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Folding of the cerebellar cortex is clade-specific in form but universal in degree

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Abstract

Like the cerebralcortex, the surface of the cerebellum is repeatedly folded. Unlike the cerebralcortex, however, cerebellar folds are much thinner and more numerous; repeatthemselves largely along a single direction, forming accordion-like folds transverseto the mid-sagittal plane; and occur in all but the smallest cerebella. We haveshown previously that while the location of folds in mammalian cerebral cortex isclade-specific, the overall degree of folding strictly follows a universalpower law relating cortical thickness and the exposed and total surface areas predictedfrom the minimization of the effective free energy of an expanding, self-avoidingsurface of a certain thickness. Here we show that this scaling law extends tothe folding of the mid-sagittal sections of the cerebellum of 53 speciesbelonging to six mammalian clades. Simultaneously, we show that each clade hasa previously unsuspected distinctive spatial pattern of folding evident at themid-sagittal surface of the cerebellum. We note, however, that the mammaliancerebellum folds as a multi-fractal object, because of the difference betweenthe outside-in development of the cerebellar cortex around a preexisting coreof already connected white matter, compared to the inside-out development ofthe cerebral cortex with a white matter volume that develops as the cerebralcortex itself gains neurons. We conclude that repeated folding, one of the mostrecognizable features of biology, can arise simply from the interplay betweenthe universal applicability of the physics of self-organization and biological,phylogenetical clade-specific contingency, without the need for invokingselective pressures in evolution.

1 | INTRODUCTION

Over 100 years ago, Ramón y Cajal (1911) established that the histological structure of the cerebellum, while distinct from that of the cerebral cortex, is nearly identical across all vertebrates examined and so invariant that Cajal referred to it as a "law of biology." Similarly, the literature on cerebellar morphology has assumed that there is invariance also on the gross morphological level, in the form of a "common plan" of folding into 10 lobules varying solely in size and degree of folding across species and clades (Sultan & Braitenberg, 1993; Sultan & Glickstein, 2007; Voogd & Glickstein, 1998). The concept of a common plan of folding of the cerebellum dates back to Stroud's (1895) conclusion that "there is a fundamental plan after which the cerebella of all mammals are formed," which implies that a human cerebellum is simply

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a "scaled-up" version of a mouse cerebellum in its morphology—even though Stroud's conclusion was reached after studying the cerebella of only cats and humans.

The cerebellum does vary widely in absolute and relative volumes of gray and white matter across mammalian species (Bush & Allman, 2003; Maseko et al., 2012). While it has been noted that there is also variation in the relative abundance of folia and sizing of subdivisions (lobules) across species (Sultan & Glickstein, 1993), these discrepancies have sometimes been attributed to functional differences in characteristic behaviors, such as the elaborate climbing skills of squirrels (Sultan & Braitenberg, 1993; Sultan & Glickstein, 2007).

During our previous comparative studies of the brains of highly diverse mammalian species (Dos Santos et al., 2017; Herculano-Houzel et al., 2006, 2007, 2011, 2014; Jardim-Messeder et al., 2017; Kazu et al., 2014; Neves et al., 2014), we have not only observed variation in the morphological appearance of the cerebellum belonging to different species, but interestingly, the shape of the midsagittal surface is distinctive to the point that cerebella can be identified as belonging to rodent, marsupial, carnivoran, artiodactyl, or primate species by simple visual inspection. Such a readily apparent clade-distinctive morphology has long been known in the cerebral cortex (Welker, 1990) but is yet to be shown in the cerebellum.

Despite the clade-specific spatial patterns of cerebral cortical folding, we have shown recently that the degree of folding, captured by the relationship between exposed cortical surface area and total cortical surface area, is fully predictable from physical principles according to a single power law that describes the conformation of minimal effective free energy, that is, the most energetically stable and therefore likely conformation, of self-avoiding expanding surfaces like the cerebral cortex (Mota & Herculano-Houzel, 2015). This power law describes how the larger the surface area of a cerebral cortex of constant thickness, or the thinner the cortex of a similar surface area across species, the more it folds—regardless of the number of cells that compose the structure (Mota & Herculano-Houzel, 2015). This power law also describes individual cerebral cortices across length scales, indicating that they are well approximated by a fractal of dimension 2.5 (Kaandorp, 1994; Losa, 2011; Wang, 2021). Fundamentally, it can be shown from first principles that the degree of folding is simply a function of the total area expressed as a multiple of the squared cortical thickness, that is, folding scales not with surface area but with the ratio between surface area and squared cortical thickness (Mota & Herculano-Houzel, 2015). This prediction corroborates previous qualitative demonstrations that, across mammalian species, thinner cortices are more folded (Manger et al., 2012; Pillay & Manger, 2007). If such a mechanism applies universally to determine the degree of folding of a layered brain structure that expands in development, then it should capture equally well the diversity in the degree of folding of the cerebellar surface across species. In this case, all else being equal, a much thinner and broader sheet like the cerebellar cortex would be expected to have much more of its surface tucked into folds than the cerebral cortex, as is the case.

Here we test the hypothesis that the same physical principles that describe the degree of folding of the cerebral cortex also apply to the cerebellum, even though the two structures originate from different anlage in the neural tube: the cerebral cortex from the dorsal ventricular zone of the second neuromere, and the cerebellum from the isthmus and first hindbrain neuromeres (Watson et al., 2016). Importantly, the pattern of neurogenesis also differs between the two cortices. In the cerebral cortex, neurogenesis occurs in an inside-out manner, with neurons mostly originating from the sub-ventricular zone and radiating *outward* as they form simultaneously gray matter and subcortical white matter. In contrast, the cerebellar cortex develops in two phases: first inside-out, as the deep nuclei and the Purkinje cells are born and connect to each other, forming the white matter core of the cerebellum; and then outside-in, as the external cerebellar germinal layer gives rise to large numbers of granule cell neurons that migrate inward, past the preexisting Purkinje cells, and lead to the formation of lobules that expand massively in surface area, much more than they gain in thickness, on top of the preexisting white matter (Goldowitz & Hamre, 1998). This differential expansion of the outer layer of the cerebellar cortex was recently shown to initiate the placement of cerebellar folds, followed by progressive subfolding of the initial folds (Lawton et al., 2019). Moreover, while the development of the cerebral cortex is largely completed prior to birth, the timing of the development of the cerebellum extends significantly postnatally (Goldowitz & Hamre, 1998) and is therefore possibly more subject to environmental influences that might affect its degree and pattern of folding. Finally, the folding of the cerebellum is distinctly two-dimensional, with folia placed mostly transversally to the midsagittal plane, in contrast to the three-dimensional folding of the cerebral cortex. Despite so many distinctions, the cerebellar cortex, like the cerebral cortex, is a self-avoiding gray matter surface that envelops white matter and deep nuclei, has a characteristic thickness, and expands through cellular proliferation and neurite elongation. Thus, if both cortices are self-avoiding surfaces, the expansion in development of which is subject to the same universal physical dictates, despite their different biological composition and connectivity, then the degree of folding of both cerebral and cerebellar cortices should arise from the same universal folding mechanism, regardless of the biology of how the tissue is formed—even if the spatial placement of the folds is somewhat variable, though still clade-specific. If this is the case, cerebellar morphology should be approximated by a fractal.

Fractals are geometric objects that are hierarchically composed of substructures of arbitrarily small scales (Losa, 2011). These substructures are moreover self-similar in the sense that they are scaled-up or scaled-down versions of each other, regardless of size. This self-similarity is typically quantified as a power law relation between the object's intrinsic and extrinsic sizes, as measured by tiling it over with tiles of a fundamental, specified size. The exponent in this relation is proportional to the so-called fractal dimension of the object. Valid across mammalian cerebral cortices, the universal gyrification relation can be rewritten suggestively as $\frac{A_T}{A_0} = (\frac{A_E}{A_0})^{\frac{5}{4}}$, where $A_0 = \frac{T^2}{k^4}$; and indeed it has recently been shown (Wang et al., 2021), by erasing structures smaller than a varying A_0, that individual primate cortices also follow a version of this law, and thus cortices approximate fractals with fractal dimension

$d_f = 5/2$.

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Here we test the hypothesis that the cerebellar cortex folds like a fractal, following a universal scaling rule analogous to the one observed in the cerebral cortex, in a self-similar manner. We proceed by determining whether the following criteria are met. First, to be universal, folding must follow a scaling rule that applies equally across the cerebella of various species and clades. Second, there must be a fundamental unit of length, or critical length, to cerebellar folia that, once reached, is followed by the formation of a new fold in an ever-repeating pattern. Finally, scaling must follow the same scaling rule at different levels *within* an individual cerebellum. At the same time, we test the prevailing assumption that all mammalian cerebella share a common spatial pattern of distribution of their folds (and therefore lobules), as well as the alternative hypotheses that (1) there is no particular order to the placement of the folds of the cerebellum across species, and that (2) like the cerebral cortex (Welker, 1990), clade-distinctive spatial patterns of folding also occur in the cerebellum.

2 | MATERIALS AND METHODS

2.1 | Experimental design

We approached the investigation of whether cerebellar folding follows a universal scaling, possibly with clade-specific spatial patterns, by generating contour tracings of the total and exposed perimeters of the cerebellar gray matter as seen in the midsagittal section of the cerebellar vermis of different mammalian species. Because cerebellar expansion in mammalian evolution occurs most obviously at the lateral hemispheres (Kielan-Jaworowska et al., 2004), the vermis is the portion of the cerebellum most likely to be conserved in structure across species, making them most directly comparable. Additionally, the midsagittal vermis is readily observable in most brain hemispheres available in various brain collections, making our analysis readily feasible and easily repeatable by other groups. Our choice of quantifying folding in the midsagittal section of the cerebellum is validated by recent analyses of cerebellar folding using a similar approach (Cunha et al., 2021; Iwaniuk et al., 2006), which found that the folding index of the midsagittal section represents the folding index of the whole cerebellum (Iwaniuk et al., 2006). Importantly, the folding index calculated by those researchers uses the surface area of the Purkinje cell layer, not the pial surface of the cerebellum; here we choose to use the pial surface instead, for two reasons. First, the cerebella we use are whole and in storage for future studies, so they cannot be stained, which precludes visualization of the Purkinje cell layer; and second, the pial surface area combined with the volume of the cerebellar cortical gray matter gives us an estimate of the average cortical thickness, which is a necessary variable for our analysis.

For the comparison of spatial patterns of cerebellar folding across species and clades, we isometrically scaled the contours so that they could be overlaid across species. Estimated variables were then subjected to mathematical analysis as described below.

2.2 | Specimens

We analyzed 1 specimen each of 53 species belonging to 6 mammalian clades: Artiodactyla ($n = 8$), Carnivora ($n = 10$), Marsupialia ($n = 5$), Perissodactyla ($n = 3$), Primata ($n = 8$), and Rodentia ($n = 19$; Table 1). All cerebella had the midsagittal surface imaged at high resolution (1200 dpi) on an HP flatbed scanner with a millimeter ruler placed on the flatbed scanner for precision and consistency.

2.3 | Measurements

We used Stereo Investigator software (MicroBrightField) to trace and measure all contours of the midsagittal cerebellar plane of each cerebellum. A virtual lens was first created to the scale of the original image for calibration. We started by tracing the total perimeter of the pial surface of the cerebellar gray matter, or P_T, with care to capture the full contour of each folium, under enough magnification that the image of the cerebellum filled the screen of a 32″ monitor (Figure 1, P_T), which amounted to a similar viewing resolution of the individual folia, over which the same Cavalieri grids were superimposed (see below). Next, a new contour traced the outer (exposed) surface of each cerebellum, from the anterior-most to the posterior-most edge of the cerebellar cortex, as if saran-wrapping the structure, to provide a measurement of the exposed perimeter (P_E) of the midsagittal cerebellar plane (Figure 1, P_E). The degree of folding in this two-dimensional plane, or folding index F, was calculated for each cerebellum as the ratio between the total perimeter and the exposed perimeter of the cerebellar gray matter on the midsagittal plane ($F = P_T/P_E$).

To estimate the average thickness of each cerebellar cortex, we used the Cavalieri probe within Stereo Investigator to obtain measurements of the area of gray matter (i.e., molecular, Purkinje, and granular cell layers indistinctly, for they cannot be distinguished at a 1200 dpi resolution) on the midsagittal plane (A_T), which when divided by the total perimeter provides a measurement of the average grey matter thickness ($T = A_T/P_T$) at that plane. Next, we determined the number of folia in the midsagittal plane (C) by counting how many foliar crowns were contained in P_T, which allowed us to determine the average length L of the cerebellar folia in each species as the ratio $L = P_T/C$ (Figure 1, right). While we define a "foliar crown" as the unit of cortical surface farthest from the white matter in any segment of cerebellar cortex between two sulci (that is, a gyrus) in the recurring folding of this cortex. Note that this procedure does not require or involve measuring the length of individual folia in order to determine the average length of cerebellar folia, L.

2.4 | Mathematical model

Perimeter measurements of the midsagittal surface of the cerebellum were used rather than estimates of the full surface area of the cerebellar cortex because the latter would be too time-consuming, and actually unnecessary given the two-dimensional nature of cerebellar folding,

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Glickstein, 1998). Additionally, it was recently shown that the cerebellar cortex folds initiate with differential expansion of the outer layer, without an obvious cellular pre-pattern, and with differential expansion of lobules that correlates with the progressive subfolding of the initial folds (Lawton et al., 2019), which is consistent with the fractal scaling of cerebellar folding that we propose here. We thus find it more likely that the placement of cerebellar folds is controlled by clade-specific genetic factors that may lead to differential patterns of cortical expansion (thus leading to different lobule lengths) and/or placement of anchoring centers (Sudarov & Joyner, 2007) that might accompany evolutionary divergence between the mammalian clades.

These considerations about the placing of the main cerebellar folds lead to the fourth evolutionary implication of our findings: If the *mechanism* of cerebellar folding is not an evolved feature, but rather a consequence of fundamental physics, with hierarchical placement of successive folds once a critical length is reached, it becomes unlikely that there is some sort of "ancestral cerebellar pattern." Our results reinforce Mota and Herculano-Houzel's proposal in 2015 that, given a set surface area and thickness, subjected to uneven forces, a sheet of gray matter will always produce the same degree of folding regardless of the mammalian clade to which it belongs, or the number of neurons it contains.

The fractal pattern of cerebellar folding revealed by our present findings begs a developmental investigation of several predictions that we can make. While our qualitative analysis was restricted to the visual analysis of already formed adult cerebella, their overlaid contours share a pattern suggestive of a hierarchical order of folding, with the specific prediction that the deepest main fissure forms first, and that the formation of the subsequent folds follows in the same order as their apparent depth in the adult cerebella. Thus, we predict that the two horizontal folds that divide the cerebellum from two halves into quarters (so to speak) are next to form after the two halves formed by the main fissure expand to the critical foliar length, given that they have the highest level of coincidence across species. As the hierarchical order of folding continues, the decreased coincidence in sulcal placement most likely arises as a result of certain lobes or lobules expanding at a faster rate than others, as suggested by Lawton et al. (2019). Thus, an uneven growth of lobules that is shared in the same manner between species of the same clade could be the mechanistic reason behind the formation of the clade-specific spatial arrangement patterns. Developmental studies would make it possible to observe empirically the order in which foliation occurs as well as how the spatial placement of the main lobes arises as the cerebellum expands. Comparative studies of cerebellar development would thus reveal how clade-specific patterns of folding arise, even as folding itself occurs predictably due to the physical properties of biological tissue.

Finally, a lingering question at this point is whether the remarkable degree of folding of even very large cerebella, such as those of humans, elephants, and cetaceans, as well as in the minute cerebella of bats, also follows the universal relationship described here while maintaining the spatial pattern that is typical of their clades. These studies, which will test the validity of our model not only in humans but also in a number of species known to have relatively larger cerebella (Clark et al., 2001; Maseko et al., 2012), whether because the number of neurons in the cerebellum is extraordinarily large (Herculano-Houzel et al., 2014) or because the cerebral cortex is relatively small in volume (Herculano-Houzel et al., 2020), are currently underway.

AUTHOR CONTRIBUTIONS

Annaleigh R. York performed research, analyzed data, and wrote the article; Chet C. Sherwood, Paul R. Manger, and Jon H. Kaas contributed research materials; Bruno Mota designed research, analyzed data, and wrote the article; Suzana Herculano-Houzel designed research, performed research, analyzed data, and wrote the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are openly available in the manuscript itself.

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