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Bok's equi-volume principle: Translation, historical context, and a modern perspective

Jack Consolini [a], Nagehan Demirci [b], Andrew Fulwider [c,d], Jeffrey J. Hutsler [e], Maria A. Holland [a,b,*]

[a] *Department of Aerospace and Mechanical Engineering, University of Notre Dame, Notre Dame, IN 46556, USA*
[b] *Bioengineering Graduate Program, University of Notre Dame, Notre Dame, IN 46556, USA*
[c] *Department of Chemical and Biomolecular Engineering, University of Notre Dame, Notre Dame, IN 46556, USA*
[d] *Department of German and Russian Languages and Literatures, University of Notre Dame, Notre Dame, IN 46556, USA*
[e] *Program in Neuroscience, University of Nevada, Reno, NV 89557, USA*

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ABSTRACT

The human brain has a complex and unique structure, characterized by intricate three-dimensional folds. These folds, and the mechanisms for their formation, have been studied for over a hundred years. Here we offer a full translation of the pivotal (1929) work by Siegfried Bok, "Der Einflußder in den Furchen und Windungen auftretenden Krümmungen der Großhirnrinde auf die Rindenarchitektur" ("The Influence of the Curvature Occurring in the Folds and Turns of the Cerebral Cortex on Cortical Architecture"). This paper established the influential equi-volume principle, which stated that cortical and laminar thicknesses, along with neuronal shape and fiber orientation, change in order to preserve relative volume throughout the folds of the cortex. We also offer a commentary on the main points of the work, looking at Bok's observations and predictions regarding the structure of neurons, cortical laminae, and the cortex itself, throughout the folds and curves of the brain. His equi-volume principle has held up to decades of experimentation and, even today, has important implications for the analysis of brain structure and function.

Statement of Significance: This manuscript presents, for the first time, a full English translation of the foundational neuroanatomy article, "Der Einflußder in den Furchen und Windungen auftretenden Krümmungen der Großhirnrinde auf die Rindenarchitektur" ("The Influence of the Curvature Occurring in the Folds and Turns of the Cerebral Cortex on Cortical Architecture"), written over 90 years ago by Siegfried T. Bok and heavily cited since then. In addition, we provide an assessment of Bok's main points, in light of his contemporaries in research at the time, as well as more recent work during the intervening decades.

1. Introduction

During gestation, the small and smooth fetal brain matures into the larger, highly convoluted brain distinctive of adult humans. For over a century, researchers from diverse disciplines (neuroanatomy, physiology, biology, engineering, etc.) have devoted their research efforts into understanding the structure and function of the brain, particularly the cerebral cortex. Although the cumulative knowledge has increased enormously over the years, many questions remain about how the cortex is arranged, and why. In particular, outstanding questions include: How do cortical structure and function vary throughout different regions of the brain? What are the meaningful subunits of the cortex (e.g. cortical columns or cortical laminae) and how do they contribute to the whole? How are the diverse functions of the cortex enabled by the structure of the cortex? Recent scientific advances now allow researchers to develop ultra-high resolution, three-dimensional, digitized laminar [1], histological [2], and anatomical [3] atlases of the human brain with outstanding precision and detail, illustrating the microscopic architecture of the cortex [4] and revealing intracortical laminar layers and columns. In many ways, these works build on the foundation of pioneers of the field working a century ago.

Many of these pioneers in the field of neuronatomy published in German. Researchers from around the world, including Germany [5], Austria [6,7], Switzerland [8], the Netherlands [9], and Hungary [10], used German as the language for scientific communication. Nowadays, however, few researchers acquire professional scientific fluency in German, and are unable to plumb the depths of these classic papers of the past. While they continue to be widely cited, many researchers

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* Corresponding author at: Department of Aerospace and Mechanical Engineering, University of Notre Dame, Notre Dame, IN 46556, USA.
E-mail address: maria-holland@nd.edu (M.A. Holland).

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in the present day may not have been able to read them in their entirety or capture minor or subtle points. Brodmann's classic paper on the localization of functions within the cerebral cortex is a prime example: originally published in 1909, it has been cited over 5000 times, including in major textbooks. However, until 1994, no complete English translation was available, and very few people had access to the book, much less had read it in full [11].

Here, inspired by this and other recent translation initiatives, including several in this special issue [12,13], we present a full translation of a transformational early German treatise on cortical anatomy, "Der Einfluß der in den Furchen und Windungen auftretenden Krümmungen der Großhirnrinde auf die Rindenarchitektur" ("The Influence of the Curvature Occurring in the Folds and Turns of the Cerebral Cortex on Cortical Architecture") by Siegfried Bok [9]. While the author later published in English [14,15], this earlier work has been largely inaccessible to many researchers. He even republished some of his early work in English 30 years later [16], but many of these publications, in both German and English, are quite difficult to find these days. Furthermore, an important purpose of making this translation available is to properly situate Bok as a contemporary of, and in conversation with, the pioneers of the field of neuroanatomy, including Brodmann and von Economo, rather than someone who arrived on the scene only decades later.

To that end, we begin with some context on the historical period when this piece was published, and a short introduction of some of the people and ideas that Bok was responding to (Section 2). We then offer an assessment of the work in light of the intervening ninety years of research in neuroscience and neuroanatomy. Guided by the structure of the original paper, we focus on the variation, throughout the folds of the brain, of laminar thickness (Part II, here Section 3), neuronal form (Part III, here Section 4), and cortical thickness (Part IV, here Section 5). In each of these areas, we highlight the main observations and predictions presented by Bok, examine the state of knowledge in the present day, and discuss the limitations of Bok's original work.

2. Historical context

Before addressing the work in question, we will first mention some of the significant names in the field of neuroanatomy in early 20th century, as these researchers and their ideas greatly influenced Bok.

Korbinian Brodmann (1868–1918) laid the foundations of anatomical brain mapping and cytoarchitecture of the cerebral cortex [17]. His work led to the functional parcellation of the cortex into 48 distinct areas, known as Brodmann areas, which are still widely used today [18]. His publications between 1897 and 1914 not only revealed the detailed laminar microstructure and cellular composition of the human cortex, but also the evolution of the cortex in different species. He identified the organization of the cortex into six layers, called laminae, and then quantitatively investigated the evolution of the cortex by analyzing the laminar and cortical thickness variations within and between species [19]. In this work, he found that the six-layered pattern is initially present in all animals, and becomes visible in the fetal human brain between the 6th and 8th months of gestation [20].

Constantin von Economo (1876–1931) and Georg Koskinas (1885–1975) were the next pioneers in understanding the differences in cytoarchitectural organization between cortical regions. They parcellated the cortex into 54 major areas, divided into 107 subunits, and reported the thickness, cell density, and cell size at each laminar layer. Crucially, they improved the method of measuring cortical thickness. Historically, sections were cut through an entire hemisphere (either transverse, sagittal, or coronal), resulting in oblique cuts through gyri and sulci, artificially inflating their thickness. Instead, von Economo and Koskinas cut each gyrus, sulcus, or wall section perpendicular to their axes [20–22]. With this measurement technique, they found that cortical thickness varies from 1.3 to 4.5 mm regionally, with a global mean of 2.5 mm. Their regional thickness averages correlate very strongly with data from contemporary magnetic resonance (MR) imaging and surface reconstruction techniques [23].

Both Brodmann and von Economo remarked on the variations in cortical thickness throughout the brain, noting that gyri were generally thicker than sulci [5] and that cortical thickness decreased gradually from dome (*Kuppel*) to wall (*Wand*) to valley (*Tal*) (Fig. 1A) [7]. To Brodmann, these variations likely depended on the cellular size, shape, arrangement, and density at each individual layer and at each location of the cortex; for example, densely-packed arrangements of smaller cells would result in a thinner cortex and vice versa. Von Economo and Koskinas also discovered consistent patterns of laminar thickness in each fold: the outermost layers of a dome (or gyrus) and innermost layers of a valley (or sulcus) are the thinnest, and the innermost layers of a dome and outermost layers of a valley are the thickest. Because they believed that every physiological function needs an anatomical basis, they interpreted this as a functional trait of the cortex, surmising that thicker layers are more important functionally [22]. In short, these authors believed that cytoarchitectonic differences lead to thickness changes which then result in functional differences.

In 1929, a Dutch professor of anatomy and histology named Siegfried Thomas Bok (1892–1964) published a paper titled "Der Einfluß der in den Furchen und Windungen auftretenden Krümmungen der Großhirnrinde auf die Rindenarchitektur" ("The Influence of the Curvature Occurring in the Folds and Turns of the Cerebral Cortex on Cortical Architecture"). This paper (e.g. Fig. 1B) was clearly founded upon the work of Brodmann and von Economo — both inspired by and formulated in opposition to these earlier studies. This work opens by referencing the assumptions of "modern authors" (likely von Economo) who "assume that a fold corresponds to a portion of the cortex that, aside from being a fold, has special architectural characteristics", and the "aforementioned authors" (likely Brodmann) who "believe that this curvature has no influence on cortical architecture".

3. Variation in laminar thickness throughout folds

> *"[The law of volume constancy] states that in a flat cortical section, the volume distribution among the five cell-abundant layers is the same as in a curved section, so long as no differences exist between these two sections other than those necessitated by the curvature. And, in a flat section, the thickness distribution is the same as the volume distribution, as the horizontal dimensions of corresponding layers in a section are always the same. The thickness distribution that would be displayed by the cortex if it were not curved is therefore equal to the volume distribution of the curved section". [9, translated]*

Even in Bok's time, it was already known that outer gyral folds are significantly thicker than inner sulcal folds throughout the cortex [7,19]. However, it was not known why or how this difference arose. Bok considered the hypotheses of his fellow researchers and formulated a thought experiment, attempting to rearrange an initially straight checkerboard pattern (Fig. 2A) into a curved one. Three possible configurations can be imagined, in which either the size and shape of the checkerboard squares is conserved at the cost of arrangement (Fig. 2B), or the arrangement of the checkerboard is preserved at the expense of the size (Fig. 2C) or shape (Fig. 2D) of the original squares. Although none of these patterns perfectly represents the actual configuration of cortical laminae, they most resemble the latter [24]. If arrangement and size are to be preserved at the expense of shape, this can occur in at least three different ways (Fig. 2A–C), with different effects on the total height. Applying this analogy to the cortex, then, suggests that some physical aspect of the cortical segments (corresponding to the squares of the checkerboard) *must* be changed after folding to adapt to the final curved configuration. Bok thus asserted that cortical curvature could affect cortical structure without affecting the functional properties of the cortex. This was in opposition to the ideas of Von Economo and

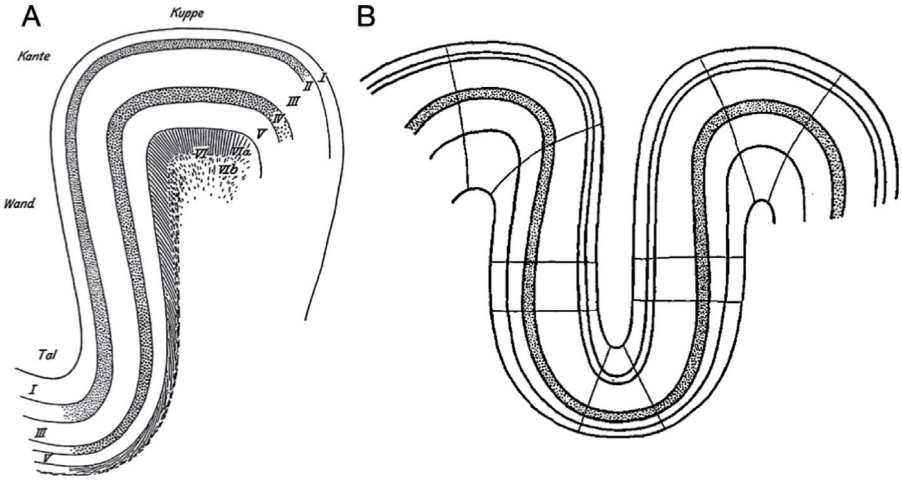

Fig. 1. Schematic drawings of the cortex depicting patterns of cortical and laminar thickness. A) Original drawing of Von Economo and Koskinas [7] depicting the six layers of the cortex at the dome (*Kuppe*), brink (*Kante*), wall (*Wand*), and valley floor (*Tal*) of the cortex. B) Original drawing of Bok [9] depicting the six layers of the cortex and cortical sections at gyri, wall, and sulci.

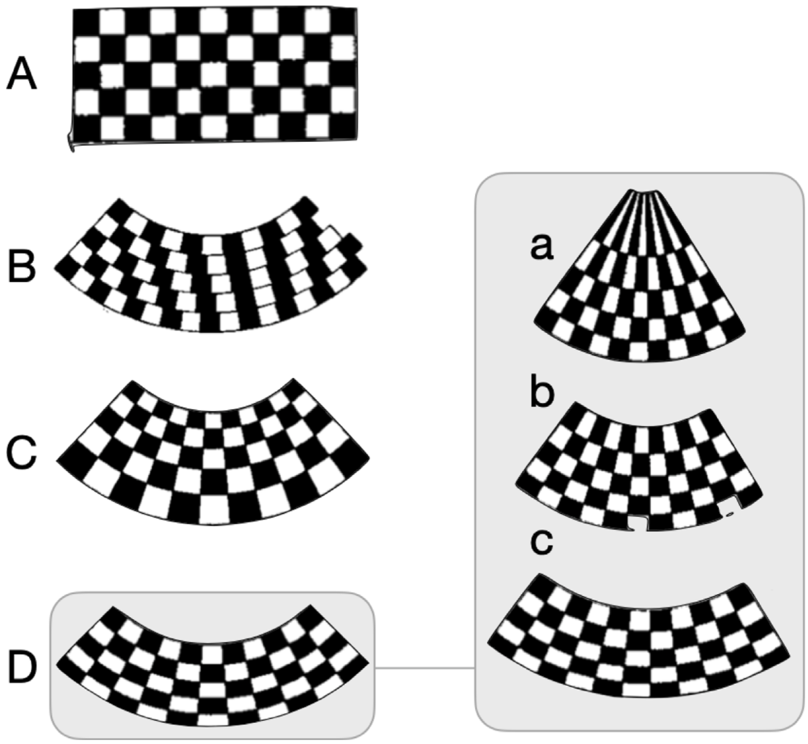

Fig. 2. Bok's visualizations of ways cortical components could change throughout curvature. (A) Initial checkerboard pattern with straight vertical and horizontal lines. Then the straight pattern is transformed into a curved one, in three different ways. (B) Squares preserve their initial size and shape, but the arrangement is altered. (C) Initial shape and arrangement are preserved but the size is altered. (D) Initial size and arrangement are preserved but shape is altered. Inset image (a–c) shows variations of how size and arrangement can be preserved by altering the dimensions (height and width) of each element. Modified from [9].

Koskinas [7], who believed that thicker layers were more important functionally.

In his manuscript, Bok qualitatively and quantitatively compared 29[1] sets of gyri, walls, and sulci in magnified, Nissl-stained folds taken from healthy adult human brains (Fig. 3, left). In visually comparing

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[1] Bok's original investigation included 17 folds, 10 extracted from a highly curved cerebral cortex, and 7 from a less curved cortex. (No information was provided regarding the individuals studied, such as their sex, age, cause of death, or why the curvature of their cortices might differ so significantly.) The 17 folds were taken from 7 regions: medial frontal gyrus (frontal lobe), insular cortex (lateral sulcus, postcentrally located), striatum (forebrain, near the subcortical basal ganglia), temporopolar cortex (temporal lobe), middle temporal gyrus (temporal lobe), basal forebrain (forebrain, below the subcortical basal ganglia), and paracentral lobe (between the frontal and parietal lobe). Some folds were taken from both the left and right hemisphere of both brains, while others were selected from only one hemisphere or only one of the individuals (for unknown reasons, perhaps because they were judged to curve too much in the out-of-plane direction). The right temporopolar cortex of the highly curved cortex was removed from the analysis because the laminar structure significantly deviated from other folds taken from the same region, leaving 16

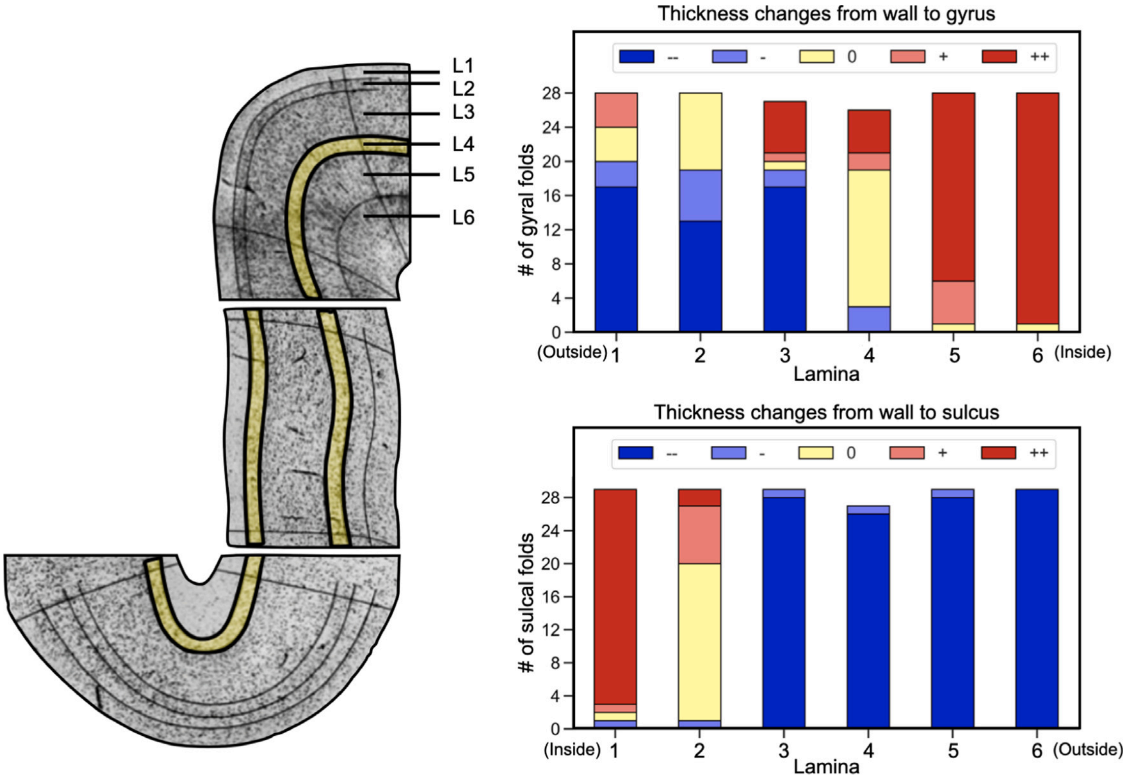

Fig. 3. Qualitative comparison of laminar thicknesses throughout a gyrus, wall, and sulcus. Left: Representative Nissl-stained folds containing gyral (top), wall (middle), and sulcal (bottom) folds from an adult cortex, modified from [9]. L2 and L4 are indicated in yellow from the sulcus to the wall and the wall to the gyrus, respectively, as Bok's qualitative analysis indicated the plane of isomorphic curvature is primarily located within them. Right: Recreation of Bok's qualitative analysis which visually compared the thickness changes (increasing, +/++; decreasing, -/- -; or staying roughly the same, 0) from the wall to gyrus (top) and from the wall to sulcus (bottom) in 29 folds. In the gyrus, LI is on the outside of the curve while L6 is on the inside, and vice versa in the sulcus. His results indicated that the second layer had the most similar thickness between the wall and the sulcus, and the fourth layer between the wall and the gyrus.

the straight walls to the curves, Bok found that the layers on the inside of the curves got thicker, and those on the outside of the curves got thinner (Fig. 3, left); the differences between gyri and sulci were even larger. This is to say that at the sulcal fundus, Lamina 1 (L1) is the thickest, while in the gyral crest, L6 is the thickest.

Although consistent with the previous discoveries of Brodmann [19] and Von Economo and Koskinas [7], Bok asserted that the laminar thicknesses did not change arbitrarily. He postulated that if the inner and outer layers curve heteromorphically (experiencing shape changes throughout curvature), than there must be a point at which the thickening and thinning trends diminish to the extent that there is no volume change. Bok called this neutral axis the *Ebene der isomorphen Krümmung* or the "plane[2] of isomorphic curvature". The plane of isomorphic curvature is not a plane in a mathematical sense, but rather a curving line (in two dimensions) or surface (in three dimensions) along which isomorphy, or similarity of form, is preserved. If the plane of isomorphic curvature is located within a certain lamina in some region of the cortex, that layer is expected to maintain relatively constant shape (and therefore, thickness). In his qualitative analysis, the innermost (with respect to the curve) granular layer showed the least thickness change in over 80% of the folds he inspected (Fig. 3, right). Thus he concluded that the plane of isomorphic curvature lay in the internal granular layer (L4) in gyri and in the external granular layer (L2) in sulci.

For his quantitative analysis, Bok first determined the boundaries of each cortical section by tracing the direction of the main dendrites, which stretch towards the pial surface in gyri and towards the white matter in sulci.[3] He then approximated the laminar thicknesses and volumes[4] of the gyral, sulcal, and wall sections from magnified photographs. From those measurements, he calculated the relative thickness and volume ($\bar{T}$ and $\bar{V}$) by normalizing by the section's *total*[5] thickness and volume, respectively.

When comparing each lamina in gyri and sulci, it is clear that relative laminar thicknesses (Fig. 4, left) differ significantly more than relative laminar volumes (Fig. 4, right). Specifically, L1 is up to 90% thinner in gyri than in sulci and L6 is up to 40% thicker, while the largest volume change is only 12%, in L1. This larger change in relative volume in L1 ($5\pm3.5\%$, mean ± SD) actually led Bok to exclude it from his analysis, and propose that the volume was only conserved in L2–L6

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folds. In each fold, he identified five cortical sections centered around a single sulcus, with a wall and a gyrus on either side. To evaluate changes in volume and thickness throughout curvature, he compared each sulcus to both of its neighboring gyri independently. Three regions were missing a second gyral section, so only 29 comparisons between gyral and sulcal sections were made.

[2] The German word *Ebene* is the mathematical word for plane, but is also used in the sense of "level" or "height". It does not imply flatness in the same way that "plane" does in English. In Bok's usage, it is implied to curve similarly to the cortex.

[3] These cortical sections should not be confused with neurobiological cortical columns, which are the smallest functional unit in the cortex ($200\,\mu m$ to $800\,\mu m$ length). However, it should also be noted that cortical columns are aligned in the same direction as the main dendrites, such that they could be used similarly to denote the edges of cortical sections.

[4] Bok actually measured surface area, which he used as a proxy for volume, based on the assumption that a reasonably straight three-dimensional fold could be simplified into a set of uniformly thick cross sections.

[5] Bok excluded L1 from his analysis post-hoc on the basis of its outsized thickness changes. Thus, the "total" thickness and volume used for normalization are only those of L2–L6. Here we report also his values for L1, normalized by the same "total".

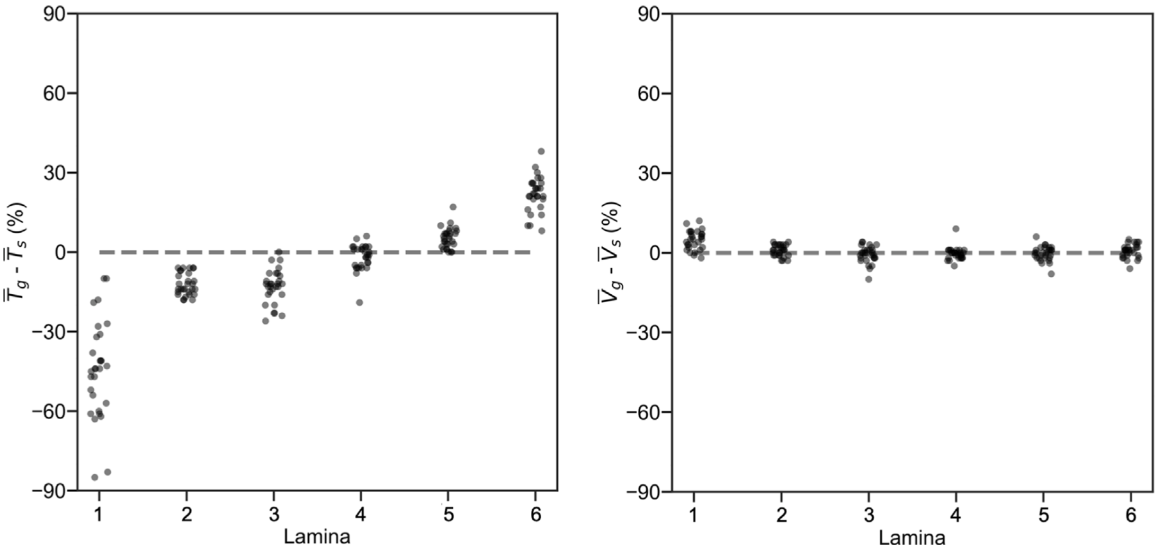

Fig. 4. Average gyral–sulcal difference in relative laminar thicknesses, $\bar{T}$ (left), and volumes, $\bar{V}$ (right), in the folds examined in [9]. Note that Bok's 'total' thickness and volume are the sum of only L2–L6, so here we calculate L1's relative thickness and volume with respect to this total.

(see footnote 5 for more information). Bok thought that its significant thickness changes were relatively too large for its considerably small volume, and attributed this to its acellular composition. However, even this change was just barely larger than the other layers (Fig. 4, right).

Based on these measurements, Bok proposed his law of volume constancy (*Volumkonstanz*), more recently referred to as the equi-volume principle, asserting that the significant changes in laminar thickness serve to maintain a constant volume of each layer throughout gyri, sulci, and the walls in between. He argued that curvature affects the structure of the folds and their laminae but not necessarily functional properties. This equi-volume principle explains the consistent curvature–thickness relationship at each layer.

3.1. Recent work

Bok's equi-volume principle has since served as an important foundation for the laminar parcellation of the cortex via *in vivo* neuroimaging, such as MRI and functional MRI (fMRI). Throughout most of the 20th century, the delineation of cortical laminae could only be done in histological sections, limiting the analysis to the manual segmentation of two-dimensional areas in *ex vivo* tissues. Advances in *in vivo* neuroimaging, particularly the development of MR imaging in the 1980's, opened the possibility of non-invasive imaging in three dimensions. This was shortly followed by the formulation of methods to segment the images produced and measure brain morphology, including cortical thickness. In the early 2000's, surface- and voxel-based Laplacian methods were developed to calculate cortical thickness by computing the gradient between equipotential pial (outer) and white matter (inner) surfaces. These methods were used to measure thickness in the brain [25–28] and other tissues [25] in two and three dimensions. The success of voxel-based Laplacian methods led to their application for parcellating cortical layers in two-dimensional histological sections and MR images [29,30]. Further refinement of the Laplacian approach introduced equi-distant cortical "layers" (not laminae in a cytoarchitectural sense), spaced evenly across the cortical profile [31].

In the 2010's, Bok's work was "rediscovered" by the neuroimaging community [32] and computational algorithms were created to apply the equi-volume principle for identification of laminar profiles in human brain MRIs [33]. The implementation of the law of volume constancy relies on the accurate location of isosurfaces (or iso*volumetric* surfaces) which divide the cortex into regions of constant relative volume [33]. This approach more accurately accounts for curvature changes than Laplacian and equidistance methods [32], producing segmentations that more accurately trace histological laminar boundaries in both human and non-human brains [33,34].

The equi-volume principle, along with Von Economo and Koskinas's atlas of neuron cell density profiles, has also been used to automate the laminar segmentation of histological images, resulting in BigBrain, a three-dimensional composition of histological images accompanied by high-resolution MR imaging and segmentations of all six cortical laminae [1,35]. Using a similar isosurface to Waehnert et al. [33], they identified the L1/L2 boundary with the same precision as manual parcellation. Similar quantitative comparisons have shown that layer profiles generated by the equi-volume model correspond closely to image intensities measured from high-resolution images [33,36,37].

3.2. Limitations and critique

While these recent works highlight the validity and applicability of Bok's equi-volume principle, recent attention on his work has also highlighted some limitations and need for re-evaluation. Firstly, Bok's identification of cortical sections were rather unclear and lacked a degree of accuracy. The lines that depict the boundaries are primarily convex-shaped in gyri, almost straight in walls, and perfectly straight in sulci (Fig. 1B), although one would expect a concave shape. These section boundaries significantly affected how surface area (again, as a proxy for volume) was measured. Bok determined the relative laminar surface areas by magnifying the sections, tracing them onto cardboard, cutting them out, and calculating the volume of the cutout using its density and mass. While this method facilitated the measurement of irregular geometries, the calculated volumes were be entirely dependent on the cortical section boundaries. For example, if the boundaries in the gyrus were drawn with a straight line similar to the sulcus (Fig. 3, left), the outer layers of the sulcus would have a smaller proportion of the total volume. Uncertainty in how to define cortical sections has resulted in different interpretations of Bok's equi-volume principle today [32]. Some adopt a curved configuration at both gyri and sulci [33], while others adopt a configuration where all boundaries are depicted as straight lines [36].

Bok's measurements were similarly dependent on his ability to reliably segment each of the six cortical laminae. Several issues arise here because, depending upon the cortical region, it is often very difficult to distinguish some layers (i.e., L2/L3 and L5/L6), causing some

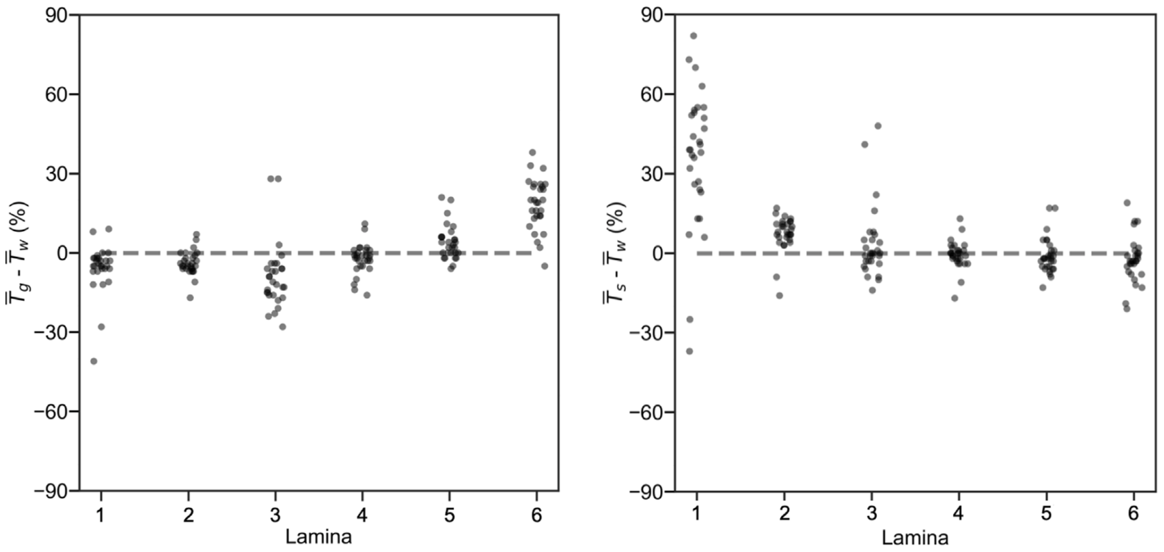

Fig. 5. Average difference in relative laminar thicknesses, $\bar{T}$ between gyri and wall (left), and between sulci and wall (right) across L1–L6 of the folds examined in [9]. Note that Bok's 'total' thickness is the sum of only L2–L6, so here we calculate L1's relative thickness with respect to this total.

researchers today to group them together in their analyses [e.g. 33,38, 39]. Additionally, even if the boundary line were more clear, the lack of a blinded expert casts doubt on the reported numbers. Bok's hypothesis could have potentially affected his segmentation of the laminae, leading him to err towards thicker inner layers and thinner outer layers. While a fully automated laminar segmentation process for the entire brain is still out of reach, the standard for studies these days is to have sections segmented by an independent, blinded expert.

Thickness measurements carried a similar lack of clarity and accuracy. Bok calculated laminar thickness by measuring the distance at an arbitrary point, offering no information as to which point or how he determined the distance. This approach fails to capture how thickness changes throughout a section, which is not equally curved throughout. Furthermore, the calculation of thickness of a curved section is not trivial; it will depend heavily on methodological choices (nearest point or orthogonal projection? Euclidean distance or distance along the curved section boundary?). Future studies attempting to replicate or test the law of volume constancy must pay particular attention to their choices in approach when determining cortical section boundaries and thickness measurements.

The location of the theoretical plane of isomorphic curvature should also be reconsidered. Bok based the location of this plane (in L4 and L2 in gyri and sulci, respectively) on his qualitative comparison of thickness changes from the wall to the curved sections (Fig. 3). However, a quantitative analysis of his own data shows that L2 actually thickens in the wall-to-sulcus transition (Fig. 5, right). Similarly, while L4 generally sees very small relative thickness deviations between the wall and both curved sections, it also deviates by up to 20% in some folds. Meanwhile, each layer (even, rarely, L1) is found to be isomorphic, or nearly so, in some folds. These data highlight a point that could have been more clear in the original paper: that the plane of isomorphic curvature is a theoretical construct, and does not neatly or consistently map onto the cytoarchitecture of the cortical laminae. While this plane may be primarily located in or near L2 and L4, it is also expected that its position will shift depending on how curved the cortex is in a given location.

While recent work has shown that segmentation based on the equi-volume principle can very accurately delineate laminae [3], there are also issues when expanding to the whole brain [32]. This appears to be less of an issue with the law of volume constancy itself, but rather in the implementation of the law. Equi-volume layering segmentation relies on the location of an isosurface that divides the cortex into regions of constant relative volume. However, as implemented, the isosurfaces over-correct for changes in curvature, at times leading to inaccurate approximations [33]. Despite the use of different smoothing methods to approximate unregistered local curvature changes, layer inaccuracies persist [32]; the solution might come through the incorporation of a curvature sensitive parameter into the method for determining the isosurface.

Another questionable aspect of Bok's analysis was his exclusion of L1 from his law of volume constancy. He believed that the layer's neuronal composition and thickness changes disqualified it, but his own measurements show that L1 largely maintains its relative volume (Fig. 4, right), with an average difference of 5 ± 3.5%. However, its exclusion can be argued on a cytoarchitectural basis. Bok's neuronal analysis (elaborated on in Section 4) showed that L1 contains almost solely horizontal cells and the dendrites of larger, inner-layer pyramidal cells, indicating that it is mostly responsible for processing inputs rather than the greater cognitive computations accomplished by the deeper layers. Some recent works have continued to exclude the first layer [35] because it shows "white-matter-like" tendencies. As each lamina independently preserves its own volume, the decision to omit or exclude the first layer can be left up to future researchers, depending on the objectives of their investigation.

4. Variations in neuronal form throughout folds

> *"[...] [T]he ganglion cells of the cerebral cortex change their form with the curvature of the cortex, and these changes in form are parallel to those of their cortical layer; they are taller and thinner in layers that are taller and thinner, and they are shorter and wider in shorter, wider layers". [9, translated]*

In the human cortex, the transition between an immature, relatively-flat cortical sheet with tightly packed cell bodies and the final mature convoluted sheet results in a distortion of the individual cell columns and the vertical fiber bundles that lie between them. As Bok noted, the distal tips of columns lying within the transition between gyral crowns and walls bow away from the crown and towards the gyral wall, while the distal ends of columns between the walls and sulcal fundi bow in the opposite direction (Fig. 3); subcortical axonal fibers are affected in much the same way.

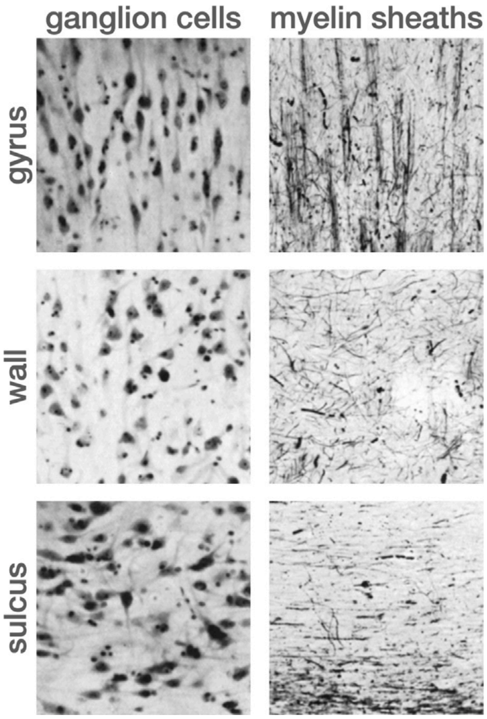

Fig. 6. Microscopic photos of the cerebral cortex in gyral, wall, and sulcal sections, showing prominent changes in cell shape and fiber orientation between locations. Left: Ganglion cells visible in Layer V from Nissl staining, magnified 200x. Cells are tall and thin in gyri and short and wide in sulci. Right: Myelin sheaths visible in the lower cortical layers from Weigert–Pal staining. Fibers are predominantly vertical in gyri and horizontal in sulci. Images modified from [9].

While investigating the changes in laminar thickness across cortical folds, Bok observed that neuronal cell bodies and the orientation of their fibers also change. Specifically, he investigated the cross-section of L5 from peak to bottom and discovered that cellular forms and myelinated fiber orientations differ distinctly between gyri, walls, and sulci (Fig. 6). As documented by Bok, the individual neuronal somata, particularly the characteristic triangular shape of the pyramidal cells (excitatory neurons that make up some 80% of the neuronal population of the cortex) changes significantly, becoming vertically elongated at the gyral crowns and foreshortened at the sulcal bottoms. At the peak, he saw that cell bodies are taller and thinner with vertically aligned fibers; at walls, cells are shorter and wider with equally horizontal and vertical fibers; and at the bottom, cells are the shortest and widest with horizontally aligned fibers (Fig. 6). Deep layer pyramidal cells within the sulcal fundi demonstrate obvious stretching of the pyramidal cell's base along with similar alternations to the basal dendrites. The purpose of these variations, as Bok suggests, is to maintain constant arrangement of neurons and constant volume of cortical layers; in fact, such shape changes are predicted by his original checkerboard thought experiment (Fig. 2).

4.1. Recent work

As discussed at length by Bok [9], cerebral cortical architecture and cell morphology are modified by the process of folding itself. However, in our current understanding, the relationship between cellular microanatomy and cortical folding is both bidirectional and complex [40]. That is, it has also long been acknowledged that cortical folding itself results from developmental events that include growth, expansion, and maturation within the cortical sheet. Specifically, the major hypotheses of the driving phenomena of cortical folding[6] are, in turn, driven by the microanatomical development of the cortex.

Nearly three decades after Bok published this paper, Mountcastle [47] formally described the cortical column, the basic unit of the cerebral cortex. In the mature brain, the six-layered cortical sheet is traversed from the pial surface to the white matter by vertical arrays of neurons, which Mountcastle named 'columns' and are still called such today [48]. During development, immature neurons (neuroblasts) adjacent to the ventricles migrate along radial glia fibers into the developing cortical plate near the brain surface. These radial glia cells serve both as precursors for additional progenitor cells and neuroblasts, as well as guides for neuroblast migration into the developing cortex. The radial unit hypothesis [49] proposes that each column in the mature cortex is formed during development by neuroblasts migrating along a single radial glia fiber, thus routing the newly born neurons in an orderly fashion up to the maturing cortical plate. This radially migrating neuron pool accounts for a large proportion of the excitatory circuitry within the cortex [50]. The arrangement of circuitry within individual columns varies between cortical regions to better serve the computational demands that each brain area must address. Such regional alterations to this circuitry are in part the basis for area identification based on laminar and cellular variation [7,19].

The tangential extent of the cortex is determined by the number of these columns; cortical area expansion is determined by the rate of mitosis within the ventricular zone protomap [51], which is known to be region-specific in the embryonic brain [52]. For example in humans, where the parietal and temporal cortex have increased expansion and folding compared to the insula and cingulate, there is a twofold increase in the density of neuronal progenitors [53]. These progenitors accumulate to a greater extent in regions that undergo greater degrees of expansion, and have also been observed to vary in a manner predictive of the formation of sulci and gyri [54]. Once neurogenesis has completed, surface expansion is driven by cellular growth, differentiation and apoptosis, and the growth and formation of connections. Differential growth of the cortical sheet results in the movement of some regions outward, becoming gyral crowns, operculum, and lobules of the brain (see [40] for a full review), while adjacent regions show relatively less movement, forming the sulci and fissures of the cortical sheet. These developmental factors are evident in the varying cytoarchitecture between regions. Transitions between distinct cytoarchitectonic regions, with distinct connectivity patterns and regional differences in neurogenesis, are thought to specifically contribute to the pattern-specific folding seen within individual species (see [55] for a review). Put another way, the differential expansion model of pattern-specific gyrification suggests that the specificity of folding is related to regional expansion, which is in turn related to the pattern specificity of cytoarchitecture. In sum, we now know that causal relationships between cortical folding and the underlying microanatomy are bidirectional: cortical folding alters the microanatomy, but microanatomy is also an important contributor to cortical folding by driving the addition of cell columns that necessarily lead to differential expansion of the cortical sheet.

4.2. Limitations and critique

Remarkably, despite not being privy to our current understanding of cortical development, a number of Bok's assertions are largely accepted to be true today. For example, in Bok's era it had been proposed that

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[6] Prominent hypotheses of cortical folding include the axonal tension theory [41], the limiting volume of the cranium [42], or a relative increase in surface expansion of the superficial layers of the cortex relative to the deep cortex [43], as well as several others (see [44]), although at least some portion of each of these theories has been found to either be incorrect or to be inadequate as a complete theory of cortical folding [e.g. 45,46].

changes in the dimensions of cortical pyramidal cells was due to a change in the orientation of their long axis rather than a reshaping of the cell body. However, Bok correctly observed that changes in cell morphology across the layers are due to a change in neuronal shape, not a rotation. In addition, he asserted that the alterations that exist in cytoarchitecture between the sulci and gyri may not reflect structural, and therefore functional, differences, because the basic constituents and connections of the cortical circuits may be maintained around these dramatic bends, a concept that he named 'constant arrangement'. Finally, his description of the curvature of cell patterning in the cortex (e.g. [9], Figure 4) is an early implicit recognition that the cortex is composed of vertical arrays of neurons, foreshadowing formal descriptions of the cortical column that would occur some 30 years later [47].

Bok's work focused on the consistent differences between distinct regions of the brain, not differences between brains from different species or from developmental timepoints in a single species. Unfortunately, several features of comparative neuroanatomy are missed because of this focus. For example, all animals begin with largely lissencephalic cortices after the start of neuronal migration; brains that will later fold dramatically show little evidence of the changes to come. Across species, increases in mitosis result in the addition of cortical columns and the expansion of the cortical sheet. Cortical sheet expansion is a fundamental driver of gyrification, and within mammalian orders, species with larger brains tend to have greater gyrification [56,57]. The magnitude of cortical expansion in mammals with gyrencephalic cortices is thought to largely be due to the addition of a specific type of radial glia cells during development. Basal radial glia cells are the progeny of apical radial glia and are not expressed in a spatially uniform fashion [44]. As the size of the neuroblast population increases in animals with larger brains, these basal radial glial cells provide additional pathways for migration. Moreover, the magnitude of basal radial glia cell expression appears to be species-specific. Mammals with gyrated cortices, such as ferrets, nonhuman primates and human primates show an abundance of these additional basal radial glia cells, while lissencephalic mammals, such as mice, primarily show only the apical radial glial cell type [44], although there is at least one exception [58]. In addition, the experimental introduction of excess basal radial glia cells in the ferret results in an increase in gyrification [59].

One significant limitation of Bok's observations of neuronal form was their qualitative nature. Indeed, he noted that it was "extremely regrettable that we cannot yet show with measurements whether these changes in the form of the ganglion cells also agree numerically with those of their cortical layers" [9]. His stated reason for this was that "[t]he individual differences in form, size, and elongation of the ganglion cells are unfortunately just too large for this question to be investigated in such a quantitative way – at least currently" [9]. In the present day, with high-resolution imaging and automated analysis tools, perhaps the time has come for a quantitative analysis of neuronal shape in the cortical laminae through the folds of the brain.

5. Variation in cortical thickness throughout folds

> *"In order to express the thickness of the cerebral cortex numerically in a way that allows us to compare different cortices with each other, the thickness must always be measured at the same curves, because – as we have seen – it changes with the curvature: it is larger in a convex curve and smaller in a concave curve. Most authors measure the cortical thickness at the peaks of folds, and this method was recommended by v. Economo as the one to be generally followed. The cortical thickness at the peaks of folds, however, still depends on the degree of curvature of this fold, which changes in different curvatures in normal as well as pathological folds". [9, translated]*

The migration of the plane of isomorphic curvature through the laminae of the cortex results in the laminar thickness changes in the gyri and sulci. The plane of isomorphic curvature serves as a pivot point for the curving cortex, in which every lamina that is between the plane and axis of curvature is thicker than in wall sections, while every lamina outside is thinner. Bok noted that L3 lies outside of the plane of isomorphic curvature in both gyri and sulci, which would explain why it was consistently found to be thinner than in wall sections (Fig. 3, right). Moreover, this property of the plane of isomorphic curvature explains why gyri are thicker than sulci. In gyri, assuming the plane of isomorphic curvature is generally found in L4 (Fig. 3, upper right), both L5 and L6 increase in thickness. In sulci, the plane of isomorphic curvature seems to be located often in L2 (Fig. 3, bottom right), meaning that only L1 increases in thickness. Because more layers increase in thickness in gyri, they are thus generally thicker than sulci.

5.1. Recent work

While Bok's equi-volume principle explains why cortical thickness changes throughout folds, it does not explain how. Here, researchers have considered both biological and mechanical mechanisms of thickness bifurcation; presumably, complex mechanical and cellular events, affecting each other simultaneously, play a coupled role in establishing these cortical thickness variations throughout the folds of the cortex. Gyri contain significantly more neurons, for instance [60]. Some authors have suggested that local increases in growth [61] or axonal fiber density [62] are responsible for increased gyral thicknesses. In addition, the distinct neuronal orientation in gyri and sulci, with long neuropils extending towards the surface in gyri and densely packed cell bodies and dendrites stretching tangentially in sulci [63–65], could potentially contribute to this thickness gap. Noticing this, Bok suggested that cortical cells respond to curvature by altering their structural properties (see Section 4 for further discussion).

Beyond imaging studies that investigate correlations between structural features, computational models of cortical folding using the framework of continuum mechanics [66] can help test hypotheses regarding the origin of regional cortical thickness patterns. For example, a combined analytical, computational, and experimental study showed that buckling of a film on a substrate of similar stiffness naturally generates thick peaks and thin valleys [67]. Other studies [68,69] have found similar results: despite starting from a uniform thickness and growing uniformly, a bifurcation occurs at buckling, whereafter gyri thicken while sulci stay the same or even thin. Interestingly, this phenomenon is only observed in soft materials; if gray matter were even ten times stiffer than white matter, these thickness differences would not develop [70].

While these results point to an important role for mechanical forces in the development of thickness differences, a mechanics-only model actually underpredicts the thickness variations seen in human brains [67]. To investigate this, we developed a model of cortical folding with heterogeneous cortical growth and compared our results to data from *in vivo* human imaging data. We found that simulations with preferentially more gyral growth were more consistent with the physiological data [70]. This is in agreement with the finding that more neurons occupy gyri than sulci [60,69].

Recently, a thorough analysis of the complex folds of the cortex using quantitative measures of surface topology revealed a strong correlation between cortical thickness and three-dimensional curvature at each depth. Cortical thickness is consistently greatest for convex shapes and smallest for concave shapes, with saddle shapes in the middle; this finding held in both humans [71] and eleven non-human primate species [57]. These support Bok's claim that thickness differences between gyri and sulci are a consequence of cortical folding.

Interestingly, while our work has suggested that the thick peaks and thin valleys should be a universal phenomenon in soft wrinkled materials, it has been noted that some systems – for example, the cerebellum

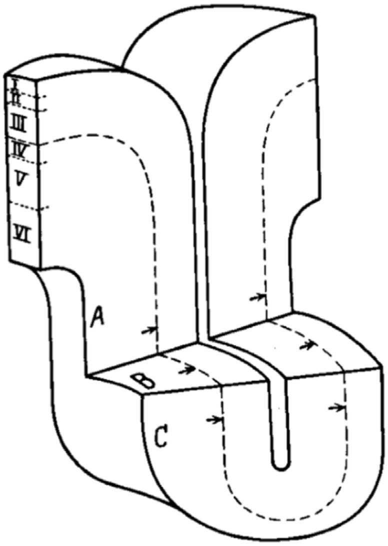

Fig. 7. Bok's Fig. 7: A schematization of the displacement of the L3/L4 boundary throughout tangential folding. Cross sections in A and C's orientation were those measured for the law of volume constancy investigation, while B is the theoretical guess of how the boundary may track when curving orthogonally to A and C's surface. Bok refers to this tangential curving as curvature of cortical folds.

and *in vitro* brain organoids – display the opposite relationship. This out-of-phase behavior between wrinkling amplitude and thickness has been termed "buckling without bending", and has been hypothesized to relate to the characteristic length scale of the tissue and its ability to flow and rearrange [72].

5.2. Limitations and critique

While our recent work has shown the wide applicability of Bok's hypothesis, it has also highlighted the role of three-dimensional shape in the determination of cortical thickness patterns. A three-dimensional view of the cortex instead of a two-dimensional cross-section demonstrates more complex folds, such as in-plane bends and gyral–sulcal junctions, more clearly. These bends of the cortex, called tangential [71] or circumferential [69] folds, are highly curved, with the inner and outer edges nearly analogous to gyral peaks and sulcal valleys, respectively. Unfortunately, this three-dimensional shape is often neglected in images of two-dimensional brain slices or images and discussions of gyri versus sulci, both in Bok's work and in the decades since.

Indeed, Bok acknowledged this implication of his equi-volume principle, noting that tangential curves (which he called "curved cortical folds") also affect thickness (Fig. 7). However, while he often attempted to choose two-dimensional slices of the brain that did not contain significant curvature out of the plane, Bok assumed them to be perfectly straight, enabling him to simplify his *equi-volume principle* into an *equi-area principle*, which was easily measurable from 2D cross-sectional images. While he found seven areas "of little curvature", which he assumed to be straight in the tangential direction (perpendicular to the plane of the slice), another 10 folds were much more curved tangentially, allowing him to investigate the effect of this tangential folding. On the inside of a tangential fold, L6 is on the inside and L1 is on the outside of the tangential curve, while on the outside, L1 is on the inside and L6 is on the outside. According to the equi-volume principle, the lower layers (L4–L6) must be thicker on the inside of a tangential fold and thinner on the outside, which is exactly what Bok observed through analyzing Nissl-stained horizontal cross sections (Fig. 7). Several recent studies also agree with this, finding that convex-shaped circumferential folds are consistently thicker than concave or saddle shaped inner ones throughout the cortex [71,73].

6. Conclusion

> *"The structure of the human cerebral cortex is considerably different at the bottom of a fold than at the peaks of the turns adjacent to this bottom, and these structural differences between the peaks and valleys of folds are found again and again to occur in the same way at every fold. The modern authors who have written about this occurrence to this point have appeared to assume that a fold corresponds to a portion of the cortex that, aside from being a fold, has special architectural characteristics; in other words, that a fold coincides with a specific cortical area that can be thought of as connected to a specific function. The architectural characteristics of this area consist of a differing distribution of thickness between the six cortical layers, a differing form of the ganglion cells, divergent fibers, and so on. In this thought process, though, it is too rarely remembered that the cortex is curved at the tops and bottoms of these folds–at the bottom in the opposite direction as at the top–and that such curvature must, geometrically speaking, profoundly influence the cortical structure". [9, translated]*

Here we have presented an overview of Bok's foundational paper on the architecture of the cortex and its laminae throughout the curves of the human brain. As summarized in the quote above, his observations span the scales, from the macroscopic thicknesses down to the microscopic form of cells and arrangement of cellular processes.

These observations formed the basis of his law of volume constancy, now more commonly referred to as the equi-volume principle, which states that layer thicknesses and cellular forms change with respect to curvature, in order to preserve the arrangement and volumes of cortical structures (laminae and columns). While Bok focused on the human brain, these thickness differences have been recently shown to be the natural consequence of folding in soft films attached to soft substrates [67] – thus, potentially applicable to other wrinkled biological tissues. His research methods and analysis were limited by the tools of that age, but the general idea of his equi-volume principle has stood the test of time. Even today, it is influencing work in the cutting-edge field of layer-MRI [1,33–35].

An important motivation for Bok's study was the claims of his contemporaries, including Brodmann [5] and Von Economo and Koskinas [7], that the structural differences between gyri and sulci indicated functional differences between them. This idea, mentioned in the very opening of his paper (and quoted at the top of this section), was deeply misguided to Bok. Instead, using a variety of approaches, from the simple checkerboard thought experiment (Fig. 2), to laminar segmentations (Fig. 3), to stained cell images (Section 4), he sought to show that many of the structural differences they had noted were simply due to the requirements of a curving object.

Towards the end of his manuscript, Bok identified the future work that was necessary to build on his hypothesis and settle the questions of structure and function in the cortex:

> *"In the future, it will [be necessary] to investigate which[...] areas are simply curved cortical sections, to which therefore no physiological meaning can be assigned, and which areas can actually be traced back to physiological differences and therefore constitute structural regions in the classical morphological-functional sense. [...] In this comprehensive discipline, this critical correction will be an enormous undertaking which, if it is to be completed with sufficient exactness, will be extremely demanding of the methods employed to achieve it". [9, translated]*

Namely, we must determine the structural differences that are the result of curvature – of different shapes, of different sizes, and of different signs, all in three dimensions – and compare those to the structural differences seen between regions. This would be, as suggested by Bok, "extremely demanding", requiring rigorous experimental or simulated data on folding in homogeneous soft materials, compared to high quality histological images from many differently-folded regions in multiple individuals, reliable segmentations by independent experts, and accompanied by reasonable estimations of the full three-dimensional local folding pattern. Then, only those features which differ from the simply-folded case would be considered as potential indications of functional differences. Essentially, Bok called for the removal of the structural differences due to curvature: the ‘‘unfolding’’ of the cortex. This work still remains for the mechanicians, neuroscientists, physicists, neuroanatomists, mathematicians, and imaging researchers of today.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics statement

This manuscript, which is based on the translation of a 90-year-old document, does not include experiments on animals or humans.

Appendix A

‘‘The Influence of the Curvature Occurring in the Folds and Turns of the Cerebral Cortex on Cortical Architecture’’

Dr. S.T. Bok
Head of Cerebral Anatomy Laboratory
Willem Arntsz Hoeve, Psychiatric Institute in Den Dolder, Holland

April 22, 1929

Translated by Andrew Fulwider

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Translator’s Notes

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Content

PART I

The structure of the human cerebral cortex is considerably different at the bottom of a fold than at the peaks of the turns adjacent to this bottom, and these structural differences between the peaks and valleys of folds are found again and again to occur in the same way at every fold. The modern authors who have written about this occurrence to this point have appeared to assume that a fold corresponds to a portion of the cortex that, aside from being a fold, has special architectural characteristics; in other words, that a fold coincides with a specific cortical area that can be thought of as connected to a specific function. The architectural characteristics of this area consist of a differing distribution of thickness between the six cortical layers, a differing form of the ganglion cells, divergent fibers, and so on.

In this thought process, though, it is too rarely remembered that the cortex is curved at the tops and bottoms of these folds—at the bottom in the opposite direction as at the top—and that such curvature must, geometrically speaking, profoundly influence the cortical structure.

The aforementioned authors clearly believe that this curvature has no other influence on cortical architecture than simply that the tangential planes and lines—the borders between layers and the tangential fibers, for example—are curved in these areas rather than running straight as they would in a flat portion of the cortex, and that the perpendicular fibers and dendrites, instead of being parallel to each other, diverge radially. All other features of the architecture in the curved portions of the cortex are discussed in the same way as features of unfolded portions; that is, specific architectural areas are discussed with respect to their functions, and these functions are thought to be localized to their respective areas.

It is, however, in no way correct to think that a curve in the cortex could only have these structural effects. Geometry tells us that the transformation of a straight-lined pattern into a curved one carries with it more numerous and varied effects than just making certain lines curved that were once straight, and making the others, which were originally perpendicular to the now curved lines, diverge radially.

To illustrate this geometric argument, a very simple geometric example is proposed in Fig. A.1. When we try to redraw the straight-lined checkered pattern denoted with *a* as a curved pattern, we notice that it is not possible to do so without disturbing certain properties of the pattern. This is not to say that the straight-lined character is lost and replaced with a curvature; that is, of course, the point of the exercise. Here, I am discussing other, much more meaningful disturbances of the original characteristics of our pattern.

We can go about this in multiple ways.

We can draw the pattern in such a way that each of the squares retains its original form and size. Of course it is necessary to slightly disturb their straight lines, but we can maintain their original width and height, and thereby their original area, as is done in *b*. We see, then, that the original, regular pattern alternating between black and white squares is lost, and of course because of the new pattern’s shape, that the outer curve consists of a longer line than the inner, meaning that more squares lie along the length of the outer curvature than along the inner. So, with this approach, the regular arrangement of the squares is lost.

If we want to maintain the original arrangement—that is, the original alternating positioning—we must make the squares on the outer

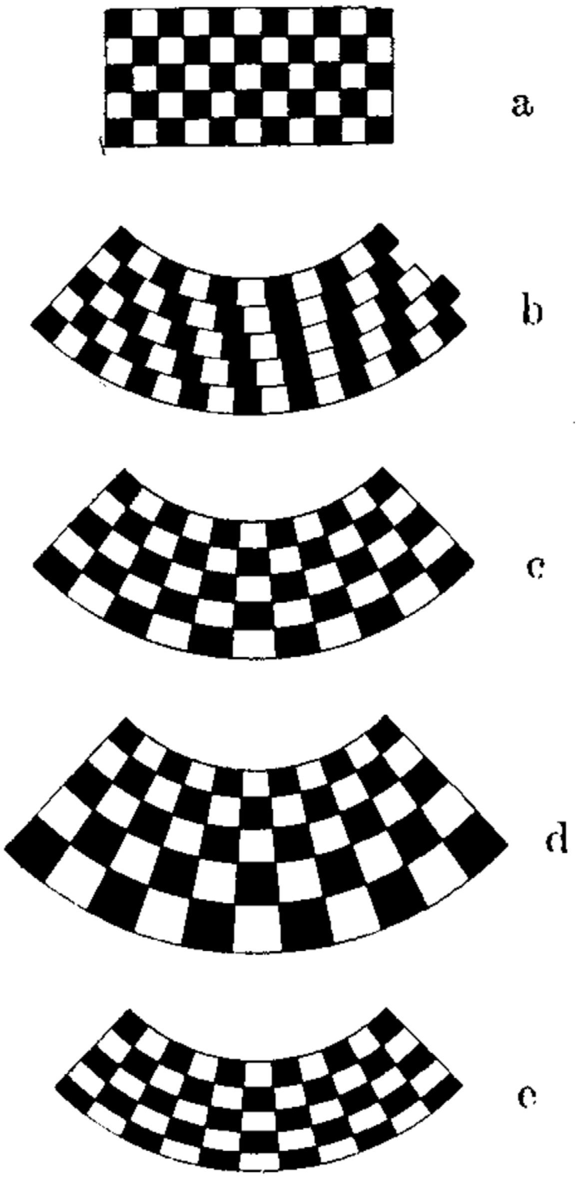


Fig. A.1. Four ways in which the straight checkered pattern can be transformed into a curved pattern: in *b* the squares retain their initial form and surface area, but their arrangement is thereby altered; in *c* the squares retain the initial arrangement and the initial height, but the width is altered; in *d* the squares retain the initial arrangement and form, but their surface area is altered; in *e* surface area and arrangement are held constant, but the squares take on different forms.

curve longer than those on the inner curve, as is done in *c* for example. However, the form of these outer squares is thereby disturbed as well as their area. To restore the original form, the outer squares must also be drawn significantly taller than the inner squares (as in *d*). However, the area is thereby altered even more. In order to maintain the original area, the outer squares must be drawn significantly shorter than the inner ones (*e*), through which the form differs even more from the original.

This example should serve to demonstrate the geometric truth that a straight-lined pattern cannot be transformed into a curved one without changing certain properties in the process. Solely geometrically, though, there is no way to know which characteristics should be lost. To some extent, we are free to choose which properties we want to maintain in the curved pattern, but others must be lost.

The cerebral cortex also shows a regular arrangement of its constituent parts, i.e. the neurons. This means that the construction thereof similarly shows a pattern, true as it may be that this pattern is much more complicated than the checkered pattern described above: the elements of the cortex have much more complicated forms, and they are not all the same as the squares in our simple checker example. Still, the cortical pattern must also adhere to the geometric rules formulated above, as these rules are valid for all spatially arranged entities. The elements of the cortex can therefore not simultaneously maintain a constant volume, a constant form, and a constant arrangement; rather, at least one of these three characteristics must change in the curves.

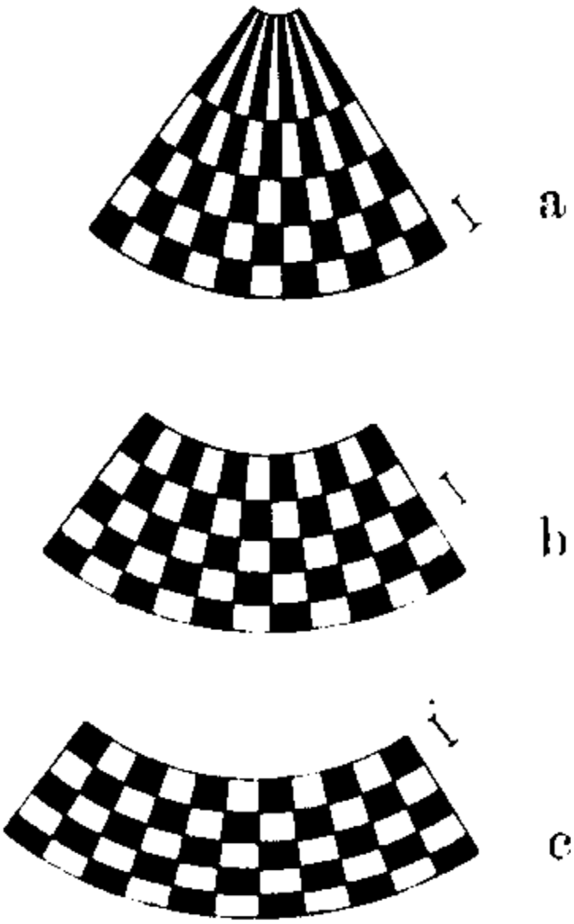


Fig. A.2. Three ways in which the straight checkered pattern from Fig. A.1 can be transformed into a curved pattern while maintaining volume and arrangement. In *a*, the outer squares retain their initial width and the inner squares are considerably narrower; in *c*, the inner squares retain their initial width and the outer squares are considerably wider. In *b*, the inner squares are slightly narrower and the outer squares are accordingly slightly wider than in the initial pattern.

In order to approach our central question, we must first know which choice nature makes in the curves of a folded cortex. An answer to this question would be interesting in two respects.

Firstly, we are interested to know which morphologic characteristics of cortical structure are maintained. We will see that the maintained characteristics are the arrangement (and also, consequently, the possibilities for adaptation) and the volume of the neurons, which are the same morphological factors that determine the function of the cortex. The cortical curvature appears therefore to occur in such a way that the cortical function is not affected.

Secondly, we are interested in knowing which characteristics change with the curvature. It has long been known that areas of the cortex with specific functions are also constructed in a specific way, and the inverse was later also accepted: that a cortical area with a specific construction serves a specific function. However, it is important to be wary of drawing conclusions about local cortical function based on certain architectural features that may be present in a cortical fold. We will see that all architectural differences between adjacent tops and bottoms of folds are only products of the local curvature and there is no evidence that the cerebral function at the bottom is different from that at the adjacent top. Finally, through knowledge of changes in architectural features due to curvature, it is possible to reveal architectural areas that are truly differentiated by function—even in a cortex as intricately folded as that of humans—by eliminating structural differences due to curvature. With this, it is also possible to correct common errors in the study of the cerebral cortex, in which architectural areas are far too often differentiated by structural differences that are only due to their curvature.

PART II

It was already known to *Brodmann* that the cerebral cortex is thinner at the bottoms of folds than at the peaks. A few years ago, *v. Economo* suggested that the distribution of cortical thickness between the six cortical layers was also different between the bottoms and tops of folds. At the tops, the lower layers are relatively thick, especially layers V and VI. At the bottoms, however, these layers are thin, and the upper layer I is much thicker than it is at the tops. The walls of folds are a middle ground between top and bottom. The state of the fourth layer, the inner nuclear layer, demonstrates these differences in thickness distribution very clearly: if it lays just under the middle of the overall cortical thickness at the wall, then we see that it is over this middle level at the peak and well under this level at the bottom of the fold. (see Fig. A.3, in which this fourth layer is dotted).

On the basis of this phenomenon, *v. Economo* constructed a theory regarding the distribution of function within curvature, also citing the notion from *Kapper* that the upper cortical layers have a receptive function and the lower layers an effectual one. In the opinion of *v. Economo*, the effectual function dominates at the peaks of folds, where the lower layers are relatively thick, and the receptive function dominates at the bottoms of folds. Curvature is, according to him, a functional entity that receives stimuli at its edges and responds from its center.

We have seen, however, that in transitioning from a straight-lined geometric pattern to a curved one, the thickness of the layers must already be changed as a result of this curving in order to retain the original arrangement of elements with constant form or constant volume. If the form of the individual elements is constant, the outer layers become thicker than the inner ones (*d* in Fig. A.1), but if the volume of the individual elements is constant, they become thinner. In *e* of Fig. A.1, the outer layer is thinner than in the straight-lined pattern *a*, and the inner layer is just as thick. Of course, volume constancy could also be achieved by drawing the outer layer with its original thickness and the inner layer significantly thicker, as is done in Fig. A.2a, or by drawing the outer layer a bit thinner and the inner layer a bit thicker, like in Fig. A.2b.

In all curves within the cerebral cortex, we see that the outer layers with respect to the curvature are thinner and the inner layers are thicker than in the adjacent flat cortical regions. (In order to avoid misunderstandings, I have chosen to always use the terms “outer” and “inner” with respect to curvature; in contrast, I use “upper” or “lower” to denote layers that are closer to the pia mater or to the white matter, or in other words, with respect to the conventional numbering of the layers from I to VI.) At the peak of a fold, the lower layers (V and VI!) are the inner layers with respect to the curvature, and at the bottom of a fold, the upper layer (I) is the inner layer: at the peak, layers V and VI are thicker than in the adjacent flat cortical region, and at the bottom, layer I is thicker than at the wall (see Fig. A.2). The inner layers are therefore in both curvatures thicker than in the adjacent flat cortex. The outer layers are thinner in both: at the bottom, the lower layers (V and VI) are thinner than in the flat wall, and at the peak, layer I is thinner. Therefore, it is possible that these changes in thickness of the cortical layers are the very same changes from our geometric pattern that maintain the volume of the layers even when they experience curvature.

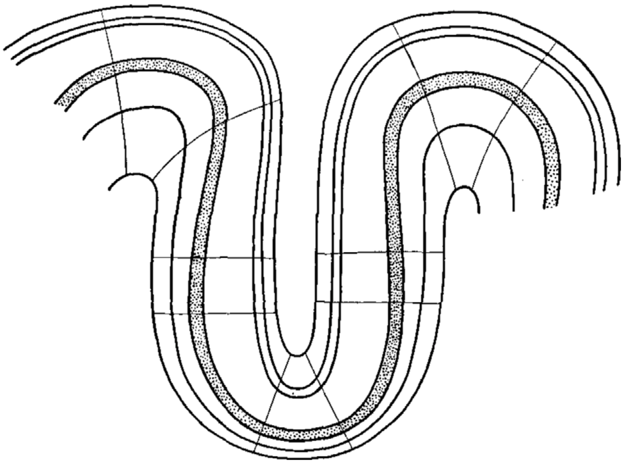


Fig. A.3. Cross-section of a cortical fold (somewhat schematized). At the bottom of the fold, the bottom cortical layers are thinner than at the fold walls, and the upper layer is thicker; however, at the peaks of the turns, the bottom layers are thicker and the upper layers are thinner than at the walls. The (dotted) fourth layer, which at the walls lies directly in the middle of the cortical thickness, is located above this middle at the peaks and below the same middle at the bottom of the fold. At the bottom of the fold, at the two walls, and at the two peaks, two lines are drawn through the cortex in the direction of the main dendrites to mark the corresponding sections of the six layers.

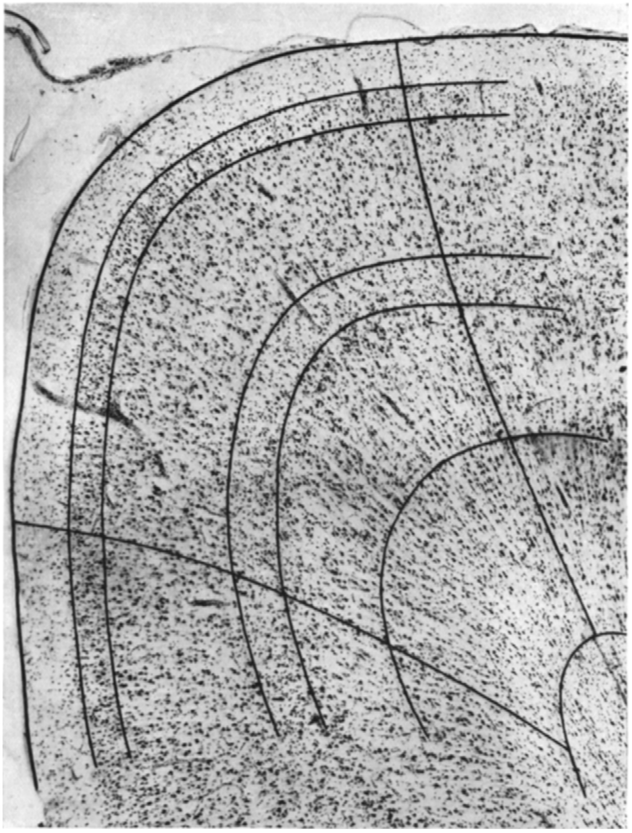


Fig. A.4. Microscopic photograph of a Nissl-stained cross-section of a human cerebral cortex (in the area of frontalis medialis). Peak of a turn (40× magnification).

This would only be the case, though, if the layer thicknesses were to vary in a very numerically specific way.

Let us think of an arbitrary part of a cortical layer, created by cutting in the direction of the main dendrites of the ganglion cells in such a way that the part in question is representative of the thickness of the layer everywhere. This section that we have created of a specific layer must correspond strictly to sections of the other layers. This correspondence between specific sections of adjacent layers is demonstrated very clearly and nicely in the fact that—among other things—the main dendrites of the ganglion cells and the perpendicular fibers all have the same direction, thereby bringing very specific positions—situated on top of one another, in a way—in the different layers, together in a morphological and undoubtedly functional coherence. In an uncurved section of the cortex (Fig. A.5), these dendrites and fibers lie parallel along the entire length. As a result, the 6 interrelated sections of the 6 layers all have the same length. In a curved section, however, these dendrites and fibers diverge outward towards the outer layers of the curvature: upwards (or towards the pia) at peaks (Fig. A.4), and downwards (or towards the white matter) at fold bottoms (Fig. A.6). At the peaks, the fold walls, and the fold bottom of Fig. A.3, two lines are drawn through the cortex in the direction of the main dendrites at each point. Each pair of lines therefore establishes the corresponding sections of the 6 layers. It can be clearly seen here that, as a result of the parallelity or the divergence of these lines, the corresponding sections in the fold wall are the same length, whereas at the peak, the sectioned part of the first layer is longer than that of the sixth and at the bottom of the fold, the sectioned part of the first layer is, conversely, shorter than that of the sixth.

If curvature were to occur in the cerebral cortex in such a way that the thickness of a layer in the curved section were the same as in an adjacent uncurved section, the volume relationship of the corresponding sections of layers within curvature would be different than in the uncurved section as a result of these differences in length: in the outer layers, where these sections are longer, the volume would be too large, and in the inner layers it would be too small. But because the outer layers in cortical curvature are thinner than in uncurved sections and the inner layers are thicker, the volume of the outer layer is reduced and the volume of the inner layer is enlarged, and if these changes in thickness occur in a very specific way, the volumes of the corresponding layer sections could be precisely corrected in such a way that they have the same relationship within curvature as they would have in the uncurved cortex.

This theory then begs the question of whether or not the changes discussed here occur in such a way that the relationship between layer volumes is one of the characteristics of the cortical structure that is maintained through curvature. In order to answer this question, the relationship between corresponding sections of layers must be measured in flat sections and nearby, diversely curved sections of the cortex, i.e. at the bottom of a fold, at the two walls of that fold, and at the peaks of the two adjacent folds. An affirmative answer would be validated if it were to be discovered through these measurements that the volumes are numerically consistent at the peaks, the walls, and the bottom. Or, to rephrase that, if each layer maintains the same percentage of the overall cortical volume in sectioned parts of the cortex at the peaks, the walls, and the bottom of a fold.

Measuring a three-dimensional volume of a cortical layer is a technically demanding prospect that can be significantly simplified with a specific schematization, the impact of which will be more precisely analyzed. A key component of this schematization is the fact that, in our investigations into folds that run straight as much as possible, we assumed that they are truly and numerically perfectly straight. In a mathematically straight fold of the cortex, the volume of corresponding sections of the cortical layers would be proportional to the area of these layers in a cross-sectional image of the fold. The measurement of three-dimensional volume can therefore be simplified into the measurement of a two-dimensional area of a cross-section.

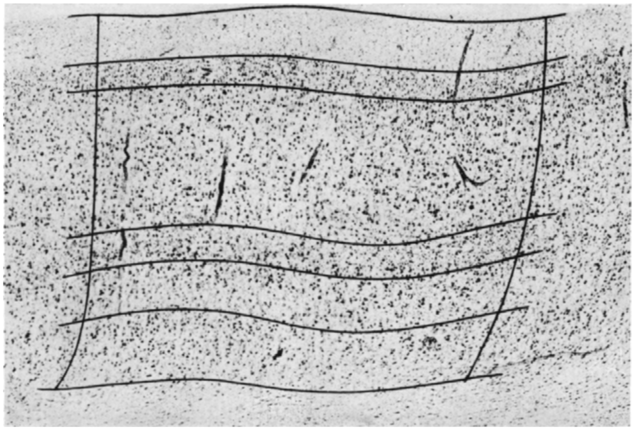


Fig. A.5. Microscopic photograph of the same cross-section as in Fig. A.4. Fold wall (40× magnification).

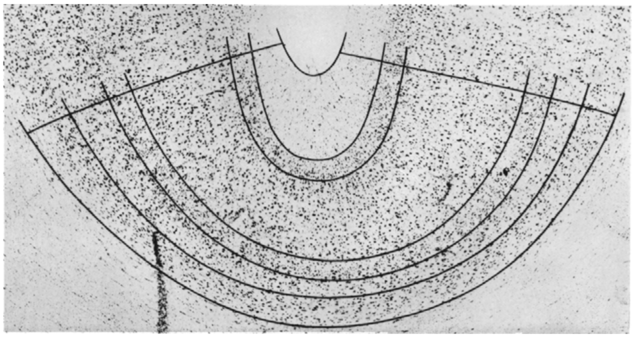


Fig. A.6. Microscopic photograph of the same cross-section as in Fig. A.4 and A.5. Bottom of fold (40× magnification).

First, cross-sections were taken from seven very straight folds, and parallel to these cross-sections, microscopic celloidin sections with 20 μ thickness were produced. After these specimens were stained using the method introduced by *Nissl* (and, for other purposes, that of *Weigert–Pal*, and a few times that of *Bielschowsky*), each specimen was photographed at 5 locations:

1. At the peak of one fold;
2. At the adjacent fold wall;
3. At the bottom of that fold;
4. At the second fold wall, and
5. At the peak of the second fold

The magnification was the same for all photographs, namely 45× (Zeiss micro planar 20 mm, plate separation 92 cm). On these photographs (the plate size was 18 × 24 cm), the boundaries of the 6 layers were inked in, and the corresponding sections of the layers were denoted with two lines, drawn through the cortex in the direction of the main dendrites (Examples in Figs. A.4, A.5, and A.6).

In order to measure the area of each layer in these cross-sections, these lines were transferred to cardboard, which was then cut along these lines. The weight of the resulting pieces, divided by the known weight of 1 cm^2 of cardboard, yielded the area of each layer section in the photograph, in cm^2. After dividing by the magnification of 45 × 45 and multiplying by 10^8, the area of each of the layer sections in the specimen can be obtained in μ^2.

But because our question does not regard the absolute volumes and rather the proportional relationship between the volumes, the area of each individual layer can simply be reported as a percent of the area of the entire cortical section. (For reasons to be discussed later, the entire cortex was regarded as only layers II through VI; in other words, layer I was omitted.) For this purpose, the cardboard weights for the corresponding sections of layers II through VI in each photograph were added, and the weights of the individual layer sections were reported as percentages of this sum.

Aside from that, in each picture, the layer thicknesses were measured in an otherwise arbitrary section.

The first seven folds were taken from a cerebrum that had relatively little curvature, not least because there are many folds to be found in such a cortex that run straight for a sufficient length. They are from different structural areas, and they were taken from as far as possible from the borders between structural areas of significantly different construction. The resulting measurements are recorded in the table on p. 694 [Table A.1] and illustrated in the graphs of Fig. A.9 under the title "Cortex with Little Curvature" (p. 702).

For each fold, 5 graphs are presented in a horizontal row.

In the first of these 5 graphs, the thickness measurements are illustrated. This graph contains 5 vertical lines, the first of which represents the first peak; the second, the adjacent fold wall; the third, the bottom of the fold; the fourth, the other wall; and the fifth, the other peak. The thickness measurements of the 6 layers are arranged on top of one another in the order of I to VI, where the measurements for layer I are presented with dotted lines. These first graphs demonstrate clearly that the cortex is thinnest at the bottom of folds (the third, or middle, vertical is the shortest) and thickest at the peaks (the first and fifth verticals are the longest).

To illustrate the unequal distribution of cortical thickness among the 6 layers, as described by *v. Economo*, more clearly, the second graph shows the layer thicknesses in percent of the entire cortical thickness. Here, as well, only the layers with abundant cells, II through VI, are considered to constitute the entire cortex. The thicknesses of these layers II through VI therefore always add up to 100%, which means that the 5 verticals are all the same length in this second graph. At the bottom of the fold (the middle, or third vertical), the lower layers V and VI make up only a small percentage of the cortical thickness (the entire vertical), at the walls (second and fourth verticals) a medium amount, and at the peaks (first and fifth verticals) the most. The fourth layer, the area of which is dotted here, is lower at the middle vertical (the bottom of the fold) than at the outer verticals 1 and 5 (the peaks). The phenomenon of *v. Economo* is therefore based in the sinking of the dotted region in this second graph, and because this sinking occurs in every investigated fold, we can be sure that this phenomenon occurs constantly and clearly in this investigation, and that the reality of this phenomenon is therefore unconditionally confirmed by this investigation. (The average displacement of the border between layers III and IV is 25% of the overall cortical thickness.)

A completely different picture comes to the foreground when we display the volume percentages graphically.

In the third graph, instead of the thickness percentages, the volume percentages are used. It becomes apparent that these volume percentages of the layers are the same for all 5 verticals: the horizontal lines show a quite straight trajectory, and the fourth layer, which is shaded here, shows no such sinking as in the thickness graphs.

In these seven straight folds, the volumes of the layers behave uniformly across the peaks, the walls, and the bottoms; the changes in thickness emphasized by v. Economo are the result of constancy of the layer volumes within these cortical curves.

The measurements of the 10 following folds do not appear to have turned out as well. The following 10 folds belong to a cortex with much more curvature and, as a result, are curved much more than the first 7 folds.

The curvature of the folds referenced here lies parallel to the surface of the cerebral surface. To me, the cerebral surface is something different from the cortical surface. The cortical surface lies between the cortex and the pia mater and follows the cortex into the depths of every fold; however, I understand the cerebral surface to be a purely conceived surface that connects the peaks of different folds and therefore does not delve into the folds: at the parietal lobe, for example, this cerebral surface lies approximately parallel to the dura mater. The curvature discussed here occurs in the direction that runs parallel to this surface, like *B* in Fig. A.7. This direction is perpendicular to the direction of the celloidin sections on which the previously discussed measurements were carried out, represented by *A* and *C* in Fig. A.7.

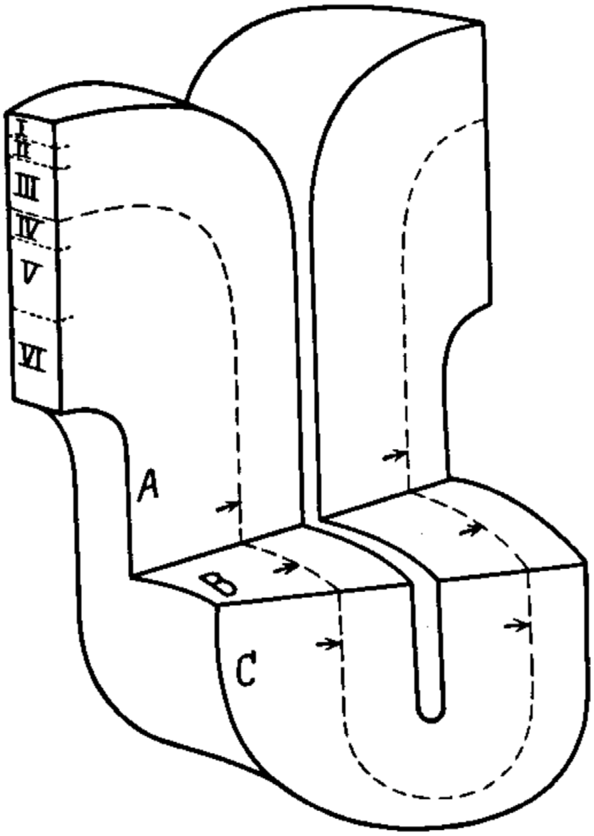


Fig. A.7. Two cross-sections (*A* and *C*) and a horizontal section (*B*) of a curved cortical fold (somewhat schematized). The border between layers III and IV, denoted with a dashed line, is centrifugally displaced in accordance with the law of constant volume, which means in the direction of the pia in the cortex of one wall (left) and in the direction of the subcortical medulla in that of the other wall (right). In the vertical slices *A* and *B* [sic], this displacement is also present even though the curvature of the fold cannot be seen as curvature in these sections.

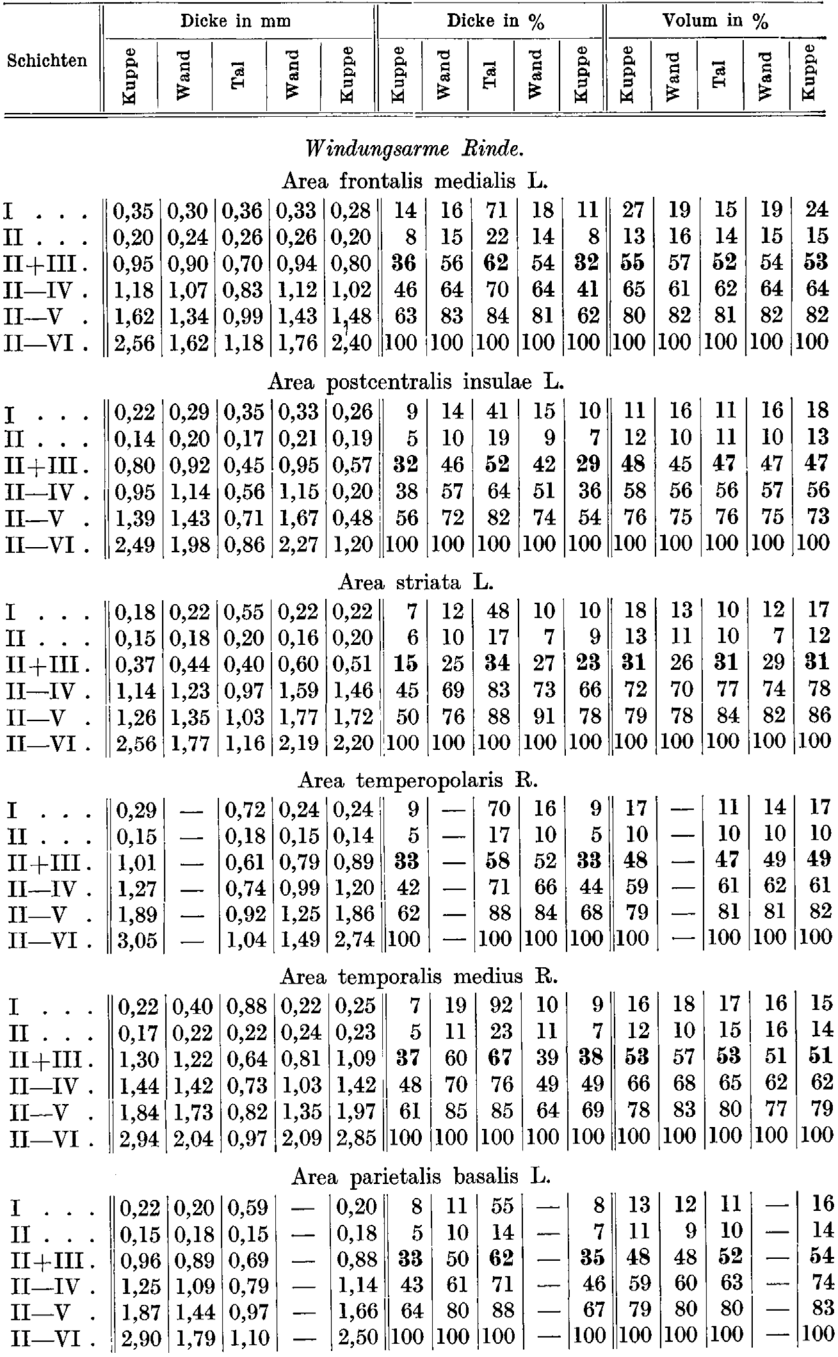
Fig. A.8 is a photograph of a section which, like the plane *B* which was just described, is oriented parallel to the cerebral surface and therefore cuts through the cortex twice, once at one wall of the fold and again at the other wall. It is clear that one of the walls is on the inner side of the curved fold, and the other is on the outer side. As a result, layer VI is the inner layer of the curve in one wall and layer I is the inner layer in the other wall.

If we denote corresponding sections of the different layers in this photograph, we clearly see that the lower layers (VI, V etc.) are shorter than the upper layers in one wall, whereas in the other wall, the upper layers are the shortest. If the volume of the cortical layers is to also remain constant through this curvature, the lower layers must become thicker in one wall while the upper layers become thicker in the other wall. In the inner wall, the fourth layer would be displaced upwards, and in the outer wall, it would be displaced downward. That is, in fact, the case. These displacements of the fourth layer caused by the curvature of the fold are denoted in Fig. A.7 with arrows.

Now, it is important to recognize that this curved fold cannot be recognized as curved in the vertical sections. Nonetheless, the fourth layer is still displaced in these sections. So, when we measure the areas

Table A.1

[Translator's note: This table does not have a caption in the original manuscript. It shows absolute and relative thicknesses (*"Dicke"*), as well as relative volumes (*"Volum"*), of the six cortical layers (*"Schichten"*) at different locations within the brain. Samples are classified as coming from areas possessing either little curvature (*"Windungsarme Rinde"*) or significant curvature *"Windungreiche Rinde"*), and are further identified by the hemisphere (*R/L*) and location from which they were taken. For each sample, values are given for each of five locations: 1. the peak (*"Kuppe"*) of one fold; 2. the adjacent fold wall (*"Wand"*) ; 3. the bottom (*"Tal"*) of that fold; 4. the second fold wall; and 5. the peak of the second fold.].



Schichten	Dicke in mm					Dicke in %					Volum in %				
	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe
Windungsarme Rinde.															
Area frontalis medialis L.															
I . . .	0,35	0,30	0,36	0,33	0,28	14	16	71	18	11	27	19	15	19	24
II . . .	0,20	0,24	0,26	0,26	0,20	8	15	22	14	8	13	16	14	15	15
II+III .	0,95	0,90	0,70	0,94	0,80	**36**	56	**62**	54	**32**	**55**	57	**52**	54	**53**
II—IV .	1,18	1,07	0,83	1,12	1,02	46	64	70	64	41	65	61	62	64	64
II—V .	1,62	1,34	0,99	1,43	1,48	63	83	84	81	62	80	82	81	82	82
II—VI .	2,56	1,62	1,18	1,76	2,40	100	100	100	100	100	100	100	100	100	100
Area postcentralis insulae L.															
I . . .	0,22	0,29	0,35	0,33	0,26	9	14	41	15	10	11	16	11	16	18
II . . .	0,14	0,20	0,17	0,21	0,19	5	10	19	9	7	12	10	11	10	13
II+III .	0,80	0,92	0,45	0,95	0,57	**32**	46	**52**	42	**29**	**48**	45	**47**	47	**47**
II—IV .	0,95	1,14	0,56	1,15	0,20	38	57	64	51	36	58	56	56	57	56
II—V .	1,39	1,43	0,71	1,67	0,48	56	72	82	74	54	76	75	76	75	73
II—VI .	2,49	1,98	0,86	2,27	1,20	100	100	100	100	100	100	100	100	100	100
Area striata L.															
I . . .	0,18	0,22	0,55	0,22	0,22	7	12	48	10	10	18	13	10	12	17
II . . .	0,15	0,18	0,20	0,16	0,20	6	10	17	7	9	13	11	10	7	12
II+III .	0,37	0,44	0,40	0,60	0,51	**15**	25	**34**	27	**23**	**31**	26	**31**	29	**31**
II—IV .	1,14	1,23	0,97	1,59	1,46	45	69	83	73	66	72	70	77	74	78
II—V .	1,26	1,35	1,03	1,77	1,72	50	76	88	91	78	79	78	84	82	86
II—VI .	2,56	1,77	1,16	2,19	2,20	100	100	100	100	100	100	100	100	100	100
Area temperopolaris R.															
I . . .	0,29	—	0,72	0,24	0,24	9	—	70	16	9	17	—	11	14	17
II . . .	0,15	—	0,18	0,15	0,14	5	—	17	10	5	10	—	10	10	10
II+III .	1,01	—	0,61	0,79	0,89	**33**	—	**58**	52	**33**	**48**	—	**47**	49	**49**
II—IV .	1,27	—	0,74	0,99	1,20	42	—	71	66	44	59	—	61	62	61
II—V .	1,89	—	0,92	1,25	1,86	62	—	88	84	68	79	—	81	81	82
II—VI .	3,05	—	1,04	1,49	2,74	100	—	100	100	100	100	—	100	100	100
Area temporalis medius R.															
I . . .	0,22	0,40	0,88	0,22	0,25	7	19	92	10	9	16	18	17	16	15
II . . .	0,17	0,22	0,22	0,24	0,23	5	11	23	11	7	12	10	15	16	14
II+III .	1,30	1,22	0,64	0,81	1,09	**37**	60	**67**	39	**38**	**53**	57	**53**	51	**51**
II—IV .	1,44	1,42	0,73	1,03	1,42	48	70	76	49	49	66	68	65	62	62
II—V .	1,84	1,73	0,82	1,35	1,97	61	85	85	64	69	78	83	80	77	79
II—VI .	2,94	2,04	0,97	2,09	2,85	100	100	100	100	100	100	100	100	100	100
Area parietalis basalis L.															
I . . .	0,22	0,20	0,59	—	0,20	8	11	55	—	8	13	12	11	—	16
II . . .	0,15	0,18	0,15	—	0,18	5	10	14	—	7	11	9	10	—	14
II+III .	0,96	0,89	0,69	—	0,88	**33**	50	**62**	—	**35**	**48**	48	**52**	—	**54**
II—IV .	1,25	1,09	0,79	—	1,14	43	61	71	—	46	59	60	63	—	74
II—V .	1,87	1,44	0,97	—	1,66	64	80	88	—	67	79	80	80	—	83
II—VI .	2,90	1,79	1,10	—	2,50	100	100	100	—	100	100	100	100	—	100

(*continued on next page*)

of corresponding parts of the cortical layers in a cross-section of the two walls, these areas are no longer proportional to the volumes of the layers; because of the displacement of the fourth layer, the measured area of the lower layers will be too big in one wall and too small in the other. In the third graph for simply curved folds, if volume is truly constant, the shaded area of layer IV will be too high or two low at the second vertical, and the opposite will be true at the fourth vertical. That turns out to actually be the case in most of the graphs from the more curved cerebrum. With less simple curvature of folds, the fourth layer is no longer always displaced in opposite directions at the two walls, so displacement in the same direction at both the second and fourth verticals can also be seen in some of the third graphs.

In curved folds, the surface areas at the two walls are not proportional to the volume, and they therefore do not lend themselves numerically to our question about volume constancy. These curved folds do not, however, experience the same disruptive effects at the

Table A.1 (*continued*).

Schichten	Dicke in mm					Dicke in %					Volum in %				
	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe
Area paracentralis R.															
I . . .	0,26	0,24	0,64	0,26	0,37	9	11	63	16	11	14	11	11	17	22
II . . .	0,13	0,13	0,13	0,13	0,13	5	6	13	8	4	8	6	6	11	10
II+III .	0,53	0,64	0,44	0,59	0,57	**18**	30	**43**	36	**17**	**28**	33	**29**	39	**30**
II—V .	1,01	1,10	0,64	0,92	1,38	34	52	63	56	41	47	54	48	61	61
II—VI .	2,99	2,10	1,01	1,65	3,44	100	100	100	100	100	100	100	100	100	100
Windungreiche Rinde.															
Area frontalis medialis R.															
I . . .	0,18	0,28	0,78	0,15	0,15	8	19	70	7	7	17	20	12	8	13
II . . .	0,11	0,12	0,12	0,11	0,11	5	8	11	5	5	9	9	6	4	9
II+III .	0,77	0,89	0,71	0,83	0,67	**34**	61	**64**	36	**32**	**51**	62	**54**	38	**47**
II—IV .	0,93	1,04	0,80	0,99	0,88	41	71	72	44	42	59	73	64	46	58
II—V .	1,41	1,28	0,95	1,52	1,36	62	87	86	67	65	78	90	82	70	78
II—VI .	2,27	1,48	1,10	2,27	2,08	100	100	100	100	100	100	100	100	100	100
Area postcentralis insulae R.															
I . . .	—	—	0,33	0,18	0,15	—	—	34	9	6	—	—	9	10	12
II . . .	—	—	0,20	0,11	0,11	—	—	21	5	4	—	—	9	6	8
II+III .	—	—	0,53	0,62	0,57	—	—	**55**	30	**23**	—	—	**39**	34	**36**
II—IV .	—	—	0,66	0,82	0,75	—	—	68	40	30	—	—	51	45	45
II—V .	—	—	0,79	1,26	1,21	—	—	81	62	49	—	—	71	67	67
II—VI .	—	—	0,97	2,03	3,47	—	—	100	100	100	—	—	100	100	100
Area striata R.															
I . . .	0,13	0,15	0,15	0,19	0,15	7	10	17	11	7	15	14	7	11	15
II . . .	0,10	0,16	0,18	0,18	0,11	5	11	21	10	5	10	12	13	9	10
II+III .	0,26	0,40	0,34	0,59	0,35	**14**	27	**38**	33	**17**	**29**	29	**29**	32	**29**
II—IV .	0,92	1,10	0,74	1,45	1,13	51	76	83	82	56	74	77	76	75	75
II—V .	1,07	1,21	0,80	1,54	1,28	59	84	89	87	63	81	85	82	87	82
II—VI .	1,80	1,44	0,90	1,78	2,01	100	100	100	100	100	100	100	100	100	100
Area temperopolaris R.															
I . . .	0,20	0,20	0,38	0,18	0,18	8	13	38	11	7	14	12	8	10	10
II . . .	0,15	0,15	0,16	0,15	0,16	6	10	16	9	6	8	10	6	9	10
II+III .	0,95	0,75	0,56	0,81	0,92	**41**	51	**56**	50	**37**	**53**	53	**40**	47	**52**
II—IV .	1,09	0,93	0,69	0,94	1,14	47	63	69	58	46	61	64	50	57	61
II—V .	1,62	1,23	0,82	1,29	1,86	70	84	82	80	75	83	85	74	79	85
II—VI .	2,32	1,46	1,00	1,60	2,48	100	100	100	100	100	100	100	100	100	100
Area temporalis medius R.															
I . . .	0,18	0,20	0,55	0,31	0,18	6	9	50	18	6	11	8	7	15	14
II . . .	0,15	0,18	0,22	0,22	0,18	5	8	20	13	6	10	8	9	12	13
II+III .	0,94	0,93	0,62	1,08	0,86	**33**	40	**57**	64	**29**	**46**	39	**44**	59	**48**
II—IV .	1,18	1,17	0,76	1,30	1,06	41	50	70	77	36	56	50	56	71	59
II—V .	1,93	1,77	0,96	1,52	1,87	68	75	88	90	64	78	74	80	87	82
II—VI .	2,85	2,35	1,09	1,70	2,93	100	100	100	100	100	100	100	100	100	100

(*continued on next page*)

peaks and bottoms of the folds. If the volume is constant, the surface area measurements of the six corresponding layer sections must still be proportionally the same at peaks and bottoms of folds.

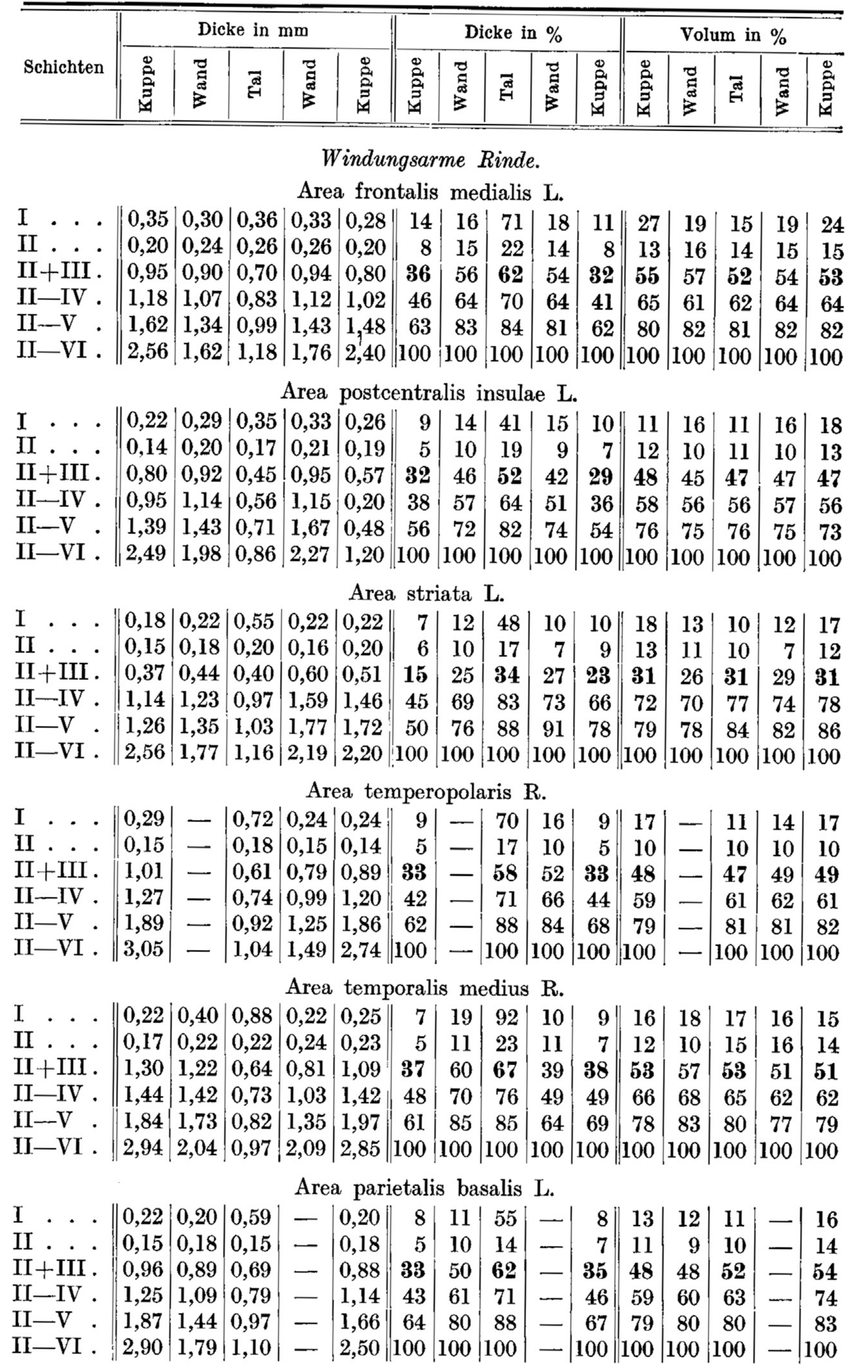
To communicate that more easily, the measurements at the walls are omitted in a fifth graph, so only the surface area measurements at the peaks and bottom of the fold are included. The three verticals in this graph are therefore identical to the first, third, and fifth verticals of the third graph. The area corresponding to the fourth layer is black here. The differences in the thickness distribution are largest between peak and bottom, and these differences are displayed in the fourth graph, in which the fourth layer is also black.

We can now see that even in the curved folds, the law of volume constance holds well: the black bands in the fifth graphs (volume graphs) are practically straight and do not show the sinking that they display in the thickness graphs to the left.

It is almost self-explanatory that in the measurement of biological objects, the results will not agree in mathematical perfection, and that the black bands—which would be mathematically perfectly straight under ideal volume constancy—display small deviations here. Nevertheless, the question should be asked whether these deviations are negligible.

It is apparent that one single curve (temporopolar area, right of the heavily curved cortex) demonstrates a very stark deviation between the bottom of the fold and the peaks. Close examination reveals an extraneous, previously unnoticed curvature at the bottom of this fold, and because of this curvature, the fold was not as deep at the studied location as on either side thereof. The bottom was also curved in a

Table A.1 (*continued*).



Schichten	Dicke in mm					Dicke in %					Volum in %				
	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe	Kuppe	Wand	Tal	Wand	Kuppe
Windungsarme Rinde.															
Area frontalis medialis L.															
I . . .	0,35	0,30	0,36	0,33	0,28	14	16	71	18	11	27	19	15	19	24
II . . .	0,20	0,24	0,26	0,26	0,20	8	15	22	14	8	13	16	14	15	15
II+III .	0,95	0,90	0,70	0,94	0,80	**36**	56	**62**	54	**32**	**55**	57	**52**	54	**53**
II—IV .	1,18	1,07	0,83	1,12	1,02	46	64	70	64	41	65	61	62	64	64
II—V .	1,62	1,34	0,99	1,43	1,48	63	83	84	81	62	80	82	81	82	82
II—VI .	2,56	1,62	1,18	1,76	2,40	100	100	100	100	100	100	100	100	100	100
Area postcentralis insulae L.															
I . . .	0,22	0,29	0,35	0,33	0,26	9	14	41	15	10	11	16	11	16	18
II . . .	0,14	0,20	0,17	0,21	0,19	5	10	19	9	7	12	10	11	10	13
II+III .	0,80	0,92	0,45	0,95	0,57	**32**	46	**52**	42	**29**	**48**	45	**47**	47	**47**
II—IV .	0,95	1,14	0,56	1,15	0,20	38	57	64	51	36	58	56	56	57	56
II—V .	1,39	1,43	0,71	1,67	0,48	56	72	82	74	54	76	75	76	75	73
II—VI .	2,49	1,98	0,86	2,27	1,20	100	100	100	100	100	100	100	100	100	100
Area striata L.															
I . . .	0,18	0,22	0,55	0,22	0,22	7	12	48	10	10	18	13	10	12	17
II . . .	0,15	0,18	0,20	0,16	0,20	6	10	17	7	9	13	11	10	7	12
II+III .	0,37	0,44	0,40	0,60	0,51	**15**	25	**34**	27	**23**	**31**	26	**31**	29	**31**
II—IV .	1,14	1,23	0,97	1,59	1,46	45	69	83	73	66	72	70	77	74	78
II—V .	1,26	1,35	1,03	1,77	1,72	50	76	88	91	78	79	78	84	82	86
II—VI .	2,56	1,77	1,16	2,19	2,20	100	100	100	100	100	100	100	100	100	100
Area temperopolaris R.															
I . . .	0,29	—	0,72	0,24	0,24	9	—	70	16	9	17	—	11	14	17
II . . .	0,15	—	0,18	0,15	0,14	5	—	17	10	5	10	—	10	10	10
II+III .	1,01	—	0,61	0,79	0,89	**33**	—	**58**	52	**33**	**48**	—	**47**	49	**49**
II—IV .	1,27	—	0,74	0,99	1,20	42	—	71	66	44	59	—	61	62	61
II—V .	1,89	—	0,92	1,25	1,86	62	—	88	84	68	79	—	81	81	82
II—VI .	3,05	—	1,04	1,49	2,74	100	—	100	100	100	100	—	100	100	100
Area temporalis medius R.															
I . . .	0,22	0,40	0,88	0,22	0,25	7	19	92	10	9	16	18	17	16	15
II . . .	0,17	0,22	0,22	0,24	0,23	5	11	23	11	7	12	10	15	16	14
II+III .	1,30	1,22	0,64	0,81	1,09	**37**	60	**67**	39	**38**	**53**	57	**53**	51	**51**
II—IV .	1,44	1,42	0,73	1,03	1,42	48	70	76	49	49	66	68	65	62	62
II—V .	1,84	1,73	0,82	1,35	1,97	61	85	85	64	69	78	83	80	77	79
II—VI .	2,94	2,04	0,97	2,09	2,85	100	100	100	100	100	100	100	100	100	100
Area parietalis basalis L.															
I . . .	0,22	0,20	0,59	—	0,20	8	11	55	—	8	13	**12**	11	—	16
II . . .	0,15	0,18	0,15	—	0,18	5	10	14	—	7	11	9	10	—	14
II+III .	0,96	0,89	0,69	—	0,88	**33**	50	**62**	—	**35**	**48**	48	**52**	—	**54**
II—IV .	1,25	1,09	0,79	—	1,14	43	61	71	—	46	59	60	63	—	74
II—V .	1,87	1,44	0,97	—	1,66	64	80	88	—	67	79	80	80	—	83
II—VI .	2,90	1,79	1,10	—	2,50	100	100	100	—	100	100	100	100	—	100

vertical plane, perpendicular to the celloidin section, in such a way that the lower layers there were the inner layers with respect to this curvature, and therefore had to be thicker than would otherwise be the case. At the third vertical, the black band was thereby displaced upwards. Numerically, it cannot be determined if the volume was actually constant in spite of this displacement, because the sectioning and the manipulation of this specimen does not allow us to determine the exact extent of this vertical curve. We must therefore omit this fold from the following numerical analysis.

The remaining deviations are small, and it seems likely that they are caused by inconsistencies in the method of measurement. If that is the case, and if these inconsistencies are not systematic (i.e. do not always influence the results in only one direction), but rather cause only random errors, the laws of statistics which are applied for such unsystematic measurement error must also be valid for the deviations found here. And that is, in fact, the case.

After omitting the single fold discussed above, 29 peaks of 16 folds were compared with the adjacent bottoms. Under ideal conditions, if volume is truly constant, the difference between the heights of the fourth layer at the peaks and the bottoms, or between the sums of the areas of layers IV, V, and VI, once at the peak and once at the bottom, would be found 29 times to be zero. The graphs, however, display the deviations:

−4%	−3%	−2%	−1%	0%	+1%	+2%	+3%	+4%	+7%
1×	2×	4×	4×	9×	3×	2×	2×	1×	1×

As illustrated in a graph (Fig. A.9, in the bottom right), these frequencies approach the theoretical frequency curve of random (unsystematic) measurement error according to *Gauss*. This agreement, which was

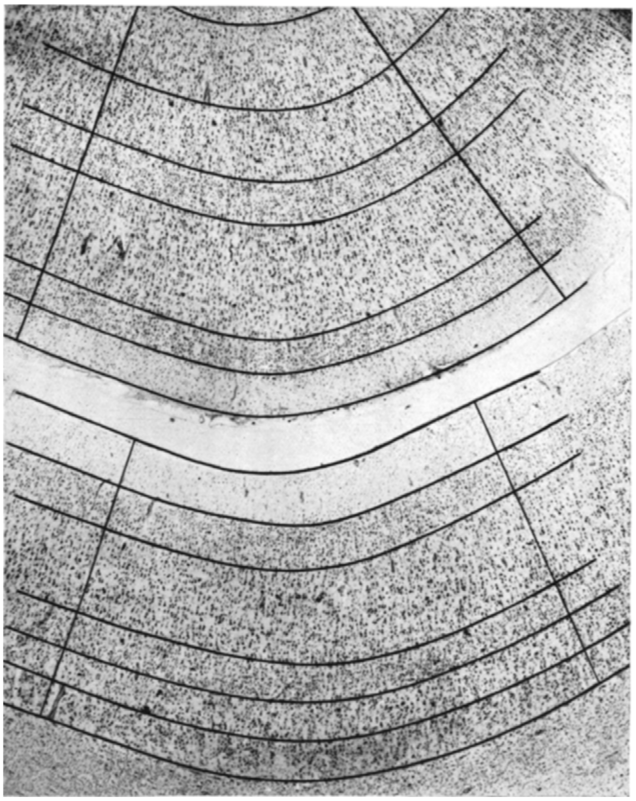


Fig. A.8. Microscopic photograph of a Nissl-stained horizontal section of a curved cortical fold (37× magnification). In the inner cortex with respect to the curvature, the fourth layer is displaced in the direction of the pia; in the outer, in the direction of the subcortical medulla. The inner cortex (top) is thicker than the outer (bottom).

achieved in spite of the small number of measurements (29), already speaks strongly to the fact that only random measurement errors are at play here.

Also in this line of questioning is whether an average difference between peak and fold bottom results from all these measurements, and whether any meaning can be inferred from this difference.

The average value was found by adding the measurements and dividing this sum by the number of measurements. The average value at the peaks was higher than that at the bottoms by only 0.1% (expressed as a percentage of the cross-sectional area of the entire cortex).

This difference of 0.1% is very small for the measurement of biological objects like these, and one is already inclined to attribute that very small error to the admittedly rather rudimentary methodology. However, a numerical basis for this conclusion can still be presented by means of statistical calculation. To this end, the mean error can be determined and the question can be asked whether or not the calculated average difference exceeds this mean error.

The mean error is calculated by adding the squares of the individual deviations and dividing this sum by the product of the number of measurements and this number minus 1 $[\sum D^2/n(n-1)]$. In this study, the mean error was found to be 0.4% (the probable error, which used to be more commonly used, is 0.3% here).

The calculated average difference in the volume distribution at the peak and the bottom of a fold, which was 0.1%, is smaller than the mean error of 0.4%. It is therefore not permissible to assign any positive meaning to the calculated average difference, the result of the measurements proves the equality of volume distribution at the peak and bottom of a fold within the bounds of accuracy for this study, given by the mean error of 0.4%.

In the graph of the error frequencies (Fig. A.9, bottom right), the average value of the difference between peak and bottom, 0.1%, is marked by an arrow. The width of the head of this arrow is equal to the mean error. The fact that the zero line goes through the arrow's head demonstrates the result described above, that the calculated value matches the ideal value for volume distribution (= 0 by ideal volume constancy) within the error of the applied method.

The miniscule average difference in the volume distribution at peak and bottom of $0.1\% \pm 0.4\%$ is a stark contrast to the average difference in thickness distribution, which is 25%.

Only one layer fails to maintain a constant volume, namely layer I. In the third graph of many folds, the dotted line that represents this first layer is not flat and horizontal, but rather lowest at the middle vertical and highest at the outer (first and fifth) verticals. This shows that its volume is smaller at the bottom of a fold than at the wall and larger at the peaks.

At the bottom of a fold, this first layer is the inner layer with respect to the curvature. When corresponding parts of the layers are sectioned off here, the first layer's part is therefore shorter than the parts of the other layers, and if thickness were constant, its volume would be too small. In order for volume to be constant, this part must be taller; in other words, layer I must become thicker than at the walls. In the thickness graphs (the first graph for each fold), we can see that layer I is indeed much thicker at the bottom of a fold (third vertical) than at the walls (second and fourth verticals). Nevertheless, its volume remains too small according to the third graphs. Its increased thickness corrects its otherwise far too small volume to some extent, but not completely, so the volume is not perfectly constant in this layer.

In the same way, layer I has a much smaller thickness at the peaks in order to reduce the otherwise far too large volume, but this reduction is not numerically sufficient to precisely maintain a constant volume.

The changes in thickness of the first layer point therefore qualitatively towards volume constancy; quantitatively, though, they are not always completely sufficient. This is the difference between the first layer and the remaining layers II through VI, in which the thickness variations also quantitatively produce volume constancy.

This first layer, the lamina zonalis, contains only individual, sparsely dispersed ganglion cells, in stark contrast to the other layers, which all contain an abundance of cells and in which the ganglion cells are arranged in a strikingly regular way. Because only these cell-abundant layers maintain their volumes precisely, there appears to be a connection between this volume constancy and the neurons. (Also, because only these cell-abundant layers show perfect volume constancy, the layer volumes in the third and fourth graphs are expressed as percentages of the overall volume of only these five layers.)

Incidentally, I have also suggested in previous studies that layer I has a systematically and genetically different importance than the deeper layers. layer I corresponds to the external veiling of the neural canal, much like the white matter of the medulla, whereas the cell-abundant layers II–VI, together with the subcortical region, originate from the shell, like the grey matter of the medulla. In this school of thought, the cell-abundant layers II–VI constitute the actual cerebral cortex and the cell-deficient layer I is better described as a sort of overlay to which primarily associative cortical fibers belong. The separation of the actual (cell-abundant) cortex into 5 layers is a secondary analysis, which must not be seen as analogous to the isolation of the first layer.

The large variety of layer construction within the cerebral cortex is also only really expressed in the cell-abundant layers II–VI, and in duplicating the layers, which occurred in the transition from the three-layer cortex to the six-layer cortex, only the cell-abundant layers are duplicated, not the lamina zonalis. In the three-layer cortex, under the pia mater comes first a cell-deficient layer, then a small-celled or granular layer, and finally a large-celled or pyramid layer; in the six-layer cortex, a cell-deficient layer (I) comes first, then a small-celled or outer nuclear layer (II), a large-celled or outer pyramid layer (III), once again a small-celled layer, the inner nuclear layer (IV), and a large-celled layer (V and VI). The small-celled and large-celled layers each appear twice here, but the cell-deficient layer is not duplicated because a second cell-deficient layer, which would be called a duplicate of the

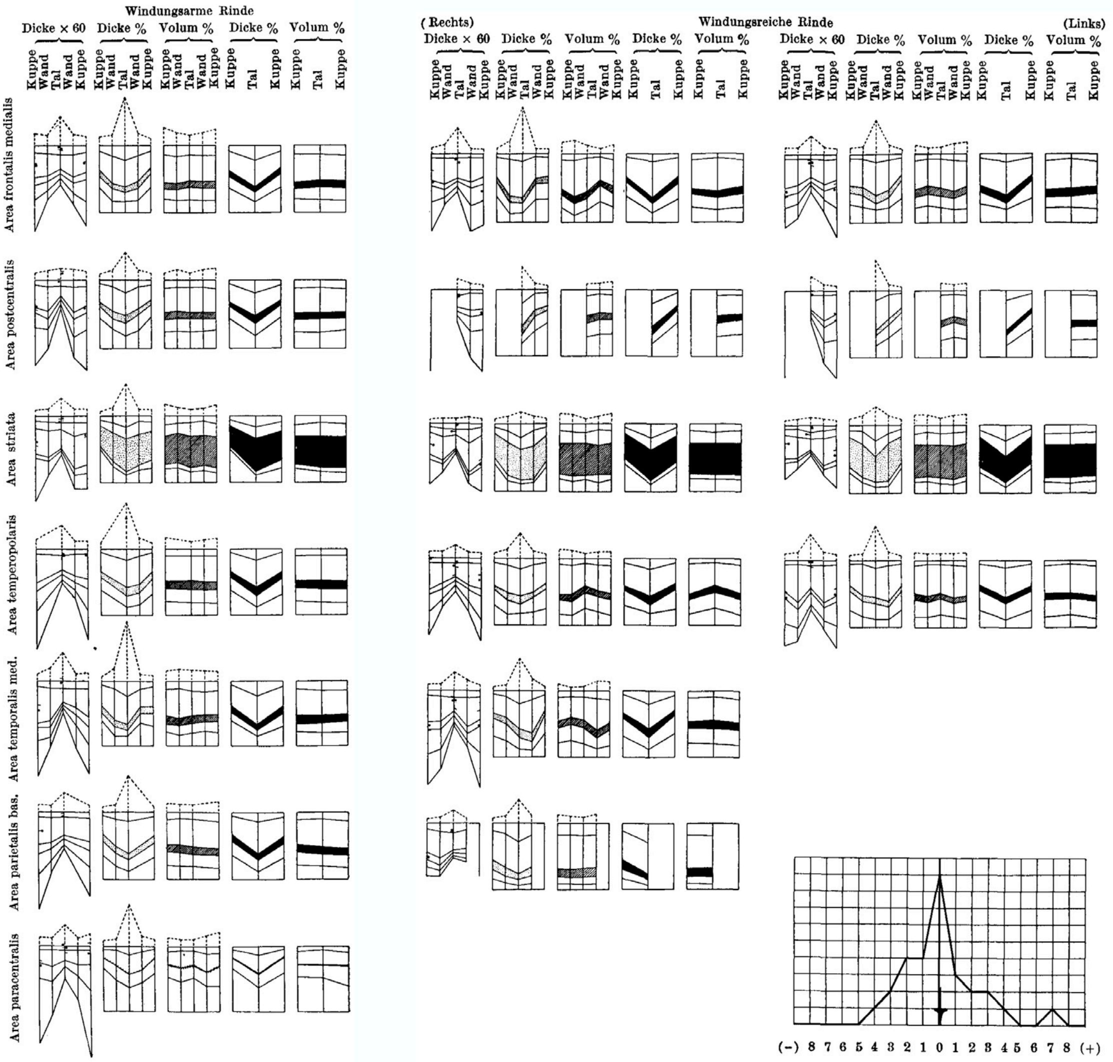


Fig. A.9. Graphical depictions of thickness and volume measurements. The five graphs in each row pertain to a specific fold. The first of the five graphs in Fig. A.9 illustrates the thicknesses of the layers (times 60), the second illustrates the same thicknesses as percents of the entire cortical thickness at that specific location, and the third illustrates the volumes of the layers in percents of the entire cortical volume at the location in question. Each of these graphs contains five verticals; the first represents the first fold peak, the second represents the adjacent fold wall, the third represents the bottom of the fold, the fourth represents the other fold wall, and the fifth represents the other fold peak. (So, these first three graphs in each row show the same data that appears in the table on page 694 ff.). The fourth and fifth graphics illustrate again the thickness and volume percents, but omit the two fold walls; that is, only the data from the fold peaks (the first and last verticals) and the bottom of the fold (middle vertical). The area of the fourth layer here is shaded black. ***The thickness distribution of the cerebral cortex between the layers shows large differences between fold peaks and the bottoms of folds: in each of the pairs of black bands, the left one (the fourth graph or the thickness graph) decreases significantly at the middle vertical (bottom of fold). The volume distribution, however, is nearly constant: the black band on the right (the fifth or volume graph) is almost perfectly horizontal.*** The curve on the bottom right illustrates the frequencies of the differences found in between the volumes of the bottom three layers in the peaks and the bottoms of the folds, normalized by the total volume of the cortex in that fold. The form of this curve resembles that of a Gaussian distribution. The arrow denotes the average difference, which is 0.1%; the tails correspond to a mean error of 0.4%. The zero line (which represents ideal constant volume) falls between these tails: *The volume distribution is therefore constant between the peaks and bottoms of folds within measurement error.* [This figure shows absolute and relative thicknesses (*"Dicke"*), as well as relative volumes (*"Volum"*), of the six cortical layers (*"Schichten"*) at different locations within the brain. Samples are classified as coming from areas possessing either little curvature (*"Windungsarme Rinde"*) or significant curvature *"Windungreiche Rinde"*), and are further identified by the hemisphere (*"Rechts"*, right, or *"Links"*, links) and location from which they were taken. For each sample, values are given for each of five locations: 1. the peak (*"Kuppe"*) of one fold; 2. the adjacent fold wall (*"Wand"*) ; 3. the bottom (*"Tal"*) of that fold; 4. the second fold wall; and 5. the peak of the second fold.].

lamina zonalis, is not to be found in the middle of the cortex above layer IV.

Why the number of layers becomes 6 or even 7 in some essays rather than 5 can be explained only by the fact that the thick inner layer of large cells can be separated further into two lower layers (V and VI) or even three (V, VI, and VII), not due to a duplication of the lamina zonalis.

The fact that the first layer, the lamina zonalis, does not have a constant volume like the other layers is just one more argument why this layer should not be considered part of the actual cortex, and why layers II through VI should be thought of as the actual cortex. All layers within the actual cortex display perfectly constant volume.

The changes in the thicknesses of the cortical layers, which occur in every curvature of the cortex, therefore occur in the exact way necessary to maintain the volume distribution of the layers in the cortex within very tight bounds in spite of these folds.

v. Economo saw in these changes in layer thickness the manifestation of a developmental stage of varying strength in the layers, and believed therefore that a thicker section of a layer could be considered to have a greater function than a thinner section of the same layer. In his opinion, the variations in thickness of a layer would therefore be manifestations of changes in the functionality of the affected layer. This conclusion, however, is completely inconsistent with the fact that these changes in thickness are precisely the changes that produce a constant volume of each layer, because this fact proves that the layers are developed to the same extent in different types of curvature. If we express the functionality of a layer in proportion to its volume, we must therefore also conclude that if the volume is constantly distributed between the layers, the functionality in individual peaks, walls, or bottoms of folds are precisely the same as well.

The distribution of volume among the cortical layers is maintained rigorously through cortical curvature, the differences in layer thickness found by v. Economo are only manifestations of this volume constancy and do not indicate any differences in the functionality of the layers.

The distribution of the entire cortical thickness among the six cortical layers changes significantly with the curvature of the cortex, as we have seen. In order to express this distribution numerically, or, in other words, to express the relative thickness of each individual layer numerically, so that the individual layers can be compared, these numbers must be independent of the degree of curvature, as this changes at different positions. The most simple way to determine these values would be the measurement of the layer thicknesses in a flat section of the cortex (with care being taken to avoid curved folds, which do not appear curved in the cross-section but nevertheless strongly influence thickness distribution!). Completely flat cortical sections of this variety are not present in many cortices. It is therefore necessary to utilize a feasibly usable method to calculate the thickness distribution, which would allow us to represent the cortex at a specific position if it were not curved.

Such a method is based in the law of volume constancy. This law states that in a flat cortical section, the volume distribution among the 5 cell-abundant layers is the same as in a curved section, so long as no differences exist between these two sections other than those necessitated by the curvature. And, in a flat section, the thickness distribution is the same as the volume distribution, as the horizontal dimensions of corresponding layers in a section are always the same. *The thickness distribution that would be displayed by the cortex if it were not curved is therefore equal to the volume distribution of the curved section*, and we can determine the latter if we section off a cortical segment in a photograph of a cross-section of a fold with the layer boundaries drawn in, e.g. at the peak of a fold, by drawing two lines through the cortex in the direction of the main dendrites of the ganglion cells, and we then determine the surface area relationship between these corresponding layer sections, e.g. by transferring the lines to cardboard, cutting the cardboard along these lines, and weighing the resulting pieces.

The precision of this method is limited by the precision with which the layer boundaries can be drawn. With the help of this method, we can determine the relationship between layer thicknesses in a curved cortex with the same precision as we can in an ideal, uncurved cortex.

PART III

In the previous chapter, we saw that the volume distribution across the six cortical layers is constant through the curvature of the cerebral cortex, and that the thickness distribution thereby changes with the curvature: the inner layers with respect to the curvature become thicker, the outer layers become thinner. But how do the neurons behave as a result of these changes in the thicknesses of the cortical layers?

If we divide a photograph of a cross-section of a fold into corresponding sections of the 6 layers using two lines drawn through the cortex in the direction of the main dendrites, and we do this both at a curve and at an adjacent flat cortical region in such a way that the two defined sections have the same surface area, then the law of constant volume distribution mandates that the two sections of one individual layer (one section in the curved cortex and the other in the flat cortex) will also have the same surface area as each other. These two layer sections do not, however, have the same form. Firstly, one is curved and the other is straight. But also, their heights and widths are different, because the layers have different thicknesses in curvature than they do in the flat cortex.

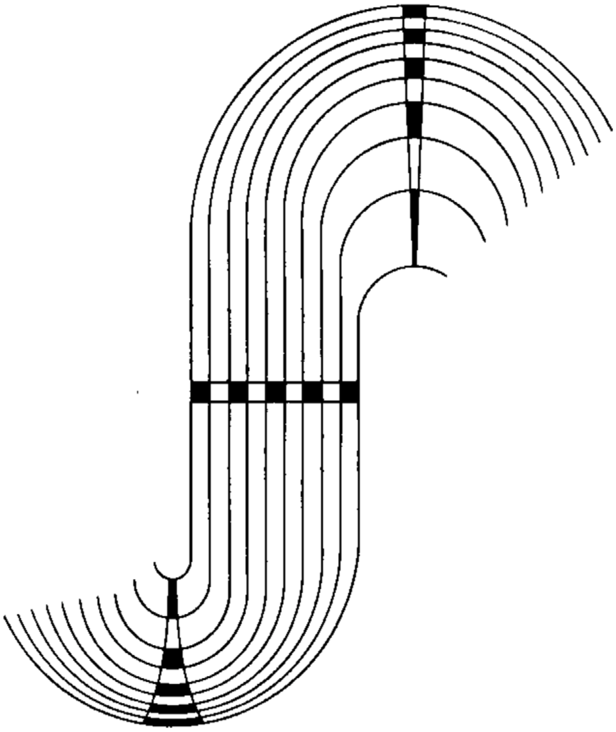


Fig. A.10. A concave and a convex curve of 9 bands of equal thickness, under the constraints of constant volume and constant arrangement, with a localization of isomorphic curvature that serves as an analog to that of the cerebral cortex. (The transitions between the straight and curved sections are schematized.)

In one layer, which is an inner layer with respect to the curvature and therefore has a larger thickness than in the flat cortex, the curved section is taller than the flat section, and because it must have the same surface area, its width in the horizontal direction is smaller (by vertical dimension or height, I mean the dimension that lies in the direction of the main dendrites, or that follows the lines from the subcortical matter to the pia mater; by horizontal dimension or width, I mean the dimension that runs parallel to the layer boundaries, or, more precisely, the tangential or horizontal fibers). In an outer layer, the relationships are obviously the opposite, because the thickness of the layer is smaller here: in this outer layer, the curved section is shorter and wider than the uncurved section.

In general, the form of an arbitrary cortical section changes with curvature by either becoming taller and thinner or shorter and wider. These changes behave in such a numerical way that the volume is maintained constant.

But how do the elements within this cortical section behave as a result of these changes in form?

Geometrically, the elements of a pattern can change in two different ways under these conditions. Allow us to choose a square as a simple pattern, divided into four component quadrants as in *a* of Fig. A.11, and to transform the large square into a rectangle whose height is half of the original height. In order to maintain the surface area, the width must then be doubled. The drawings *b* and *c* of this figure illustrate the two ways in which the components can change: in *b*, they have maintained their original form but changed their arrangement; in *c*, they have maintained their original arrangement but changed their form.

The question must then be asked, whether the form or the arrangement of the neurons is maintained as the thicknesses of the cortical layers change?

If a change in form occurs in an overall figure, and the components of the figure maintain the same arrangement, the components necessarily also display change in form, as we have seen. It is also clear that

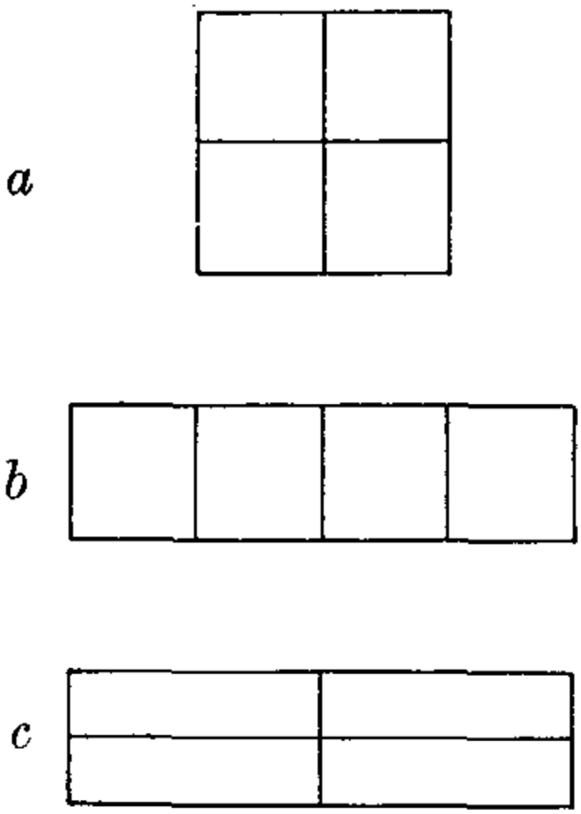


Fig. A.11. Two ways in which assembled parts of a whole figure can change in a transformation that changes the whole figure while keeping area constant. In *b*, the constituent squares retain their initial form, but their arrangement is changed; in *c*, their arrangement is unchanged but their form changes accordingly.

this change in the form of the components is analogous to that of the overall figure: the large square of our Fig. A.11*a* becomes a rectangle in *c*, the width of which is four times its height, and the component squares also become rectangles that are four times wider than they are tall.

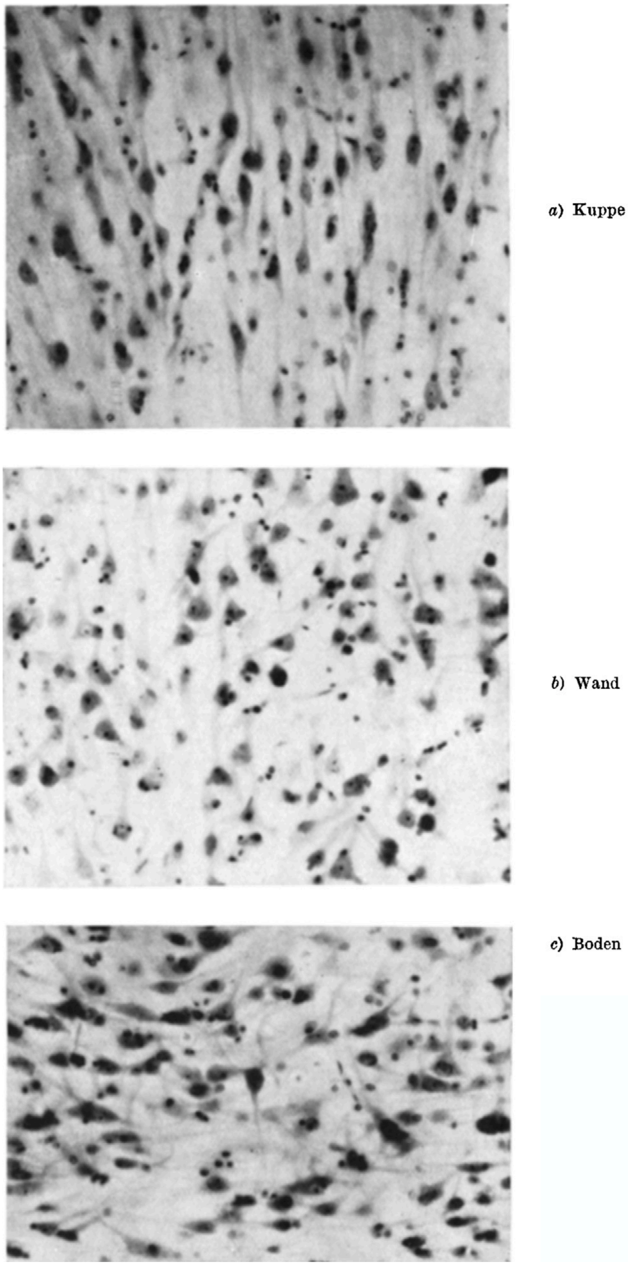
The arrangement of the neurons can therefore only be maintained through the curvature of the cortex if they display a change in form similar to that of their layers.

In the inner layers of a cortical curve, the layers are transformed in such a way that their vertical dimension becomes larger and their horizontal dimension becomes smaller; in the outer layers, on the other hand, their horizontal dimension becomes larger and their vertical dimension becomes smaller. If the arrangement is to be held constant, the ganglion cells of the inner layers with respect to the curvature must display a larger vertical dimension and a smaller horizontal dimension; they must, in other words, become taller and thinner than the ganglion cells of the same layer in the adjacent, uncurved cortex. And, in the outer layers, they must be shorter and wider than the corresponding cells in the uncurved cortex.

If we compare the cellular forms between the flat and curved sections of our samples, we can easily see that these changes in cellular form, which are necessary for the arrangement of the neurons to be constant, truly do occur in every cortical curvature.

Because they are proportional to the changes in the thickness of the layer in question, they occur most strongly in the layers whose thicknesses change most strongly. As we will analyze even more closely in the following chapter, these are layers V and VI. At the peak of a fold, these are the innermost layers with respect to the curvature.

Their thicknesses increase significantly there, almost by a factor of two compared to the fold wall. At the bottom of a fold, they are the outermost layers and therefore become significantly thinner, mostly by a factor of two to three. These layers therefore have a four to six times larger thickness at the peak of a fold than they do at the bottom of the fold. Sections of these layers with equal volumes therefore have a four to six times larger height at the peak than at the bottom, and their width decreases by the same factor. Such a strong change in form only occurs in these layers.


a) Kuppe

b) Wand

c) Boden

Fig. A.12. Three microscopic photos of the fifth layer of a Nissl-stained cross-section of the cerebral cortex (200× magnification). At the peak of the fold (a), the ganglion cells tall and narrow, at the fold wall (b), the ganglion cells are shorter and wider, and at the bottom of the fold (c), they are so short and so wide that their horizontal dimension exceeds the vertical.

Figs. A.12 and A.13 show photographs of the ganglion cells in the fifth layer at the peak of a fold, the fold wall, and the bottom of the fold, Fig. A.12 with a specimen colored according to *Nissl*, and Fig. A.13 with a specimen saturated with silver according to *Bielschowsky*. The change in the form of these cells is immediately apparent. At the peak, where the fifth layer is tall and the section in question is tall and thin, the cells

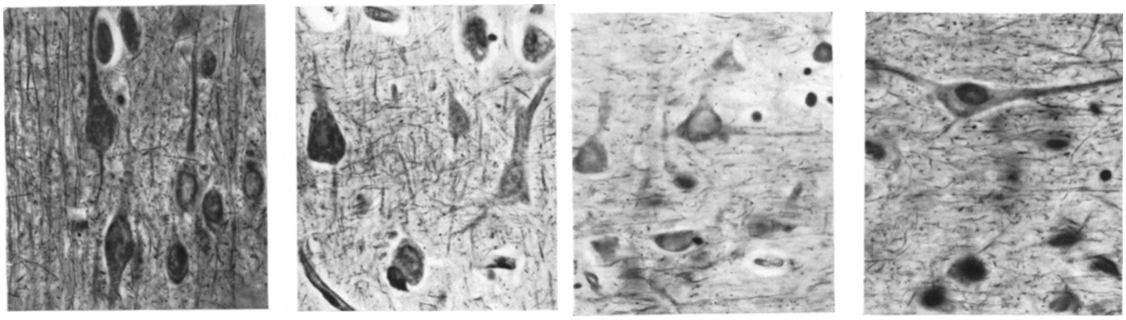

a) Kuppe
b) Wand
c) Zwischen Wand und Boden
d) Boden

Fig. A.13. Four microscopic photographs of the fifth layer of a Bielschowsky-stained cross-section of the cerebral cortex. (a) At the peak of the fold, (b) the fold wall, (c) between wall and bottom, (d) at the bottom of the fold (in all the pictures, the pia is at the top). At the peak, the cells are taller and narrower; at the bottom, shorter and wider than at the wall. The primary axis of the cells is always the vertical; also, at the transition between the wall and the bottom, the neurites extend towards the bottom. At the peak of the fold, the vertical fibers prevail; at the bottom, the horizontal (540× magnification).

are similarly tall and thin (Figs. A.12a and A.13a); at the wall, they are thinner and wider (Figs. A.12b and A.13b); at the bottom of the fold, where the layer has a very small height and the section in question is therefore very short and very wide, the ganglion cells are also very short and very wide (Figs. A.12c and A.13d). They are so short and so wide here, in fact, that their horizontal dimension is larger than their vertical dimension and their largest dimension is thereby horizontal, as opposed to in the other cortical segments, where it is vertical.

The differences in the forms of the ganglion cells in the fifth layer are therefore not at all questionable, but rather quite clear: at the peak, the already vertical orientation of the cortical cells is accentuated by an elongation of the vertical dimension and a shortening of the horizontal, so that these cells become thin shapes that are oriented vertically. At the wall, they are more plump, and at the bottom of the fold, the horizontal dimension overtakes the vertical so strongly that the cells are again quite thin shapes, but this time oriented horizontally.

The horizontal elongation of the ganglion cells of the lower cortical layers at the bottom of a fold has been known for quite some time. One group of authors sees this structural peculiarity as an indication of the existence of a specific cytoarchitectural cortical region; the other group thinks this horizontal positioning is caused by the exertion of many horizontal fibers passing under the cortex of the fold bottom from one peak to the other; they think that the ganglion cells are simply rotated 90° so that instead of standing vertically as in the rest of the cortex, they have fallen over here and are lying horizontally. They think, in other words, that the cells actually do have a constant form.

If the latter theory were to be correct, not only would the largest dimension of the cell be horizontal, but also the main structural axis. In most cortical cells, the structural axis is vertical: the pyramid cells, for example, generally resemble a pyramid, the base of which is oriented downward, i.e. towards the subcortical matter, so that the cell is wide on the bottom and gradually becomes thinner towards the top; the neurite extrudes from the bottom or the base (generally from the center of this surface); the main dendrite extends from the upper peak and towards the pia mater. If the theory of cellular turning were correct, this main structural axis of the ganglion cells would be horizontal, so the neurite and the main dendrite would have to extend in horizontal directions, the neurite towards one peak and the main dendrite towards the other. These two horizontal extensions of the cell body, which extend diametrically to each other, would also have to display strongly different thicknesses, as one extends from the basal half of the pyramid and the other from the half with the peak (Fig. A.14, top right).

If, however, the horizontal elongation of these cells occurs because the cell form changes with the form of the layer to which it belongs in order to maintain a constant arrangement of the cells, then the cells would not be turned and the main axis would still be vertical, just shorter than the lateral elongation.

In this case, the neurite would still extend from the bottom surface, i.e. towards the subcortical matter, and the cell would maintain its vertical axis of symmetry (Fig. A.14, bottom right).

Microscopic observation of the Bielschowsky specimens shows that the neurites of these cells extend from the bottom surface, and that they are only vertically symmetrical (Fig. A.13d). Reality therefore reflects the theory which states that the cell form changes with the form of the layer in question, and it contradicts the theory which states that the cells are somehow turned.

Furthermore, the theory of the cells being somehow turned also contradicts the way in which the sections of the lower layers at the bottom of a fold, with horizontal cells, transition into the adjacent sections with vertical cells.

This transition is not abrupt, but rather gradual, much like the gradual decrease in the thicknesses of the lower layers from the bottom of a fold to the fold wall. If the cells at the bottom of the fold were turned 90°, the gradual nature of their transition would dictate that they display a smaller and smaller rotation in this region of transition until that rotation reaches 0° in the vicinity of the fold wall; in other words, the cells would have to be diagonal in this transitional region (Fig. A.14, top).

In the transitional region, however, the cells are certainly not diagonal. They always appear as orthogonal, i.e. with one axis being vertical and the other axis being horizontal. Only the height of the cell changes in the vertical direction, and only the width changes in the horizontal direction, as is demonstrated in Fig. A.13c with a microscopic photograph of the fifth layer in the transition from peak to fold bottom.

The nucleus of the cell also changes with the form of the cell body: in thin cells with dominant vertical dimensions, the largest axis of the nucleus is also vertical, whereas in the cells with large horizontal elongation, the largest axis of the nucleus is horizontal.

In the transition region, the largest axis of the nucleus is again not diagonal; the vertical nuclear axis simply becomes smaller and smaller as we progress from the peak to the bottom of the fold, so that the vertical ellipsoid first becomes a sphere and then eventually a horizontal ellipsoid.

So, the ganglion cells of the cerebral cortex change their form with the curvature of the cortex, and these changes in form are parallel to those of their cortical layer; they are taller and thinner in layers that are taller and thinner, and they are shorter and wider in shorter, wider layers (of course, with the restriction that only cells of the same layer are compared to one another).

It is extremely regrettable that we cannot yet show with measurements whether these changes in the form of the ganglion cells also agree numerically with those of their cortical layers. The individual differences in form, size, and elongation of the ganglion cells are unfortunately just too large for this question to be investigated in

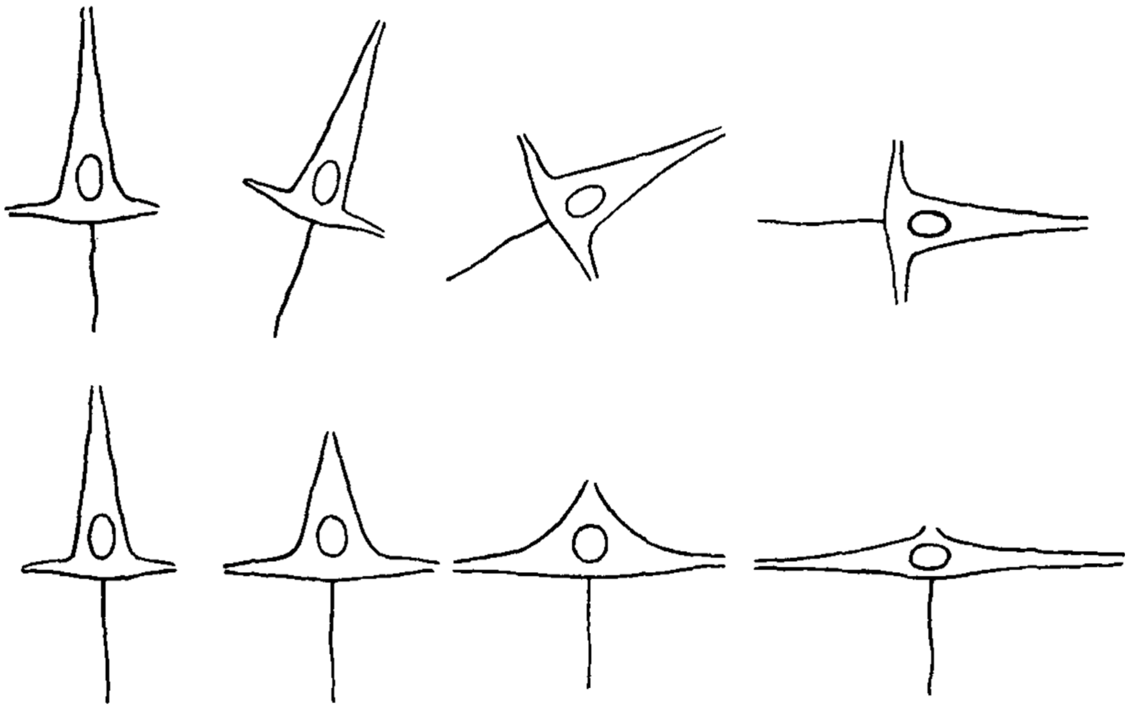


Fig. A.14. Above: illustration of the old understanding of horizontal extension of ganglion cells in the lower layers at the bottom of the cortical folds as occurring through rotation. In the transition states, the cells would then have to be tilted and in the bottom of the fold, the neurite would have to protrude horizontally in the extension of the long axis of the nucleus. Below: the understanding represented here: the change of form the ganglion cells must display in order to retain a constant arrangement through cortical folds. The main axis of the cell is still the horizontal, but through elongation of the horizontal. In the transition states, the cells remain vertically oriented, and at the bottom of the fold, the neurite can protrude vertically in the direction of the shorter axis.

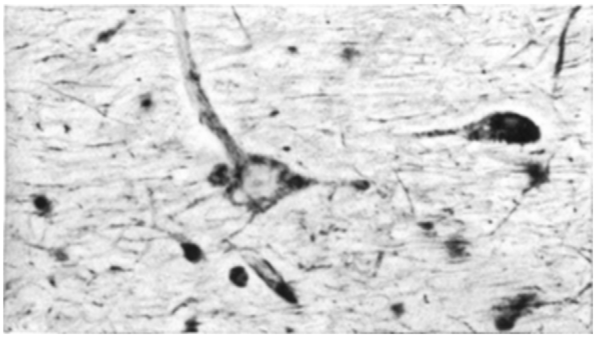


Fig. A.15. A ganglion cell of the fifth layer at the bottom of a fold with a strongly developed main dendrite (540× magnification). The main axis of the cell is the vertical (Bielschowsky-stained).

such a quantitative way—at least currently—as the question of the volume constance in the layer volumes. But, even without proving this numerical agreement through measurements, we can say that the agreement between the changes in the form of the cells and their layers is very strong [see Fig. A.15].

Nowhere have I encountered a cell which changes form in a way that does not qualitatively reflect the changes in the thickness of the layer to which it belongs, nor have I made any observation which could cause an impression that there exists a qualitative difference between the size of the changes in the form of the layer and the cells therein.

We can therefore conclude from the above discussion that the ganglion cells of the cerebral cortex change their form with the curvature of the cortex in such a way that is geometrically necessary in order to maintain an unchanged arrangement, even if we do not know to which degree of precision these changes in form reflect this geometric necessity.

Studying the nerve fibers leads to the same conclusion.

In the cerebral cortex, the vast majority of the nerve fibers are either vertical or horizontal: there are very few slanted fibers. We can see how a geometric pattern of vertical and horizontal lines changes as the entire pattern is drawn taller and thinner or shorter and wider while the volume is maintained.

Fig. A.16 shows a square in which the same number of vertical and horizontal lines are regularly distributed. At the bottom of the figure, the square is transformed into a rectangle with one third the height and three times the width of the square, making its surface area the same as that of the square. The number of vertical lines remains constant, as well as the number of horizontal lines. Their separation, however, is changed. The distance between the horizontal lines is only one third of their separation in the square, as the entire height of the pattern is only one third of the original pattern. So, the horizontal lines have moved closer to one another. In the same way, we can understand that the vertical lines have moved further away from each other until their separation became three times what it was in the square. If we can view a circular part of this pattern (just like we can view a circular part of a cortical specimen under a microscope), we can see just as many horizontal lines as vertical lines in the square, whereas we see mostly horizontal lines in the horizontal rectangle, these lines having moved much closer to each other than they are in the square, and only a few vertical lines very far from each other. The number of vertical lines in this field of view is only one ninth of the number of horizontal lines, which shows that the ratio of horizontal lines to vertical lines changes proportionally to the square of the overall height of the pattern.

If the height of our overall pattern is increased instead of decreased, as is the case on the right side of Fig. A.16, we see primarily vertical lines in our circular field of vision for the same reasons: the horizontal lines are so far away from one another that we only see them occasionally here and there.

If the arrangement of the neurons in the cerebral cortex is maintained in spite of the changes in thickness experienced by the layers within curvature, the same conditions apply as in the geometric pattern

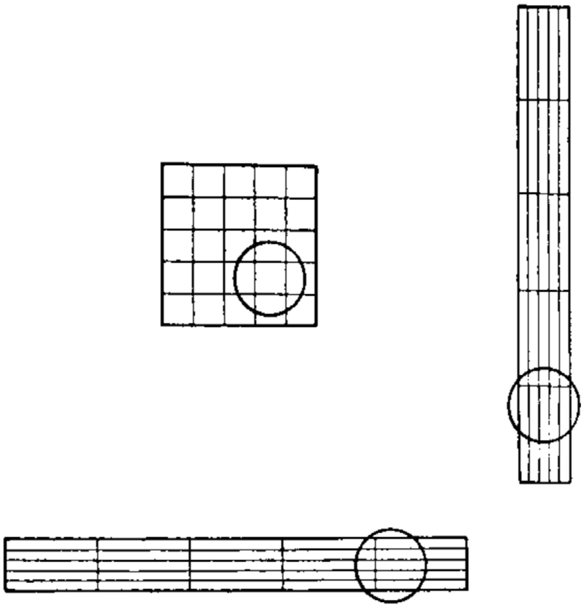


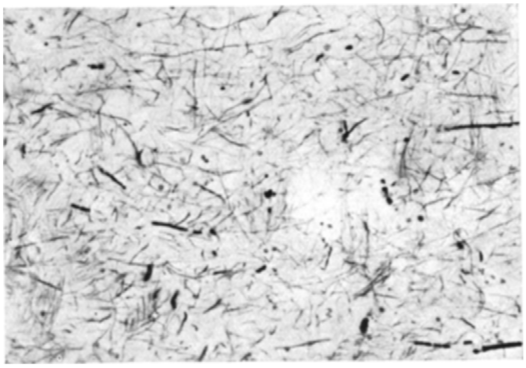
Fig. A.16. The impact of a transformation of a square with equal numbers of horizontal and vertical lines into rectangles which have widths or heights three times those of the original, but which retain the area of the original. In the bottom rectangle, the horizontal lines moved closer to each other, and the verticals moved away from each other. In the circle, there are 9 times as many horizontal lines as there are vertical lines, as opposed to the original, in which there are equal numbers of both.

in Fig. A.16; the number of vertical and horizontal fibers must remain constant in analogous layer sections, despite the fact that these sections become taller and proportionally thinner or shorter and proportionally wider than they are in the uncurved cortex. In thinner sections of a cortical layer, the horizontal fibers must be most apparent when inspected under a microscope; in thicker sections, the vertical. These differences must be very pronounced, especially because the ratio between the horizontal and vertical fibers changes proportionally to the square of the layer thickness.

And that is, in fact, the case, as is immediately illustrated by the microscopic photographs in Fig. A.13, which are taken of the fifth layer of a *Bielschowsky* saturated specimen of the cerebral cortex. *At the wall of a fold (second photograph), we see approximately the same number of horizontal and vertical fibers. At the bottom of the fold, where these layers are thinner, we primarily see horizontal fibers packed closely together (fourth photograph), and only a few scattered vertical fibers. At the peaks, on the other hand, where these layers are thick (first photograph), we find primarily vertical fibers and only a few horizontal.*[7]

This contrast between the peaks, where the vertical fibers dominate in the lower layers, and the bottoms, where the horizontal dominate, is even more evident in the fiber specimens. This can be explained by the fact that the fiber sheathing of the neurites begins a small distance away from the ganglion cells. In order to make this clear, let us think of a vertical neurite which protrudes from a ganglion cell on the boundary between layers V and VI in a flat cortical section, and takes on a myelin sheath at half the thickness of layer VI. So, if this layer is 10 μ thick, the myelin sheath in this layer is 5 μ long. If we imagine this layer becoming two times thinner, and we accept that the unmyelinated section of the neurites maintains the same length, the myelin sheath then begins at the lower boundary of the sixth layer, e.g. this fiber is no longer myelinated within the cortex. So, in the fiber specimens, many vertical fibers of the lower layers are absent at the bottoms of folds. Now, let us think of layer VI as becoming twice as thick. The myelin sheath once again begins 5 μ under the ganglion cell and is therefore 15 μ long within the sixth layer. Initially, it was only 5 μ long. A twofold increase in the layer thickness in this case therefore corresponds to a threefold elongation of the myelin sheath.

a) Kuppe



b) Wand

c) Boden

Fig. A.17. Three microscopic photographs of the lower layers of the cortex in a cross-section of a fold in which the myelin sheaths are stained with the Weigert–Pal technique. At the peak of the fold (*a*), the vertical fibers appear most frequently, at the fold wall (*b*), there are about as many horizontal fibers as vertical, and at the bottom of the fold (*c*), horizontal fibers appear much more often.

If the length of the unmyelinated beginning part of the neurites changes disproportionately to the layer thickness, the vertical fibers will be even more dominant in a thicker section of a layer than would be the case only due to the change in the layer's form. The horizontal fibers will similarly be even more dominant in a thinner section.

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[7] Of the few fibers that are skew in the uncurved cortex, most of them are essentially horizontal at the bottom of a fold because the horizontal component of their diagonal direction is elongated and the vertical component is made smaller, so the angle at which they are askew is decreased; at the peaks, they are essentially vertical. The fibers that appear to be diagonal in the fold walls therefore largely seem to disappear at the bottoms and peaks of folds.

Fig. A.17 shows three microscopic photographs of a cross-section of a cortical fold, in which the myelin sheaths are colored with the method from *Weigert–Pal–Kulchitsky*. They are, again, omitted in the lower layers. At the wall (middle photograph), we see approximately the same number of horizontal and vertical fibers; at the peak (top photograph), we see almost exclusively vertical fibers; at the bottom (bottom picture), almost exclusively horizontal fibers. The fibers in these last two photographs of the curved cortical sections are much more closely packed than in the middle photograph of the uncurved cortex.

These differences between the fibers at the bottoms and peaks of the folds are so large, and these images seem to be so fundamentally opposed, that it is nearly impossible to immediately understand that these two images are transformations of the same basic image, and this is challenging to understand even with the help of the analysis above. Nevertheless, while following the cortex from the bottom of a fold to its peak, one can observe these two images gradually transition into each other, and the completely unexpected degree to which they differ can be explained by the discovery that the ratio of these two groups of fibers in the same layer changes with the square of the layer's thickness, and that the length of the unmyelinated initial segment of the neurites is relatively constant.

These differences between the bottom of a fold, where the lower layers appear to contain almost exclusively horizontal fibers, and the peak, where the same layers appear to contain almost exclusively vertical fibers, is so apparent that we can understand why many cerebral anatomists studying the myeloarchitectonic regions of the cerebral cortex have understood the bottoms and peaks of folds as distinct myeloarchitectonic regions.

This is even more understandable because the upper cortical layers contain relatively few myelinated fibers, and the strongest changes of the fiber complex determined by the curvature (which occur in the lower layers, where the thickness changes are most pronounced) occur in the same layers that, to some extent, define the fiber complex of the entire cortex due to the abundance of myelinated fibers in those layers. And also because these changes caused by the curvature are often larger than the differences between actual myeloarchitectonic cortical regions not caused by curvature. And finally, the theory that specific myeloarchitectonic regions exist in the bottoms of folds is supported by the fact that the vertical and horizontal fibers, the ratio of which is changed by curvature, appear to serve two different functions, as the horizontal fibers are typically associated with an associative function and the vertical fibers with a projective one. The changes of the fiber complex caused by the curvature certainly suggest a functional difference, namely a change in the relationship between the associative and the projective functions of the cortex.[8]

Even though these reasons might understandably lead to an assumption that different myeloarchitectonic fields exist at the peaks and bottoms of folds, the analysis of cortical curvature presented here proves that the strong differences in their myeloarchitectonic character are products of the fact that the arrangement of the neurons is maintained through curvature. Therefore, the evidence does not indicate the existence of functional differences.

So, in cortical curvature, the neurons of the cerebral cortex show the very changes in their form that are required to maintain a constant arrangement of these neurons. Whether these changes in form are also numerically consistent with the conditions of constant arrangement cannot be shown in this work, as the required measurements were provisionally deemed too difficult due to the strong individual variations of the cortical neurons. That having been said, the subjective impression is that they cannot numerically deviate much from the ideal conditions of a constant arrangement. *I therefore believe that I am entitled to the conclusion that the neurons of the cerebral cortex seek to maintain their arrangement through cortical curvature, and that they are completely (or nearly completely) successful in doing so*.

The suggestion of this analysis, that the neurons display a constant arrangement, is consistent with the results of our analysis of the changes in the layer thicknesses. In the second chapter, we found that these changes in thickness were the product of the layers maintaining a constant volume. Without delving much deeper into that, a constant arrangement of specific layers also logically follows from these changes in thickness.

The changes in the thicknesses of the cortical layers are the same type as those in Figure *e* of Fig. A.1. In this figure, the checkered pattern is drawn as a curved pattern in such a way that the squares maintain a constant volume and a constant arrangement. In *b* of the same figure, however, the squares still show a constant volume, but the layer thicknesses remain unchanged. The difference between these two figures is the fact that in *b*, a combination of constant volume and constant form exists (which necessitates that the arrangement of the squares is changed), whereas in *e*, a combination of constant volume and constant arrangement exists (which necessitates changes in the layer thicknesses). The constant volume of the layers, achieved through the thicknesses of the layers, is the same as is shown in figure *e*, and is combined with the constant arrangement of specific components. This is a unanimous indication that the small components of the layers, the neurons, show a constant arrangement.

The constant arrangement of the neurons in the cerebral cortex in the curvature of the cortex results, as we have seen, firstly in a radial orientation of the main axis of the ganglion cells and the extension and retraction of the nerve fibers, secondly in a changing form of the ganglion cells, which become taller and thinner in a thicker layer and shorter and wider in a thinner layer than they would be in the uncurved cortex, and thirdly in changes of the fiber complex, which shows more vertical fibers in thicker sections and more horizontal fibers in similarly formed thinner sections of the layers.

PART IV

In order to maintain a constant volume and a constant arrangement through the curvature of the cerebral cortex, the elements of this cortex—the neurons as well as the layer sections—must undergo a change in form consisting of an enlargement of the vertical dimension innermost layer with respect to the curvature and a proportional shrinking of the horizontal dimension thereof, as well as the inverse in the outermost layer: a shrinking of the vertical and a proportional enlargement of the horizontal dimension thereof. In these two extreme layers—the outermost and the innermost—these changes in form are the most pronounced, and because they manifest in opposite ways, they deviate from each other here more strongly than anywhere else. In layers closer to the middle of the cortex, these changes in form become more and more minute, and the layers are therefore less differentiated, until eventually, between the inner layers where the elements become taller and the outer layers where they become shorter, a layer must exist in which the elements maintain the same height and therefore also the same width as in the flat cortex; or in other words, in which no changes in form occur at all.

In the schematic drawing in Fig. A.10, in which 9 bands of the same thickness go through two curves while maintaining volume constance, we can see that the squares in the straight section become tall and thin in the inner bands of the curves, as opposed to short and broad in the outer bands, but that in each curve, there is a specific band in which the square has remained a square. Of course, this formulation is not perfectly correct, as the square in the curved section is bound by four lines, two of which (the upper and lower ones) are curved and the other two diverge, which means that the square is curved. Aside from that

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[8] I notice that these functional differences suggested by the changes in the myeloarchitectonic character between the bottoms and peaks of folds is different from the functional difference suggested by the changes in layer thickness and formulated in the theories of *v. Economo*.

curvature, though, its form is unchanged: its height and average width are the same as in the uncurved pattern.

The curvature therefore has a different influence on the elements in this special layer than on the elements in the other layers. The elements in the other layers are firstly curved, but secondly, the relationship between their vertical and horizontal dimensions is also changed so that a square is transformed into a (curved) rectangle. In the one special layer, though, the elements are only curved, and aside from that, no other changes in form occur. To succinctly describe this special way in which the curvature manifests in this layer, it can be called *isomorphic curvature*. The remaining layers show a *heteromorphic curvature*.

It is clear that purely isomorphic curvature can only occur at as thin a layer as imaginable, as a thicker layer, even one with isomorphic curvature, can still be divided into a number of thinner layers, and only one of these layers can then show isomorphic curvature; the inner and outer layers would then necessarily have heteromorphic curvature. We must therefore speak of a single *plane of isomorphic curvature*.

The thickness gained by the cerebral cortex in a curve is connected to the location of this plane of isomorphic curvature. This is because every layer inside this plane (i.e. between this plane and the axis of curvature) is thicker than in the flat cortex and every layer outside this plane is thinner. If this plane were to lie towards the center of the curvature, fewer layers would be thick and more would be thin, which would mean that the overall cortex would be thinner. If this plane were more peripherally located, more layers would be thick and fewer would be thin, so the cortex would be thicker.

In the three figures in Fig. A.2, the plane of isomorphic curvature is at different heights: in *a* it is in the upper (=inner) layer, in *b* in the middle layer, and in *c* in the lower (=outer) layer. The pattern *a* is the thickest and the pattern *c* is the thinnest of the three.

In order to analyze the changes in the overall cortical thickness, we must first understand the positioning of the plane of isomorphic curvature, and we must seek to prove which factors determine this positioning.

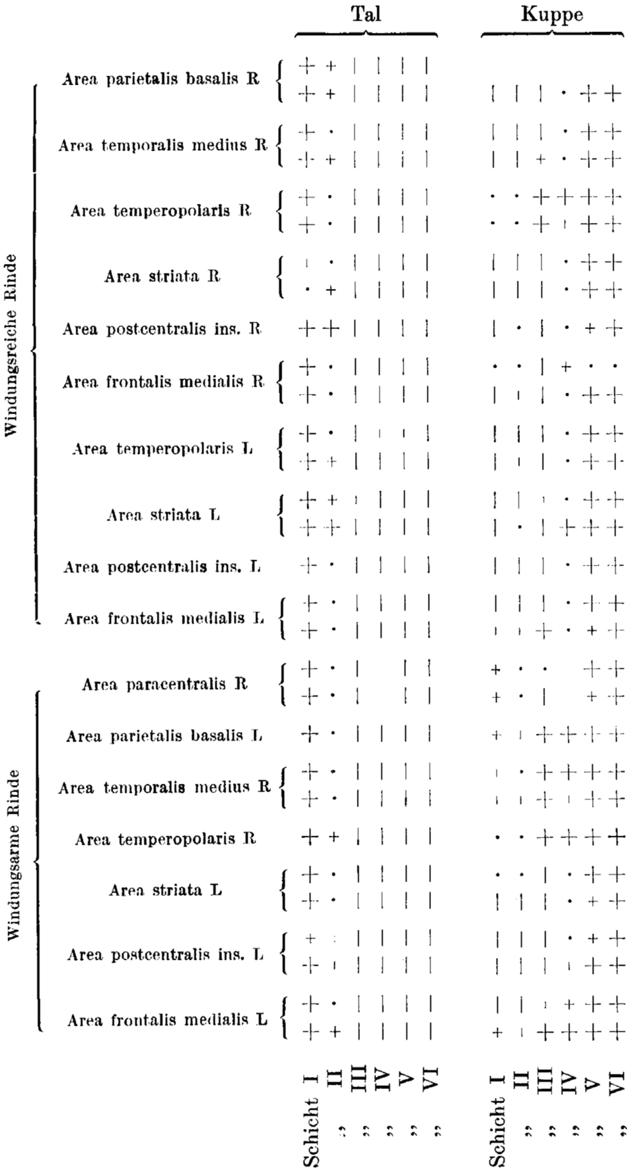
The positioning of the plane of isomorphic curvature can be determined in two different ways. Because the elements at this plane have the same vertical and horizontal dimensions as in analogous sections in the adjacent flat cortex, we can determine in every curvature, the level in the cortex at which the vertical dimension is maintained, or we can determine the level at which the horizontal dimension is maintained.

We will begin with the method of the constant vertical dimension.

This method only allows for rough approximations, as the cortical layers are the smallest analogous parts that can be designated in a curve and in the adjacent flat cortical section in order to measure the heights thereof. Within the thicknesses of the layers, it is impossible to accurately bound analogous cortical components. Furthermore, all of the layers are not so distinctly defined that changes in their thicknesses can be measured with sufficient precision. We must therefore be satisfied here with rather rough findings. It is helpful that the plane of isomorphic curvature not only shows constant thickness, but that it is also located between layers which are thicker in curvature on one side and thinner in curvature on the other.

For every transition from a flat cortical section to a curved one, it must therefore be determined which of the 6 layers become thicker and which become thinner, as well as which, if any, maintain the same thickness. The flat—or relatively flat—cortical sections are located at the fold walls, and every fold wall transitions into two different curvatures, one at the peak of the fold and the other at the bottom of the fold. For each completely measured fold, then, the changes in absolute cortical thickness can be studied at four such transitions from flat to curved cortex, once for the 1. first wall into the first peak, 2. then for the second wall into the second peak, 3. thirdly for the first wall into the bottom of the fold, and 4. fourthly for the second wall into that bottom.

All of these changes in thickness are simply illuminated by the graphs of absolute layer thicknesses given in Fig. A.9, i.e. by the first graph in each row. When a specific layer becomes thicker in the transition from the first wall (second vertical) into the first peak (first vertical), for example, the lines defining this layer diverge in the graph from the second to the first vertical. If the layer were to become thinner in this transition, the lines would converge.



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Windungsreiche Rinde	Area parietalis basalis R	+	+	|	|	|	|						
		+	+	|	|	|	|	|	|	|	·	+	+
	Area temporalis medius R	+	·	|	|	|	|	|	|	|	·	+	+
		+	+	|	|	|	|	|	|	+	·	+	+
	Area temperopolaris R	+	·	|	|	|	|	·	·	+	+	+	+
		+	·	|	|	|	|	·	·	+	|	+	+
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	Area striata L	+	·	|	|	|	|	·	·	|	·	+	+
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		Schicht I	„ II	„ III	„ IV	„ V	„ VI	Schicht I	„ II	„ III	„ IV	„ V	„ VI

Fig. A.18. Changes in the thickness of the cortical layers at transitions from flat cortical sections into concave (top) and convex (bottom) curved sections. + indicates the layer is thicker in the curved section, - indicates the layer is thinner in the curved section, and . indicates the layer is equally thick in the curved section as in the flat section. The six symbols in each column represent the six layers at the same transition.

In Fig. A.18, for every transition and for every layer, whether the layer becomes *thicker* or *thinner* as a result of the curvature is represented with + or -, and if the same thickness is maintained, this is represented with a point. A vertical column of six signs tells us about the changes in thickness in the six layers in one transition. The transitions from wall to fold bottom are assembled in the top table, and the transitions from wall to peak in the bottom table.

In the transitions from wall to fold bottom (top table), we can see that layers III through VI always get thinner (minus sign), that layer I gets thicker (plus sign), and that layer II maintains the same or approximately the same thickness (point, or a small minus or plus sign) in the majority of cases. At the bottom of the folds, the plane of isomorphic curvature therefore always lies in the second layer or very close to it.

In the bottom table, in which the transitions from wall to peak are collected, no such perfect regularity exists. Nevertheless, this table illuminates a preference for the fourth layer. At the peaks, the plane of isomorphic curvature lies mostly in or near the fourth layer, even if not as consistently as it lies in the second layer at the fold bottoms. At the peaks where it does not lie in the fourth layer, it lies closer to the surface in the third or second layer.

The second layer of the cerebral cortex is the outer or first nuclear layer, the fourth is the inner or second nuclear layer.[9] The plane of isomorphic curvature therefore shows a tendency to localize itself in a nuclear layer. In the concave curvature of the fold bottom, it regularly lies in the first nuclear layer; in the convex curvature of the peak, it mostly lies in or near the second nuclear layer. In both cases, this is whichever nuclear layer is the innermost between the two with respect to the curvature. The results from this first method can therefore be summarized as follows: *the plane of isomorphic curvature shows a tendency to localize itself in whichever nuclear layer is the innermost with respect to the curvature. This is always achieved quite precisely in the concave curves (fold bottoms), but only in the majority of cases in the convex curves: in the remaining cases, it mostly lies more off-center*.

The second method for determining the plane of isomorphic curvature is based on the constant horizontal dimension. This method is much more exact than the first method, but its results are unfortunately so strongly influenced by fold curvature that it fails to offer us any meaningful results in spite of its exactness.

If we think of the cortex in a cross-section of an ideally straight fold as being divided into a large number of very thin layers, and we define two segments of the cortex, one in a flat section and one in a curved section, with lines drawn through the cortex in the direction of the main dendrites, we thereby also define two segments of each very thin layer, one flat and the other curved. If the two cortical sections we define have the same surface area, according to the law of volume constance, the two segments of each layer will also have the same surface area as each other. The more inner layers of the curved section will be shorter than the flat section of the same layer, as measured along the layer boundary, and the more outer layers will be longer. The curved layer in which the plane of isomorphic curvature lies will have the same length as the flat section of the same layer. So, if we measure the width of a cortical segment along a line that runs parallel to the layer boundaries, which we have previously called a horizontal line, and we always do this for analogous layers in the two segments, we will find the same width for the curved segment and the uncurved segment at the plane of isomorphic curvature. At planes which lie inside this plane of isomorphic curvature with respect to the curvature, the width of the curved segment is smaller than that of the uncurved segment, and at planes outside this plane, it is larger. In this way, the plane of isomorphic curvature can be determined.

It is not necessary for us to define two segments with the same surface area, because if the surface area of one of these segments is larger by some factor, its width at the plane of isomorphic curvature will be larger by the exact same factor: *The surface areas of the two cortical segments defined on the photograph are proportional to their widths at the plane of isomorphic curvature*.

To determine the plane of isomorphic curvature by means of the second method, one segment is defined on the photograph each for a flat and a curved section of the cortex, and the lengths of the different layer boundaries drawn in these segments were measured with a curvimeter. Then, the relationship between the surface area of the two cortical segments is determined (for example, by weighing cardboard pieces cut into those shapes) and each length belonging to the segment is divided by this relationship. If, then, the widths of the two segments are compared, which is made possible in this way, the widths of the curved segment at the inner layers will be shorter than those of the uncurved section, and they will be longer in the outer layers. The plane of isomorphic curvature is located in the layer with one boundary that is too short and another that is too long. And the location of this plane within this layer can be interpolated with a precision that is dependent only on the precision of the measurements and the definition of the segments.

The results achieved through this second method are included in the graphs of the absolute layer thicknesses [(Fig. A.9)] in the form of small dashes. They are not automatically the same as the results of the first method, which is a product of the fact that the studied folds are not ideally straight, and that every deviation from this straightness has a specific and very large impact on the results of these measurements.

We saw on p. 697 ff. that in a simply curved fold, one wall is the inner wall with respect to the curvature and the other wall is the outer wall; or in other words, that the cortex is curved concavely in one wall and convexly in the other. Further down (p. 731), we will see that the thicknesses of the cortex change with the curvature, that it becomes thinner in concave curvature and thicker in convex curvature. In the cross-section of a curved fold, the cortex is therefore thicker at one wall and thinner at the other than it would be if the fold was straight, and the surface area of a cortical section in our photograph will therefore be too big at one wall and too small at the other.

Because the lengths of the layer boundaries are not subject to this influence, as they lie parallel to the axis of the fold curvature, and the segments at the peaks and fold bottoms do not, this unmeasurable influence of the fold curvature results in a proportional displacement of the levels found by means of the second method, which are displaced upward at the peaks and downward at the fold bottoms by convex wall curvature, and conversely downward at the peaks and upward at the bottoms by concave wall curvature.

The magnitudes of these displacements cannot be determined by measuring the cross-sectional photographs. Nevertheless, the order of magnitude thereof can be read from these graphs and an approximate correction can be made thereby.

The graphs of the R. area temporalis medius in the heavily curved cortex belong to a simply curved fold. In the third graph, the fourth layer is higher at the second vertical than at the first and third, which means that the volume of the fifth and sixth layers was found to be too large at this wall. Those layers are too thick here, so the curvature of this wall made the lower cortical layers thicker and is therefore a convex curvature. The dash between the first and second verticals in the first graph predicts the plane of isomorphic curvature to be too low, and the dash between the second and third verticals predicts it to be too high. At the other wall, there are contradictory conditions: layer IV is too low at the fourth vertical of the third graph, so the wall curvature is concave and the dash between the third and fourth verticals is too low.

The difference in height between the dashes at the two peaks, located between the first and second as well as between the fourth and fifth verticals in the first graph, is 1.5 times the difference between the heights of layer IV at the second and fourth verticals in the third graph; the height difference between the two dashes at the bottom, at the third vertical, is the same as the difference between the heights of layer IV at the second and fourth verticals in the third graph. The influence of the fold curvature on the values found for the location of the plane of isomorphic curvature can therefore be somewhat corrected by displacing the dashes at the peaks in the same direction, with 1.5 times the magnitude of the difference between the heights of layer IV at the second and fourth verticals in the third graph of the fold in question, and by displacing the dashes at the bottom in that amount in the opposite direction. No further explanation is needed, as this correction

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[9] The conventional adjectives: “inner” and “outer” are not used with respect to the curvature here, as in all other parts of this article, but rather with respect to the height. For this reason, I choose the name “first nuclear layer” for layer II and “second nuclear layer” for layer IV.

is extremely crude and does not change the fact that the accuracy of this second method is permanently lost in curved folds. Nevertheless, this correction was calculated and represented in all of the thickness graphs with points. The positions of these points, understandably, still do not agree with the results of the first method, and they do not represent constancy of layer volumes.

Only a measurement of three-dimensional (spatial) cortical segments could accurately predict the position of the plane of isomorphic curvature through the second method. As of now, I do not intend to make such spatial measurements.

So it must be left to future studies to answer the question of whether isomorphic curvature is also localized in the inner nuclear layer even with respect to curvature of folds. In the folds studied by me, this does appear to be the case. Through this, a cortical section curved in two directions at once could display isomorphy at two different planes simultaneously, and the consequences of opposing or agreeing heteromorphy would have to combine in different ways at different layers. This could possibly explain why some curvatures appear to show isomorphy in two non-adjacent layers at once, and between these two layers, appear to be allomorphically curved.

So, the plane of isomorphic curvature lies in the innermost nuclear layer with respect to the curvature in the majority of cases (more than 80%). From this, two characteristics of cortical curvature follow, both of which are quite interesting.

Firstly, this means that the third layer always lies outside the plane of isomorphic curvature, both in concave and convex curves, and it is therefore thinner in every cortical curve than in adjacent flat cortical sections. In the two transitions from the flat cortex at a fold wall, once into the concave curvature of the fold bottom and once into the convex curvature of the peak, we generally see that each layer gets thinner in one transition and thicker in the other. Only this third layer tends to become thinner in both curves.

I am of the opinion that this characteristic of cortical curvature does not have any further meaning. The other characteristic, which will be discussed now, gives us more information about the factors that influence the localization of the plane of isomorphic curvature.

Because the plane of isomorphic curvature is mostly localized in the inner nuclear layer with respect to the curvature, the other nuclear layer is outside this plane and, as a result, is thinner than in the uncurved cortex. *In most curvatures, one of the two nuclear layers maintains its thickness and the other becomes thinner than in the uncurved cortex, which means that no nuclear layer becomes thicker*.

There are very few exceptions to this rule, which namely occur in the peaks of folds in which the layer of isomorphic curvature is located in the third or even the second layer as opposed to the fourth. There, the second nuclear layer (layer IV) is located inside the plane of isomorphic curvature and therefore becomes thicker. This gain of thickness, which only occurs at a few positions, is quite small, as the displacement of the plane of isomorphic curvature occurs very far from the midpoint of the curvature.[10] This midpoint of curvature is located in the subcortical region, and the radius of the second nuclear layer includes the (large!) thickness of the fifth and sixth layers as well as a considerable distance into the white substance. A small displacement of the plane of isomorphic curvature away from this axis therefore numerically constitutes only a very small fraction of the radius of curvature and causes only a small increase in the thickness of the second nuclear layer.

In the concave curvature of the fold bottom, a displacement of the same size would cause a much larger increase in thickness. Firstly, the plane of isomorphic curvature lies in the first nuclear layer here and therefore exists near the inner layer boundary with respect to the curvature. Secondly, in its concave curvature, the cortex must only surround the pia mater, whereas it must curve around the subcortical white matter in its convex curvature. This means that the radius of curvature of the plane of isomorphic curvature is very small (the curvature is very pronounced) at the bottom of a fold, and a displacement away from the axis of curvature would result in a very pronounced increase in the thickness of the first nuclear layer. It is therefore very much worth mentioning that a displacement of this plane into the third layer at the bottom of a fold was only found twice, and that this displacement was extremely small in both cases. As a result, the associated increases in the thickness of the nuclear layer were also small.

So, In the curvature of the cerebral cortex, the nuclear layers show no increase in thickness, or, in exceptional cases, only a small increase in thickness. An increase in the thickness of a nuclear layer means that the small ganglion cells (which are smaller in the nuclear layers than in other layers) become taller and narrower. *The small ganglion cells therefore do not become narrower, or, at the very most, become only slightly narrower in the curvature of the cerebral cortex*.

The ganglion cells becoming narrower can only be avoided if the small cells in the outer nuclear layer with respect to the curvature become shorter and wider. We have seen that the outer nuclear layer gets thinner in curvature. The small cortical cells do get wider as a result of that, but they remain constrained by the necessary minimum, which we want to see.

In most of the curvatures, the extent to which the cells of a nuclear layer become wider (and this layer thinner) is determined by the fact that the plane of isomorphic curvature is localized in the other nuclear layer, so that layer therefore has a constant thickness and its cells undergo no changes in form. If the increase in the width of the former cells were smaller, the outer nuclear layer would also become thinner to a smaller extent, which could only be the case if the plane of isomorphic curvature were displaced more outward—away from the axis of curvature—, e.g. outside the other nuclear layer. This other layer would then become thicker than in the flat cortex, and its cells would also become thinner. Such a thinning of the small cortical cells, however, occurs very rarely—as we have seen. The widening of the small cells in one nuclear layer occurs in such a way that it sufficiently prevents the thinning of the other small cells in most cases. It only barely falls short of that mark in the exceptional cases, in which the small cells of the other nuclear layer show a slight thinning.

Conversely, this widening also does not regularly exceed this measurement. That occurs only where the plane of isomorphic curvature inside the inner nuclear layer with respect to the curvature, when both nuclear layers become thinner than in the uncurved cortex. This occurs only in very few exceptional cases, which can be seen in the table.

Because the small cells of the cerebral cortex become at most only slightly thinner, the small cells of one of the two nuclear layers must become wider, and this widening remains constrained by the necessary minimum.

If a ganglion cell of the cerebral cortex becomes thinner, this generally means that its smallest dimension becomes smaller, as the typical cortical cell has a smaller (horizontally measured) width than its (vertically measured) height. *The plane of isomorphic curvature is therefore localized in such a way that the smallest dimension of the small ganglion cells does not become smaller, or becomes only slightly smaller*.

This rule also governs the changes in thickness displayed by the entire cortex in curvatures, as this depends on the localization of the plane of isomorphic curvature, which we saw on p. 722.

At the bottom of a fold, this plane of isomorphic curvature lies in or near the second layer. Because the first layer is the innermost layer with respect to the curvature, only one layer (and two at a few folds) lies inside the plane of isomorphic curvature here, and four layers lie outside. At the bottom of a fold, then, only one layer becomes thicker than in the uncurved cortex and four layers become thinner: the entire cortex is therefore thinner here than at the fold wall.

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[10] The idea of a midpoint of the curvature (or, spatially speaking, an axis of curvature) cannot be perfectly conceived, as the different layers are not curved exactly concentrically and therefore do not have exactly the same midpoint of curvature.

In the transition into the peak of a fold, the plane of isomorphic curvature lies mostly in the fourth layer, which means approximately in the middle of the uncurved cortex. Here, then, half of the cortex becomes thinner, and half becomes thicker. If these two changes occur to the same extent, the overall cortex will become thicker than at the wall (if the thickness at the wall is 100, and the increase and decrease in the thicknesses of the two halves are twofold, then the thickness of the upper half at the peak is $1/2 \times 50 = 25$, and the thickness of the lower half is $2 \times 50 = 100$, so the thickness of the overall cortex is 125, which is 25% more than at the wall). The lower half of the cortex is, however, closer to the axis of curvature than the upper half, and its thickness therefore increases more than the upper half decreases. The result is an even stronger increase in the thickness of the cortex at the peaks of folds.

The fact that the cerebral cortex is thinner at the bottoms and thicker at the peaks of folds than it is at the adjacent walls therefore follows from the rule that the smallest dimension of the small ganglion cells does not become smaller.

This rule appears to not apply as strictly as the law of constant volume, as we have seen: this becomes clear at certain curves, even if the deviations are not especially large. It has not yet been established whether these deviations only appear to be such, e.g. whether they are actually caused by the curvature of the folds. The consequences of curved folds add to the consequences of the cortical curvature in the tops and bottoms of folds analyzed here in such a complicated way that it is not yet possible to conduct a sufficient analysis. If they actually are deviations—but still quite small ones, as we have seen—then it seems quite possible to me that the influence of cortical thickness on the localization of the plane of isomorphic curvature is at play here. If, for example, a lack of space existed for which a reduction in cortical thickness could compensate, this reduction could be achieved through a displacement of the isomorphy away from the axis of curvature, which would necessitate a small thinning of the small cells in the second nuclear layer that would otherwise not occur. A clue in that direction is offered by the displacement of isomorphy away from the axis of curvature at the bottom of an insular fold. This displacement is the strongest that I have seen, and the fold in question touches the claustrum here, which lays on the striatum: cortex, claustrum, and striatum are only separated from each other by thin lamellas of white substance. It is conceivable that at the bottom of this fold, there would not be sufficient space, and the cortex would seek to become thinner. Such a reduction in cortical thickness, caused by external conditions, would only cause a small thinning of the small cortical cells.

In order to express the thickness of the cerebral cortex numerically in a way that allows us to compare different cortices with each other, the thickness must always be measured at the same curves, because—as we have seen—it changes with the curvature: it is larger in a convex curve and smaller in a concave curve. Most authors measure the cortical thickness at the peaks of folds, and this method was recommended by *v. Economo* as the one to be generally followed. The cortical thickness at the peaks of folds, however, still depends on the degree of curvature of this fold, which changes in different curvatures in normal as well as pathological folds. Atrophic folds, for example, have especially strongly curved peaks. The thickness at the peaks is therefore not a reliable measurement for comparing different cortices with each other.

The simplest solution would be to only measure the thickness of uncurved cortical sections. But because these do not exist in many cortices, it is still necessary to utilize an applicable method to calculate the thickness that the cortex would have at a specific location if it were not curved there. Such a method follows from the described transformation equalities.

In a curved and a corresponding, ideally flat cortical section, let us imagine two segments with the same surface area, defined by lines drawn on the cross-sectional photograph in the direction of the main dendrites. The surface area of the uncurved, and therefore rectangular segment is equal to the product of its thickness and its length, e.g. the length of the plane of isomorphic curvature in this segment. The thickness of the uncurved section can therefore be calculated as the surface area of the segment divided by the length of its plane of isomorphic curvature. But because this surface area is equal to that of the curved segment, and also the length of the isomorphic planes of each segment are the same length, as we saw on p. 722, we can also find the thickness of the uncurved segment by using the length of the plane of isomorphic curvature in the curved segment. *We can therefore determine the ideal cortical thickness at a cortical curve by defining an arbitrary segment and dividing the surface area thereof by the length of its plane of isomorphic curvature.*

Unfortunately, this method is not very precise, as we are not yet able to precisely determine the location of the plane of isomorphic curvature. It is, however, more precise than the methods currently in use.

With this analysis of isomorphy, all of the currently known changes that affect the structure of the cerebral cortex in the curvature of the tops and bottoms of folds can be summarized in laws. Collectively, these laws govern these changes unambiguously, and they can be formulated as follows:

In the curvatures of the cerebral cortex, the volume and arrangement of the constituent parts—like the neurons, for example—are held constant. The form of the neurons and the thicknesses of the layers must therefore change, and these changes occur in such a way that the ganglion cells of the nuclear layers do not become thinner and, where it is necessary that they become wider, do so as little as necessary; in other words, in such a way that the smallest dimension of the small ganglion cells either does not or barely does become smaller.

PART V

In the previous chapter, it was shown that until now, the recognized differences in the structure displayed by the cerebral cortex at the bottoms, walls, and peaks of folds were all consequences of the cortical curvature that occurs at the folds. The structural pattern of the bottom of the fold is a geometric transformation of the structural pattern of a flat cortex into a concavely curved one, and at the peaks of folds, into a convexly curved one.

Transformations can occur in very different ways, depending on the properties that are preserved through the transformation, or the “transformation constants”. In the curvature of the cerebral cortex, there are three such constants to be found, which together distinctly determine all the details of this transformation:

1. Constant volume of the component parts (i.e. the neurons);
2. Constant arrangement of these parts;
3. No reduction in and minimal enlargement of the smallest dimension of the small ganglion cells.

Of these three, we found that the first law, that of volume uniformity, is very strictly valid, namely within the accuracy of our measurement methods, which yielded a mean error of 0.004. There is also nothing to indicate that the second law, that of arrangement uniformity, is any less strict—we were not, however, able to substantiate this through our measurements. The third law, which restricts the reduction of the smallest dimension of the small ganglion cells as well as minimizes the enlargement of the same, appears to be less strictly applied; some deviations from this law exceed multiple percentage points. The possible causes for this deviation from the third transformation constant, which is by no means confirmed and is undoubtedly quite small, have not been more closely investigated.

The specific changes that occur in the structural picture due to the curvature transformation are the following.

The inner layers with respect to the curvature are thicker in the curved cortex than in the flat cortex. The ganglion cells therein are taller and markedly thinner, the vertical fibers are closer to each other, and the horizontal fibers are further from one another than in the flat cortex. The outer layers with respect to the curvature are, in contrast, thinner, the ganglion cells therein are shorter and wider, the vertical fibers are further from each other, and the horizontal fibers are closer than in the flat cortex.

The differences in the relationship between the number of vertical and horizontal fibers that can be seen in identically formed layer areas are quite large because they are proportional to the square of the layer thickness. Upon examination of fibers, it can be seen in the fifth and sixth layers of the bottom of a fold, where these layers are very thin, that the fibers are almost exclusively horizontal. At the peak, where these layers are much thicker, the fibers are mostly vertical. In these layers, the form variation of the ganglion cells as a result of this extreme change in thickness is also very apparent: at the peak, these cells are tall and thin, or decidedly vertical, whereas at the bottom, they become so significantly broadened that their width vastly exceeds their height and they become horizontal.

In a concave curve—at the bottom of a fold, for example—only layer I is thicker than in the flat cortex, layer II is often about the same thickness, and the remaining layers (III through VI) are thinner than in the flat cortex. In a convex curve, like at the peak of a fold, layers V and VI are always thicker, layer VI mostly displays the same thickness as in the flat cortex, and layers III, II, and I are then thinner. The entire cortex, as a result, is thicker in convex curves and thinner in concave curves than in uncurved sections.

Because of the curvature that occurs in the folds, corresponding changes will occur in the walls of these folds as well.

The sections of the cerebral cortex that are known either through clinical or physiological experience to serve different functions have also been known for a long time to display different structural construction types. Later, it was accepted that the inverse was also true—that all cortical areas which display different structures must serve different functions. The question then becomes whether the structural differences that occur in the transformation of a flat cortex into a curved one have a functional meaning.

This functional meaning could manifest in one of two ways: either the curvature could be a morphologic consequence of the function localized to this area, or the curvature could—by changing the form of the neurons—influence the local function.

The possibility that local character of the cortical function at some position might cause morphological changes in the neurons which would result in the cortex becoming curved—in order for these neurons to better serve this specific function, for example—is not likely. This is because the localization of such a specific function would then have to necessitate characteristics that would justify the peculiar structure of a curve, such that the localization of the function would cause the formation of the curve.

Namely in the configuration of the different cortical folds, we see certain coincidences that must be grounded in the spatial form of the folds. For example, in a simply constructed fold, concave cortical curvature appears on either side of the bottom of the fold just as convex curvature appears the same distance from the peak of a fold: The fact that the distances from the two convex curves to the concave curve located between them are generally the same is a consequence of the fact that the two adjacent turns lie in the same level—namely against the wall of the cranial cavity, and is therefore grounded in the spatial form of the folds. If these curves were instead caused by local functional characteristics—of which there would have to be two types, one to cause convex curves and one to cause concave curves—it would be quite odd that every time, on both sides and the same distance from the first type of functional characteristic, the second type of function would be localized.

There are more such coincidences that I want to just briefly reference.

In a curved fold, the two walls display curvatures that fit into each other like a cast model in its mold. In every such instance, the two walls are curved in the opposite direction and in such a way that their pial surfaces display the same radius of curvature, a fact that is also grounded in the spatial form of the folds. It must be regarded as highly improbable that a wide range of special functions would be localized in such a way in the flat cortex that the resulting curvatures would always result in folding together cortical areas with opposing localized functions that occur in exactly the right proportions to make these sections fit perfectly into one another.

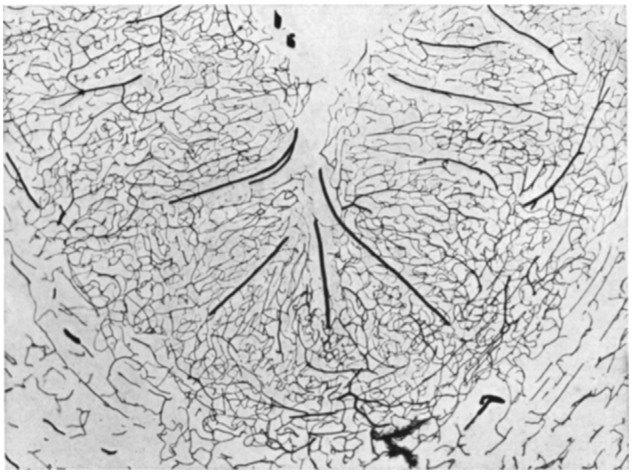

Fig. A.19. The vessels of the human cerebral cortex at the bottom of a fold (Injection preparation 30×, as in Figs. A.20 and A.21).

It is therefore extremely unlikely that cortical curvature is the consequence of local neurons altering their form to satisfy a localized characteristic of cortical function.

Is it possible that curvature might then cause specific functional differences where it occurs?

Only a physiological investigation could provide an answer to this question. Morphology can only provide clues to point to a possible answer: these clues must then proceed from the question of which morphological characteristics are maintained through curves and which vary.

The arrangement and volumes of the Neurons are maintained. The arrangement of the neurons is connected most closely to the function of the neurons in question, as their capabilities are determined by their arrangement. The fact that this very arrangement is maintained therefore already points to the likelihood that function is similarly maintained. The volume constancy also points in this direction, as an increase or decrease in volume normally corresponds with an increase or decrease in functional capacity.

The form of the neurons and the thicknesses of the layers vary within curves, which means the relationship between the horizontal and vertical dimensions of the neurons (including the dendrites and axons as well as the body of the cell) is also changed. These changes occur, however, in such a way that a dendrite or axon shortens itself when ganglion cells move closer to it and elongates when other cells are moved further away. This means that the dendrites and axons are arranged how they must be arranged in a curved cortical section to maintain the wiring possibilities of different neurons. The shortening or elongation required for this constant capacity is the only thing that occurs in cortical folds that could have a functional meaning. However, this meaning still seems quite small to me: the function of a motor cell in the frontal horn of the spinal cord is not dependent on whether the muscle to which it is innervated is close to or very far from the spinal cord. It appears certain to me that the absolute length of the extensions of the neuron has a much smaller impact on the function than the arrangement of the neurons themselves, which impacts the function by determining with which other neurons these extensions may connect. Geometrically, it is not possible to maintain both the length of the extensions and the arrangement of the neurons within a curve.

Fig. A.20. The vessels of the human cerebral cortex at the wall of a fold (the bottom of which is depicted in Fig. A.19).

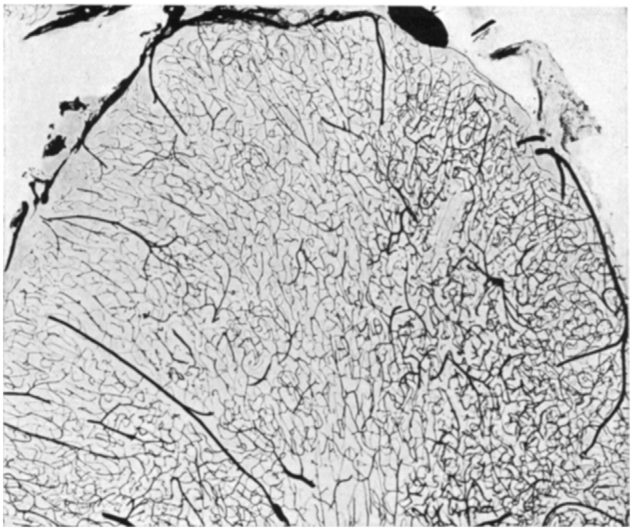

Fig. A.21. The vessels of the human cerebral cortex at the peak of a fold (adjacent to the fold in Figs. A.19 and A.20).

One of the two characteristics must be lost, and we see that the arrangement is maintained and the length of the extensions changes according to the distances between connected neurons. In other words, only the property that has very little to no functional meaning is changed, and the properties that have significant functional meanings are held constant, so that the functional meaning of the constant properties vastly outweighs the functional meaning of the variable properties.

It logically follows that the cortical function is not changed throughout curvature. It is certainly clear that we currently have not a single piece of morphologic evidence which would lead us to assume that cortical folds have any influence on proximal cortical function.

It certainly also logically follows that a different type of curvature would not leave cortical function so unchanged as the type that is determined by the three forms of transformation described above. In a different type of curvature, either the neuron arrangement or the neuron volume would vary with the curves. *Therefore, perhaps due to the physiological requirement that the cortical function not be influenced by the curvature of the cortex, we must investigate why the cortex curves in such a way that it can be described by the transformation laws described above.*

For the first two forms of transformation (the constancy of volume and arrangement), this is readily clear: In order to maintain function, the wiring of the neurons must remain the same and therefore the arrangement of the neurons must remain as similar as possible. The volume of the neurons must also not be changed. But the third law, that a reduction of the smallest dimensions of the small ganglion cells must not occur, appears to also be connected to this necessity, as it is very certainly realistic to think that of all possible changes in the form of the ganglion cells, a reduction in the smallest dimension is the most significant. It is then also believable that this third law is less strict than the first two, as this change in dimension would have less functional impact than a change in neuron arrangement or neuron volume. It is still possible, however, that completely different—i.e. morphologic—factors (like a resistance to deviation in form, which would be most pronounced specifically when it came to reduction of size in the smallest cells) could be the cause of this third law.

The possibility that the need for constant cortical function is the foundational cause of the threefold nature of the cortical curvature is obviously in no way proven by these facts; rather, it is only proposed as a possibility that might be more closely investigated.

However, we can still find an argument in support of the possibility that the pattern of neurons curves in this specific way so as to not affect the function of the neurons in the way in which the pattern of the cortical blood vessels curve.

While the neurons maintain their arrangement and volume in the curves of the cortex, thereby changing their form (arrangement, volume, and form cannot all three be geometrically maintained, as we have seen), a different decision is made with the pattern of the blood vessels: the vascular loops principally display a constant form and constant size, thereby changing their arrangement in curves. Figs. A.19 through A.24 display microscopic photographs of a specimen of the cerebral cortex in which the blood vessels were injected with dye.[11]

Whereas the ganglion cells are strongly shortened and horizontally elongated in the lower layers (V and VI) at the bottom of a fold, and the horizontal fibers are very closely packed while the vertical fibers are quite distant from each other, we see in Figs. A.19 and A.22 that the vascular loops have the same form and the same size here as they do in the uncurved section of the cortex (Figs. A.20 and A.23), and that the relationship between the horizontal and vertical vessels does not experience a change. Only in the peak of a fold, when these layers are significantly thicker and compressed, do the vascular loops become (still only slightly) narrower. The arrangement of the vascular loops is, however, very drastically changed within cortical curves, even though that is not necessarily obvious to the eye: in the outer layers with respect to the curvature, like layer VI at the bottom of a fold, there is a much higher number of adjacent loops than in the corresponding section of the inner layers (I and II), even though this section of the inner layers is much shorter and the vascular loops are the same size (see also Figures. 26 and 28 in Pfeifer, 1.c.).

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[11] This injection preparation is the intellectual property of Dr. *H. M. de Burtlet*, Conservator of the anatomical laboratory of the Imperial University at Utrecht.

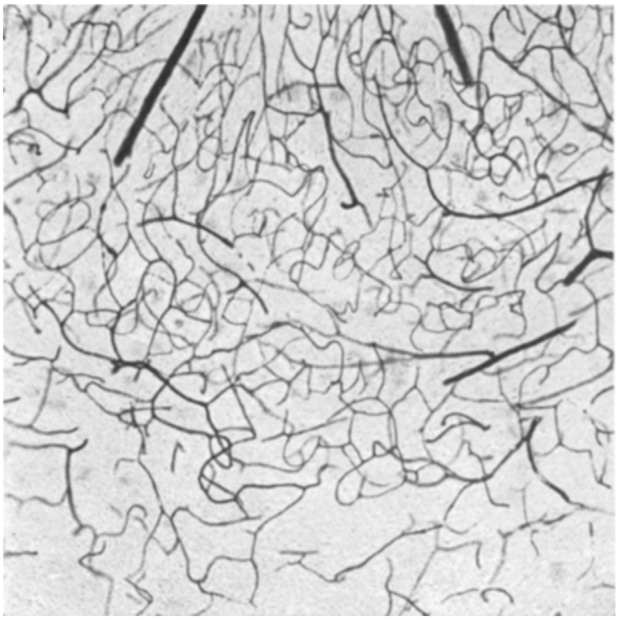

Fig. A.22. The vessels of the lower cortical layers at the bottom of a fold (part of Fig. A.19, magnified a further 75×).

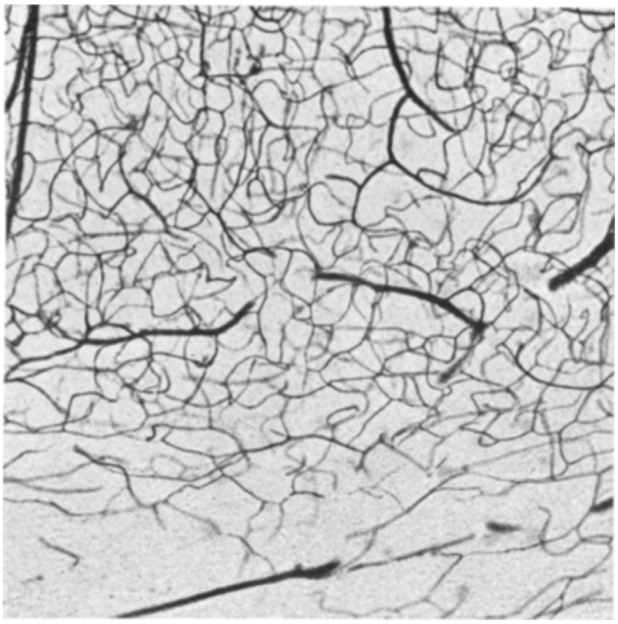

Fig. A.23. The vessels of the lower cortical layers at the wall of a fold (part of Fig. A.20, magnified a further 75×).

The vascular loops also display a tendency to maintain their form. They display only minor deviations from this form in the same cortical areas where the change in neuron form is especially strong.

The different organ systems located in the cortex evidently curve in different ways. The neurons have a constant arrangement; the vascular loops maintain a constant form. The neuron pattern curves in the way that is geometrically depicted in Fig. A.1e, and the vascular pattern in the way depicted in Fig. A.1b. The geometric possibility chosen in each case must therefore depend on the type of organ in question.

This very strongly suggests that the transformation in each case is chosen to maintain the function of the affected organ.

The function of the vessels is dependent on different factors than that of the neurons. For the function of the neuron apparatus, the immediate wiring of the individual neurons is of the utmost importance; the wiring of the vessels, however, is barely even taken into consideration for the function of the vascular system: if each vascular loop only receives a sufficient blood supply, its function is practically guaranteed—independent of the path the blood takes to reach it. For the humeral supply to the tissue, however, the total length of the vessels and the absolute distances to the neighboring vessels are very important, in contrast to the minimal importance the distance between two connected neurons and the lengths of their fibers. The neurons only sacrifice their vertical and horizontal dimensions, which have very little to no influence on their function, and they maintain their arrangement, which is extremely meaningful for their function, constant. *The vascular loops, on the other hand, sacrifice their arrangement and opt instead to maintain their vertical and horizontal dimensions and thereby their overall length (in analogous cortical sections with the same volume), which means that they sacrifice the morphological characteristics that have little meaning to their function while maintaining those that are important to their function*.

Fig. A.24. The vessels of the lower cortical layers at the peak of the fold (Part of Fig. A.21, magnified a further 75×).

This juxtaposition between the types of curves displayed by the neurons and the vessels comprises an argument in favor of the notion I defend above—namely, that the neuronal function goes unchanged through cortical curvature.

v. Economo constructs a special theory about the function distribution in curvature on the basis of the architectural differences between the tops and bottoms of folds. In the significant thickness of the lower layers at the peaks and the upper layers at the bottoms, he saw a strong evolution in these layers and thought therefore that the functions bound to these layers would be strengthened at these positions. The upper layers have a receptive function according to *Ariens Kappers*, and the lower layers an effectual one. As a result, *v. Economo* concluded that the curves at their edges—or at the bottom of the adjacent folds—had a primarily receptive function, and at their center—at the peak—a primarily effectual one.

We have already seen that we may not speak here of a strong change in these layers, as only the thicknesses increase and not the volumes thereof. The argument on which the argument of *v. Economo* is based is thereby proven incorrect. From this fact, the question could be asked whether the notion of different functions being localized to the tops and bottoms of folds can justifiably be maintained.

The structural differences that have been recognized to this point between the tops and bottoms of folds are all consequences of the

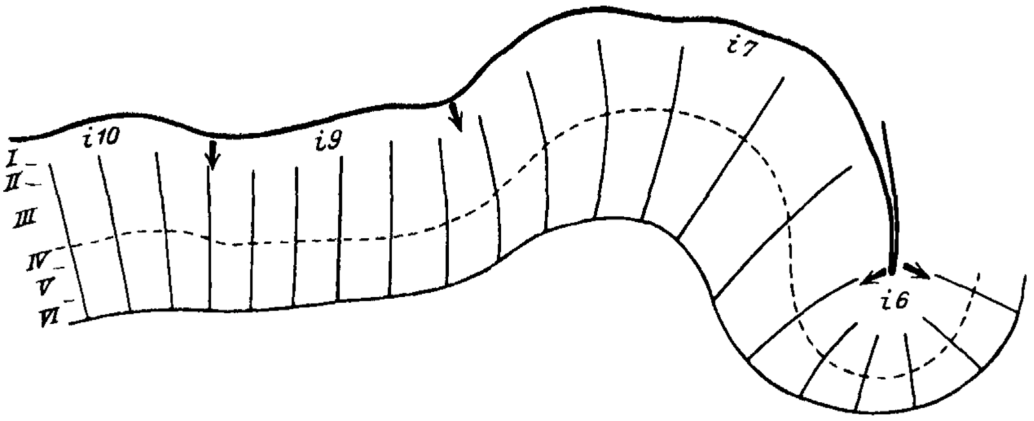

Fig. A.25. Contours of a photographic depiction of the human insular cortex as published by *Rose*, with arrows drawn by him at his proposed borders of different architectural areas. These arrows fall at the borders of differently curved cortical sections. The dashed line, drawn by me between layer III and layer IV, is higher in the convexly curved sections and lower in the concavely curved sections than it is in the flat section. The convex cortical sections are thicker—and the concave sections thinner—than the flat section.

curvature itself, and we have seen that these curves and all of their morphological consequences are not likely to cause functional differences. I am therefore of the opinion that not only is the basis of *v. Economos* argument invalid, but that the notion itself, that function is separated among sections of folds, is not likely to explain the true situation. In any case, there is currently not a single piece of morphological evidence which points to the presence of functional differences between the bottom of a fold, the walls of the fold, and the adjacent peaks.

In its generality, this statement is obviously only valid for the folds that lie together with their adjacent peaks within a single structural cortical region in the classical morphological sense, and not for a fold in which a boundary between two classical structural regions with fundamentally different structure separates the bottom from the wall, for example. For the investigation described above to not be disturbed by the presence of such boundaries, the measured specimens were all cut from central parts of classical structural regions.

Even if a cortical fold has no influence on the type of cortical function, it nevertheless has a strong quantitative influence, as the existence of folds means a significantly larger surface area of the cortex and as a result a significant increase in the overall cortical volume. It is therefore likely, as many authors have already suggested, that the folds and thereby the cortical curvature exist in order to amplify the cortical function. This amplification of the function at a specific location indicates a certain character about the function; this character is not, however, restricted to single cortical curves and also not different in each curve. It is much more bound to a larger area into which most folds, with their bottoms and their walls and their adjacent peaks, fall entirely—commonly along with many similar folds and curvature complexes. The question of which factors determine where and in which direction the folds occur so as to increase cortical volume in such a location falls outside the scope of this work.

Analysis of the cortical curvature has indicated a second cause of structural differences in the cerebral cortex that has not yet been recognized as such, namely the curvature itself. The fact that different areas of the cortex display different structures has always been traced back to functional differences. We know now that there are two types of structural differences: one that is a consequence of a specific function, and a second that is caused by cortical curvature. This second type is very likely not caused by functional differences, and we have certainly not found any evidence so far that it exists so as to allow for these functional differences.

I would therefore like to suggest that the cortical regions in which structural characteristics are entirely explained as consequences of curvature, and which, as a result, offer no morphological reason for us to assume they exist in service of a specific type of function, should not be given the name “structural region”, but rather the name “curved cortical section”, and that the name “structural region” should be used only in the classical morphological-functional sense, reserved for the cortical regions in which the structural character is not explained by the curvature and to which a specific type of function is likely localized.

The discipline of designating cortical areas has – until now – resigned itself to designating areas of the cortex in which structure is different from that of the other areas. In the future, it will need to investigate which of these areas are simply curved cortical sections, to which therefore *no* physiological meaning can be assigned, and which areas can *actually* be traced back to physiological differences and therefore constitute structural regions in the classical morphological-functional sense. Only in this way can it correct the mistakes that it has made by designating structural regions, to which a physiological meaning is also assigned, in such regions where structural differences are only caused by the curvatures occurring in the region. In this comprehensive discipline, this critical correction will be an enormous undertaking which, if it is to be completed with sufficient exactness, will be extremely demanding of the methods employed to achieve it.

This is not the appropriate place to present all the relevant architectural works to the reader and to analyze them in this way, as the purpose of this article is only to explain the principle of the influence of curvature on cortical structure. However, I can certainly say that I have gotten the impression that if we were to differentiate these works into two periods, a classical foundation and a modern development, the results of the classical period would remain almost completely unchanged in light of this critical recall study, which is to say that the cortical regions described in this period actually do have physiological foundations, but the results of the modern development period are very different, as in this period especially, very many cortical regions are denoted where only cortical curvature is present.

The fact that curved cortical sections are understood to be structural regions is further exacerbated by the fact that they display rather “omnilaminar” structural differences, which, as we know, is a strong indicator of the presence of a region boundary in the field of designating cortical regions. A curve, of course, causes changes in almost every layer, meaning that only one layer can curve isomorphically, and even that does not always occur.

All too often, the concavely curved cortical sections at the bottom of folds are understood as structural regions with special functions. It is unsurprising that the flat cortical sections in the walls are also denoted as specific regions in order to differentiate these sections without curvature from the sharply curved sections at the tops and bottoms of the folds. And from this analysis of the structural characteristics of these sections, we can understand the reason for the observation made by *Beck* that the two regions on either side of the bottom of a fold commonly display a marked uniformity in their structure. These sections are the two walls of the fold, and in straight folds, these walls have the same curvature (of infinitely large radius) and they must therefore display the same structure. Only a curve of the fold itself could cause differences between the two walls. We then also find that curved folds are denoted as region boundaries by modern authors.

We also understand that the transitions between curved and uncurved cortical sections are commonly described as specific structural regions.

The drastic curves that occur at the bottoms or tops of folds are not the only areas that have been denoted as structural regions with their own function. More moderate curves that occur in overall relatively uncurved sections have also been described as structural regions.

I only want to cite one single example so as to allow the reader to recognize how vital it is to critically rework the entire field of cortical region denotation, differentiating between curves and structural regions in the classical morphological-functional sense. This example was taken from the recent work of *Rose* on the insular lobe.

Within the classical insular regions, *Rose* differentiates a great number of structural areas and describes their differences with the help of many photographs. From one of these photographs, Fig. A.25 shows the location of the Pia mater, the border between layers III and IV (dashed), the border between cortex and medulla, and the arrows drawn by *Rose* at the borders of his proposed structural regions *i6*, *i7*, *i9*, and *i10*.

All of the structural regions denoted by *Rose* in this picture coincide with sections of the cortex that display a specific curvature. The first arrow from the left lies between a convexly curved section and an uncurved section, the second between that uncurved section and a second convexly curved section, the third between this convex section and a concave section at the bottom of a fold, and the fourth between this concave section and another uncurved section. In Fig. A.25, I have drawn in the directions of the main dendrites with radial lines. In the two convex sections of the pia, these lines diverge to the top, in the uncurved section, they are parallel to each other, and in the concave section, they converge. The curvatures are therefore noticeable throughout the entire cortex, and not, for example, only due to irregularities of the lamina zonalis; the areas denoted by *Rose* therefore coincide perfectly with different curved cortical sections.

The structural differences that he describes between these regions are also the exact same differences that must occur within curvature. The inner layers with respect to the curves are called “strongly developed”, which we would only call “thicker” in accordance with the aforementioned analysis. The ganglion cells located therein are thinner, the cortex is thicker in the convex curves and thinner in the concave curves, etc.

Because the photographed section was not taken perpendicularly to all axes of curvature, we cannot measure whether or not the differences here quantitatively agree with the consequences of curvature. Qualitatively, the agreement is so strong, even despite the many different types of curvature, that it must be regarded as likely that only curves and the consequences thereof exist here. With more precise measurements, it is possible that some hidden structural region would be uncovered here. The work of *Rose*, however, has not done this and has only denoted structural regions where only curved cortical sections exist.

This example should suffice to show that just an understanding of the consequences of cortical curvature makes it possible to denote structural regions with certainty even in curved cortices like that of the human. In order to do so, the regions with different structures must all be identified, as has already been done in recent years in cytoarchitectonics and myeloarchitecture, and then for each of these regions, it must be determined whether or not their structural character is a result of their curvature (which will be especially difficult within folds). Only the structural differences that are not identical to the consequences of curvature can then be assessed as indicators of structural regions.

Only in this way can the actual structural differences within the human cerebral cortex, which coincide with functional differences, be perfectly identified. We will then also be in a better position to construct accurate assessments of phenomena like the gradation of *Vogt-Beck* and the transgyral adaptation described by *Gurewitsch* and *Chatschaturian*. The former phenomenon has so far been noticed in the fact that certain parts of the cortex at the peaks of a series of adjacent folds show a gradual change in structure in spite of the fact that between these parts, regions with different structures exist in the bottoms and walls of folds. These intermediate regions are, however, unlikely to be just curved sections, so it would be possible (and, I believe, even probable) that the gradation is actually a structural change that occurs in a large cortical area and proceeds uninterrupted.

Hopefully, the omission of the influence experienced by cortical structure due to cortical curvature will contribute in this way and analogous ways to a deeper understanding of the variations of cortical structure which are bound to variations in function.

PART VI

1. At a given fold in the human cerebral cortex, both volume and arrangement of the neuronal parts arranged within the cortex are held constant, and the smallest dimension of the small ganglion cells (which, in cells located in the nuclear layer, is the width) does not get appreciably smaller.
2. This consistent behavior of the volume and arrangement geometrically implies that the form of the neurons and the thicknesses of the layers both must change in the folds. With respect to the folds, the inner layers become thicker and the outer layers become thinner than in the unfolded cortex. In a thicker section of a layer, the ganglion cells become taller and narrower, and the vertical fibers are most prominent, whereas in a thinner section, the ganglion cells are shorter and wider, and the horizontal fibers are most prominent. Between these two extremes, there exists a level with isomorphic curvature in which the neuron form is constant. This level is found in one of the two innermost cortical layers with respect to the fold.
   On page 732, a method is proposed to determine how thick a folded section of the cortex would be if it were not folded. On page 706, a method is proposed to determine with great accuracy how the thickness would then be distributed among the different layers. Through these measurements, different cortices and different cortical locations can be compared.
3. These changes in cortical structure through a cortical fold provide no evidence that the cortical function in the folded section differs from that of the directly adjacent unfolded section. Most likely, it is the same, as the morphological factors that we are inclined to believe influence the function or are influenced by the type of function are the very same factors that are held constant in the folds. (Perhaps the requirement that the functionality of the neuron apparatus remains unchanged in a fold is even what defines these folds. The fact that the pattern of the vascular cortex appears to curve in a different way than that of the neurons, namely with consistency in the volume and form of the vascular mesh, which affects the vascular function as little as possible, also points to this possibility.)
4. Areas of the cortex in which structural features are entirely due to the effects of curvature should not be thought of as separate structural areas, but rather curved cortical sections. The designation of structural area is thereby reserved only for the classical morphological-functional definition, which implies that the structural features of the area in question cannot be explained by just the curvature and therefore appears to be bound to some specific type of function.
5. In modern teaching of cortical areas, many areas are accepted as structural areas where only curved cortical sections exist. As such, it is often accepted that the bottom of a fold belongs to a different structural area than the walls, which again belong to

different structural area than the adjacent peaks, and to each of these areas, a specific type of function was thought to be localized. For example, *v. Economo* accepted that the cortex at the bottom of a fold had a primarily receptive function compared to the primarily effectual function at the adjacent peaks, as the upper layers (called “receptive” by *Ariens Kappers*) are thickest at the bottoms of folds and the lower (effectual) layers are thickest at the peaks. At the 17 folds measured here, however, it was shown that the structural differences between different regions of the folds can be completely attributed to the different curvatures (concave at the bottoms, approximately zero at the walls, and convex at the peaks). The changes in layer thicknesses, for example, correspond to the constant volume of each layer, which was found to be exactly valid within the error bounds of the measurement methods (of which the mean error is 0.4%). In general, it is very likely that no functional difference exists between various regions within a fold. At the very least, there are no morphological reasons to believe these regions perform different functions.

6. The definition of structural areas in the cerebral cortex must therefore be reestablished, omitting the structural differences that are only the result of curvature.

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Appendix B. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.brain.2022.100057.

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