images show slices through the brain at the mid-ventricular level (top row) and at the level of the centrum semiovale (bottom row) between 26 and 39 week gestational age (adapted from [19]). We see clearly the first folds appearing around 27-29 weeks.

Before we further speculate about brain shape and brain architecture, we must first be able to find good quantitative measures of folding that go beyond the description of elite brains. A simple way to quantify these convolution is through the so-called *gyrification index*.

Consider the brain slice shown in Figure 2.5. One can measure both the length of its contour by following every nooks and crannies, or the length of a taut string around it. The ratio between the two lengths is the gyrification index of this shape. By construction, its smallest value of one is attained when the shape is smooth and increases as the shape becomes increasingly more folded into itself. Mathematically, the gyrification index of a two-dimensional shape is the ratio

of its contour length by the length of its convex hull. A convex hull of a shape is the smallest convex set that contains it, that is the smallest shape such any two points in the convex hull are joined by a line segment that completely lies within the the convex hull. Similarly for a three-dimension shape, the convex hull is the ratio of the surface area of the shape by the surface area of its convex hull.

Similarly, for a three-dimensional shape like the brain, we can measure the surface area of the brain from the reconstruction of MRI slices as described in the previous chapter and measure the area of a smooth membrane that we would wrap around the brain like a cling film. The ratio of the brain surface area by the smooth film surface area is the gyrification index (GI) of the brain. A smooth brain like the manatee's will have an index close to one whereas the highly folded healthy human brain is around 2.56, with typical variations between 2.4 and 2.8, and no significant differences between men and women [39]. This high index is a direct consequence of the rapid areal increase of the brain cortex seen in Figure 2.1.

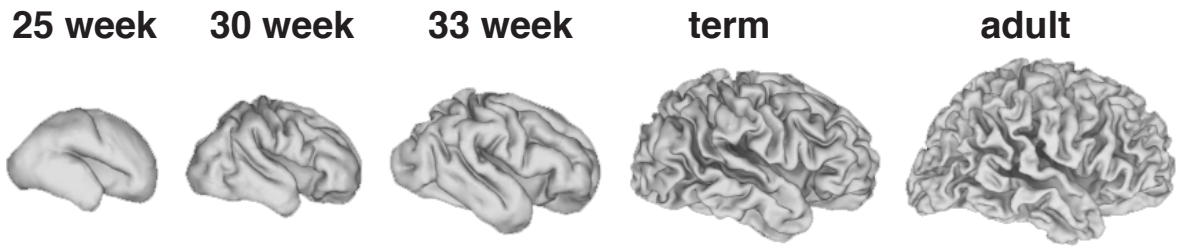

Figure 2.4: Progressive gyrification of the human brain from the early formation of a fold at week 25 to the adult brain. In this reconstruction, only the white matter is shown, not the overlaying cortex (adapted from a figure made by the van Essen lab).

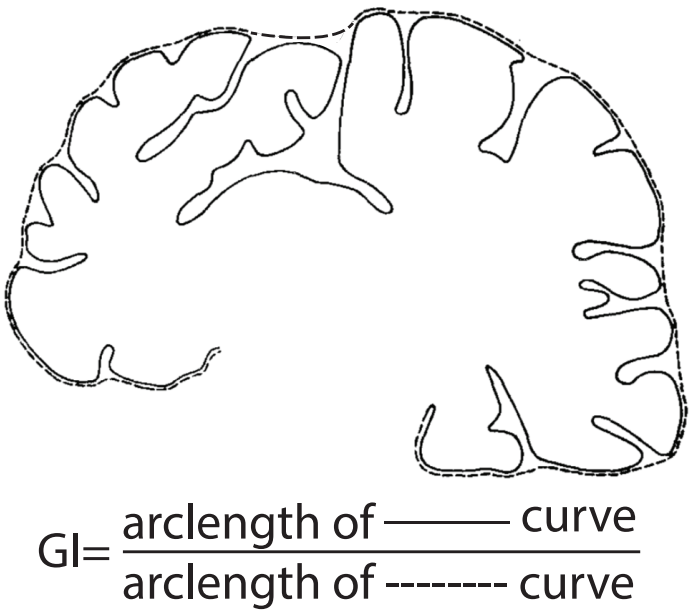

Figure 2.5: The gyrification index (GI) of a brain slice is obtained by taking the ratio of the total arclength of the brain contour (solid curve) by the total arclength of a string pulled along the outer contour (dashed curved). In this case the gyrification index was measured to be 2.95 (modified from Figure 1 of [39])

2.3 The animal brain

Erasistratus of Ceos (304-250 B.C.) compared brains of different animals and reasoned that human superiority comes from the complexity of the convolutions. In the words of Galen: "*The cerebrum which has many folds, and the cerebellum, even more than the cerebrum, was provided with many varied convolutions. So we learn that in compared to other animals–deer, hare, that far excels in running – man is far superior to the other animals in thinking. Hence, this organ is large and has many folds.*" [22]

Studying brain folds in different mammals is particularly interesting as they present many different sizes and shapes. The smallest mammal that presents folding is the ferret with a few simple folds reminiscent of the main fissure lines found in the human brain and, to a first approximation, larger animals or animals that are thought to be intelligent presents more complex convolutions. Have we finally found a good measure to distinguish ourselves within the animal kingdom? We can use the gyrification index to sharpen our argument and study how convolutions depend on brain weight. As a first comparison, consider our primate family. The diversity of brain size and shape can be appreciated in Figure 2.6. Armed with such knowledge and collecting other data sets from the literature, we can go ahead and measure precisely the gyrification indices of different primates.

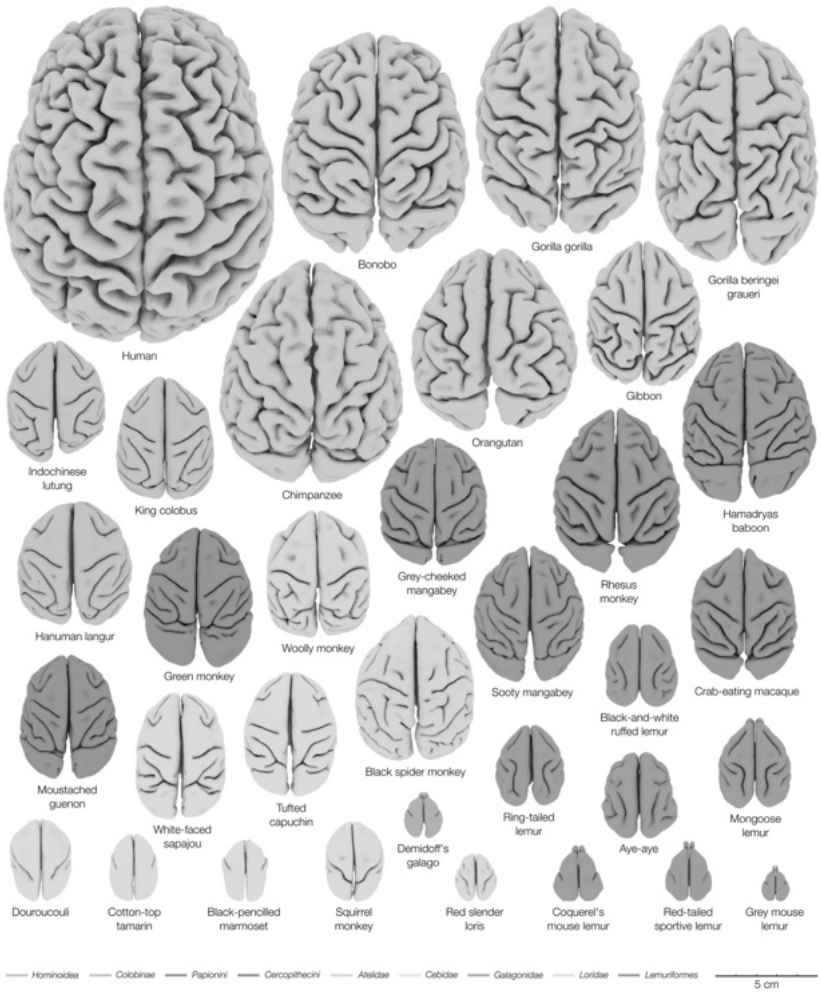

Figure 2.6: Dorsal view of the reconstructed cerebral hemispheres of 34 different primate species (figures adapted and courtesy of Katja Heuer and Roberto Toro [14])

We can divide primates into two main groups, the *anthropoids* including ourselves and our close cousins the apes and monkeys, and the *prosimians* our more distant relatives, including lemurs and lorisids. From an allometric perspective, we show, in Figure 2.7, a log-log plot of the gyrification index as a function of the brain weight for 44 different primate species. There are two interesting observations to draw from this plot. First, there is a clear general trend of overall increase in convolution complexity as a function of brain weight. Larger brains are more convoluted. Second, the actual increase for the two groups is different with a much more pronounced (faster) increase in complexity with brain weight for anthropoid. As discussed in the previous chapter, this difference points to differences in overall brain architecture. It is possible that anthropoids have developed mechanisms that allow for faster increase of brain area, hence managing to pack more cognitive power in that crucial cortical region. Finally, we see that humans sit nicely at the top of the scale with both the bigger and more complex brain.

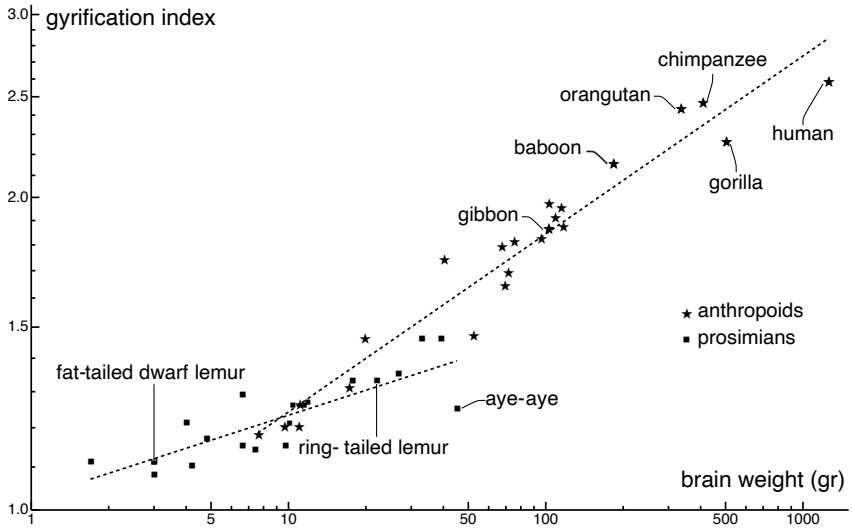

Figure 2.7: Gyrification index of primates (divided into prosimians and anthropoid) agains brain weight showing an overall increase of gyrification with weight. The dashed line shows the best fit allometric scaling for both groups (data from [38])

Before we celebrate our convolution superiority, we should compare ourselves with other class of mammals. We learned from our investigation of brain weights that there is much to learn by comparing different groups of mammals. In Figure 2.8, we pool data for 91 mammalian species. Again, we observe that different groups have different scalings but, unsurprisingly, cetaceans distinguish themselves again by both size and complexity. Flipper the dolphin is laughing at us once more.

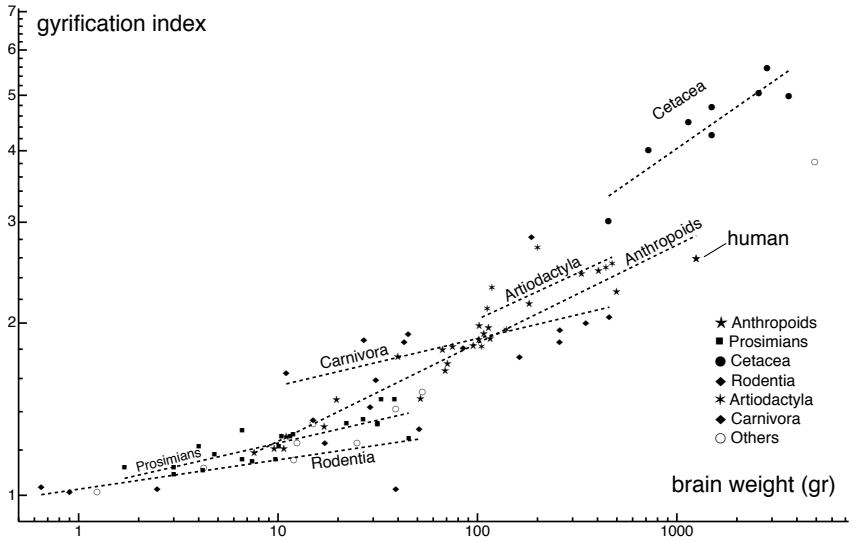

Figure 2.8: Gyrification index of mammals agains brain weight. The dashed line shows the best fit allometric scaling for each group (data from [38]).

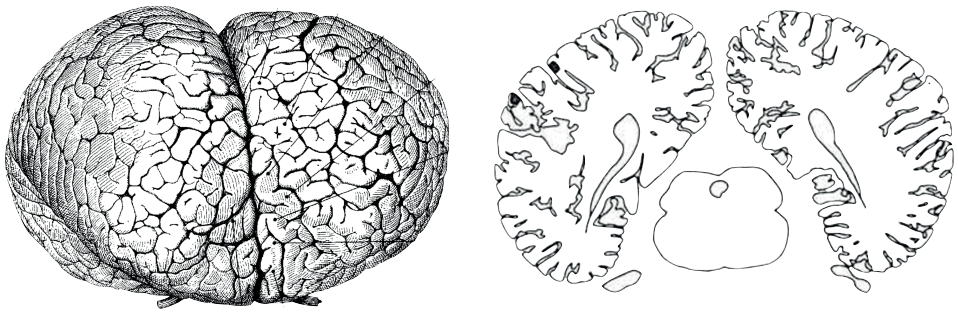

Figure 2.9: The brain of the Common bottlenose dolphin (*Tursiops truncatus*) shows extreme gyrification. Sketch and section adapted from [21] and [24], respectively.

What can we conclude from our investigation? It seems that for a given architecture associated with each groups, convolutions scale with brain size. As far as we are concerned, in the allometric world there is nothing exceptional about where we sit. We are below the dashed line, showing a less-than-average performance in our group and if we were to draw any partial conclusions from this graph, we would conclude that we are nothing but a scaled-up version of anthropoids.

We have learned that much like brain mass, convolution is a blunt measure that cannot truly reveal many functions of the brain. Yet, the complex appearance of the brain raises many enticing questions. Is it a by-product of the expansion of the cortical layer that has no room left to go but folds into itself? Or is its organisation the result of the compartmentalisation of functions, creating dedicated regions of highly connected neurons dedicated to particular tasks? To address these questions, we must first understand how these patterns emerge through development.

2.4 Brain morphogenesis

Brain folding, or gyrification, is a crucial aspect of brain development that allows for the rapid tangential expansion of the cerebral cortex while maintaining a compact volume [28, 35]. Sev-

eral hypotheses have been proposed to explain the mechanisms driving cortical folding during brain development. An older theory is that the *skull-constraint hypothesis*, suggests that the rigid skull restricts brain growth, forcing the cortex to fold as it expands (Fig. 2.10). However, this has largely been discounted as the skull accommodates brain growth [3] (See Fig. 2.11).

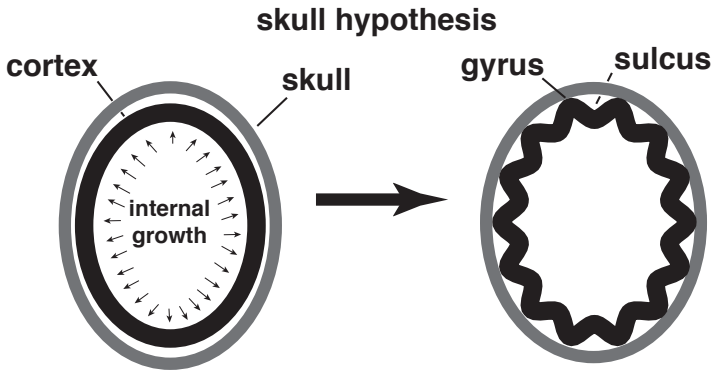

Figure 2.10: The skull hypothesis. If the brain expands faster than the skull it will push against the skull the skull and be forced to fold back on itself.

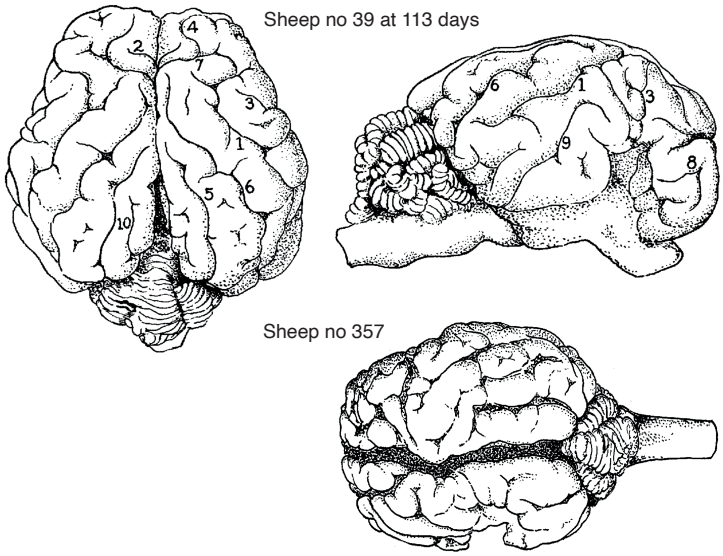

Figure 2.11: Top: Normal gyrification of a sheep's brain at term (113 days gestation). Bottom: If part of the hemisphere is removed during gestation, the right hemisphere still shows regular gyrification showing that folding is not due to a mismatch between brain and skull growth (adapted from Barron [3]).

A popular theory among neuroscientists is the *axonal tension hypothesis*, which posits that tension in axons connecting distant regions of the brain pulls cortical areas together, leading to the formation of gyri. Additionally, patterned growth models propose that localized differences in neuronal proliferation and migration drive the formation of primary folds in consistent regions. However, theory, simulations, and experiments on ferret brains (Fig. 2.13) have clearly established that axonal tension cannot be the prime driver of folding [37, 13].

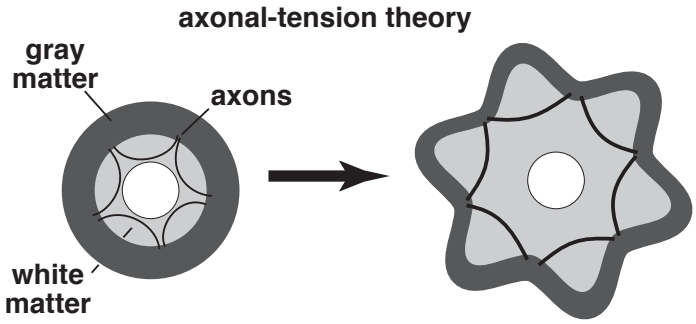

Figure 2.12: The axonal-tension theory assumes that axons are laid early in the development and connect different regions. As the brain expands, they act as cables preventing these regions to expand outward; (b) the differential-growth theory uses the fact that the cortical layers expand tangentially much faster than the core white matter resulting into an elastic instability.

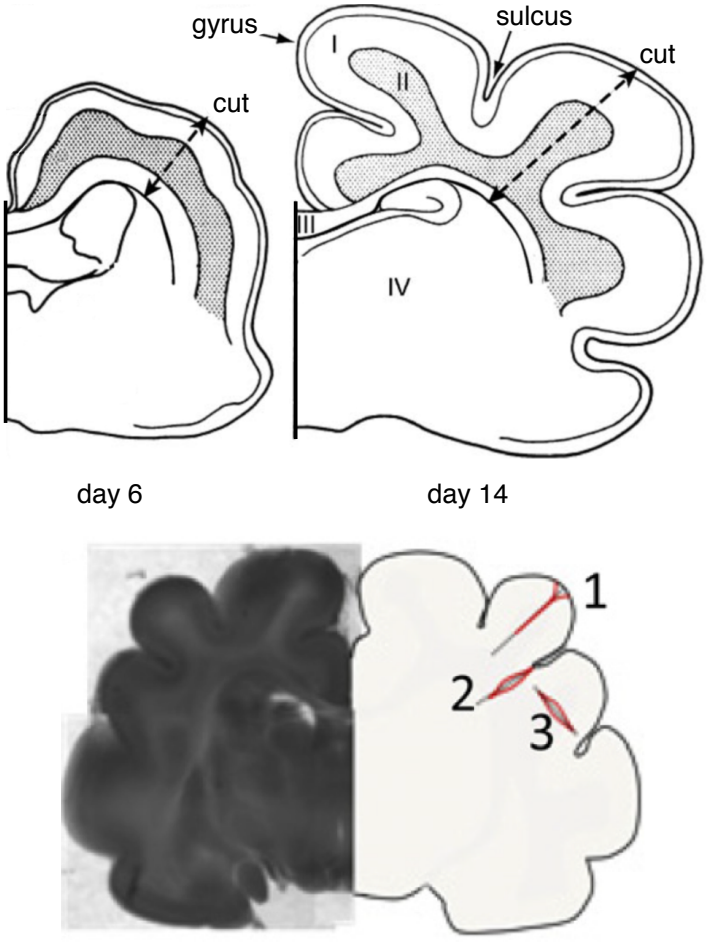

Figure 2.13: To test between the two main proposed mechanisms, cuts can be made in the Ferret brain at different points in development. At 6 days after birth the ferret brain is still smooth but is convoluted at day 14. Transverse cuts reveal basic properties of the internal stresses within the tissues, and in particular if the tissue is in tension or in compression along the direction perpendicular to the cut (Adapted from [37].)

The third theory, shown in Fig. 2.13 is the *differential tangential growth hypothesis*, which

proposes that since the outer layers of the cortex grow more rapidly than the underlying layers, a compressive stress is induced that leads to mechanical buckling and folding. This minimal hypothesis accounts for the basic pattern observed and is sufficient to explain the observed variations of thickness between gyri and sulci [16, 15]. The wrinkling instability [1, 2] is now recognised as the main factor for folding, including by David van Essen, the initial promoter of axonal tension theory, who wrote: "*the relatively rapid tangential expansion of the cortex has emerged as a driving factor*" [11], relegating axonal tension as a secondary, but potentially important, factor in shaping finer details of brain geometry, such as white matter organization [12]. Importantly, disruptions in the folding process can lead to developmental abnormalities linked to conditions such as epilepsy, autism, and schizophrenia [8], but the precise effects on folding are difficult to pinpoint exactly due to the complexity of these conditions. Hence, gyrification by itself has not yet been conclusively used as a biomarker [34].

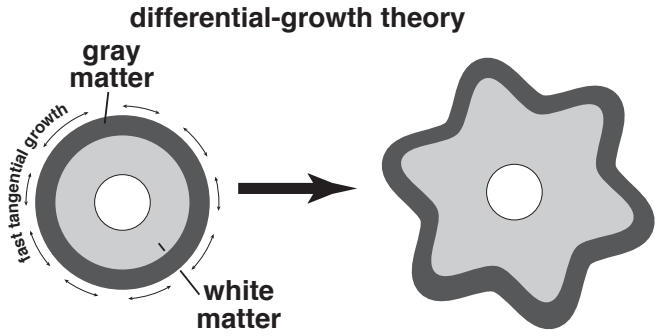

Figure 2.14: The differential-growth theory uses the fact that the cortical layers mad of grey matter grows tangentially much faster than the core white matter resulting into an elastic instability.

2.4.1 Wrinkling models

From a mathematical perspective, we can ask the simple question: assuming that the brain folds solely through differential growth, what can we predict? Are these predictions consistent with other observations?

The first thing that a mathematical modeller does is to throw away aspects of the problem that may be important to match the precise details of the observations but are mostly irrelevant to capture their main features. If asked how a car works, the modeller will dispense of all gizmos until they get to four wheels and the engine. Indeed, the placement of the cup holders is important for the passenger comfort but useless to understand the idea behind the internal combustion engine.

In our case, we want to know how differential growth can create patterns in the first place. To do so, we simplify the problem to its simplest non-trivial core and consider a block made out of two incompressible tissues, one large one representing the white matter and one thin layer on top of it representing the expanding cortex as shown in Figure 2.15.

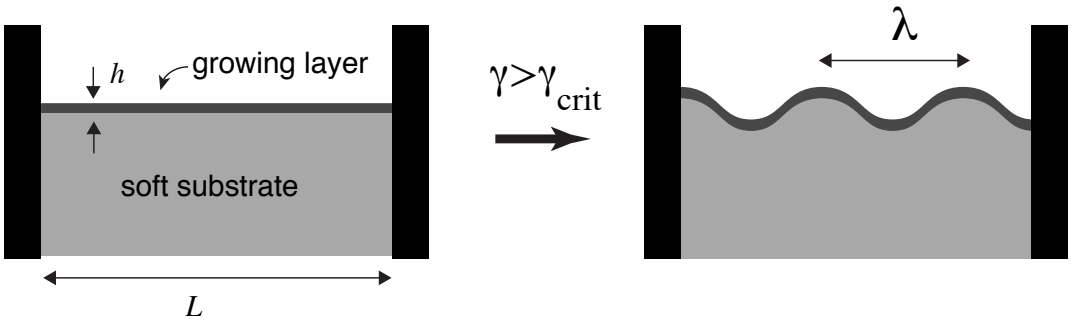

Figure 2.15: A toy model for wrinkling due to differential growth is a growing thin layer of thickness h on a soft (non-growing) substrate. If the top layer was neither attached nor constrained, it would grow to a longer layer of length $(1-\gamma)L$. When attached and constrained by the ends, this layer becomes compressed. At a critical value of the growth parameter γ, the system becomes mechanically unstable and develops wrinkles of wavelength λ (peak to peak distance).

We further assume that the tissue can only deform in the plane and is free to slide vertically at the two ends. The two tissues may have different *moduli* expressing the fact that for a given force a piece of either material may be easier to stretch than the other. This relative effect is contained in a single parameter μ, such that $\mu > 1$ expresses the fact that the bottom material is softer (i.e. easier to stretch) than the top one, which will be assumed here.[1] Differential growth is expressed by assuming that the bottom layer does not grow and the top layer growth is defined by a parameter $\gamma > 0$. If we were to cut out the top layer and let it grow freely, it would increase its length from L to $(1+\gamma)L$, while keeping its thickness h constant. The problem is then to find at which value of $\gamma = \gamma_{\text{crit}}$ the top layer becomes mechanically unstable and wrinkles with a typical wavelength λ. These initial wrinkles will, with further growth, develop into characteristic folds that are observed. The evolution of wrinkles into folds is described in [32]. Yet, the type of patterns obtained in a growing two-layer system is quite complicated and depends on multiple factors. Whereas we have made some progress in the last 10 years, much remains to be understood.

A relatively straightforward mathematical analysis of the equation governing the deformation of a growing beam on a substrate reveals that the critical growth and wavelength are:

$$\gamma_{\text{crit}} = \frac{3^{2/3}}{4}\mu^{-2/3}, \qquad \lambda = \frac{2\pi}{\sqrt[3]{3}}\, h\, \mu^{1/3}.$$

The numbers appearing in these relations are not important and depends on the particular hypotheses made to solve the problem. Much more interesting are the relationships with respect to the relative stiffness parameter μ and the thickness h. If we eliminate μ from the two equations, we obtain

$$\lambda = \pi \frac{h}{\sqrt{\gamma_{\text{crit}}}}.$$

[1] Given two tissues, one can in principle test their stiffness by a simple stretch-extension experiment where the stretch as a function of the applied force is measured. In the simplest setting, these experiments lead to the determination of the so-called *Young's modulus* that provides a measure of the material stiffness and is expressed in pascals (the units of pressure). Yet, brain tissues are so delicate and soft that these 'simple' experiments are extremely difficult to perform especially in live developing embryos and much research in recent years has been devoted to finding ways to measure brain properties [5].

What we also learn from this formula is the following series of qualitative relationships:

More growth $\Longrightarrow$ more wrinkles	$\gamma \nearrow \Rightarrow \lambda \nearrow$
A ticker layer $\Longrightarrow$ less wrinkles	$h \nearrow \Rightarrow \lambda \nearrow$
A thinner layer $\Longrightarrow$ more wrinkles	$h \searrow \Rightarrow \lambda \searrow$

How do these simple observations compare with the human brain? Clearly, it is not possible to *experiment* on human brains by varying the parameters appearing in these relations. However, we can *observe* different pathological situations where such variations naturally occur.

2.4.2 Pathological convolutions

Brain development is tightly regulated. Hence, it is not surprising that major developmental failures are associated with either a lack of wrinkling or excessive convolutions. Both brain malformations are observed and shown in Figure 2.16. *Lissencephaly*, literally meaning 'smooth brain' is a rare brain disorders associated with severe developmental delays and poor prognosis, where the brain or some regions appear smooth. It can be traced back to defective neuronal migration during gestation preventing the formation of the characteristic six layers present in a healthy cortex. Whereas normal human cortex has a typical well-regulated thickness of about 2 to 4 mm, lissencephalic brains have a thickness of 10 to 20 mm. According to our toy model, an increase of thickness of a factor five would imply a wavelength five times larger, that may not result at all in any folding (since the brain surface is curved and of a given size, a long theoretical fold may not actually fit within the domain and will be altogether absent). This trend is consistent with the observations

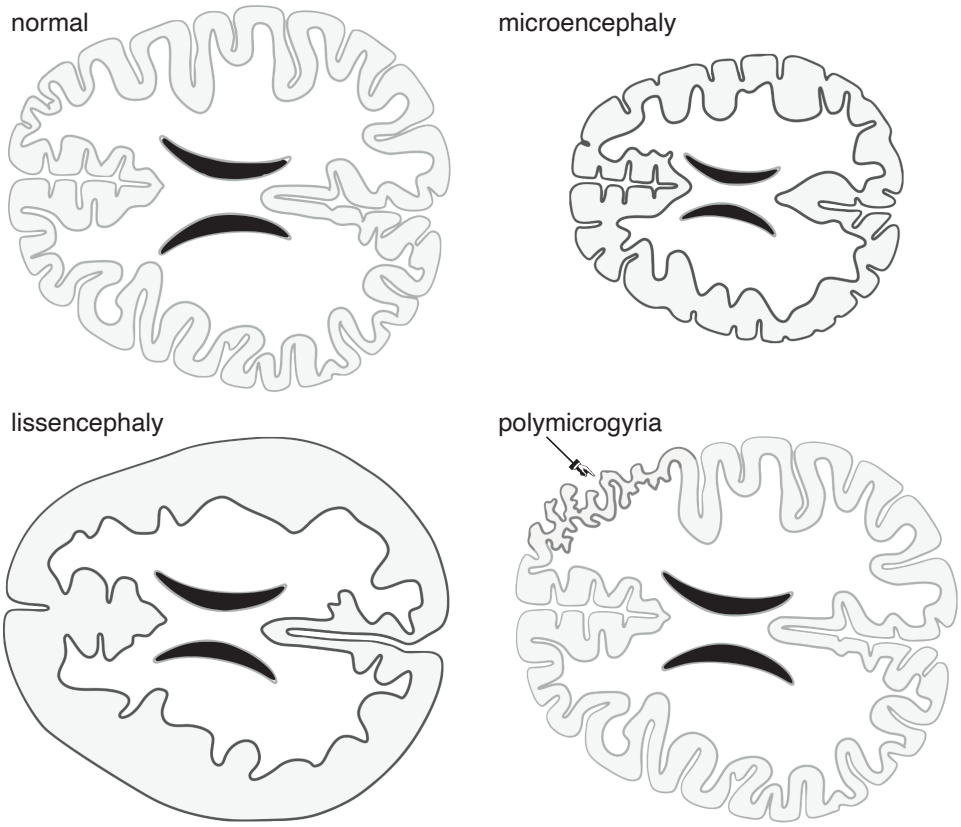

Figure 2.16: Schematic of horizontal sections through the cerebral cortex of a normal human brain compared to those of patients with cortical malformation: microcephaly, lissencephaly, and polymicrogyria (adapted from [10]).

At the other end of the spectrum, *polymicrogyria* is a condition associated with excessive wrinkling and many (poly) small gyri (microgyri) in some parts of the brain. It is first detected during convolution formation starting around week 20 but is believed to be caused earlier on by the defective proliferation and migration of *neuroblasts*, the cells that will develop into a neuron after migration. Depending on the affected region, polymicrogyria is associated with different symptoms which typically include seizures, developmental delays, and weakened muscles. Similarly, it has been shown that smaller local variations in the gyrification index are commonly observed in major psychiatric disorders such as schizophrenia, bipolar disorder, major depressive disorder, and autism spectrum disorder [29]. For instance, abnormal cortical folding in the Broca area, associated with language, is observed in schizophrenia [36] .Schizophrenia is a very serious condition often described as a disorder of thought, language, and communication. One of the morphological characteristics of polymicrogyria is that the cortex is abnormally thin due to malformation of the L5 layer. Again, this observed trend is consistent with our simple analysis that predicts smaller wrinkles for thinner growing layers.

2.5 Curvature and thickness

It is easy to criticise our toy model and decide that it is irrelevant for the study of brain folding. It is not a model yet, but a proto-model needed to understand, in the simplest of settings, what are the shapes that can result from having a rapidly growing tissue on a substrate. Since it captures some qualitative aspects of the problem, we can now build a more realistic theoretical model based on the same idea or develop experimental set-up with similar mechanisms.

Morphoelasticity, is a relatively new scientific discipline that uses mathematical ideas based on continuum mechanics to model the growth and remodelling of biological materials. In particular, it can be applied to formulate better models for brain growth. In simple geometries, it can be used to refine our initial model and obtain better understanding of folding mechanism and pattern generation.

In a recent collaboration with the group of my colleague Ellen Kuhl at Stanford, we studied a problem related to variations in brain thickness. The *cortical thickness* is the distance between the white matter and pial interface. In 1909, the famous German neurologist Korbinian Brodmann, known for drawing the first map of the cerebral cortex based on regional variations in structure, made an interesting observation: gyri, the elevated visible part of the wavy pattern, are usually thicker than sulci, the lower hidden part of the pattern as shown in Figure 2.17. We confirmed this early observation by looking at 564 healthy adult human brains and for each one measuring the gyral and sulcal thicknesses of 58 gyral and 62 sulcal regions. The 32,712 gyral regions have mean thicknesses of 2.87, whereas the 34,968 sulcal regions average 2.47 mm. There is doubt, from the data, that the difference is systematic and statistically significant. But, how does this variation come about? And, is it related to any particular function?

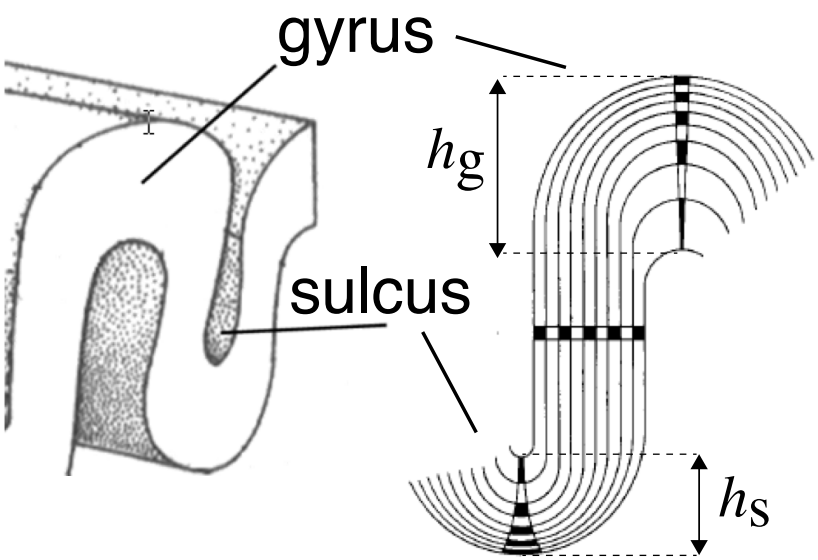

Figure 2.17: A systematic trend observed in the brain is that the cortical thickness h_{g} of gyri is larger than the cortical thickness h_{s} of sulci (Adapted from Bok 1929.)

A traditional explanation for observed patterns in biology is that a specific feature is the result of a genetic coding. A pattern or a structure emerges from the precise positional information provided by the variations of chemicals called morphogens throughout the tissue. In our case, a possible mechanism is that there are distinguished positions on the developing brain cortex that experience more growth. The cells at that location integrate the information provided by gradients of morphogens to divide more than neighboring cells. It is therefore natural that these positions are both thicker and end up as gyri. Indeed, simulations of growing tissues based on this idea confirm the formation of gyri at places with extra growth. However, it does not imply that morphogens are necessary for this pattern to develop.

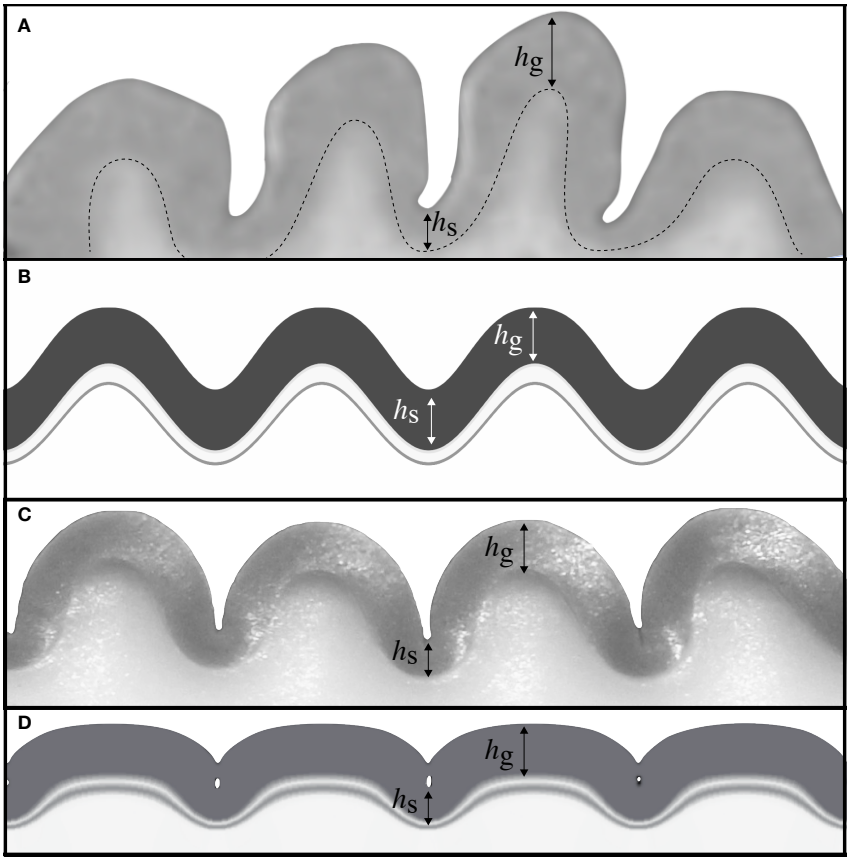

Figure 2.18: Brain slice showing gyri and sulci (A). A combined mathematical (B), experimental (C), and computational (D) analysis of the wrinkling instability show that gyri are always thicker than sulci as observed in the brain (adapted from [15]).

An alternative explanation is that the difference in thickness naturally happens during the instability. We tested this hypothesis by computing the change in thickness through the wrinkling instability. We showed that, systematically, gyri are *always* thicker than sulci through the instability. We further confirmed this result by direct simulations of growing tissues and by considering the patterns obtained by a swelling gels glued to another, non-swelling, gel to mimic the physical process. In all cases, we found that gyri are thicker than sulci as a result of the instability as shown in Figure 2.18. Hence, there is no need for extra information provided by mysterious morphogens and Ockam's razor suggests that it is the likeliest explanation for the observation.

Another interesting consequence of this theory is what happens to patterns growing on curved domain of various size. A direct consequence of the relation linking wavelength to growth is that for folds to develop, a domain L needs to long enough compared to the wavelength λ. Since mammalian brains are divided into a right and left hemisphere, we have $L = \pi R/2$ where R is the brain's radius. Hence for a fixed thickness h, which is typically around 2 mm, and small enough brains, no fold will develop. This simple prediction is consistent with the observations that we drew out of Figure 2.6 in which we saw that small primate brains are smooth and single folds appear at a critical brain size, and more generally in the mammalian brains as shown in Figure 2.19.

The same analysis of patterns on curved surfaces has another effect. The gyrification patterns still appear but they are delayed with respect to the flat solution [18]. The more curved the surface, the more growth is required to start forming a pattern. Therefore, if the top layer grows

on an ellipsoid, it will develop gyrification patterns first on the flat part of the ellipsoid, not the curved end. This delay is also consistent with the observations that patterns appear first on flat parts of the developing brain. It also implies that on an elongated brain, large folds will develop along the main axis as can be seen in the dolicocephalic brains of the capybara and lion in Figure 2.19.

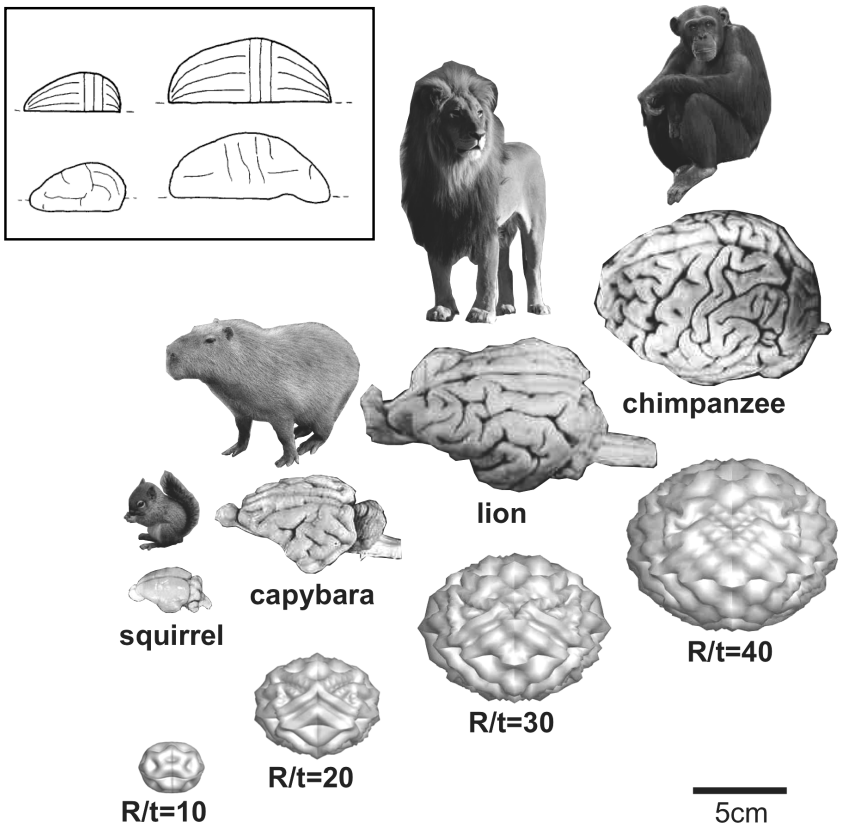

Figure 2.19: Mammalian brains vary greatly in size, shape, and gyrification but only marginally in cortical thickness. Simulations of spheroid with growing cortical layer and varying radius-to-thickness ratio predict an increase in gyrification (adapted from [4]) with absolute brain size and an alignment of the gyrification patterns for elongated brains (insert adapted from [33]).

Epilogue

There have been exciting developments in recent years about the use of geometric measures to study the brain. Apart from the gyrification index, there are much more refined measures to quantify the brain. One idea is to express the shape of the brain has a sum of multiple shapes with different spatial frequencies, much like we would characterise the shape of a violin string by its harmonics. This so-called *mode decomposition* of the brain has been shown to be particularly good at capturing brain dynamics [25] as well as a biomarker for early psychosis [6]. These last studies suggest that there is an intricate relationship between brain function and geometry.

When we look at a section of the brain, we clearly see isolated modules corresponding to well-defined regions. These regions are connected to each other by axons and naturally interact during normal brain function. For instance, visual information is being transported from the eye to the back of the brain for processing. Hence, rather than looking at the details of the geometry, it may be useful to study the brain as a network of connected regions. Mathematically, we can use graph theory to characterise these connections and develop a general theory of the brain

based on the particular topology of these graphs. In the next Lecture, we will discuss this approach that has been particularly successful in understanding brain functions and is now central to many aspects of neuroscience.

Appendix: Computation of the gyrification index of Gauss' brain using a half-ellipsoid model

I present the computation of the gyrification index (GI) of a human brain by modelling it as a half-ellipsoid, including the base area in the surface area calculation. Recall that the gyrification index is a quantitative measure of cortical folding in the brain, defined as the ratio of the total cortical surface area (including hidden areas within sulci) to the outer surface area. Modelling the brain as a geometric shape allows for estimation of expected surface area based on volume, facilitating the calculation of the GI.

From historical records, we known the volume and the total cortical area as measured by Rudolf Wagner's son Hermann in his thesis dissertation in 1864. Hence we need to approximate the outer area. For any given shape, surface area and volume are related by $A = kV^{2/3}$, where k depends on the shape (try to find k for a sphere as an exercise). Here, we will model the brain as a half-ellipsoid. Therefore, the steps involve calculating the volume and surface area of the half-ellipsoid, determining the proportionality constant k in the formula $A = kV^{2/3}$, and computing the GI based on estimated brain measurements.

2.6 Volume of the Half-Ellipsoid

The volume of a half ellipsoid with semi-axes a, b, and c is

$$V = \frac{2}{3}\pi abc. \tag{2.1}$$

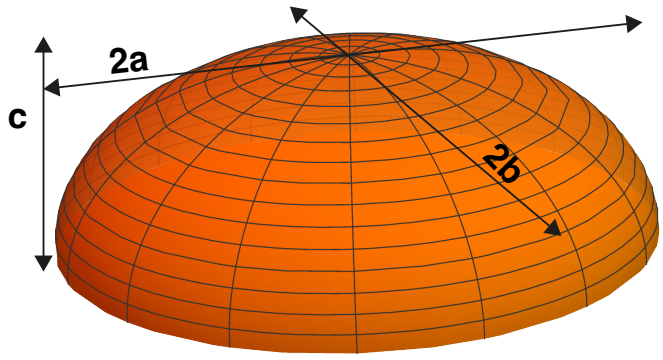

Figure 2.20: We model the brain as a half-ellipsoid with semi-axes a, b, c.

The total surface area A includes the lateral surface area A_{lateral} and the base area A_{base}. The base ares is simply the area of the ellipse with semi-axes a and b:

$$A_{\text{base}} = \pi ab. \tag{2.2}$$

However, there is no simple formula for the area of an ellipsoid. Hence, we use Knud Thomsen's approximation:

$$A_{\text{full}} \approx 4\pi \left(\frac{a^p b^p + a^p c^p + b^p c^p}{3} \right)^{1/p}, \tag{2.3}$$

where $p \approx 1.6075$.

Next we compute both quantities (Volume and Area) for typical values of the human brain with $a = 8\,\text{cm}$, $b = 7\,\text{cm}$, and $c = 5\,\text{cm}$ to obtain

$$V = \frac{2}{3}\pi abc \tag{2.4}$$

$$\approx 586.43\,\text{cm}^3. \tag{2.5}$$

The areas are

$$A_{\text{lateral}} \approx\approx 276.92\,\text{cm}^2, \quad A_{\text{base}} \approx 175.93\,\text{cm}^2. \tag{2.6}$$

Using

$$V^{2/3} = (8.362\,\text{cm})^2 \approx 69.943\,\text{cm}^2, \tag{2.7}$$

and the formula $k = A/V^{2/3}$, we obtain

$$k = \frac{A}{V^{2/3}} = \frac{452.85\,\text{cm}^2}{69.943\,\text{cm}^2} \approx 6.476. \tag{2.8}$$

Let us use this value to find the exposed area of Gauss's brain with mass $m = 1,492\,\text{g}$. A typical density for brain is $\rho \approx 1.04\,\text{g/cm}^3$, hence

$$V = \frac{m}{\rho} = \frac{1,492\,\text{g}}{1.04\,\text{g/cm}^3} \approx 1,434.62\,\text{cm}^3, \tag{2.9}$$

and

$$V^{2/3} = (11.267\,\text{cm})^2 \approx 126.90\,\text{cm}^2. \tag{2.10}$$

Therefore, the expected outer surface area A_{model} is

$$A_{\text{model}} = kV^{2/3} = 6.476 \times 126.90\,\text{cm}^2 \approx 822.19\,\text{cm}^2. \tag{2.11}$$

These estimates are consistent with measurements on the brain that give estimates for the total surface of cortex cerebri between 1800 and 2500 cm^2 and visible surface of cortex cerebri between 600 and 900 cm^2 [30, 17].

Knowing that $A_{\text{total}} = 2,195.88\,\text{cm}^2$, we can now compute the gyrification index as

$$GI = \frac{A_{\text{actual}}}{A_{\text{model}}} = \frac{2,195.88\,\text{cm}^2}{822.19\,\text{cm}^2} \approx 2.67. \tag{2.12}$$

This value of the GI is within the typical range for healthy human brains, which generally ranges from 2.0 to 3.0, with an average around 2.5.

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