

Neuro-evolutionary evidence for a universal fractal primate brain shape

Reviewed Preprint

Revised by authors after peer review.

About eLife's process

Reviewed preprint version 2

April 9, 2024 (this version)

Reviewed preprint version 1

December 14, 2023

Sent for peer review

September 18, 2023

Posted to preprint server

August 21, 2023

Yujiang Wang , Karoline Leiberg, Nathan Kindred, Christopher R. Madan, Colline Poirier, Christopher I. Petkov, Peter N. Taylor, Bruno Mota

CNNP Lab (.), Interdisciplinary Computing and Complex BioSystems Group, School of Computing, Newcastle University, Newcastle upon Tyne, United Kingdom • Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom • UCL Institute of Neurology, Queen Square, London, United Kingdom • School of Psychology, University of Nottingham, Nottingham, United Kingdom • Department of Neurosurgery, University of Iowa, USA • metaBIO Lab, Instituto de Física, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

 https://en.wikipedia.org/wiki/Open_access

 Copyright information

Abstract

The cerebral cortex displays a bewildering diversity of shapes and sizes across and within species. Despite this diversity, we present a universal multi-scale description of primate cortices. We show that all cortical shapes can be described as a set of nested folds of different sizes. As neighbouring folds are gradually merged, the cortices of 11 primate species follow a common scale-free morphometric trajectory, that also overlaps with over 70 other mammalian species. Our results indicate that all cerebral cortices are approximations of the *same* archetypal fractal shape with a fractal dimension of $d_f = 2.5$. Importantly, this new understanding enables a more precise quantification of brain morphology as a function of scale. To demonstrate the importance of this new understanding, we show a scale-dependent effect of ageing on brain morphology. We observe a more than four-fold increase in effect size (from 2 standard deviations to 8 standard deviations) at a spatial scale of approximately 2 mm compared to standard morphological analyses. Our new understanding may therefore generate superior biomarkers for a range of conditions in the future.

eLife assessment

This study presents **valuable** framework and findings to our understanding of the brain as a fractal object by observing the stability of its shape property within 11 primate species and by highlighting an application to the effects of aging on the human brain. The evidence provided is **solid** but the link between brain shape and the underlying anatomy remains unclear. This study will be of interest to neuroscientists interested in brain morphology, and to physicists and mathematicians interested in modeling the shapes of complex objects.

Introduction

The morphological complexity of the mammalian cerebral cortex has fascinated scientists for generations, with cortices across and within species exhibiting a large diversity of shapes and sizes. Such diversity is not arbitrary, however. The mammalian brain folds into stereotypical, hierarchically-organized structures such as lobes and major gyri. In fact, qualitative and quantitative regularities in cortical scaling have often been suggested and observed [1, 2, 3, 4]. More specifically, through modelling the mechanism of cortical folding from a statistical physics approach, we have previously derived a theoretical scaling law relating pial surface area A_t , exposed surface area A_e , and average cortical thickness T :

$$A_t T^{\frac{1}{2}} = k A_e^{\frac{5}{4}}. \quad (1)$$

This scaling law, relating powers of cortical thickness and surface area metrics, was shown to be valid across mammalian species [5] and within the human species [6], as well as to the structures and substructures of individual brains [7, 8]. Notably, across all these cases the dimensionless offset k is shown to be near invariant. However, this universality, presumed to be arising from universal physical principles and evolutionarily conserved biomechanics, says little about what that cortical shape actually is, beyond a constraint binding three morphometric parameters. In this paper, we take Eqn. (1) as an empirical starting point to create a new and hierarchical way of expressing cortical shape. Specifically, we introduce a coarse-graining procedure that renders cortical shapes at different spatial scales, or resolutions. We show that the *shapes of primate cerebral cortices at each spatial scale can be understood as approximations of the same universal self-similar archetypal form.*

Besides revealing a symmetry in nature hidden under much apparent complexity, our results indicate a conservation of some quantities across evolution. We will show that these results further provide us with a new and powerful tool to express and analyse cortical morphology. As an example, we will calculate the effects of human ageing across spatial scales and show that the effects are highly scale-dependent.

2 Coarse-graining Method

The universal scaling law (Eqn. 1) can be rewritten in a suggestive way

$$\frac{A_t}{A_0} = \left(\frac{A_e}{A_0} \right)^{1.25}, \quad (2)$$

where the $A_0 = \frac{T^2}{k^4}$ is a fundamental area element that defines the threshold between gyrencephaly (folded cortex) and lissencephaly (smooth cortex) when $A_t = A_e = A_0$. For a constant k the value of A_0 is a multiple of T^2 , indicating that cortical thickness determines the size of the smallest possible gyri and sulci.

This re-writing highlights a new perspective, or interpretation of the scaling law: it now suggests a relationship between intrinsic and extrinsic measures of cortical size²: A_t and A_e respectively, measured in units of A_0 . This is reminiscent of fractal scaling [9], where a complex shape reveals ever smaller levels of self-similar detail as it is probed in ever smaller scales (or equivalently, higher resolutions), represented here by A_0 . The scaling, or power exponent between the measured intrinsic and extrinsic sizes is the so-called fractal dimension.

Although actual fractals are mathematical abstractions, they can often be defined as the limit of iterative processes. Many structures in nature, and in particular biology [10, 11, 12, 13, 14, 15, 16], are good approximations of a fractal. Equation (2) is suggestive, but not proof, that cortices are among these forms, with a fractal dimension of $1.25 \times 2 = 2.5$ (the factor 2 being the topological dimension of areas). Indeed, fractal scaling for various aspects of cortical morphology has often been postulated [17, 18], with a number of recent papers making use of MRI data [19, 20, 21]. Most recently published estimates of fractal dimension for the whole cortex are indeed close to 2.5 [22, 23, 24].

Here, for the first time, we propose to directly construct morphologically plausible realisations of cortices at any specified spatial scale, or resolution. This is achieved through a coarse-graining method that removes morphological details smaller than a specified scale while preserving surface integrity. For example, at a set scale of 3 mm, sulcal walls that are less than 3 mm apart would be removed, and the neighbouring gyri would be fused. This method is a new systematic way of expressing cortical shape, in terms of a flow of morphometric measurements as spatial scale varies. By examining how areas scale across coarse-grained realisations of actual primate cortices, we will be able to directly verify cortical self-similarity.

As a starting point for such a coarse-graining procedure, we suggest to turn to a well-established method that measures fractal dimension of objects: the so-called box-counting algorithm [25, 26]. Briefly, this algorithm fill the object of interest (say the cortex in our case) with boxes, or voxels of increasingly larger sizes and counts the number of boxes in the object as a function of box size. As the box size increases, the number of boxes decreases; and in a log-log plot, the slope of this relationship indicates the fractal dimension of the object. In our case, this method would not only provide us with the fractal dimension of the cortex, but, with increasing box size, the filled cortex would also contain less and less detail of the folded shape of the cortex. Intuitively, with increasing box size, the smaller details below the resolution of a single box would disappear first and increasingly larger details will follow – precisely what we require from a coarse-graining method. We therefore propose to expand the traditional box-counting method beyond its use to measure fractal dimension, but to also analyse the reconstructed cortices as different realisations of the original cortex at the specified spatial scale.

Concretely, our proposed method requires the bounding pial and white matter surfaces of the cortical ribbon as input. We obtained these surfaces based on reconstructions from magnetic resonance imaging data in 11 different primate species (see Suppl. S1). Algorithmically, we then segment the space between the original pial and white matter surfaces into a 3D grid of boxes of the desired scale λ , where each box is a cube of dimensions $\lambda \times \lambda \times \lambda$. We also term the 3D grid of cubes “voxelisation”, as it effectively captures the shape of the cerebral cortex as voxels in 3D space (Fig. 1B bottom row). At any given scale, or voxel size, this process effectively erases morphological features (folds) that are smaller than the cube size. Visually, increasing the voxel size appears as if the cortex is “melting” and “thickening” (Fig. 1, and videos: <https://bit.ly/3CDqZQ>).

The observation that with increasing voxel sizes, the coarse-grained cortices tend to be smoother and thicker is particularly interesting: the scaling law in Eq. 3 can be understood as thicker cortices (T) form larger folds (or are smoother i.e. less surface area A_f) when brain size is kept constant (A_e). This way of understanding has also been vividly illustrated by using the analogy of forming paper balls with papers of varying thickness in Mota *et al.* [4]: to achieve the same size of a paper ball (A_e), the one that uses thicker paper (T) will show larger folds (or is smoother i.e. less surface area A_f) than the one using thinner paper. The scaling law can therefore be understood as a physically and biologically plausible statement, and here, we are encouraged that our algorithm yields results in line with the scaling law.

A more technical and detailed description and discussion of the algorithm is provided in [Suppl. S2](#). Note this method has also no direct dependency on the original MR image resolution, as the inputs are *smooth* grey and white matter surface meshes reconstructed from the images using strong (bio-)physical assumptions and therefore containing more fine-grained spatial information than the raw images (also see [Suppl. S3](#)).

Finally, to analyse the scaling behaviour of the different coarse-grained realisations of the same brain, we apply an isometric rescaling process that leaves all dimensionless shape properties unaffected (more details in [Suppl. S4.1](#)). Conceptually, this process fixes the voxel size, and instead resizes the surfaces relative to the voxel size, which ensures that we can compare the coarse-grained realisations to the original cortices, and test if the former, like the latter, also scale according to [Eqn. \(1\)](#). Resizing, or more precisely, shrinking the cortical surface is mathematically equivalent to increasing the box size in our coarse-graining method. Both achieved an erasure of folding details below a certain threshold.

3 Results

3.1 All primate brains follow the same scaling law across spatial scales

We have analysed cortices of 11 different primate species (see [Suppl. S1](#)): aotus, cebus, chimpanzee, colobus, galago, human, lagotrix, lophocebus, macaque, marmoset, and pithecia, and various cohorts of human subjects. We applied our coarse-graining procedure to their pial and white matter surfaces, and empirically determined (i) that all species followed a power law (linear regression $R_2 > 0.999$ for all species); (ii) the slope of said power law is $\alpha = 1.255$ on a group level (CI: [1.254 1.256]) using linear mixed effect modelling (see [Fig. 2](#) for visualisation, and [Suppl. S4](#) for a detailed breakdown by species); and importantly, (iii) all species also show a similar offset $\log k \approx -0.65263$, with a standard deviation of intercept across species estimated at 0.02 from linear mixed effect modelling in $\log k$.

Taken separately, the scaling for each species is proof that their cortices are self-similar with the same scaling: they each approximate a fractal with fractal dimension $d_f = 2.5$. Considering all species together, different species also overlap substantially (similar offset), and only differ from each other in the range of scales over which the approximation is valid (see [Suppl. S4.2](#) and [S5](#)). Thus, as [Fig. 2](#) illustrates, the data supports a *universal* scaling law across primate species and spatial scales:

$$A_t(\lambda)T(\lambda)^{\frac{1}{2}} = kA_e(\lambda)^{\frac{5}{4}}, \quad (3)$$

with $k = 0.2277$.

3.2 Primate brains at different spatial scales are morphometrically similar to each other and other mammalian species

To better characterise the coarse-grained cortices in terms of their similarity in offset, we use a previously introduced [\[27\]](#) set of independent morphometric measures, K , I and S , that summarise the shape of the cortex in a natural and statistically robust way. In this framework, isometrically scaled copies of the same shape all map onto a line along the $I = \log A_t + \log A_e + \log T^2$ direction, which is perpendicular to a $K \times S$ plane that fully summarises their shape. $K = \log A_t - \frac{5}{4} \log A_e + \frac{1}{4} \log T^2$ is the direction defined by the offset k of the scaling law [Eqn. \(1\)](#), while direction $S = \frac{3}{2} \log A_t + \frac{3}{4} \log A_e - \frac{9}{4} \log T^2$ captures the remaining information about shape, and can be regarded as a simple measure of morphological complexity. Ref [\[27\]](#)

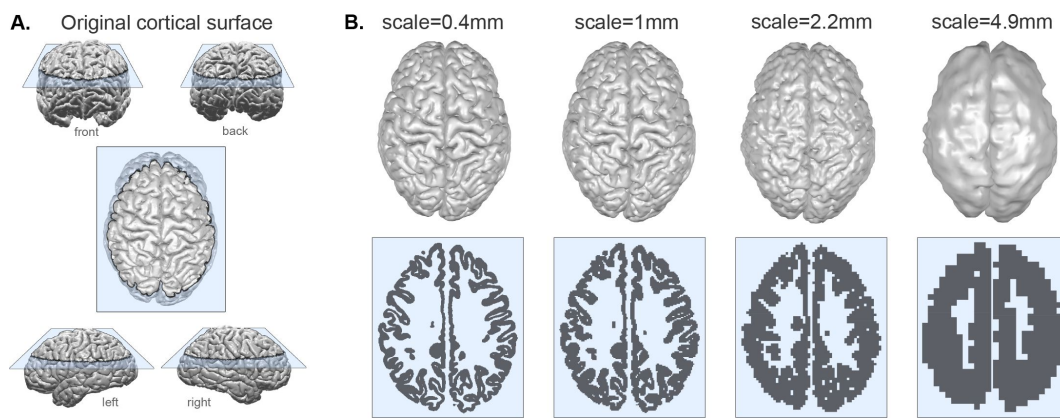


Figure 1

Coarse-graining a cortex at different scales.

A: Example original pial surface from a healthy human viewed from varying angles. **B:** Same example cortical surface from A, coarse-grained to different spatial scales. Top row shows resulting pial surfaces (with a small amount of smoothing applied for visualisation purposes here). Bottom row shows the corresponding voxelisation at each scale through the slice indicated by blue plane in panel A.

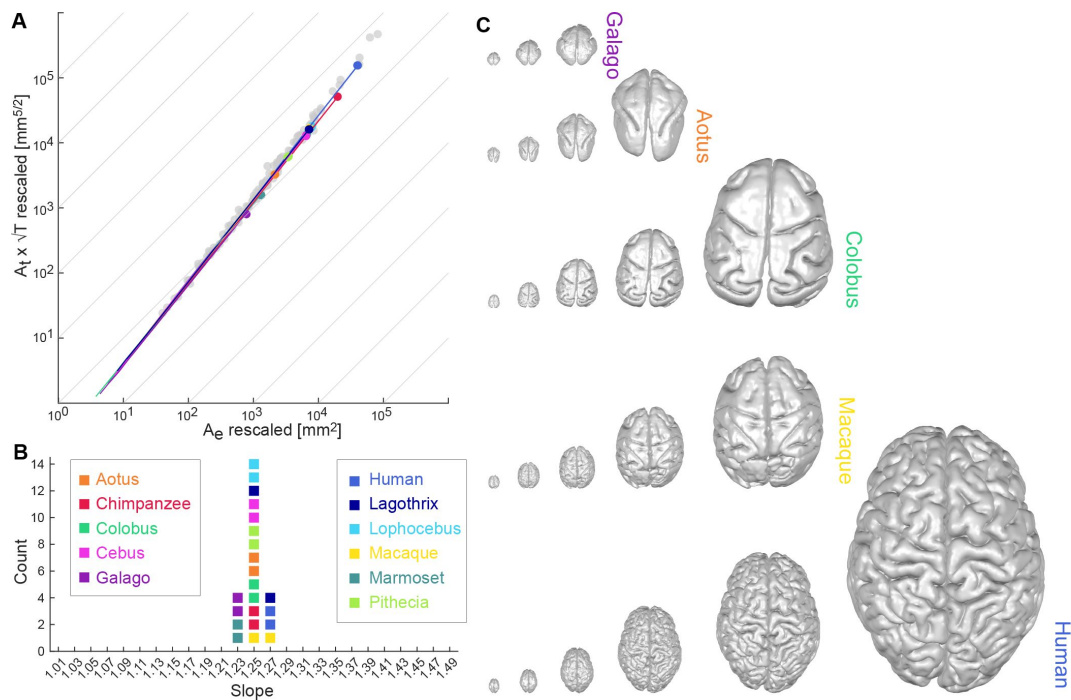


Figure 2

Universal scaling law for 11 coarse-grained primate brains.

A: Coarse-grained primate brains are shown in terms of their relationship between $\log_{10}(A_t \times \sqrt{T})$ vs. $\log_{10}(A_e)$. Each solid line indicates a cortical hemisphere from a primate species. Thin grey lines indicate a slope of 1 for reference. Filled circles mark the data points of the original cortical surfaces. Grey data points are plotted for reference and show the comparative neuroanatomy dataset across a range of mammalian brains [5]. **B:** Slopes (α) of the regression of data points in A for each species. For each species, two data points are shown, one per hemisphere. Colour-code for each species is maintained throughout the whole figure. **C:** Rescaled brain surfaces visualised for five example species at different levels of coarse-graining.

provides a detailed derivation and demonstration of the superior sensitivity and specificity of these new morphometric measures. The advantage of using this framework here is that we can assess the offset K (and shape term S) without interference by isometric size effects, including any re-scaling procedures. In other words, the following results are independent of the isometric size of the brain surfaces analysed.

One can directly compute the values of K and S for any cortex-like object, thus ascribing to it a point in the $K \times S$ plane. But a fuller expression of a particular shape is captured by the *trajectory* of said object as a function of coarse-graining in the $K \times S$ plane. This is a very convenient and informative way of summarising shape: self-similar objects correspond to straight trajectories as the $K \times S$ plane is in log-log space. In particular, objects without any folds or protrusion (i.e., convex, such as the box with finite thickness in [Fig. 3 A](#)) correspond to the line $K = -\frac{1}{9}S$, as $A_e = A_t$ for all levels of coarse-graining. Horizontal trajectories (constant K) represent fractal objects with fractal dimension $d_f = 2.5$ ([Fig. 3 B](#)). And finally, in the $K \times S$ plane, a shape is said to be “universal” for a set of objects when their trajectories overlap, so that they can all be regarded as coarse-grained versions of one another ([Fig. 3 C](#)).

From this perspective, the regularity observed in primate cortices is remarkable ([Fig. 3 D](#)). The value of K is nearly invariant in all cases, in parallel to what was found in [\[4\]](#). But, over all levels of coarse-graining, K also remains near-invariant in all *trajectories* as S decreases, resulting in a set of horizontal lines that largely overlap with each other and other mammalian species. The variance in K across scales and all 11 species is < 0.01 , which is at least an order of magnitude lower than the variance in S . Primate brains therefore have all three characteristics of self-similarity, fractality (with $d_f = 2.5$), and universality (invariant K for all scales and species) at the same time.

Thus, coarse-grained primate cortical shapes are morphometrically similar to, and in terms of the universal law, ‘as valid as’ actual existing mammalian cortices³. In contrast, we tested various non-brain shapes, and while e.g. the walnut, and bell pepper shapes form (partially) straight lines, they vary in both K and S (see [Suppl. S6](#)). These shapes may have a fractal regime, but their fractal dimension is not 2.5, nor is their shape similar to primate or mammalian brains in terms of K or S . Furthermore, [supplementary S7](#) underscores the algorithmic and statistical robustness of these results using multiple realisations of the coarse-graining procedure on the same shape. In this framework, our main result can thus be expressed simply: for all the cortices we analysed, and for none of the non-cortices, coarse-graining will leave K largely unaffected, while morphological complexity S will decrease.

3.3 Morphometric measures as functions of scale reveal scale-specific effects of ageing

In the final part of our work, we show how our algorithm and the associated new understanding of brain morphology may become useful in applications. As an example, we will focus on how the ageing process affects human cortical morphology across scales. In [Fig. 4 A](#), we compare the total surface area $A_t(\lambda)$ as a function of scale λ for a young (20 year old) vs. an old (80 year old) group of human brains. Strikingly, the difference in A_t between the groups takes a U shape, where the strongest effect is seen at approx 2 millimeter (older subjects have higher A_t). For scales over approx 5 mm, and under 0.5 mm the difference become relatively small, suggesting the ageing process has less effect on the largest and smallest cortical morphological features. Finally, we reproduced these results in an independent dataset in [Suppl. S8.2](#).

In this particular example, the dramatic scale-dependency of morphological measures can be visually and intuitively understood by looking at the reconstructed surfaces at each scale: [Fig. 4 B](#) shows some coronal slices of the cortical surface. At scale 0.27 mm, the gyri in the younger subjects are densely packed, but the older subjects show the expected widening between gyral

walls and decrease in gyral surface area at the crown (see e.g. [28, 26] for recent investigations and references therein). At 1.86 mm, the younger cortices have already partially “melted”, erasing most small sulci between the densely packed gyri. In the older humans, however, the gyri are less dense, the sulci more open, and thus, at 1.86 mm, most gyri and sulci have not been erased yet. At scale 7.94 mm, both young and old brains have “melted” down to similarly near-lissencephalic shapes. For a more detailed multiscale investigation over the entire human lifespan, please refer to our new preprint [?]

More broadly, one can regard the melting process as a way of determining how cortical area is allocated across different scales. As the cortex ‘melts’, the contributions to the total area from features smaller than the cut-off scale are eliminated. In the example in Fig. 4, for instance, we can say about half ($10_{5-4.7} = 10_{0.3} \approx 2$) the total area in the 80 y.o. cortices is present in features smaller than 4 mm.

From an application perspective, this example here illustrates clearly that the surface area difference between older and younger subjects at “native” scale (i.e. original freesurfer surfaces) is negligible (effect size smaller than 2 standard deviations). However, in our analysis across scales, there is a clear optimal scale at approx. 2 mm where the effect size is maximised between older and younger subjects (effect size is approx-8 standard deviations). For most classification applications, the scale-dependent morphometrics therefore represent a huge advance over the native scale.

4 Discussion

We have devised a new way of expressing the shape of the mammalian cerebral cortex, as the flow in the values of morphometric measures over a range of spatial scales. This was achieved by coarse-graining cortical surfaces, erasing morphological features smaller than the specified scale, while preserving surface integrity. After applying this method to the cortices of 11 primate species, we have shown that all these diverse shapes are approximations of *the same archetypal self-similar (fractal) shape*. Most of their morphological diversity can be ascribed to the species-specific ranges of spatial scales over which each approximation is valid, with the smallest scale being an invariant multiple of cortical thickness. This was a proof-by-construction of fractality, a step beyond the usual box-counting approach, which also yields scale-dependent morphometrics. As a proof-of-principle we showed that healthy human ageing has highly scale-dependent effects in a range of morphometrics.

Compared to previous literature, we can summarise our main contribution and advance as follows: (i) We are showing for the first time that representative primate species follow the exact same fractal scaling – as opposed to previous work showing that they have a similar fractal dimension [29, 30], i.e. slope, but not necessarily the same offset, as previous methods had no consistent way of comparing offsets. (ii) Previous work could also not show direct agreement in morphometrics between the coarse-grained brains of primate species and other non-primate mammalian species. (iii) Demonstrating in proof-of-principle that multiscale morphometrics, in practice, can have much larger effect sizes for classification applications. This moves beyond our previous work where we only showed the scaling law across [4] and within species [6], but all on one (native) scale with comparable effect sizes for classification applications [6].

In simple terms: we know that objects can have the same fractal dimension, but differ greatly in a range of other shape properties. However, we demonstrate here, that representative primate brains and mammalian brain indeed share a range of other key shape properties, on top of agreeing in fractal dimension. This suggests a universal blueprint for mammalian brain shape and a common set of mechanisms governing cortical folding. As a practical additional outcome of our

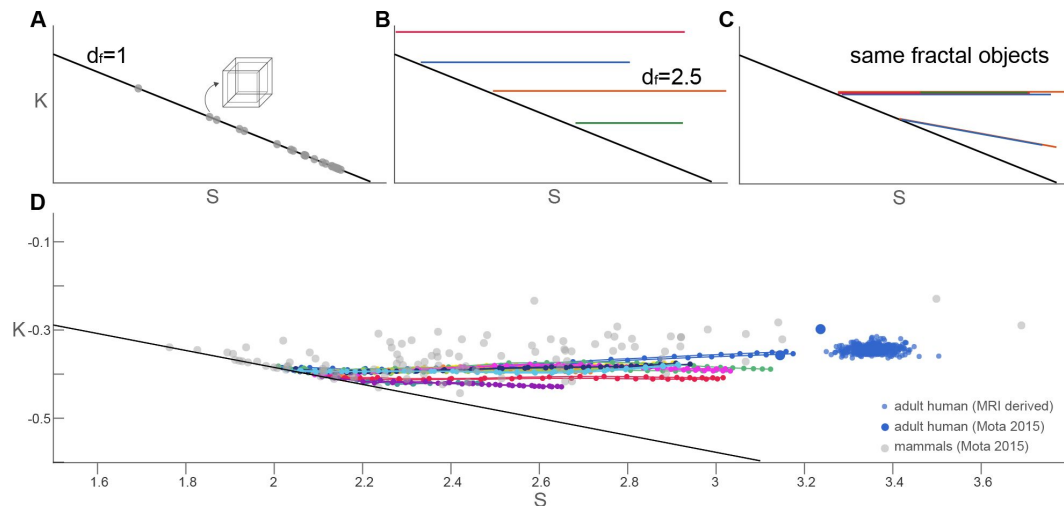


Figure 3

Trajectories of coarse-grained primate cortices and other mammalian and human brains in $K \times S$ plane.

A: Straight trajectories indicate self-similarity (described by a scaling law). In particular, the black line here indicates objects with $A_e = A_t$ for all scales, such as the box of finite thickness with a fractal dimension $d_f = 1$ (grey data points). This line is reproduced in all subpanels for reference. **B:** Morphological trajectories of multiple hypothetical fractal objects are shown which. A flat trajectory (constant K) correspond to $d_f = 2.5$ in this space. However, these objects are clearly different fractals with different values of K . **C:** Hypothetical objects with overlapping straight morphological trajectories indicate multiple realisations of the same fractal object. Flat trajectories (constant K) correspond to $d_f = 2.5$. The two hypothetical objects with a decreasing $K(S)$ correspond to $2 < d_f < 2.5$. **D:** Projecting our actual data into the normalised $K \times S$ plane showing the coarse-grained primate brains (same as in Fig. 2) as data point connected with solid lines (colour-code same as Fig. 2). Different mammalian brains are shown as grey scatter points, and adult human data points are blue.

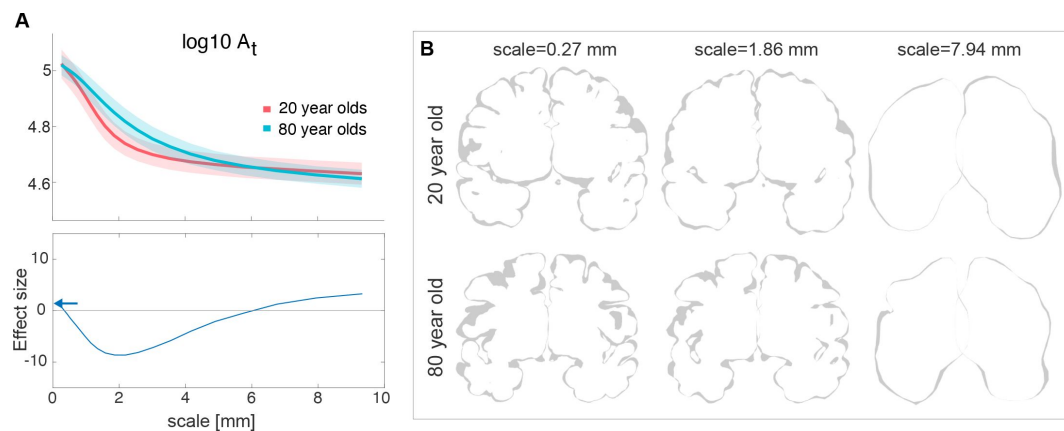


Figure 4

Human ageing shows differential effects depending on spatial scale.

A: Top: $A_t(\lambda)$ is shown for a group of 20-year-olds (red, $n=27$) and a group of 80-year-olds (blue, $n=86$). Mean and standard deviation are shown as the solid line and the shaded area respectively. Bottom: Effect size (measured as ranksum z-values) between the older and younger groups at each scale. Positive effect indicates a larger value for the younger group. Blue arrows indicate the effect size at “native scale” i.e. using the original freesurfer grey and white matter meshes. **B:** Coronal slices of the pial surface of an example 20-year-old subject and an 80-year-old subject at different scales (columns).

study, we could show that our novel method of deriving multiscale metrics of brain shape can differentiate subtle shape changes much better than the metrics we have been using so far at a single native scale.

Expressing cortical morphology as a function of scale is more detailed than a list of summary morphometric measures, and more informative than the mere listing of every sulcus and gyrus. We propose this new syntax as the basis for a more rigorous characterisation of brain morphology and morphological changes. A clear advantage is that some biological processes may only act on a specific spatial scale, leaving other scales untouched (ageing in our example). By disambiguation of the spatial scale, it allows for an extra dimension of understanding, and tracking of biological processes. In the future, this approach can also be extended to cortical development and to various degenerative [6] and congenital [27] neuropathic conditions, especially if combined with a regionalised version of this method applied to specific cortical regions [7] or local patches [8].

Empirically, the main result of this paper is the demonstration of a universal self-similar scaling (Eqn. 3) for primate, and presumably mammalian cortices. There are two aspects of this universality: first that for each and every cortex the value of K remains the same for all scales as one removes substructures smaller than a varying length scale (or equivalently, that the fractal dimension is almost exactly 2.5 in all cases). Second, that the value of K for the cortices of different species is approximately the same, as previously observed (Eqn. 1) across species [5] and individuals [6]. One could imagine a set of shapes for which one but not the other aspect of the universality in K holds true. However, the fact that both universalities hold true is significant. It suggests the existence of a single highly conserved mechanism for cortical folding, operating on all length scales self-similarly with only a few morphological degrees of freedom. It also hints at the possibility of deriving cortical scaling from some variational principle. Finally, this dual universality is also a more stringent test for existing and future models of cortical gyrification mechanisms at relevant scales, and one that moreover is applicable to individual cortices. For example, any models that explicitly simulate a cortical surface could be directly coarse-grained with our method and compared to actual human and primate data provided here.

The scaling itself does not imply or favour any particular proposed gyrification model (ours [5] included), and all results in this paper are agnostic about this choice. Indeed, our previously proposed model [5] for cortical gyrification is very simple, assuming only a self-avoiding cortex of finite thickness experiencing pressures (e.g. exerted by white matter pulling, or by CSF pressure). The offset K , or ‘tension term’, precisely relates to these pressures, leading us to speculate that subtle changes in K correlate with changes in white matter property [6, 27]. In the same vein of speculation, the scale-dependence of K shown in this work might therefore be related to different types of white matter that span different length scales, such as superficial vs. deep white matter, or U-fibres vs. major tracts. However, there are also challenges to the axonal tension hypothesis [31]. Indeed, white matter tension differentials in the developed brain may not explain location of folds, but instead white matter tension may contribute to a whole-brain scale ‘pressure’ during development that drives the folding process overall. Aside from speculations about the biological interpretation, the simplicity of the highlighted scaling law parallels many complex phenomena in nature that display simple and universal scaling that can be derived from first principles [32, 33, 34]. In addition, recent results suggest simplicity and symmetry are generically favoured on statistical-ensemble grounds by evolution [35]. Our model correctly predicts the scaling law (Eqn. 1), but a more complete explanation for cortical gyrification is probably far more complex [36] than can be accounted by such a simple model.

One specific example of said complexity are the exact patterns, locations, depth, and features of gyri and sulci. We know such patterns to be, for example, variable but also somewhat heritable in humans, whilst in macaques such patterns are relatively preserved across the species. Our work does not explain any of these observations, nor are the coarse-grained versions of human brains

supposed to exactly resemble the location/pattern/features of gyri and sulci of other primates. The similarity we highlighted here are on the level of summary metrics, and our goal was to highlight the universality in such metrics to point towards highly conserved quantities and mechanisms.

More broadly, the interaction between brain development and evolution may also benefit from a scale-specific understanding. This may be important in elucidating what in cortical morphology is selected for by evolution, what is determined by physics; what is specified by genes, and what is emergent. For example, one can estimate the number of structural features at each scale ($A_t(\lambda)$ as multiples of $A_0(\lambda)$), and it will be interesting to correlate this number to other quantifiers of cortical structure, such as number of neurons [4], number of functional areas [37] or the number of cortical columns [38], possibly over different stages of development. Generally, the larger the cortical feature (i.e. from gyri to functional areas to lobes to hemispheres), the earlier during development it appears [39, 40], and more broadly it is conserved over kinship [41] and phylogeny [42, 43]. It thus seems likely that comparative neuroanatomical methods [44, 45] may be directly used to identify and contrast structures in coarse-grained cortices of more highly gyrified species with their analogues in less-gyrified species. One could then perhaps specify when evolution conserves and when it invents old and new cortical features.

Our work here was limited to summary descriptors of entire cortical hemispheres, but future work will explore extensions of these methods to lobes and cortical areas, similarly to [7, 8]. This will generate precise characterisations of the morphological differences between phylae and across developmental stages, and perhaps pinpoint the time and location of morphological changes leading to congenital and neurodegenerative conditions. Ultimately, we hope this new framework for expressing and analysing cortical morphology, besides revealing a hitherto hidden regularity of nature, can become a powerful tool to characterise and compare cortices of different species and individuals, across development and ageing, and across health and disease.

Acknowledgements

We thank members of the Computational Neurology, Neuroscience & Psychiatry Lab (www.cnnp-lab.com) for discussions on the analysis and manuscript, and Dirk Jan Ardesch and Martijn van den Heuvel for helpful discussions and NHP brain surface data. P.N.T. and Y.W. are both supported by UKRI Future Leaders Fellowships (MR/T04294X/1, MR/V026569/1); Y.W. and K.L. are further supported by the EPSRC (EP/Y016009/1, EP/L015358/1). B. Mota is supported by Fundação Serrapilheira Institute (grant Serra-1709-16981) and CNPq (PQ 2017 312837/2017-8).

Supplementary

S1 Primate species and their cortical surface reconstruction

With the exception of the marmoset data, all other cortical surface reconstructions were based on healthy individual brains.

S1.1 Human data

To study healthy human adults, we used the Human Connectome Project (HCP) MRI data, available at <https://db.humanconnectome.org/> [46], obtained using a 3T Siemens Skyra scanner with 0.7 mm isotropic voxel size. We used the HCP minimally pre-processed FreeSurfer data output, which provided the pial and white matter surface meshes we required. We selected five random subjects in the age category 22-25 y.o. and show one example subject (103414) in the main text, and the remaining subjects in [Suppl. S4](#).

To study the alterations associated with human ageing, we used T1 and T2 weighted MRI brain scans from The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset (available at <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/> [47, 48]). Cam-CAN used a 3T Siemens TIM Trio System with 1 mm isotropic voxel size (for more details see [47, 48]). From the Cam-CAN dataset we retained 644 subjects that successfully completed preprocessing (with FreeSurfer *recon-all*) without errors. From these subjects we selected all subjects between the ages of 17-25 inclusive (forming the 20 y.o. cohort, $n=27$); we also selected all subjects between the ages of 77-85 inclusive (forming the 80 y.o. cohort, $n=86$).

To confirm the ageing results, we also obtained an independent dataset from the Nathan Kline Institute (NKI)/Rockland sample [49] (http://fcon_1000.projects.nitrc.org/indi/pro/nki.html) using the same procedure as described for the CamCAN dataset.

The MR images of both CamCAN and NKI datasets were first preprocessed by the FreeSurfer 6.0 pipeline *recon-all*, which extracts the grey-white matter boundary as well as the pial surface. These boundaries were then quality checked by visual inspection for particularly the young and old cohorts and manually corrected where needed.

For all three datasets, we obtained the pial and white matter surfaces for further analysis. In the current work, the analysis is always hemisphere based, as in our previous work [5, 6]. We did not perform a more regionalised analysis, which is also possible [7, 8]. Future work using the principle demonstrated here can be directly extended to derive regionalised measures across scales.

S1.2 Non-human primate data

S1.2.1 Macaque

Rhesus Macaque MRI scans were carried out at the Newcastle University Comparative Biology Centre. Macaques were trained to be scanned while awake and sat in a primate chair. Both T1 weighted MP-RAGE and T2 weighted RARE sequences were acquired, using a vertical MRI scanner (Biospec 4.7 Tesla, Bruker Biospin, Ettlingen, Germany).

Scans were processed using a custom macaque MRI pipeline, incorporating ANTs, SPM, FreeSurfer and FSL. Briefly, this involved the creation of precursor mask in SPM, denoising (ANTs *DenoiseImage*) and debiasing (ANTs *N4BiasFieldCorrection*, and Human Connectome *BiasField-Correction* script), creation of a final mask in SPM and then processing in FreeSurfer (using a modified version of the standard FreeSurfer processing pipeline). Reconstructed pial and white matter surfaces were visually quality controlled in conjunction with the MR images.

S1.2.2 Marmoset

The marmoset MRI structural scan was collected as part of the development of the NIH marmoset brain atlas [50, 51]. Data was collected *ex vivo* from a 4.5-year-old male marmoset using a T2-star weighted 3D FLASH sequence using a horizontal MRI scanner (Biospec 7 Tesla, Bruker Biospin, Ettlingen, Germany).

A total of ten scans were collected and averaged into one final image. In combination with scans from other modalities, cortical boundaries were manually delineated on each coronal slice. Boundaries were then refined through comparisons with other atlases. Volumetric data was then converted to surfaces using a custom pipeline involving an intermediate generation of high-resolution mesh data [52], decimation [53], and remeshing. Reconstructed pial and white matter surfaces were visually quality controlled in conjunction with the MR images.

S1.2.3 Other NHP

The remaining NHP MRI and subsequent brain surface extraction is detailed in [54], [55], and provided to the authors in a processed format. Briefly, a range of specialised scanners were used to acquire optimal images for each species. FreeSurfer 6.0 with some modifications was used for surface reconstruction, complemented by FSL, ANTS, and Matlab. All surfaces were visually inspected for accuracy and consistency across datasets.

S1.3 Comparative neuroanatomy data

The comparative neuroanatomy dataset for different mammalian species is the same as previously published [5]. Note that for this dataset, we only had numerical values for the total and exposed surface area, as well as average cortical thickness estimates. We did not perform any analysis across scales in this dataset (hence surfaces were not required), but only used it as a reference dataset.

S2 Coarse-graining algorithm

The core coarse-graining algorithm underpinning our analyses takes pial and white matter surfaces from the cortical surface reconstruction (Suppl. S1) as inputs and at any specified spatial scale λ “voxelises” the gray matter ribbon at the specified resolution. To achieve this, we set up a 3D voxel grid, where each grid voxel is of size $\lambda \times \lambda \times \lambda$.

In detail, we assign all voxels in the grid with at least four corners inside the original pial surface to the pial voxelization. We then assign voxels with all eight corners inside the original white matter surface to the white matter voxelization. Finally, subtracting the white matter voxelisation from the pial voxelisation, we obtain the grey matter voxelisation (Fig. 1B bottom row). The pial surface voxelisation is designed such that neighbouring gyri can fuse if their separation is smaller than the scale of interest, whilst not growing the cortex outwards. The white matter surface voxelisation allows the walls of each gyrus to thicken and fuse inwards. Visually, this process looks as if the cortex is “thickening” inwards and smoothing on the outside.

From the voxelised cortex at each scale λ , we can then obtain coarse-grained pial and white matter surfaces, and extract estimates of global morphometric measures such as the average cortical thickness $T(\lambda)$, the total cortical surface area $A_t(\lambda)$, and the exposed surface area $A_e(\lambda)$. For each λ , we derived an outer isosurface equal to 0.5 for the pial voxelisation (voxel values are 1 within the voxelised pial surface and 0 otherwise). This isosurface is then defined as the coarse-grained pial surface at this scale. The surface area of this isosurface is used as $A_t(\lambda)$. The exposed surface area $A_e(\lambda)$ is subsequently derived from the convex hull of the pial isosurface. Finally, the cortical thickness $T(\lambda)$ is estimated as $\frac{V_G(\lambda)}{A_t(\lambda)}$, where $V_G(\lambda)$, which is the estimated grey matter volume,

derived from the number of grey matter voxels, is multiplied by the voxel volume. These global morphometric measures are summary statistics of the shape of the brain at each particular scale, capturing information about both their intrinsic geometry ($A_t(\lambda)$, $T(\lambda)$) and extrinsic geometry ($A_e(\lambda)$). In this manner, for each cortex, we obtain not just one set of summary morphometric measures, but rather a set of measures as functions of λ . A detailed walk-through of the coarse-graining algorithm and estimation of morphometric measures is provided on Github: <https://github.com/cnnp-lab/CorticalFoldingAnalysisTools/blob/master/Scales/fastEstimateScale.m>.

Note that although this process is inspired by the box-counting algorithm, it is different from box-counting and related convolution-based algorithms: we do not simply apply successive convolutions with an increasing kernel size (or equivalent), which effectively would achieve a uniform and spatially isometric “smearing” of the original cortical shape to a given scale, rather than a targeted erasure of *surface* details smaller than said scale. As a result, this method yields

well-defined and well-behaved white and gray matter surfaces. Thus, one can apply all the usual analytical tools to these realisations that are applicable to actual cortices. Note that our approach is more comparable in its principles to the calculation of the outer smoothed pial surface in FreeSurfer [56], which utilises a dilation *and* erosion convolution to effectively erase details below a certain scale. Of course, our proposed procedure is not the only conceivable way to erase shape details below a given scale; and we are actively working on related algorithms that are also computationally cheaper. Nevertheless, the current version requires no fine-tuning is computationally feasible and conceptually simple, thus making it a natural choice for introducing the methodology and approach.

Given how broadly it has been verified, we expect the observed universality in cortical self-similar scaling to be robust to the details of the coarse-graining algorithm. It would be very informative to test this proposition in future. For example, an alternative method inspired by [57] could be implemented, eschewing voxelization and dealing only with the flow of nested surfaces with self- and mutual- avoidance explicitly implemented. Going in the opposite direction, more detailed models for the mechanisms of cortical folding (see e.g. [58]) can be regarded as a type of reverse melting, and could perhaps be implemented and tested in a similar fashion as fine-graining procedures.

S3 Influence of original image resolution

In this supplementary section, we want to demonstrate the relatively weak effect of the original image resolution on our analysis outputs. To this end, we used five example HCP subjects, who were scanned at 0.7mm isotropic image resolution, and downsampled their images to 1mm isotropic images. We then proceeded with our analysis using two freesurfer outputs. (1) the HCP freesurfer pipeline output optimised for the 0.7mm resolution, and (2) a standard freesurfer pipeline output on the 1mm downsampled images. We proceeded with these two sets of surfaces in our analysis and show the resulting morphology measures in **Fig. S3.1**.

We observe a relatively weak difference between these two sets of inputs/surfaces. Both sets largely follow the same trajectory across scales. Especially in the exposed area, the within and between subject differences are noticeably larger than between image resolutions. In total area and thickness, some small but systematic differences are seen in all subjects between the scales of 1- 2mm. These are most likely differences in the cortical morphology reconstruction in the freesurfer surfaces using the two different resolution images as input. However, in none of these resulting morphology measures do we see an artifact specifically at 0.7 or 1mm. Any differences between image resolutions only result in subtle changes in the freesurfer meshes, which are smooth. *Our analysis method therefore has no direct dependency on the image resolution*, as our inputs are these smooth freesurfer meshes.

S4 Scaling properties by species

S4.1 Obtaining the scaling law

From the coarse-grain procedure (**Fig. 1**), we obtain surface meshes for the pial and white matter surface at each spatial scale. From those, we derive exposed area, total pial surface area, and average cortical thickness as described in Methods. However, the coarse-graining procedure, by itself, barely changes the exposed surface area, and only changes the total surface area minimally (**Fig. S4.1 A**). As the voxel size changes at each scale, it only starts to affect the exposed area at very large scales, where effectively the voxels are no longer a good description of the shape of the skull. Thus, if we scatter the raw data points from the coarse-graining procedure in the plane of the scaling law, there is barely any variance in the data (**Fig. S4.1 B**). Even after zooming in, we see an almost vertical line (**Fig. S4.1 B**). This is expected and is not evidence for or against our hypothesis.

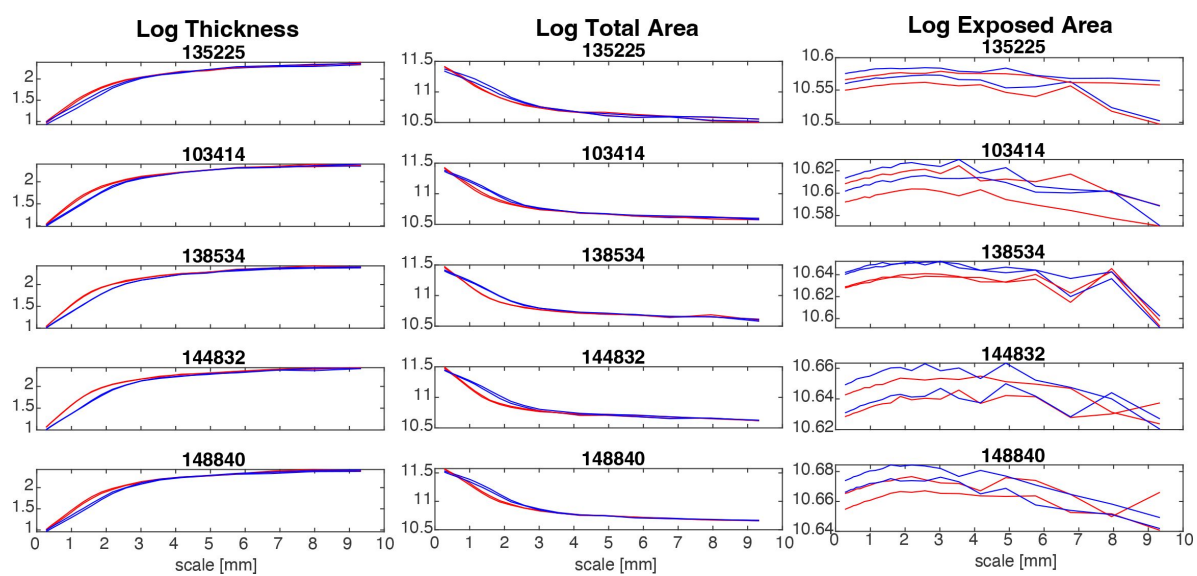


Figure S3.1

Effect of using different original image resolution in five example HCP subjects.

In all plots, red lines indicate an original image resolution of 0.7mm isotropic, whereas blue line indicate an original image resolution of 1mm isotropic. Both hemispheres are shown for each subject.

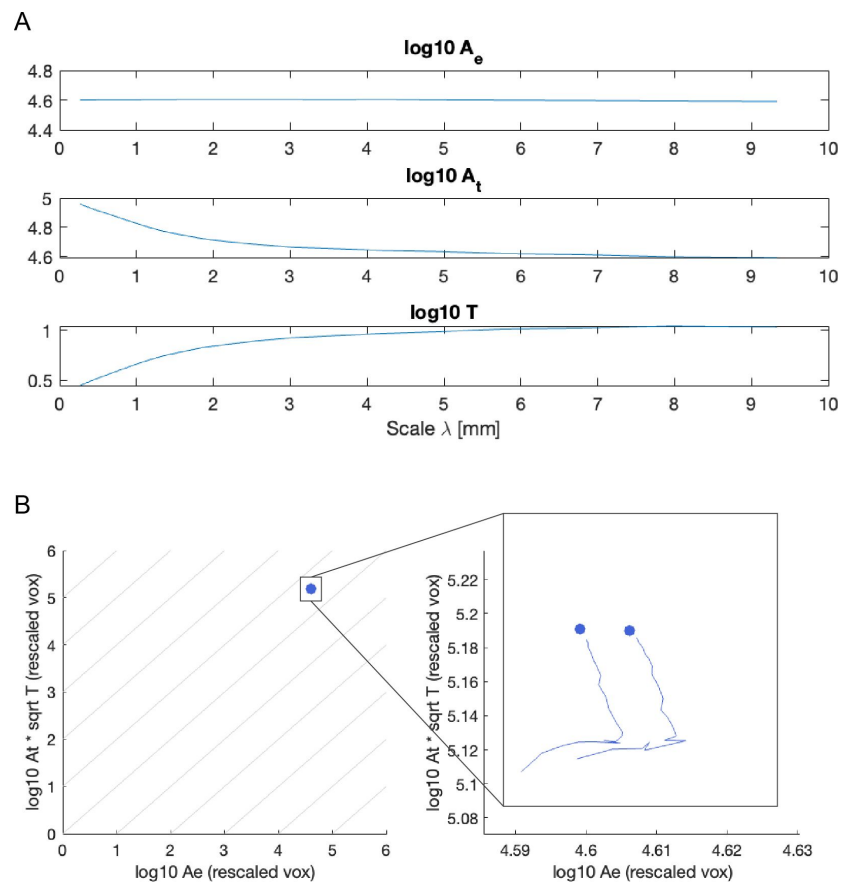


Figure S4.1

Unscaled quantities cannot be used to verify scaling law.

A: The exposed surface area A_e barely changes across scales, and A_t only changes minimally. **B:** Plotted in the scaling law plane (as **Fig. 2**) the data points barely have any variance, and overlap each other substantially. Even after zooming in, the trace for the coarse-graining procedure (solid line) is virtually a vertical line (with a small artifactual 'tail' coming from very large voxel sizes).

Instead, we need to transform the data into a perspective that makes sense to be seen in the scaling law plane. Instead of thinking of the coarse-graining procedure as a process that re-renders the cortex at increasing voxel sizes, we can instead think of the procedure as rescaling the original cortical mesh into increasingly smaller sizes, and re-rendering it with the same fixed voxel size. The analogy using Britain's coastline is that instead of measuring the coastline with increasingly smaller rulers, we resize the map of the coastline to increasingly smaller sizes, but keep the size of the ruler the same. Both procedures are equivalent and produce the same fractal dimension.

To achieve this procedure, we re-scaled our measurements of A_e , T and A_t by the voxel size (λ) and a fixed factor (l_r):

$$\begin{aligned} A_e^r &= \frac{A_e}{(\lambda \times l_r)^2} \\ A_t^r &= \frac{A_t}{(\lambda \times l_r)^2} \\ T^r &= \frac{T}{(\lambda \times l_r)}. \end{aligned} \quad (4)$$

As we used isometric cubes as voxels, the voxel size refers to the length of a single side. E.g. $\lambda = 1$ if we used a isometric $1 \times 1 \times 1 \text{ mm}_3$ voxel.

$$l_r = \frac{1}{\lambda_s} \times \frac{I_s}{I_o}, \quad (5)$$

l_r is a fixed factor for each cortical hemisphere, and does not change with λ . We use it to systematically shift all the data points within a range, such that the re-scaled quantities are not larger than those from the original cortical meshes. One can easily verify that l_r will not change the slope or offset of any scaling law, but simply represents a constant shift to all data points. In our data, some of the re-scaled quantities would indeed be larger than those from the original cortical meshes, as the voxel size we choose is limited at the smaller end only by computational resources. In other words, we can use very small voxel sizes (relative to the mesh), which after re-sizing would yield very large values of A_e , A_t , and T . To avoid this, we chose l_r simply as the ratio of the I (isometric term) of the mesh at the smallest scale we used relative to the original mesh, divided by the λ of the smallest scale:

where λ_s is the smallest voxel size used for a particular cortex, I_s is the corresponding I for this cortex at the smallest voxel size.

Finally, I_o is the I term for the original cortical mesh. Indeed, the ratio of $\frac{I_s}{I_o}$ is always close to, but larger than one in our dataset. Thus, we can see in **Fig. 2 A** that most traces start very close to the original data point, indicating that our finest scale is reconstructing the original surfaces well.

Note that the re-scaling is isometric, meaning that it only affects I , but does not change the data in the $K \times S$ plane (**Fig. 3**). Rescaling by a factor proportional to λ_2 can therefore be understood as distributing the data points along the I axis, while l_r can be understood as fixing the position in the I axis relative to the I of the original mesh.

Fig. 2 A is produced with these rescaled quantities as described above. The only final step in producing **Fig. 2 A**, and in calculating the associated slopes, is the removal of artifactual data points where $\frac{A_t}{A_e} < 0$, which can occur at very large voxel sizes relative to the cortical mesh.

The algorithmic implementation in MATLAB can be found on Github: <https://github.com/cnnp-lab/CorticalFoldingAnalysisTools/blob/master/Scales/fastEstimateScale.m>, as part of our Cortical Folding Analysis MATLAB package <https://github.com/cnnp-lab/CorticalFoldingAnalysis> which also has been recently updated with a graphical user interface.

S4.2 Species-specific details

In the following, we will show the detailed data for each species in terms of their scaling behaviour in **Fig. S4.2**. Videos for all species, showing the pial surface at each scale can be found under <https://bit.ly/3CDoqzQ> for review purposes. Final versions of all underlying data, analysis code, and videos will be published on Zenodo and eLife upon acceptance of the paper.

Given the demonstrated overlap between species, and if their cortices are all approximations of the same form, how can one tell apart their cortices? The answer is that all approximations have a range of validity, which varies between cortices. For a gyrified cortex of area A_t , the coarse-graining will remove details of ever-increasing scale, lowering $A_t(\lambda)$ until attaining lissencephaly for $A_e(\lambda_{lys}) = A_t(\lambda_{lys})$. Indeed, it follows from rewriting *Eqn. (3)* in the form of *Eqn. (2)* that a given cortex' shape will be comprised of self-similar structures with areas ranging from $A_0 = g_{-5}A_t$ at their smallest to A_t at their largest, where g is the gyrification index $g = \frac{A_t}{A_e}$. Whenever this self-similar scaling is valid, A_0 acquires a further interpretation as the typical size of the smallest structures in a cortex: patches smaller than that must be approximately smooth. Consequently, $N_{structures} \simeq \frac{A_t}{A_0} = g^5$ estimates the number of morphological features in each cortex (and adds a new interpretation for the gyrification index). For example, we estimate the human in our dataset to have about 105 morphological features in each cortical hemisphere, and the galago to have about 4 such morphological features. The corresponding $N_{structures}(\lambda)$ estimates how this number changes over coarse-graining. *Suppl. S5* later provides a more detailed discussion on this topic.

S5 Morphometric relations and the range of validity of the fractal approximation

There are many geometrical quantities that describe aspects of entire cortical hemispheres. But most information contained in such summary morphometric measures is captured, exactly or to good approximations, by the three used in *Eqn (1)*: the pial (or total) surface area A_t , exposed surface area A_e , and average cortical thickness T . Other quantities, like the gyrification index $g = \frac{A_t}{A_e}$, or the Grey Matter and Total volumes, can be expressed as products of power laws of these quantities; and the logarithm of products of power laws are linear combinations of the logarithms of the constituting variables, with their exponents as coefficients. Thus, the morphology of a given cortex can be fairly summarized as point in a 3-dimensional morphometric space with components given by $\log A_t$, $\log A_e$ and $\log T^2$ (the last exponent guarantees all axes have the same dimension of $\log[Area]$).

This logarithmic structure guarantees that the quantities denoted by products of power laws of the original variables correspond to vectors in the morphometric space: the increase and decrease of their values occur along these vectors, and the planes perpendicular to each vector denote all configurations with the same value for the associated variable. For example, $G = \log g = \log A_t - \log A_e$, the point in the morphometric space associated with the gyrification ratio value $\frac{A_t}{A_e}$, defines a displacement along a vector with coefficients $\{1, -1, 0\}$.

The quantities K , S and I used in Sec. 3.2 likewise correspond to displacements along specific directions in morphometric space, which are all orthogonal to one another. These can be normalized, so that the sum of their squared coefficients equals unity. In this case, expressing cortical shape in the morphometric space in terms of the original variables or the new variables amounts simply to a rotation: a change of orthonormal base.

Figs. 2 and **3** can be then regarded as particular 2D snapshots, taken from a certain direction, of a 3D set of points.

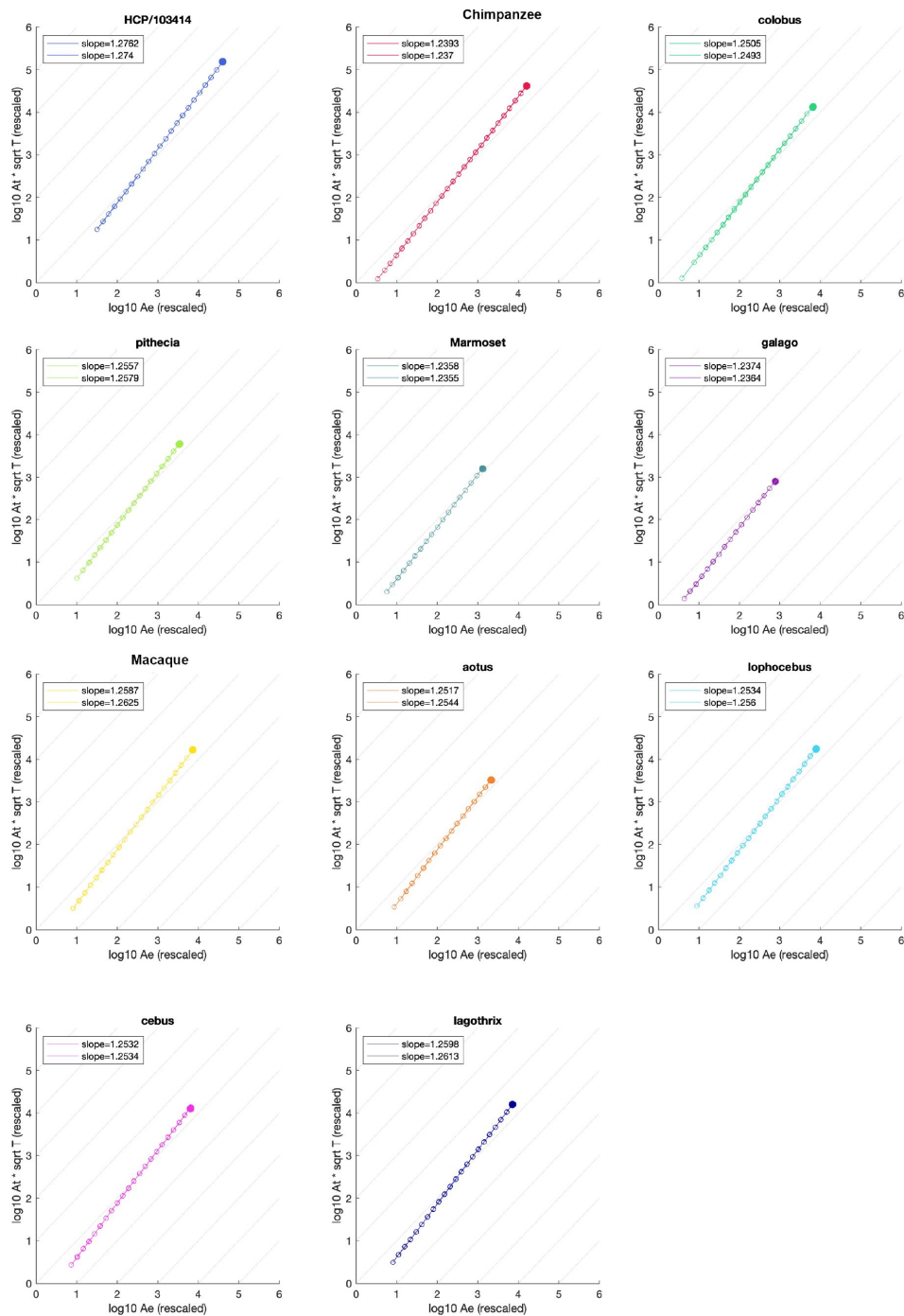


Figure S4.2

Detailed scaling plots for each species.

Filled circle is the original mesh, empty circle are data points from the coarse-graining algorithm. Empty circles are connected by a line for visualisation. Two hemispheres are analysed separated for each species, although data points overlap substantially in plot. Slope estimates are given at top left corner in each plot.

Of particular note, those vectors with a sum of coefficients equal to zero correspond to dimensionless variables. Any such vector is perpendicular to the I direction, and lie on the $K \times S$ plane.

In this framework, we can picture the step-wise coarse-graining of a cortex, as described in Sec. 3.1, as a trajectory in this morphometric space. Empirically, Sec. 3.1, as codified by [Eqn. 3](#), find that the trajectories in morphometric space for all studied primates are linear, and largely overlap along a line of constant K . For cortical morphology, the first fact implies scale-invariance, the second implies universality.

Aging, development, and the progression of neurodegenerative conditions likewise each correspond to different morphometric trajectories.

Now consider a morphometric trajectory, corresponding to the coarse-graining of a cortex up to the point of lissencephaly, i.e., to the spatial scale λ_{lys} such that $A_t(\lambda_{lys}) = A_e(\lambda_{lys})$. In the idealized case (but very close to empirical, as seen in Sec. 3.1), all points along the trajectory should follow [Eqn \(3\)](#), starting at the original values for the morphometric measures and ending at the intersection of the $K = \text{constant}$ coarse-graining trajectory and the $g = 1$ line that defines the limit for lissencephaly (points with $g < 1$ are geometrically possible, but are largely avoided by the trajectories of actual cortices, although not by those of all shapes; see S6.1). This trajectory spans a range of values for each morphometric measure: for dimensionless morphometric measures, such span is fully specified by [Eqn \(3\)](#). For all others, one needs also to specify the voxel rescaling. The scheme described in [Sec.S4.1](#) simply guarantees that, for a constant

$k = A_t A_e^{-\frac{5}{4}} T^{\frac{1}{2}}$, the fundamental area element $A_0 = \frac{T^2}{k^4} = \frac{A_e^5}{A_t^4}$ (and thus also the average thickness T) is kept constant for all realisations of the coarse-graining process. We can regard these as approximations of the same original cortex, all drawn with the same resolution, but in ever smaller isometric sizes.

This choice of spatial scale then allows our identification of A_0 as the typical size of the smallest morphological features in a given cortex. Equivalently, it is also the area of the largest possible lissencephalic cortex for a given average cortical thickness, just at the cusp of the onset of gyrencephaly.

This same choice also enable us to easily compute the expected span of the various morphometric measures over coarse-graining, assuming the universal scaling: each will range between its original value (expressed as a function of the original values for A_t , A_e and T), and its value at spatial scale λ_{lys} , where $A_t(\lambda_{lys}) = A_e(\lambda_{lys}) = A_0$: we simply replace A_t and A_e by A_0 , and T by $\sqrt{A_0 k^4}$. The ratios between the initial and final values of all morphometric measures will be given as powers of g , imbuing the gyrification index with a new significance.

We list below the exspans for all such morphometric measures ($S = \log s$, $K = \log k$ and $I = \log v_I$)

Morphometric measure	Original Value =	Span $\times$	Value at lissencephalic limit
T^2	T^2	1	$A_0 k^4$
A_0	$\frac{A_e^5}{A_t^4}$	1	A_0
A_e	A_e	g^4	A_0
A_t	A_t	g^5	A_0
V_{total}	$\approx \frac{2}{9\sqrt{3\pi}} A_e^{\frac{3}{2}}$	g^6	$\approx \frac{2}{9\sqrt{3\pi}} A_0^{\frac{3}{2}}$
V_{GM}	$A_t T$	g^5	$A_0^{\frac{3}{2}} k^2$
g	$\frac{A_t}{A_e}$	g	1
$N_{features}$	$\approx \frac{A_t^5}{A_e^5}$	g^5	1
k	$A_t A_e^{-\frac{5}{4}} T^{\frac{1}{2}}$	1	k
s	$A_t^{\frac{3}{2}} A_e^{\frac{3}{4}} T^{-\frac{9}{2}}$	$g^{\frac{21}{2}}$	k^{-9}
v_I	$A_t A_e T^2$	g^9	$A_0^3 k^4$
$\hat{k}$	$A_t^{\frac{4}{\sqrt{42}}} A_e^{-\frac{5}{\sqrt{42}}} T^{\frac{2}{\sqrt{42}}}$	1	$\hat{k}$
$\hat{s}$	$A_t^{\frac{2}{\sqrt{14}}} A_e^{\frac{1}{\sqrt{14}}} T^{-\frac{6}{\sqrt{14}}}$	$g^{\frac{18}{\sqrt{14}}}$	$\hat{k}^{-3\sqrt{3}}$
$\hat{v}_I$	$A_t^{\frac{1}{\sqrt{3}}} A_e^{\frac{1}{\sqrt{3}}} T^{\frac{2}{\sqrt{3}}}$	$g^{3\sqrt{3}}$	$A_0 \hat{k}^{\sqrt{14}}$

S6 Validation with non-brain shapes

We chose to apply our coarse-graining procedure to a range of shapes to validate our algorithm, and we included both negative and positive controls.

As a first positive control, we used a simple box with finite thickness (i.e. we simulated a inner “white matter” surface and an outer “grey matter” surface, both being a cube, one positioned inside the other). A schematic is shown in **Fig. S6.1**. We know based on theoretical consideration that this box must be aligning exactly with the $K = -\frac{1}{9}S$ line, as its A_t must be the same as its A_e at every stage of coarse-graining, which also implies a “fractal dimension” of 1. This is exactly the case in our plot of K against S , as all the grey data points from the coarse-graining algorithm align on $K = -\frac{1}{9}S$ (thick black line).

As negative controls, we included three non-brain shapes, a bell pepper, two walnut halves, and a coarse outline of a bust/figurine known as Laurana. All three of these shapes show a self-similar, or fractal, regime (corresponding to partially straight trajectories in $K \times S$) in our coarse-graining procedure, but their trajectories in $K \times S$ space are not flat (**Fig. S6.1**), meaning their fractal dimensions are distinct from 2.5. Their trajectories also do not overlap with each other, indicating that they are fundamentally different shapes.

The human brain is included here as a reference and shows a clear flat trajectory (**Fig. S6.1**) as presented in the main text. Also worth noting, after the human trajectory intersects the $K = -\frac{1}{9}S$ line, it veers off to follow the line closely, indicating that the A_e and A_t remain the same with further steps of coarse-graining. Effectively, the human brain transitions to be lissencephalic convex structures once their fractal regime ends. For simplicity, we excluded these lissencephalic data points of extreme coarse-graining from the results in the main text.

S7 Validation with randomising grid for coarse-graining

To assess robustness of the coarse-graining algorithm, we ran 30 different realisations of the algorithm, but with a small random shift of the grid position relative to the surface meshes. The shift is chosen to be within the radius of λ . This allows subtle changes in the voxelisation at the boundary of grey matter and white matter. Interestingly, over five different human individuals, we observed subtle changes in the values S over the 30 realisations, and to a lesser degree K (**Fig.**

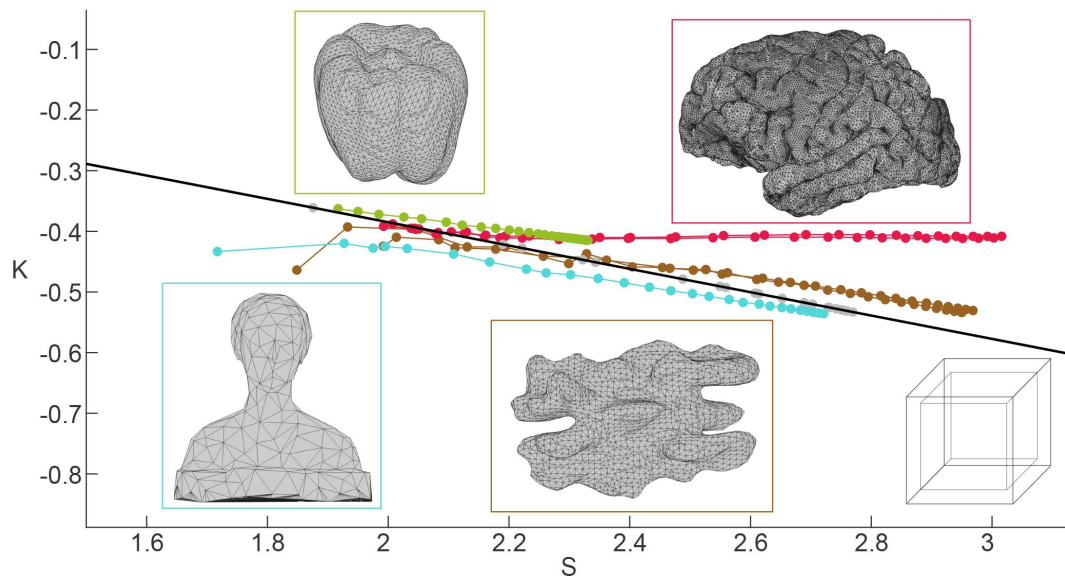


Figure S6.1

Scaling behaviour of various shapes in $K \times S$ space.

Thick black line indicates $K = -\frac{1}{9}S$ and a gyrification index $g = \frac{A_t}{A_e} = 1$. Points above and below the line have, respectively, $g > 1$ and $g < 1$. Colour-coded boxes show the shape of the objects we analysed. For simplicity we show the outer “pial” surface of each object. In the case of the box, we indicated both outer and inner surfaces. Green data points correspond to the bell pepper, red to the human brain, cyan to the ‘Laurana’ bust, brown to the walnut, and grey to the box of finite thickness.

S7.1 [↗](#)). Additionally, the variation between individuals, especially in K at smaller spatial scales, is far greater than the variation introduced by the jittered realisations. These results suggest that the coarse-graining algorithm is extremely robust towards subtle changes at the grey or white matter boundary, especially far away from the lissencephalic limit.

S8 Ageing process

S8.1 All morphometric variables

In the main text, we used the ageing process as an example for scale-dependent biological process. For completeness, here we also show all the morphometric variables across scales in the 20 y.o. and 80 y.o. cohort in **Fig. S8.1** [↗](#), and the corresponding effect sizes in **Fig. S8.2** [↗](#). As expected, A_e shows very little difference between the two cohorts. I , S , and T show some effects at scales smaller than 4 mm, but the effect decreases monotonously for higher scales. K demonstrates a more complex scale-dependent effect: larger K in younger subjects at small scales of 0.25 mm (in agreement with previous native scale analyses [\[6\]](#)), smaller K in younger subjects at scales of approx. 2 mm, and a return to larger K in younger subjects at large scales of more than approx. 5 mm. Note, however, that despite these large effect sizes, the actual change of values of K is within the range of variation expected across species (seen in the main text). The range of variation of K is approx 0.04 here, and at least an order of magnitude smaller than the range of variation in S (approx 1.5).

S8.2 Confirmation in independent dataset

To confirm that our observed ageing effect was not driven by sample or data-specific properties, we also analysed an independent dataset (NKI) with the same methods (see Section S1). Here, we show the equivalent figures to **Fig. S8.1** [↗](#) and **Fig. S8.2** [↗](#) for the NKI data in **Fig. S8.3** [↗](#) and **Fig. S8.4** [↗](#). The same qualitative patterns can be seen in all plots, including the scale-specific effects in K and A_e at around 2 mm.

References

- [1] Zhang Kechen, Sejnowski Terrence J. (2000) **A universal scaling law between gray matter and white matter of cerebral cortex.** :5621–5626 <https://doi.org/10.1073/pnas.090504197>.
- [2] Francis Cassot, Frederic Lauwers, Sylvie Lorthois, Prasanna Puwanarajah, Henri Duvernoy (2009) **Scaling laws for branching vessels of human cerebral cortex.** *Microcirculation*, **16**:331–344 <https://doi.org/10.1080/10739680802662607>.
- [3] Karbowski Jan (2011) **Scaling of brain metabolism and blood flow in relation to capillary and neural scaling.** *PLoS ONE*, **6** <https://doi.org/10.1371/journal.pone.0026709>.
- [4] Mota Bruno, Herculano-Houzel Suzana (2014) **All brains are made of this: A fundamental building block of brain matter with matching neuronal and glial masses** *Frontiers in Neuroanatomy*, **8** <https://doi.org/10.3389/fnana.2014.00127>.
- [5] Mota Bruno, Herculano-Houzel Suzana (2015) **Cortical folding scales universally with surface area and thickness, not number of neurons** *Science* :74–77 <https://doi.org/10.1126/science.aaa9101>
- [6] Wang Yujiang, Necus Joe, Kaiser Marcus, Mota Bruno (2016) **Universality in human cortical folding in health and disease.** *PNAS*, <https://doi.org/10.1073/pnas.1610175113>

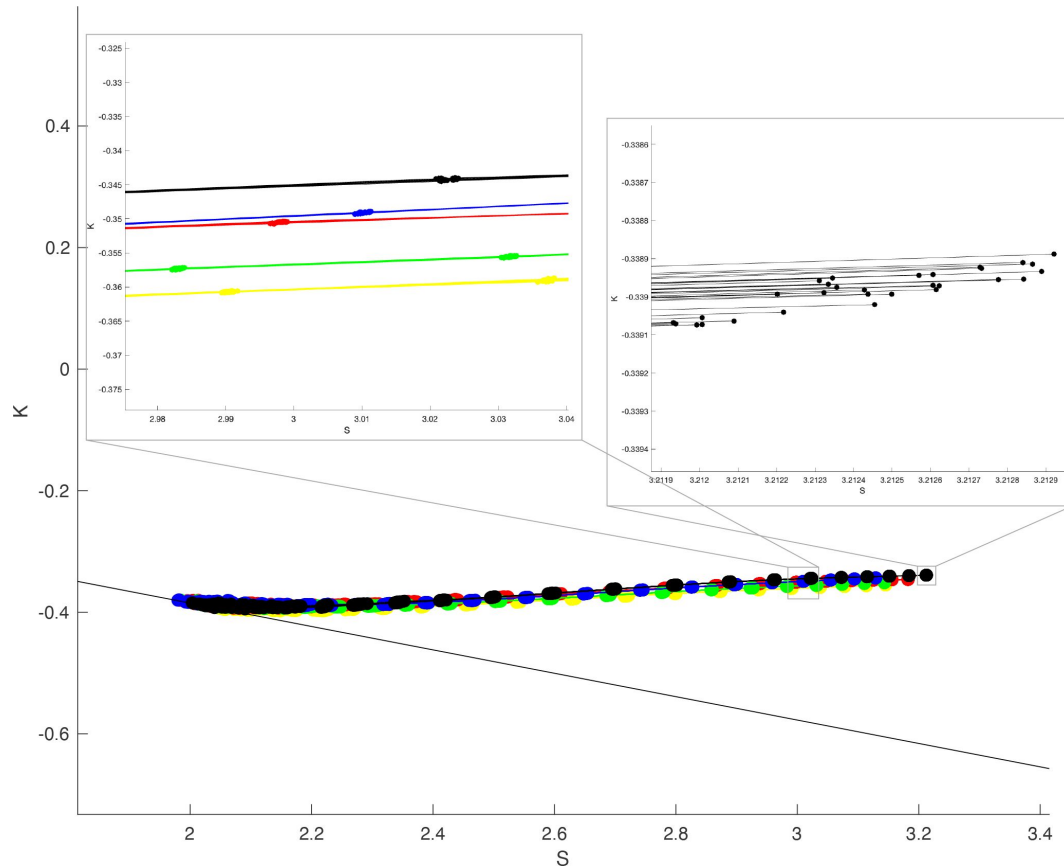


Figure S7.1

Randomising grid for coarse-graining yields very consistent results within individuals in $K \times S$ space.

Thick black line indicates $K = -\frac{1}{9}S$ and a gyrification index $g = \frac{A_t}{A_e} = 1$. Each colour in the plot indicates a different human individual (HCP 103414 - yellow, 135225 - red, 138534 - green, 144832 - blue, 148840 - black, respectively). 30 jittered grid outputs are shown for each individual, lines connect datapoints of the same jittered version. Zoomed in panels show that the jittered outputs have far less variation within than between individuals.

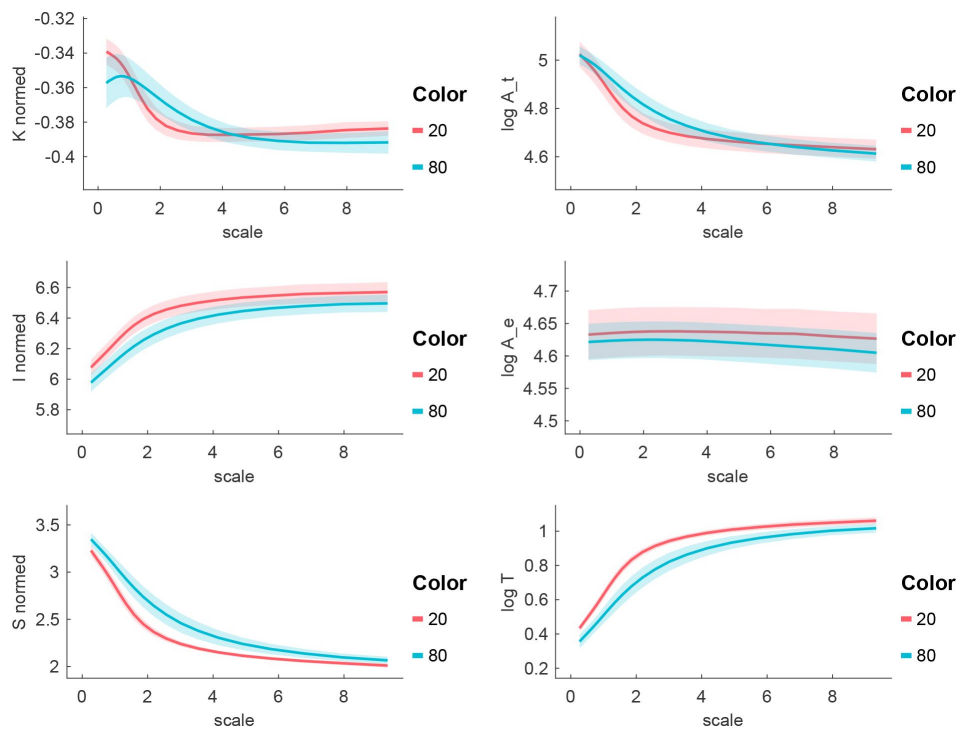


Figure S8.1

All morphological variables across scales in the 20 y.o. and 80 y.o. cohort.

Each panel shows a morphological metric, and data is shown for a group of 20-year-olds (red, n=27) and a group of 80-year-olds (blue, n=86). Mean and standard deviation are shown as the solid line and the shaded area respectively.

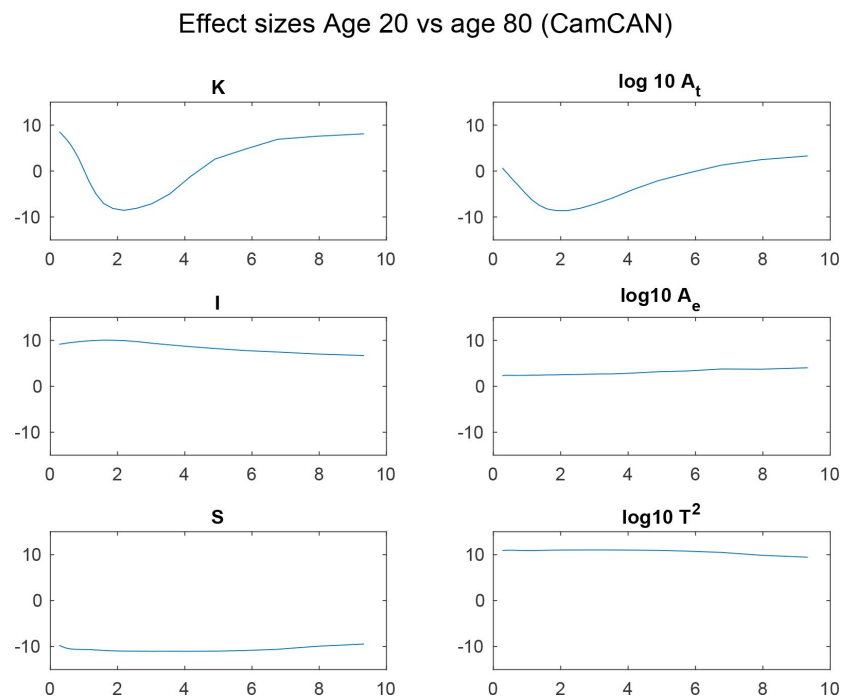


Figure S8.2

Effect size between the 20 y.o. and 80 y.o. cohort in all morphological variables.

Each panel shows a morphological metric, and data is shown for a group of 20-year-olds (red, n=27) and a group of 80-year-olds (blue, n=86). Effect size is measured as the ranksum z statistic between the two groups.

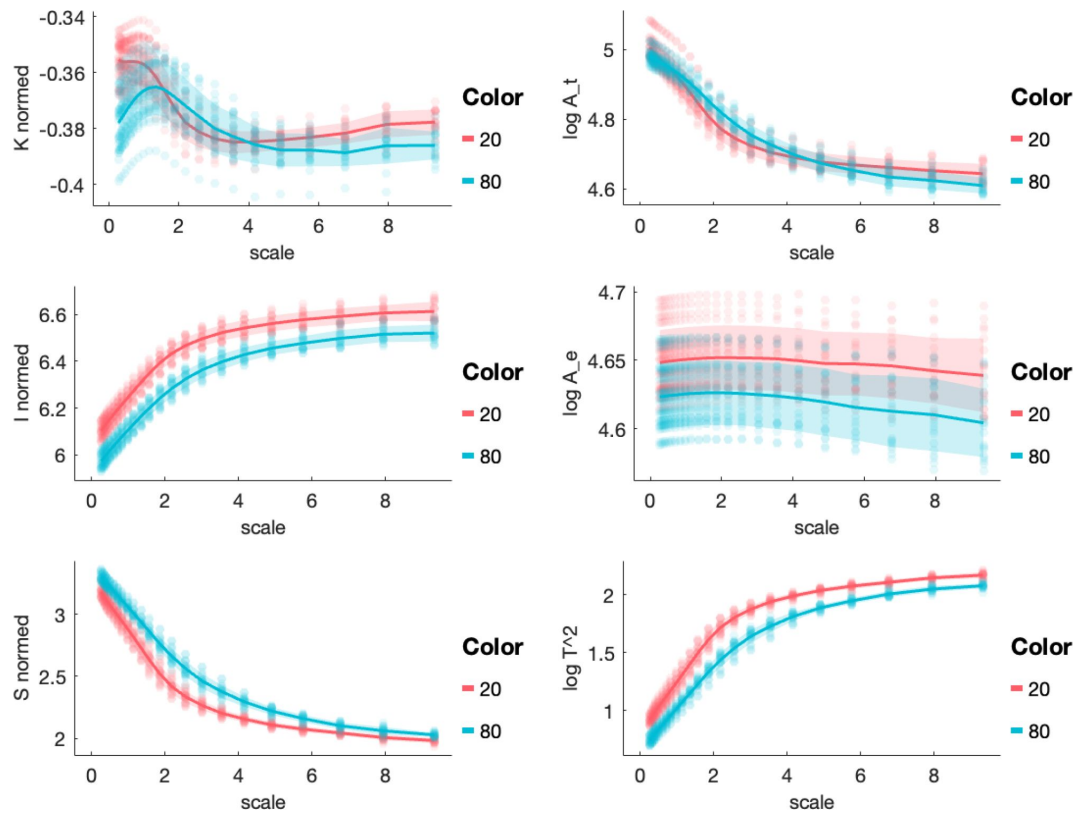


Figure S8.3

All morphological variables across scales in the 20 y.o. and 80 y.o. cohort in a separate (NKI) dataset.

Each panel shows a morphological metric, and data from an independent dataset (NKI) is shown for a group of 20-year-olds (red, n=10) and a group of 80-year-olds (blue, n=10).

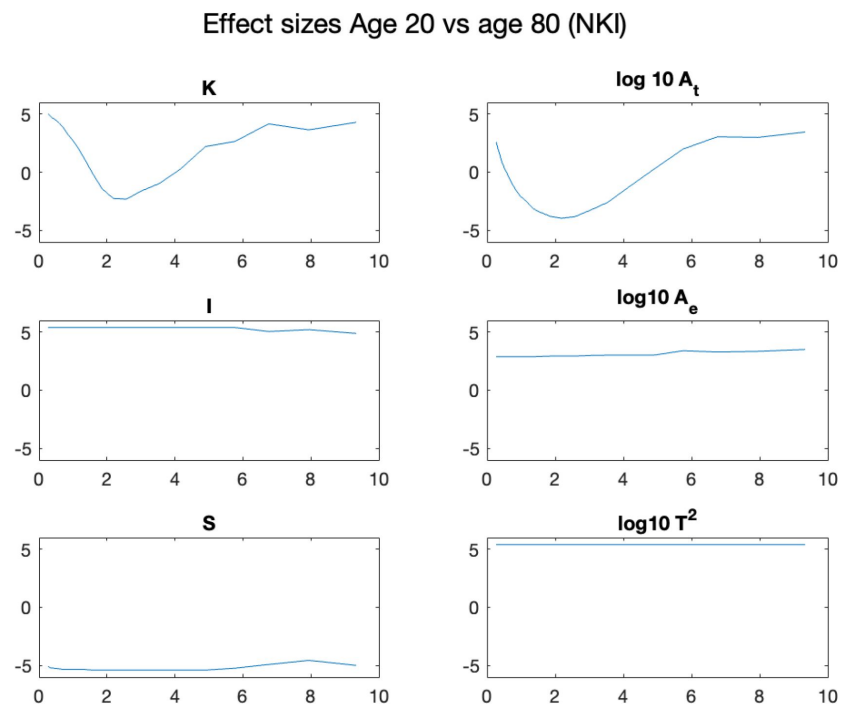


Figure S8.4

Effect size between the 20 y.o. and 80 y.o. cohort in all morphological variables in a separate (NKI) dataset.

Effect size is measured as the ranksum z statistic between the two groups. Mean and standard deviation are shown as the solid line and the shaded area respectively.

- [7] Wang Yujiang, Necus Joe, Rodriguez Luis, Taylor Peter, Mota Bruno (2019) **Human cortical folding across regions within individual brains follows universal scaling law.** :1–8 <https://doi.org/10.1038/s42003-019-0421-7>
- [8] Leiberg Karoline, Papasavvas Christoforos, Wang Yujiang, Bruijne Marleen de, Cattin Philippe C., Cotin Stéphane, Padoy Nicolas, Speidel Stefanie, Zheng Yefeng, Essert Caroline (2021) **Local morphological measures confirm that folding within small partitions of the human cortex follows universal scaling law** *Medical Image Computing and Computer Assisted Intervention – MICCAI 2021*, :691–700
- [9] Mandelbrot. B. B. (1983) **The fractal geometry of nature.**
- [10] Elston G. N., Zietsch Brendan (2005) **Fractal analysis as a tool for studying specialization in neuronal structure: the study of the evolution of the primate cerebral cortex and human intellect** :217–227
- [11] Plank Michael J., Benhamou Simon (2008) **Random walk models in biology.** <https://doi.org/10.1098/rsif.2008.0014>
- [12] Ionescu Clara, Oustaloup Alain, Levron François, Melchior Pierre, Sabatier Jocelyn, De Keyser Robin (2009) **A model of the lungs based on fractal geometrical and structural properties** *IFAC Proceedings Volumes*, :994–999 <https://doi.org/10.3182/20090706-3-FR-2004.00165>
- [13] Losa. Gabriele (2011) **Fractals in Biology and Medicine.** <https://doi.org/10.1002/3527600906.mcb.201100002>
- [14] Klonowski. Wlodzimierz (2016) **Fractal Analysis of Electroencephalographic Time Series (EEG Signals),** :413–429 <https://doi.org/10.1007/978-1-4939-3995-425>
- [15] Antonio Di Ieva (2016) **Springer Series in Computational Neuroscience** *The Fractal Geometry of the Brain.* <https://doi.org/10.1007/978-1-4939-3995-4>
- [16] Reznikov Natalie, Bilton Matthew, Lari Leonardo, Stevens Molly M., Kröger Roland (2018) **Fractal-like hierarchical organization of bone begins at the nanoscale.** <https://doi.org/10.1126/science.aao2189>
- [17] Free S. L., Sisodiya S. M., Cook M. J., Fish D. R., Shorvon S. D. (1996) **Three-Dimensional Fractal Analysis of the White Matter Surface from Magnetic Resonance Images of the Human Brain.** :830–836 <https://doi.org/10.1093/cercor/6.6.830>
- [18] Kiselev Valerij G., Hahn Klaus R., Auer Dorothee P. (2003) **Is the brain cortex a fractal?** :1765–1774 [https://doi.org/10.1016/S1053-8119\(03\)00380-X](https://doi.org/10.1016/S1053-8119(03)00380-X)
- [19] Marzi Chiara, Giannelli Marco, Tessa Carlo, Mascalchi Mario, Diciotti Stefano (2021) **Fractal analysis of mri data at 7 t: How much complex is the cerebral cortex?** *IEEE Access*, 9:69226–69234 <https://doi.org/10.1109/ACCESS.2021.3077370>
- [20] Jao Chi-Wen, Lau Chi, Lien Li-Ming, Tsai Yuh-Feng, Chu Kuang-En, Hsiao Chen-Yu, Yeh Jiann-Horng, Wu Yu-Te (2021) **Using fractal dimension analysis with the desikan–killiany atlas to assess the effects of normal aging on subregional cortex alterations in adulthood.** <https://doi.org/10.3390/brainsci11010107>

- [21] Meregalli Valentina, Alberti Francesco, Madan Christopher R., Meneguzzo Paolo, Miola Alessandro, Trevisan Nicolò, Sambataro Fabio, Favaro Angela, Collantoni Enrico (2022) **Cortical complexity estimation using fractal dimension: A systematic review of the literature on clinical and nonclinical samples** *European Journal of Neuroscience*, **55**:1547–1583 <https://doi.org/10.1111/ejn.15631>
- [22] King Richard D., Brown Brandon, Hwang Michael, Jeon Tina, George Anuh T. (2010) **Fractal dimension analysis of the cortical ribbon in mild Alzheimer’s disease.** *NeuroImage*, **53**:471–479 <https://doi.org/10.1016/j.neuroimage.2010.06.050>
- [23] Madan Christopher R., Kensinger Elizabeth A. (2016) **Cortical complexity as a measure of age-related brain atrophy.** :617–629 <https://doi.org/10.1016/j.neuroimage.2016.04.029>
- [24] Marzi C., Giannelli M., Tessa C., Mascalchi M., Diciotti S. (2020) **Toward a more reliable characterization of fractal properties of the cerebral cortex of healthy subjects during the lifespan.** <https://doi.org/10.1038/s41598-020-73961-w>
- [25] Kochunov Peter, Thompson Paul M., Coyle Thomas R., Lancaster Jack L., Kochunov Valeria, Royall Donal, Mangin Jean-François, Rivière Denis, Fox Peter T. (2007) **Relationship among neuroimaging indices of cerebral health during normal aging.** *Human Brain Mapping*, **29**:36–45 <https://doi.org/10.1002/hbm.20369>
- [26] Madan. Robust Christopher R. (2019) **estimation of sulcal morphology.** <https://doi.org/10.1186/s40708-019-0098-1>
- [27] Wang Yujiang *et al.* (2021) **Independent components of human brain morphology.** <https://doi.org/10.1016/j.neuroimage.2020.117546>
- [28] Jin Kaide, Zhang Tianqi, Shaw Marnie, Sachdev Perminder, Cherbuin Nicolas (2018) **Relationship Between Sulcal Characteristics and Brain Aging** *Frontiers in Aging Neuroscience*, **10** <https://doi.org/10.3389/fnagi.2018.00339>
- [29] Hofman. Size Michel A. (1985) **and shape of the cerebral cortex in mammals.** *Brain, Behavior and Evolution*, **27**:28–40 <https://doi.org/10.1159/000118718>
- [30] The M A Hofman. (1991) **fractal geometry of convoluted brains.** *Journal für Hirnforschung*, **32**:103–111
- [31] Xu Gang, Knutsen Andrew K., Dikranian Krikor, Kroenke Christopher D., Bayly Philip V., Taber Larry A. (2010) **Axons Pull on the Brain, But Tension Does Not Drive Cortical Folding.** <https://doi.org/10.1115/1.4001683>
- [32] Barenblatt. G.I. (1996) **Cambridge Texts in Applied Mathematics** *Scaling, Self-similarity, and Intermediate Asymptotics: Dimensional Analysis and Intermediate Asymptotics.*
- [33] West Geoffrey B., Brown James H., Enquist Brian J. (1997) **A General Model for the Origin of Allometric Scaling Laws in Biology.** <https://doi.org/10.1126/science.276.5309.122>
- [34] Gagler Dylan C., Karas Bradley, Kempes Christopher P., Malloy John, Mierzejewski Veronica, Goldman Aaron D., Kim Hyunju, Walker Sara I. (2022) **Scaling laws in enzyme function reveal a new kind of biochemical universality** *Proceedings of the National Academy of Sciences*, <https://doi.org/10.1073/pnas.2106655119>

- [35] Johnston Iain G., Dingle Kamaludin, Greenbury Sam F., Camargo Chico Q., K. Doye Jonathan P., Ahnert Sebastian E., Louis Ard A. (2022) **Symmetry and simplicity spontaneously emerge from the algorithmic nature of evolution.** <https://doi.org/10.1073/pnas.2113883119>
- [36] Quezada Sebastian, van de Looij Yohan, Hale Nadia, Rana Shreya, Sizonenko Stéphane V, Gilchrist Courtney, Castillo-Melendez Margie, Tolcos Mary, Walker David W (2020) **Genetic and microstructural differences in the cortical plate of gyri and sulci during gyrification in fetal sheep.** :6169–6190 <https://doi.org/10.1093/cercor/bhaa171>
- [37] Molnár Zoltán, Kaas Jon H., de Carlos Juan A., Hevner Robert F., Lein Ed, Němec Pavel (2014) **Evolution and development of the mammalian cerebral cortex.** *Brain, Behavior and Evolution*, **83**:126–139 <https://doi.org/10.1159/000357753>
- [38] Kaas. Evolution Jon H. (2012) **of columns, modules, and domains in the neocortex of primates.** :10655–10660 <https://doi.org/10.1073/pnas.1201892109>
- [39] Zilles Karl, Palomero-Gallagher Nicola, Amunts Katrin (2013) **Development of cortical folding during evolution and ontogeny.** :275–284 <https://doi.org/10.1016/j.tins.2013.01.006>
- [40] Garcia Kara E. *et al.* (2018) **Dynamic patterns of cortical expansion during folding of the preterm human brain.** :3156–3161 <https://doi.org/10.1073/pnas.1715451115>
- [41] Pizzagalli Fabrizio *et al.* (2020) **The reliability and heritability of cortical folds and their genetic correlations across hemispheres.** <https://doi.org/10.1038/s42003-020-01163-1>
- [42] Heuer Katja, Gulban Omer, Bazin Pierre-Louis, Osoianu Anastasia, Valabregue Romain, Santin Mathieu, Herbin Marc, Toro Roberto (2019) **Evolution of neocortical folding: A phylogenetic comparative analysis of mri from 34 primate species** *Cortex*, **118**:275–291 <https://doi.org/10.1016/j.cortex.2019.04.011>
- [43] Valk Sofie L. *et al.* (2020) **Shaping brain structure: Genetic and phylogenetic axes of macroscale organization of cortical thickness** *Science Advances*, <https://doi.org/10.1126/sciadv.abb3417>
- [44] Mars Rogier B., Neubert Franz-Xaver, Verhagen Lennart, Sallet Jerome, Miller Karla L., Dunbar Robin I., Barton Robert A. (2014) **Primate comparative neuroscience using magnetic resonance imaging: Promises and challenges** *Frontiers in Neuroscience*, **8** <https://doi.org/10.3389/fnins.2014.00298>
- [45] Croxson Paula L, Forkel Stephanie J, Cerliani Leonardo, Thiebaut de Schotten Michel (2017) **Structural Variability Across the Primate Brain: A Cross-Species Comparison** :3829–3841 <https://doi.org/10.1093/cercor/bhx244>
- [46] Van Essen D. C. *et al.* (2012) **D. C. Van Essen, K. Ugurbil, E. Auerbach, D. Barch, T. E. J. Behrens, R. Bucholz, A. Chang, L. Chen, M. Corbetta, S. W. Curtiss, S. Della Penna, D. Feinberg, M. F. Glasser, N. Harel, A. C. Heath, L. Larson-Prior, D. Marcus, G. Michalareas, S. Moeller, R. Oostenveld, S. E. Petersen, F. Prior, B. L. Schlaggar, S. M. Smith, A. Z. Snyder, J. Xu, and E. Yacoub. The Human Connectome Project: A data acquisition perspective.** *NeuroImage*, **62**(4):2222–2231, October 2012. ISSN 1053-8119. doi:10.1016/j.neuroimage.2012.02.018. URL <http://www.sciencedirect.com/science/article/pii/S1053811912001954>. <https://doi.org/10.1016/j.neuroimage.2012.02.018>

- [47] Shafto Meredith A *et al.* (2014) **The cambridge centre for ageing and neuroscience (cam-can) study protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing.** *BMC neurology*, **14**
- [48] Taylor Jason R, Williams Nitin, Cusack Rhodri, Auer Tibor, Shafto Meredith A, Dixon Marie, Tyler Lorraine K, Henson Richard N, *et al.* (2017) **The cambridge centre for ageing and neuroscience (cam-can) data repository: structural and functional mri, meg, and cognitive data from a cross-sectional adult lifespan sample.** *Neuroimage*, **144**:262–269
- [49] Nooner Kate *et al.* (2012) **The nki-rockland sample: A model for accelerating the pace of discovery science in psychiatry** <https://doi.org/10.3389/fnins.2012.00152>
- [50] Liu Cirong, Ye Frank Q., Yen Cecil, Newman John D., Glen Daniel, Leopold David A., Silva Afonso C. (2018) **A digital 3D atlas of the marmoset brain based on multi-modal MRI.** *NeuroImage*, **169**:106–116 <https://doi.org/10.1016/j.neuroimage.2017.12.004>
- [51] Liu Cirong *et al.* (2020) **A resource for the detailed 3d mapping of white matter pathways in the marmoset brain.** *Nature Neuroscience*, **23**:271–280 <https://doi.org/10.1038/s41593-019-0575-0>
- [52] Madan. Christopher R. (2015) **Creating 3D visualizations of MRI data: A brief guide** *F1000Research*, **4** <https://doi.org/10.12688/f1000research.6838.1>
- [53] Madan. Christopher R (2016) **Improved understanding of brain morphology through 3d printing: A brief guide** *Research Ideas and Outcomes*, **2** <https://doi.org/10.3897/rio.2.e10398>
- [54] Ardesch Dirk Jan, Scholtens Lianne H, de Lange Siemon C., Roumazeilles Lea, Khrapitchev Alexandre A, Preuss Todd M, Rilling James K, Mars Rogier B, Martijn P (2022) **van den Heuvel. Scaling Principles of White Matter Connectivity in the Human and Nonhuman Primate Brain.** *Cerebral Cortex*, **32**:2831–2842 <https://doi.org/10.1093/cercor/bhab384>
- [55] Bryant Katherine L. *et al.* (2021) **Diffusion MRI data, sulcal anatomy, and tractography for eight species from the Primate Brain Bank.** *Brain Structure and Function*, **226**:2497–2509 <https://doi.org/10.1007/s00429-021-02268-x>
- [56] Schaer M., Cuadra M. B., Tamarit L., Lazeyras F., Eliez S., Thiran J. P. (2008) **A Surface-Based Approach to Quantify Local Cortical Gyrification.** *IEEE Transactions on Medical Imaging*, **27**:161–170 <https://doi.org/10.1109/TMI.2007.903576>
- [57] Yu Chris, Brakensiek Caleb, Schumacher Henrik, Crane Keenan (2021) **Repulsive surfaces.** <https://doi.org/10.1145/3478513.3480521>
- [58] Raznahan Armin, Shaw Phillip, Lalonde Francois, Stockman Mike, Wallace Gregory L., Greenstein Dede, Clasen Liv, Gogtay Nitin, Giedd Jay N. (2011) **How Does Your Cortex Grow?** *7174–7177* <https://doi.org/10.1523/JNEUROSCI.0054-11.2011>

Article and author information

Yujiang Wang

CNNP Lab (,) Interdisciplinary Computing and Complex BioSystems Group, School of Computing, Newcastle University, Newcastle upon Tyne, United Kingdom, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, UCL Institute of Neurology, Queen Square, London, United Kingdom

For correspondence: Yujiang.Wang@newcastle.ac.uk

Karoline Leiberg

CNNP Lab (,) Interdisciplinary Computing and Complex BioSystems Group, School of Computing, Newcastle University, Newcastle upon Tyne, United Kingdom

Nathan Kindred

Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom

Christopher R. Madan

School of Psychology, University of Nottingham, Nottingham, United Kingdom

Colline Poirier

Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom

Christopher I. Petkov

Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, Department of Neurosurgery, University of Iowa, USA

Peter N. Taylor

CNNP Lab (,) Interdisciplinary Computing and Complex BioSystems Group, School of Computing, Newcastle University, Newcastle upon Tyne, United Kingdom, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, UCL Institute of Neurology, Queen Square, London, United Kingdom

Bruno Mota

metaBIO Lab, Instituto de Física, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

Copyright

© 2023, Wang et al.

This article is distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use and redistribution provided that the original author and source are credited.

Editors

Reviewing Editor

Jessica Dubois

Inserm Unité NeuroDiderot, Université Paris Cité, Paris, France

Senior Editor

Yanchao Bi

Beijing Normal University, Beijing, China

Reviewer #2 (Public Review):

In this manuscript, the authors analyze the shapes of cerebral cortices from several primate species, including subgroups of young and old humans, to characterize commonalities in patterns of gyrification, cortical thickness, and cortical surface area. The authors state that the observed scaling law shares properties with fractals, where shape properties are similar across several spatial scales. One way the authors assess this is to perform a "cortical melting" operation that they have devised on surface models obtained from several primate species. The authors also explore differences in shape properties between brains of young (~20 year old) and old (~80) humans. A challenge the authors acknowledge struggling with in reviewing the manuscript is merging "complex mathematical concepts and a perplexing biological phenomenon." This reviewer remains a bit skeptical about whether the complexity of the mathematical concepts being drawn from are justified by the advances made in our ability to infer new things about the shape of the cerebral cortex.

(1) The series of operations to coarse-grain the cortex illustrated in Figure 1 produces image segmentations that do not resemble real brains. The process to assign voxels in downsampled images to cortex and white matter is biased towards the former, as only 4 corners of a given voxel are needed to intersect the original pial surface, but all 8 corners are needed to be assigned a white matter voxel. The reason for introducing this bias (and to the extent that it is present in the authors' implementation) is not provided. The authors provide an intuitive explanation of why thickness relates to folding characteristics, but ultimately an issue for this reviewer is, e.g., for the right-most panel in Figure 2b, the cortex consists of several 4.9-sided voxels and thus a >2 cm thick cortex. A structure with these morphological properties is not consistent with the anatomical organization of typical mammalian neocortex.

(2) For the comparison between 20-year-old and 80-year-old brains, a well-documented difference is that the older age group possesses more cerebral spinal fluid due to tissue atrophy, and the distances between the walls of gyri becomes greater. This difference is born out in the left column of Figure 4b. It seems this additional spacing between gyri in 80 year olds requires more extensive down-sampling (larger scale values in Figure 4a) to achieve a similar shape parameter K as for the 20 year olds. The authors assert that K provides a more sensitive measure (associated with a large effect size) than currently used ones for distinguishing brains of young vs. old people. A more explicit, or elaborate, interpretation of the numbers produced in this manuscript, in terms of brain shape, might make this analysis more appealing to researchers in the aging field.

(3) In the Discussion, it is stated that self-similarity, operating on all length scales, should be used as a test for existing and future models of gyrification mechanisms. Given the lack of association between the abstract mathematical parameters described in this study and explicit properties of brain tissue and its constituents, it is difficult to envision how the coarse-graining operation can be used to guide development of "models of cortical gyrification."

(4) There are several who advocate for analyzing cortical mid-thickness surfaces, as the pial surface over-represents gyral tips compared to the bottoms of sulci in the surface area. The authors indicate that analyses of mid-thickness representations will be taken on in future work, but this seems to be a relevant control for accepting the conclusions of this manuscript.

<https://doi.org/10.7554/eLife.92080.2.sa1>

Reviewer #3 (Public Review):

Summary: Through a rigorous methodology, the authors demonstrated that within 11 different primates, the shape of the brain followed a universal scaling law with fractal properties. They enhanced the universality of this result by showing the concordance of their results with a previous study investigating 70 mammalian brains, and the discordance of their results with other folded objects that are not brains. They incidentally illustrated potential applications of this fractal property of the brain by observing a scale-dependant effect of aging on the human brain.

Strengths:

- New hierarchical way of expressing cortical shapes at different scales derived from previous report through implementation of a coarse-graining procedure
- Investigation of 11 primate brains and contextualisation with other mammals based on prior literature
- Proposition of tool to analyse cortical morphology requiring no fine tuning and computationally achievable
- Positioning of results in comparison to previous works reinforcing the validity of the observation.
- Illustration of scale-dependance of effects of brain aging in the human.

Weaknesses:

- The notion of cortical shape, while being central to the article, is not really defined, leaving some interpretation to the reader
- The organization of the manuscript is unconventional, leading to mixed contents in different sections (sections mixing introduction and method, methods and results, results and discussion...). As a result, the reader discovers the content of the article along the way, it is not obvious at what stages the methods are introduced, and the results are sometimes presented and argued in the same section, hindering objectivity.

To improve the document, I would suggest a modification and restructuring of the article such that: 1) by the end of the introduction the reader understands clearly what question is addressed and the value it holds for the community, 2) by the end of the methods the reader understands clearly all the tools that will be used to answer that question (not just the new method), 3) by the end of the results the reader holds the objective results obtained by applying these tools on the available data (without subjective interpretations and justifications), and 4) by the end of the discussion the reader understands the interpretation and contextualisation of the study, and clearly grasps the potential of the method depicted for the better understanding of brain folding mechanisms and properties.

<https://doi.org/10.7554/eLife.92080.2.sa0>

Author Response

The following is the authors' response to the original reviews.

Public Reviews:**Reviewer #1 (Public Review):**

This study examined a universal fractal primate brain shape. However, the paper does not seem well structured and is not well written. It is not clear what the purpose of the paper is. And there is a lack of explanation for why the proposed analysis is necessary. As a result, it is challenging to clearly understand what novelty in the paper is and what the main findings are.

We have now restructured the paper, including a summary of the main purpose and findings as follows:

“Compared to previous literature, we can summarise our main contribution and advance as follows:

- (i) We are showing for the first time that representative primate species follow the exact same fractal scaling – as opposed to previous work showing that they have a similar fractal dimension [Hofman1985, Hofman1991], i.e. slope, but not necessarily the same offset, as previous methods had no consistent way of comparing offsets.
- (ii) Previous work could also not show direct agreement in morphometrics between the coarse-grained brains of primate species and other non-primate mammalian species.
- (iii) Demonstrating in proof-of-principle that multiscale morphometrics, in practice, can have much larger effect sizes for classification applications. This moves beyond our previous work where we only showed the scaling law across [Mota2015] and within species [Wang2016], but all on one (native) scale with comparable effect sizes for classification applications [Wang2021].

In simple terms: we know that objects can have the same fractal dimension, but differ greatly in a range of other shape properties. However, we demonstrate here, that representative primate brains and mammalian brain indeed share a range of other key shape properties, on top of agreeing in fractal dimension. This suggests a universal blueprint for mammalian brain shape and a common set of mechanisms governing cortical folding. As a practical additional outcome of our study, we could show that our novel method of deriving multiscale metrics of brain shape can differentiate subtle shape changes much better than the metrics we have been using so far at a single native scale.”

We plan to use the second paragraph as a plain-language summary of our work.

Additionally, several terms are introduced without adequate explanation and contextualization, further complicating comprehension.

We have now made sure that potential jargon is introduced with context and explanation. For example in Introduction: “This scaling law, relating powers of cortical thickness and surface area metrics, [...]”

Does the second section, "2. Coarse-graining procedure", serve as an introduction or a method?

We have now renamed this section to “Coarse-graining Method” to indicate that this is a section about methods. However, to describe the methods adequately, we also expanded this section with introductory texts around the history and motivation of the method to provide context and explanations, as the reviewer rightly requested.

Moreover, the rationale behind the use of the coarse-graining procedure is not adequately elucidated. Overall, it is strongly recommended that the paper undergoes significant improvements in terms of its structure, explanatory depth, and overall clarity to enhance its comprehensibility.

To specifically explain the rationale behind the coarse-graining method, we added several clarifications, including the following paragraph:

“As a starting point for such a coarse-graining procedure, we suggest to turn to a well-established method that measures fractal dimension of objects: the so-called box-counting

algorithm [Kochunov2007, Madan2019]. Briefly, this algorithm fills the object of interest (say the cortex in our case) with boxes, or voxels of increasingly larger sizes and counts the number of boxes in the object as a function of box size. As the box size increases, the number of boxes decreases; and in a log-log plot, the slope of this relationship indicates the fractal dimension of the object. In our case, this method would not only provide us with the fractal dimension of the cortex, but, with increasing box size, the filled cortex would also contain less and less detail of the folded shape of the cortex. Intuitively, with increasing box size, the smaller details, below the resolution of a single box, would disappear first, and increasingly larger details will follow – precisely what we require from a coarse-graining method. We therefore propose to expand the traditional box-counting method beyond its use to measure fractal dimension, but to also analyse the reconstructed cortices as different realisations of the original cortex at the specified spatial scale.”

Reviewer #2 (Public Review):

In this manuscript, Wang and colleagues analyze the shapes of cerebral cortices from several primate species, including subgroups of young and old humans, to characterize commonalities in patterns of gyrification, cortical thickness, and cortical surface area. The work builds on the scaling law introduced previously by co-author Mota, and Herculano-Houzel. The authors state that the observed scaling law shares properties with fractals, where shape properties are similar across several spatial scales. One way the authors assess this is to perform a "cortical melting" operation that they have devised on surface models obtained from several primate species. The authors also explore differences in shape properties between the brains of young (~20 year old) and old (~80) humans. My main criticism of this manuscript is that the findings are presented in too abstract a manner for the scientific contribution to be recognized.

We recognise that our work is at the intersection of complex mathematical concepts and a perplexing biological phenomenon. Therefore, our paper has to strike a balance between scientifically accurate and succinct descriptions whilst giving sufficient space to provide context and explanations.

Throughout, we have now added text to provide more context, but also repeat key statements in plain-english terms.

For example, we added the following text to highlight our key contributions.

“In simple terms: we know that objects can have the same fractal dimension, but differ greatly in a range of other shape properties. However, we demonstrate here, that representative primate brains and mammalian brain indeed share a range of other key shape properties, on top of agreeing in fractal dimension. This suggests a universal blueprint for mammalian brain shape and a common set of mechanisms governing cortical folding. As a practical additional outcome of our study, we could show that our novel method of deriving multiscale metrics of brain shape can differentiate subtle shape changes much better than the metrics we have been using so far at a single native scale.”

(1) The series of operations to coarse-grain the cortex illustrated in Figure 1, constitute a novel procedure, but it is not strongly motivated, and it produces image segmentations that do not resemble real brains.

To specifically explain the rationale behind the coarse-graining method, we added several clarifications, including the following paragraph:

“As a starting point for such a coarse-graining procedure, we suggest to turn to a well-established method that measures fractal dimension of objects: the so-called box-counting algorithm [Kochunov2007, Madan2019]. Briefly, this algorithm fills the object of interest (say

the cortex in our case) with boxes, or voxels of increasingly larger sizes and counts the number of boxes in the object as a function of box size. As the box size increases, the number of boxes decreases; and in a log-log plot, the slope of this relationship indicates the fractal dimension of the object. In our case, this method would not only provide us with the fractal dimension of the cortex, but, with increasing box size, the filled cortex would also contain less and less detail of the folded shape of the cortex. Intuitively, with increasing box size, the smaller details, below the resolution of a single box, would disappear first, and increasingly larger details will follow – precisely what we require from a coarse-graining method. We therefore propose to expand the traditional box-counting method beyond its use to measure fractal dimension, but to also analyse the reconstructed cortices as different realisations of the original cortex at the specified spatial scale.”

We also note in several places in the text that the coarse-grained brains are not to be understood as exact reconstructions of actual brains, but serve the purpose of a model:

“[...] nor are the coarse-grained versions of human brains supposed to exactly resemble the location/pattern/features of gyri and sulci of other primates. The similarity we highlighted here are on the level of summary metrics, and our goal was to highlight the universality in such metrics to point towards highly conserved quantities and mechanisms.”

“Note, of course, that the coarse-grained brain surfaces are an output of our algorithm alone and not to be directly/naively likened to actual brain surfaces, e.g. in terms of the location or shape of the folds. Our comparisons here between coarse-grained brains and actual brains is purely on the level of morphometrics across the whole cortex.”

The process to assign voxels in downsampled images to cortex and white matter is biased towards the former, as only 4 corners of a given voxel are needed to intersect the original pial surface, but all 8 corners are needed to be assigned a white matter voxel (section S2). This causes the cortical segmentation, such as the bottom row of Figure 1B, to increase in thickness with successive melting steps, to unrealistic values. For the rightmost figure panel, the cortex consists of several 4.9-sided voxels and thus a >2 cm thick cortex. A structure with these morphological properties is not consistent with the anatomical organization of a typical mammalian neocortex.

Specifically on the point on increasing cortical thickness with increased level of coarse-graining, we have now added the following paragraph:

“The observation that with increasing voxel sizes, the coarse-grained cortices tend to be smoother and thicker is particularly interesting: the scaling law in Eq. 1 can be understood as thicker cortices (T) form larger folds (or are smoother i.e. less surface area A_t) when brain size is kept constant (A_e). This way of understanding has also been vividly illustrated by using the analogy of forming paper balls with papers of varying thickness in [Mota2015]: to achieve the same size of a paper ball (A_e), the one that uses thicker paper (T) will show larger folds (or is smoother i.e. less surface area A_t) than the one using thinner paper. The scaling law can therefore be understood as a physically and biologically plausible statement, and here, we are encouraged that our algorithm yields results in line with the scaling law.”

(2) For the comparison between 20-year-old and 80-year-old brains, a well-documented difference is that the older age group possesses more cerebral spinal fluid due to tissue atrophy, and the distances between the walls of gyri becomes greater. This difference is born out in the left column of Figure 4c. It seems this additional spacing between gyri in 80-year-olds requires more extensive down-sampling (larger scale values in Figure 4a) to achieve a similar shape parameter K as for the 20-year-olds. A case could be made that the familiar way of describing brain tissue - cortical volume, white matter volume, thickness, etc. - is a more direct and intuitive way to describe differences between young

and old adult brains than the obscure shape metric described in this manuscript. At a minimum, a demonstration of an advantage of the Figure 4a and 4b analyses over current methods for interpreting age-related differences would be valuable.

We have demonstrated the utility of our new shape metrics in a separate paper [Wang2021]. However, we agree with the reviewer that, in this specific instance, it is much easier to understand the key message without considering the less traditional metrics. We have therefore completely revised this part of the Results section to highlight the advantage of multiscale morphometrics, and used the traditional metric of surface area to illustrate the point. The reasoning in surface area is much easier to follow, both visually and conceptually, exactly as the reviewer described.

(3) In Discussion lines 199-203, it is stated that self-similarity, operating on all length scales, should be used as a test for existing and future models of gyrification mechanisms. First, the authors do not show, (and it would be surprising if it were true) that self-similarity is observed for length scales smaller than the acquired MRI data for any of the datasets analyzed. The analysis is restricted to coarse (but not fine)-graining.

To clarify this point, we have added a supplementary section and the following sentence: “Note this method has also no direct dependency on the original MR image resolution, as the inputs are smooth grey and white matter surface meshes reconstructed from the images using strong (bio-)physical assumptions and therefore containing more fine-grained spatial information than the raw images (also see Suppl. Text 3).”

We are indeed sampling at resolutions down to 0.2mm, which is below MR image resolution. The reviewer is, however, correct that we are only coarse-graining, not “fine-graining”. Coarse-graining, here, relates to more coarse than the smooth surface meshes though, not the MR image.

Therefore, self-similarity on all length scales would seem to be too strong a constraint. Second, it is hard to imagine how this test could be used in practice. Specific examples of how gyrification mechanisms support or fail to support the generation of self-similarity across any length scale, would strengthen the authors' argument.

We agree that spatial scales much below 0.2mm resolution may not be of interest, as these scales are only measuring the fractal properties, or “bumpiness”, of the surface meshes at the vertex level. We have therefore revised our statement in Discussion and clarified it with an example: “Finally, this dual universality is also a more stringent test for existing and future models of cortical gyrification mechanisms at relevant scales, and one that moreover is applicable to individual cortices. For example, any models that explicitly simulate a cortical surface could be directly coarse-grained with our method and compared to actual human and primate data provided here.”

Some additional, specific comments are as follows:

(4) The definition of the term A_e as the “exposed surface” was difficult to follow at first. It might be helpful to state that this parameter is operationally defined as the convex hull surface area.

We agree and introduced this term now at first use: “The exposed surface area can be thought of as the surface area of a piece of cling film wrapped around the brain. Mathematically, for the remaining paper it is the convex hull of the brain surface.”

Also, for the pial surface, A_t , there are several who advocate instead for the analysis of a cortical mid-thickness surface area, as the pial surface area is subject to bias depending

on the gyrification index and the shape of the gyri. It would be helpful to understand if the same results are obtained from mid-thickness surfaces.

This point is indeed being investigated independently of this study. Our provisional understanding is that in healthy human brains, at native scale, using the mid (or the white matter) surface introduced a systematic offset shift in the scaling law, but does not affect the scaling slope of 1.25. However, this requires a more in-depth investigation in a range of other conditions, and in the context of the coarse-grained shapes, which is on-going. Nevertheless, the scaling law, at first introduction already, has been using the pial surface area [Mota2015] and all subsequent follow-up studies followed this convention. To make our paper here accessible and directly comparable, we therefore used the same metric. Future work will investigate the utility of other metrics.

(5) In Figure 2c, the surfaces get smaller as the coarse-graining increases, making it impossible to visually assess the effects of coarse-graining on the shapes. Why aren't all cortical models shown at the same scale?

The purpose of rescaling the surfaces is to match the scaling plot (Fig 2A) directly, which are showing shrinking surface areas A_e and A_t with increasing coarse-graining. Here, we are effectively keeping the size of the box constant and resizing the cortical surface instead, which is mathematically equivalent to changing the box size and keeping the cortical surface constant.

An alternative interpretation of the “shrinking” is, therefore, that with increasingly smaller cortical surfaces, the folding details disappear, as we require from our coarse-graining method. This is also visually apparent, as the reviewer points out. We have added this to the explanation in the text.

If we, however, changed the box size instead, the scaling law plot would be meaningless: for example, A_e would barely change with coarse-graining. We would therefore have needed to introduce more complexity in our analysis in terms of how we can measure the scaling law. Thus, we opted to present the simpler method and interpretation here.

Nevertheless, we agree that a direct comparison would be beneficial and have thus added the videos for each species in supplementary under this link: <https://bit.ly/3CDoqZQ> Upon completed peer-review, we hope to integrate these directly into eLife's interactive displays for this figure.

(6) Text in Section 3.2 emphasizes that K is invariant with scale (horizontal lines in Figure 3), and asserts this is important for the formation of all cortices. However, I might be mistaken, but it appears that K varies with scale in Figure 4a, and the text indicates that differences in the S dependence are of importance for distinguishing young vs. old brains. Is this an inconsistency?

We agree that it may be confusing to emphasise a “constant K ” in the first set of results across species, and then later highlight a changing K in the human ageing results. To clarify, in the first set of results, we find a constant K relative to a changing S : the range in K across melted primate brains is less than 0.1, whereas in S it is over 1.2. In other words, S changes are an order of magnitude higher than K changes. Hence, we described K as “constant” relative to S .

Nevertheless, K shows subtle changes within individuals, which is what we were describing in the human ageing results. These changes are within the range of K values described in the across species results.

However, in the interest of clarity, we followed the reviewer's suggestion of simplifying the last set of results on human ageing and therefore the variable K in human ageing now only

appears in Supplementary. We have now added clarifications to the supplementary on this point.

Reviewer #3 (Public Review):

Summary:

Through a detailed methodology, the authors demonstrated that within 11 different primates, the shape of the brain matched a fractal of dimension 2.5. They enhanced the universality of this result by showing the concordance of their results with a previous study investigating 70 mammalian brains, and the discordance of their results with other folded objects that are not brains. They incidentally illustrated potential applications of this fractal property of the brain by observing a scale-dependent effect of aging on the human brain.

Strengths:

- New hierarchical way of expressing cortical shapes at different scales derived from the previous report through the implementation of a coarse-graining procedure.*

Positioning of results in comparison to previous works reinforcing the validity of the observation.

- Illustration of scale-dependence of effects of brain aging in the human.*

Weaknesses:

- The impact of the contribution should be clarified compared to previous studies (implementation of new coarse graining procedure, dimensionality of primate brain vs previous studies, and brain aging observations).*

We have now made these changes, particularly by adding two paragraphs to the start of Discussion. One summarising the main contributions above previous work, and one paraphrasing the former in plain English for accessibility.

- The rather small sample sizes, counterbalanced by the strength of the effect demonstrated.*

We have now increased the sample size of the human ageing analysis substantially to over 100 subjects and observe the same trends, but with an even stronger effect. We therefore believe that this revision serves as an additional internal validation of our data and methods.

- The use of either averaged or individual brains for the different sub-studies could be made clearer.*

We have now added this to our Suppl methods: with the exception of the Marmoset, all brain surface data were derived from healthy individual brains.

- The model discussed hypothetically in the discussion is not very clear, and may not be state-of-the-art (axonal tension driving cortical folding? cf. <https://doi.org/10.1115/1.4001683>).*

We have now added this citation to our Discussion and given it context:

“Indeed, our previously proposed model [Mota2015] for cortical gyrification is very simple, assuming only a self-avoiding cortex of finite thickness experiencing pressures (e.g. exerted by white matter pulling, or by CSF pressure). The offset K , or 'tension term', precisely relates to these pressures, leading us to speculate that subtle changes in K correlate with changes in white matter property [Wang2016, Wang2021]. In the same vein of speculation, the scale-dependence of K shown in this work might therefore be related to different types of white matter that span different length scales, such as superficial vs. deep white matter, or U-fibres vs. major tracts. However, there are also challenges to the axonal tension hypothesis [Xu2010]. Indeed, white matter tension differentials in the developed brain may not explain location of folds, but instead white matter tension may contribute to a whole-brain scale 'pressure' during development that drives the folding process overall.”

Reviewer #3 (Recommendations For The Authors):

Many thanks to the authors for this elegant article. I will only report here on the cosmetics of the article.

We thank the reviewer for their kind words and attention to detail and have made all the suggested changes and revised the paper generally for readability, grammar and spelling.

p2: last line of abstract: 'for a range of conditions in the future'.

p3 l.37: I would not self-describe this method as elegant as this is a subjective property .

p3 l.38: 'that will render' -> I wouldn't use the future here.

p.4 l.59: double spacing before ref [9]?

p.6 l.99: 'approximate a fractal' -> why is 'a' italicized?

p.7 fig.2: I would expect the colours to be detailed in the legend. Are there two data points per species because both hemispheres are treated separately?

p.9 l.134-135: 'similar to and in terms of the universal law 'as valid as' -> please add commas for reading comfort: 'similar to, and, in terms of the universal law, 'as valid as'.

p.9 l. 141: For all the cortices we analysed.

p.9 Fig 3: I find the colours a bit confusing in Figs B and C. I find Fig C a bit confusing: what are all the lines representative of, and more specifically, the two lower lines with a different trajectory?

p.10 l.155: '1500' -> '~1500'.

p.13 l. 209: either 'speculate that' of 'wonder if'.

p.14 l.232: 'neuron numbers' -> 'number of neurons'.

p.26 S2 second paragraph: 'gryi' -> 'gyri'.

p.30 l.3: please refrain from starting a sentence with I.e..

p.30 last line before S3.2: 'The algorithmic implementation in MATLAB can be found on Zenodo: TBA' - I guess this is linked to you disclosing the code upon acceptance, but please complete before final submission.

p.34 middle/bottom of page: 'The scheme described in Sec. S3.1' -> double spacing before S3.1?

p.35 l.1: 'We simply replace' -> 'we simply replace' (no capital).

p.36 Fig S5.1: explicit the same colouring of the points and boxes in legend

p.38 Fig. S6.1: briefly describe the use of colours in the legend.

p.39 Fig. S7.1: detail colours in the legend.

p.41 Fig. S7.3: detail colours in the legend.