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A tension-based theory of morphogenesis and compact wiring in the central nervous system.

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Many structural features of the mammalian central nervous system can be explained by a morphogenetic mechanism that involves mechanical tension along axons, dendrites, and glial processes. In the cerebral cortex, for example, tension along axons in the white matter can explain how and why the cortex folds in a characteristic species-specific pattern. In the cerebellum, tension along parallel fibers can explain why the cortex is highly elongated but folded like an accordion. By keeping the aggregate length of axonal and dendritic wiring low, tension should contribute to the compactness of neural circuitry throughout the adult brain.

The central nervous system (CNS) comprises a diverse collection of neural structures, each with a distinctive shape and an intricate internal architecture. Questions about morphogenesis - how these structures attain their particular shapes during development - have intrigued neuroscientists for more than a century, but many mechanistic issues remain unresolved. Here, I propose that mechanical tension, working against internally generated hydrostatic pressure, is a major driving force for many aspects of CNS morphogenesis. The clearest examples supporting this hypothesis are the cerebral cortex and cerebellar cortex, which in many species have extensive convolutions that allow a large surface area to fit within the available cranial volume. For example, the human cerebral cortex attains a surface area of about 1600 cm^2, nearly three times what it would be in the absence of convolutions[1, 2]). For a given species, the folds have a consistent position in relation to identified cortical areas in some regions, but in other regions the pattern shows marked individual variability[3, 4]. Tension-based morphogenesis can account for the variability as well as the consistency of convolutions in terms of underlying patterns of connectivity between cortical areas.

Tension has previously been suggested to contribute to morphogenesis in the peripheral nervous system[5, 6] and in various non-neural cells and tissues[7-9]. However, its relevance for CNS development has received surprisingly little consideration. The prospect of a major role for tension arises because of two basic anatomical characteristics of CNS tissue. First, many structures have pronounced *anisotropies* in the orientation of axons, dendrites, and glial processes. If these processes are under tension, their springiness will make the tissue elastic, but the elasticity will not be uniform along all axes. Instead, the mechanical compliance should be lowest (resistance to stretching highest) along the axis of preferred orientation. Accordingly, tissue expansion should occur preferentially along axes having greater compliance. The second characteristic involves *projection asymmetries*, in which the trajectories of processes arising or terminating in a given region are biased towards one side. A prime example is the cerebral cortex, whose long-distance connections enter and leave the cortex exclusively through the underlying white matter. During cerebral growth, tension along axons acting in concert should pull strongly interconnected regions towards one another while allowing weakly connected regions to drift apart. The combined effects should keep wiring length short and overall neural circuitry compact.

Computer designers strive to place electronic components efficiently, yet invariably devote far more space to wiring than to computation and memory combined[10]. Likewise, the nervous system devotes most of its space to non-synaptic wiring, even though minimizing wiring length has been proposed as an important design principle of neural architecture[11-16]. One example of compact wiring (also called “component placement optimization”[14]) is the layout of areas across the surface of the cerebral cortex, as connections occur with high probability between adjacent areas but with low probability between distant areas[14, 17-19]. The suggestion[14,20, 21] of extending this type of analysis to the third dimension is taken up here, allowing the generality of compact wiring to be assessed.

Are neurons under tension?

The macroscopic mechanical properties of biological tissue depend on the active and passive mechanical characteristics of its microscopic constituents[22, 23]. For neural tissue, the most relevant structures are its elongated axons, dendrites, and glial processes. Five characteristics relevant to morphogenesis have been demonstrated for the axon-like neurites that neurons and neuronal cell lines extend *in vitro* . (1) Neurites growing on an adhesive substrate generate substantial mechanical tension (stress)[24, 25] - averaging around 150 µdyne for chick sensory neurons[26]. Given a neurite diameter of 1 µm or less (S. Heidemann, personal communication), this corresponds to an impressive 1% of the specific tension that mammalian skeletal muscle can exert[27]. (2) When a neurite is transiently stretched, its length increases in proportion to applied tension, indicating simple elastic behavior[25]. (3) When resting tension is fully released, a neurite initially shortens only slightly; if pushed further, it becomes wavy like a compressed rubber band[28]. (4) Neurites display visco-elastic properties under sustained stretching, as the initially elevated tension passively relaxes to a lower level over a period of minutes[28]. (5) Active elongation (towed growth) occurs when tension is maintained above a threshold level, and active retraction occurs when tension is fully released[26, 28]. Collectively, these passive and active mechanical properties allow neurites to adjust their length by a negative feedback mechanism that tends to maintain a steady tension, much as a fishing line is reeled in or out to regulate tension on the line.

The macroscopic mechanical properties of the brain *in vivo* are consistent with neurite properties observed *in vitro*. Brain tissue springs back to its original position after transient deformation, indicating that many cellular processes are elastic and under resting tension. Supporting this inference is the widespread occurrence of straight or smoothly curved neuronal processes, particularly in early development[29, 30]. Curved trajectories suggest tension coupled with displacement by pressure from neighboring axons, analogous to the arc on a fishing line caused by a breeze. There are also many processes with wavy or curled profiles (at least at the time of tissue fixation)[29-31], suggesting that tension is not universal. However, to play a role in morphogenesis, tension need only be present on many processes much of the time, not on all of them at all times.

Neurons generally establish long-distance connections early in development. To cope with embryonic growth and shape changes, axons must therefore adjust their length continually, with some growing much faster than others and some actually shortening, for example, as the cortex folds. Tension, working through passive viscoelasticity plus active growth and retraction, is an ideal feedback signal for regulating axonal length *in vivo*, just as it does *in vitro*. This feedback mechanism evidently persists into adulthood, given that extrinsic forces such as tumors cause gradual tissue deformations without axonal breakage. A corollary requirement is that mechanical adhesion between pre- and post-synaptic partners must occur at CNS synapses, to avoid their coming apart when under tension. Evidence for strong synaptic adhesiveness comes from the observation that mechanical homogenization of brain tissue yields a large pool of synaptosomes - subcellular components whose pre- and post-synaptic membranes remain tightly apposed[32].

If neuronal and glial processes are under tension, what prevents them from all concurrently shortening, leading to a smaller brain that is fully relaxed? CNS tissue lacks a rigid structural framework to prevent such a collapse; tension must instead be counterbalanced by hydrostatic pressure to establish biological "tensegrity"[9, 33]. All cells have an intrinsic pressure differential across their plasma membrane, resulting from active transport mechanisms that regulate osmotic balance, but there are also important extrinsic sources of pressure discussed below.

Patterns of tissue growth.

Morphogenetic shape changes involve interactions among three factors: the local forces that cells generate as they grow and migrate; the mechanical properties of the immediately surrounding tissue; and any extrinsic forces arising from tension or pressure generated at a distance. We first consider a simple situation involving tissue that is mechanically isotropic (because its axons, dendrites, and glial processes are randomly oriented) and is not subject to external forces. If all cells grow at similar rates, the tissue would expand equally in all directions. This may explain the compact, rounded shape of many subcortical nuclei, whose cellular architecture is relatively isotropic[34, 35].

In contrast, tissue expansion should generally be nonuniform if the cellular architecture is anisotropic or if external forces are biased (Fig. 1). For example, Figure 1A schematizes a radially anisotropic architecture, in which cellular processes are elongated along the vertical (radial) axis. If these processes are under tension, the radial axis would be mechanically stiffer than the tangential axes. Generalized cellular growth would lead to preferential expansion along the path of least resistance, i.e., in the tangential plane. This bias may contribute to the sheet-like expansion of several radially anisotropic structures, including the embryonic neuroepithelium[36], cerebral cortex[35], and retina[35]. However, these structures also have a standing pressure differential across their surface[37, 38], maintained by a steady production of cerebrospinal fluid (aqueous humor, for the eye). As in a balloon, this internal pressure would cause surface tension that stretches the sheet (Fig. 1B). Experimentally reducing intracerebral pressure[39] or intraocular pressure[40] reduces the rate of tangential growth, but the tissue remains a thin sheet, suggesting that both pressure and radial architecture contribute to anisotropic growth.

Not suprisingly, forces arising from surrounding non-neural structures can also affect the shape of the brain. For example, deformation of the skull arising from premature closure of cranial sutures, leads to corresponding changes in brain shape[41]. However, morphogenetic forces operate in the other direction as well. In cases of hydrocephalus, for example, abnormal expansion of the brain markedly impacts the size and shape of the skull.

Cerebral cortex: whether and where to fold.

The cerebral cortex forms as a smooth sheet populated by neurons that proliferate at the ventricular surface and migrate outward along radial glial fibers (Fig. 2A). But why does the cortical sheet remain smooth (lissencephalic) in some species, particularly those with small brains, yet become highly convoluted (gyrencephalic) in others, particularly those with large brains? The primary reason is that cortical surface area increases disproportionately with brain size. For example, in humans, cortical surface area is 1700-fold greater than in shrews (~40-fold in linear dimensions), whereas cortical thickness is only 6-fold greater[42]. Most of this bias is attributable to the aforementioned preference for tangential versus radial expansion. The remainder arises because the volume of neocortical gray matter, expressed as a percentage of total brain volume, increases with brain size - from about 13% for basal insectivores[43] to 50% for humans[42]. This reflects differences in the duration of neurogenesis, which increases steeply with brain size for the cerebral cortex and less steeply for subcortical structures[44-46], leading to a systematic increase in the ratio of cortical to subcortical neurons. From this perspective, convolutions increase with brain size primarily because the expansion of the cortical sheet outpaces the minimal area needed to envelop the underlying cerebral volume.

When convolutions occur, what determines the spatial pattern of folding? Previous hypotheses about cortical folding have emphasized mechanisms intrinsic to the cortical gray matter[3, 47, 48], such as differential growth of different layers[49]. However, folding patterns can be dramatically altered by prenatal lesions that are likely to perturb long-distance connections[20, 50, 51], suggesting a major role for extrinsic factors.

Two observations suggest that tension along axons in the white matter is the primary driving force for cortical folding. First, the cortical sheet is physically tethered from only one side, initially by radial glial processes (Fig. 2A), followed soon thereafter by connections between cortex (including the cortical subplate) and various subcortical nuclei[52]. Tension along inwardly directed processes would provide a cohesive force that works against intraventricular hydrostatic pressure to insure that the cortical mantle remains tightly wrapped around the subcortical interior. Second, specific cortico-cortical projections are established early (Fig. 2B), as evidenced by neurons that send axons across the corpus callosum even while still migrating to the cortex[53,54] and by topographically organized projections between visual areas in the macaque that are established while convolutions are forming[30] (see also ref. [20]). Tension along obliquely oriented axonal trajectories between nearby cortical areas would generate tangential force components that tend to induce folds at specific locations in relation to areal boundaries (Fig. 2B,C). If developing CNS axons generate even a modest fraction of the specific tension measured *in vitro*, then populations of axons pulling in concert should have ample strength to cause folding of the highly pliable embryonic cortical sheet.

The cortex can fold in either of two polarities. In an *outward fold*, the crease is directed away from the interior, forming the crown of a gyrus and reducing the distance within white matter between opposite banks of the fold. Tension would pull strongly interconnected regions towards one another, forming an outward fold along their common border (heavy lines, Fig. 2B,C). In an *inward fold*, the crease is directed towards the interior, forming the fundus of a sulcus. This slightly increases the distance within the white matter that separates opposite banks, so it provides no direct advantage for wiring length in the immediate vicinity. However, geometrical constraints require an inward fold between each pair of outward folds. In a general tug-of-war among many pathways competing for different folding patterns, sparse projections would generally be ineffective at resisting tissue displacements that force their axons to elongate. Consequently, outward folds should tend to occur between neighboring areas that are only weakly interconnected (fine lines, Fig. 2B,C). Altogether, tension-induced folding should contribute to compact wiring for the cortex as a whole.

When a paperback book is folded, adjacent pages slide relative to one another. When the cortex folds, sliding between layers should also occur, but to a lesser degree because of stretching and shearing forces that alter cellular morphology and the thickness of different layers. Along inward folds, cells in deep layers should be stretched tangentially and compressed radially, making these layers thinner. In contrast, along outward folds, cells in deep layers should be stretched radially, making these layers thicker (Fig. 2D). These predictions closely match the characteristic differences in cortical architecture of gyral versus sulcal regions of the adult cortex[55], suggesting that differential growth of cortical layers is a consequence, not a cause, of the forces that induce folding.

Compact cortical wiring.

The macaque monkey is a good testbed for analyzing the compactness of cortical wiring and the relevance of tension-based morphogenesis to cortical folding, because its convolutions are stereotyped and its cortico-cortical connections have been intensively studied[17]. Figure 3 shows the location of a number of well-studied cortical areas or functionally related sets of areas in the macaque in relation to major cortical folds. The upper panels show a computerized reconstruction of the right hemisphere, viewed in its original configuration (upper left), and after computational smoothing to better reveal the interior of sulci (upper right). On the lower right is a cortical flat map[56] of the entire hemisphere (after introducing cuts that reduce distortions in surface area). The gyral and sulcal pattern on the cortical map is indicated by white lines for the crests of outward (gyral) folds and black lines for inward (sulcal) folds.

A striking example of compact wiring involves areas V1 (red) and V2 (orange), which contain separate, mirror-image representations of the contralateral visual hemifield and are linked by massive reciprocal connections[57]. In the intact hemisphere the two representations are brought into close proximity and approximate register by outward folds running along the V1/V2 border[20, 57]. This is illustrated for points near the vertical meridian (green and yellow) and the horizontal meridian (blue and black). Topographically corresponding loci in V1 and V2 are close together in 3-dimensional space, as shown on a parasagittal slice through the cortex (left center), even though loci near the horizontal meridian are widely separated on the flat map and in the embryonic hemisphere prior to folding[30]. The alignment between V1 and V2 maps is less precise medially, in the vicinity of the calcarine sulcus, but is still better than if the folding pattern were random.

Table 1 documents the excellent correlation between qualitatively assessed connection strengths and the polarity of folding that occurs close to the border between adjacent areas or regions identified in Figure 3. Strongly interconnected regions are consistently separated by an outward fold, whereas weakly connected regions are consistently separated by an inward fold. These regions collectively occupy more than half of the cortical surface, signifying that compact wiring is a widespread characteristic in the macaque. A survey of other species supports the generality of this conclusion. Examples include the consistent occurrence of the V1/V2 boundary along outward folds in humans[58], Cebus monkeys[59], and cats[60], and the consistent positioning of somatosensory and motor cortex on opposite banks of an inward fold in primates, carnivores, and rodents[3].

Compact wiring of a system as a whole does not imply that all individual pathways are as short as possible. Indeed, many individual pathways would be much shorter if the cortex were folded differently. Also, some of the folds shown in Fig. 3 do not run exactly along the borders between functionally defined subdivisions. Lastly, strong connections between opposite banks are lacking for some outward folds, such as that in the interior of area V1 (along the medial wall of the hemisphere). However, each of these characteristics is to be expected when minimizing the aggregate length of connections in a highly interconnected network. In general, tension-based folding may necessitate some folds that are neutral or even disadvantageous with regard to local connection lengths in order to better approach a global minimum.

Tension-based morphogenesis also suggests a basis for individual variability in brain morphology. No two brains are identical in the detailed pattern and position of convolutions, nor in the size and exact connectivity patterns of various cortical areas. For example, the surface area of V1 in the macaque varies by more than two-fold across individuals, yet inward cortical folds consistently run close to the V1/V2 boundary[61], as expected if folding is dominated by V1-V2 connections. Elsewhere, where competing pathways are evenly balanced, small individual differences in the relative sizes of areas or the strengths of pathways could tilt the balance between two or more qualitatively different folding patterns (e.g., one sulcus versus two in a given region). These are analogous to local minima in the overall “energy landscape” that characterizes possible states of a system[62]. The number of local minima generally increases with the complexity of the system, suggesting a basis for the notably high variability of convolutions in the human brain[4]. A corollary is that whether a particular cortical area ends up on a gyrus or in a sulcus may be of little import for the specific computations mediated by that area, as long as the system as a whole has attained a near-minimal aggregate wiring length (for a given set of connections and topological arrangement of areas across the cortical sheet).

A related issue concerns the nature and magnitude of any selective advantage that is conferred by an optimal pattern of cortical folds compared to various sub-optimal configurations, such as a hypothetical cortex that is equally convoluted but whose folds are positioned randomly. While this type of problem is difficult to attack experimentally, the conceptual issue is important in evaluating compact wiring and tension-based morphogenesis from an evolutionary perspective.

Generalizations to other structures.

Given the variety in cellular architecture and connectivity patterns that occur in different embryonic CNS structures, to what extent can tension-based morphogenesis account for the great diversity of shapes evident in the adult CNS? Examples involving the cerebellum and the retina suggest that the explanatory power of the hypothesis is quite broad.

The cerebellum has a distinctive dual anisotropy in its cellular architecture, in which Purkinje cell dendrites and ascending axons of granule cells are aligned parallel to the radial axis, whereas the large contingent of parallel fibers is aligned along a single axis in the tangential plane. If these processes are all under tension, the resistance to stretching would be relatively high along both the radial axis and the axis of parallel fibers, leaving the axis orthogonal to parallel fibers as a single path of least resistance (inset, Fig. 4). This can explain why the disk-shaped embryonic cerebellum grows preferentially along this axis into a ribbon that, when unfolded, is often 10-fold or more longer than wide[63, 64].

Why is the cerebellum much more convoluted than the cerebrum, despite its smaller size? This outcome is predictable from the fact that cerebellar cortex is much thinner than cerebral cortex and is wrapped around a small subcortical volume (few nuclei, minimal ventricular space, and little white matter because of the absence of cortico-cortical connections). The accordion-like configuration of the cerebellar sheet may reflect shearing forces that differ according to the axis of folding. Folding occurs primarily along the axis of parallel fibers ("with the grain"), which allows parallel fibers to slide relative to one another without changing in length (Fig. 4). Folding "against the grain" (orthogonal to parallel fibers) should be resisted because it would impose additional stretching of parallel fibers along each outward fold. Unlike cerebral cortex, the specific locations of cerebellar folds cannot be based on patterns of cortico-cortical projections, because such connections are altogether absent in cerebellar white matter. Undiscovered asymmetries in the connectivity of afferent inputs (mossy fibers and climbing fibers) might influence where folds occur, but a plausible alternative is that the positioning of cerebellar folds (as distinct from their orientation) is largely arbitrary with respect to connection patterns or functional subdivisions of the cerebellum.

In the retina, many species have a specialized foveal region that subserves high visual acuity[65]. A prominent morphological characteristic of the fovea is a tangential displacement of retinal ganglion cells, away from the region of maximal cone density, which occurs during late embryonic and early postnatal development[66]. Prior to this displacement, ganglion cells initially direct their axons outward from the center of the presumptive fovea, and at some distance away these axons aggregate into fiber bundles (arcuate fascicles) that loop around to reach the optic disk[67] (Fig. 5A, B). If ganglion cell axons are physically anchored where they join the arcuate fascicles, tension along them would include a tangential component that pulls ganglion cell bodies away from the center of the fovea, with bipolar and cone cell processes trailing because cone cell bodies are anchored at the outer retinal surface (Fig. 5C, D). Displacements should be largest in the center of the fovea, where the ratio of ganglion cells to cones is maximal and where the tethering capacity of foveal cones is weakened by a postnatal reduction in diameter that is associated with an increase in visual acuity[66]. Towards the periphery, each ganglion cell is anchored to progressively more cones (via intervening bipolar cells), which can explain the progressively closer alignment between ganglion cells and the cones they subserve (Fig. 5D). The reduction in retinal thickness in the foveal pit is thought to be functionally significant because it reduces light scatter and improves optical image quality right where visual acuity is highest[65]. Thus, tension-driven retinal morphogenesis may have an adaptive role that involves more than just reducing wiring length.

Concluding remarks.

In a classic analysis of growth and form D'Arcy Thompson[22] discussed how tension and pressure can interact with structural anisotropies and asymmetries to determine the shape of biological structures. He successfully applied this perspective to a variety of peripheral body parts and even to plants, but not to the brain. The present theory of tension-based morphogenesis of the CNS can be viewed as a natural, albeit belated extension of his pioneering ideas. While clearly speculative, the theory offers a simple and coherent explanation for many diverse aspects of CNS structure and development, and it already is supported by numerous lines of evidence.

Four major arenas are ripe for future investigation. (1) It is important to determine the mechanical properties of CNS tissue, especially structures with anisotropic cellular architecture, and to measure the physical forces (tension and pressure) actually generated during morphogenesis. (2) A much wider range of species and structures should be examined to determine the generality of compact wiring in the adult and the degree to which the pattern of development is consistent with tension-based morphogenesis. Of particular interest are structures such as the hippocampus and olfactory bulb, whose distinctive architecture and connectivity patterns may be responsible (by way of tension) for their unique shapes in the adult. (3) Experimental perturbations to distinguish between alternative models are needed. Do specific alterations in neural connectivity caused, for example, by congenital developmental abnormalities (e.g., lissencephaly[68, 69]), early surgical lesions[50, 51], or genetic mutations[70], cause shape changes consistent with tension-based morphogenesis but not with other models? (4) Computer simulations can test whether the specific sequence of shape changes that occur during development of particular CNS regions can be replicated using plausible assumptions about forces and cellular dynamics, along with quantitative information about connectivity patterns. Collectively, these tests should reveal the degree to which tension-based morphogenesis and compact wiring represent fundamental principles of neural development and function.

Morphogenesis entails an intricate choreographing of physical forces that cause differential tissue growth and displacement. Does this entail an elaborate set of developmental instructions, transcending those needed to regulate the processes of neural proliferation, migration, axonal pathfinding, and synapse formation? If morphogenesis is driven largely by tension, the answer is no. Instead, the specificity of shape changes would largely be a byproduct of factors that dictate the connectivity and topology of the underlying neural circuitry. This constitutes an attractively efficient strategy for sharing the heavy instructional burden needed to guide neural development.

Figure Legends

Fig. 1. Mechanical factors contributing to anisotropic tissue growth. A. Preferential tangential growth of a radially anistropic tissue (a schematic embryonic neuroepithelium). If cellular processes are under tension, the radial (vertical) axis would be mechanically stiffer than the tangential axes. If cells grow by exerting uniform pressure in all directions, expansion would occur preferentially along tangential axes, i.e., the path of least resistance ($dx, dy > dz$). This anisotropic expansion would occur if growth is mediated by passive visco-elastic tissue, and also if cells show active growth properties, as long as growth rates *in vivo* are proportional to tension, just as *in vitro*[26]. B. Balloon-like expansion of a quasi-spherical sheet (the embryonic neuroepithelium) surrounding a fluid-filled ventricular space that generates outward pressure (large arrows). This causes surface tension in the neuroepithelial wall (small arrows) and also a compressive force along the radial axis, adding to the bias for tangential expansion arising from the radial anisotropy schematized in panel A.

Fig. 2. Tension-mediated folding of cerebral cortex. A. Early in development, neurons (black) migrate to the cortical plate along radial glial cells (red), differentiate, and emanate axons . B. Many axons reach specific target structures prior to the onset of cortical folding. Tension along them (arrows) would pull strongly interconnected regions together and allow weakly interconnected regions to drift apart. C. This leads to outward folds that separate strongly interconnected regions, and inward folds that separate weakly interconnected regions. Connections with subcortical structures (not shown) may also influence cortical folding, though to a lesser degree because of smaller tangential force components. D. Cortical folding causes shearing that tends to stretch the radial axis (dashed lines). Compensatory tangential forces (small arrows) would tend to thicken the deep layers along outward folds and the superficial layers of inward folds, making their constituent cells (green) taller and thinner. The converse should occur in superficial layers of outward folds and deep layers of inward folds. Additional tangential force components associated with axons in the white matter (bold arrows) should enhance these effects on deep layers and counteract them in superficial layers.

Fig. 3. Compact wiring of cerebral cortex in the macaque monkey, revealed by folding patterns in relation to areal boundaries and connection patterns. Lateral views of the right hemisphere are shown before (upper left) and after (upper right) extensive smoothing. A cortical flat map[17, 56] (lower right) includes cuts through the middle of V1, rather than its perimeter as done in previous macaque flat maps. The map shows outward folds (white), inward folds (black), and selected cortical areas[17, 56]. Selected points in the contralateral visual hemifield (lower left) are represented on a parasagittal slice through occipital cortex (left center) and on the 2-D cortical map, based on reported topographic organization[57, 61]. The connectivity and folding patterns indicate that wiring is compact (see Table 1 and text). Abbreviations: arcuate sulcus (AS), auditory (Aud), central sulcus (CeS), inferior occipital sulcus (IOS), intraparietal sulcus (IPS), lunate sulcus (LS), posterior parietal (PP), somatosensory (SS), sylvian fissure (SF).

Fig. 4. Dual anisotropies in the mammalian cerebellum. Purkinje cell dendrites and ascending axons of granule cells are aligned along the radial axis, and parallel fibers in the superficial layers are aligned along one tangential axis (medio-lateral in many regions), jointly accounting for the ribbon-like elongation of cerebellar cortex (inset). Afferent fibers might bias the position at which folds occur if they preferentially distribute to opposite banks of outward folds, as shown hypothetically for a mossy fiber.

Fig. 5. Tension-mediated formation of the fovea. A. Bird’s-eye view of neonatal retinal ganglion cell axons radiating outward from the presumptive foveal region and joining into arcuate fascicles. B. Cross-sectional view at the same stage, showing ganglion cells positioned directly over the cones they subserve. C. Bird’s-eye view of ganglion cell distribution in the adult fovea, showing the displacement away from the center to form the foveal pit. D. Cross-sectional view, showing an offset between ganglion cells that are weakly tethered by cones in the fovea but no offset for the strongly anchored ganglion cells in the periphery.

Table 1. Connection strength and folding polarity in macaque cerebral cortex

Areas	Connection Strength	Folding Polarity	Location of Fold(s)	Reference
V1 ↔ V2	Strong	outward	lunate, calcarine, inferior occipital sulci	57
Somatosensory (1,2,3,5,7b, SII)	Strong	outward	postcentral gyrus, inferior parietal lobule	71-73
4 ↔ 6	Strong	outward	precentral gyrus	71, 74
8 ↔ 46	Strong	outward	prearcuate gyrus	75, 76
3b ↔ 4	Weak	inward	central sulcus	71, 72
visual ↔ somatosensory	Weak	inward	intraparietal sulcus	72, 77
auditory ↔ somatosensory	Weak	inward	Sylvian fissure	73, 78
6 ↔ 8	Weak	inward	arcuate sulcus	74, 76

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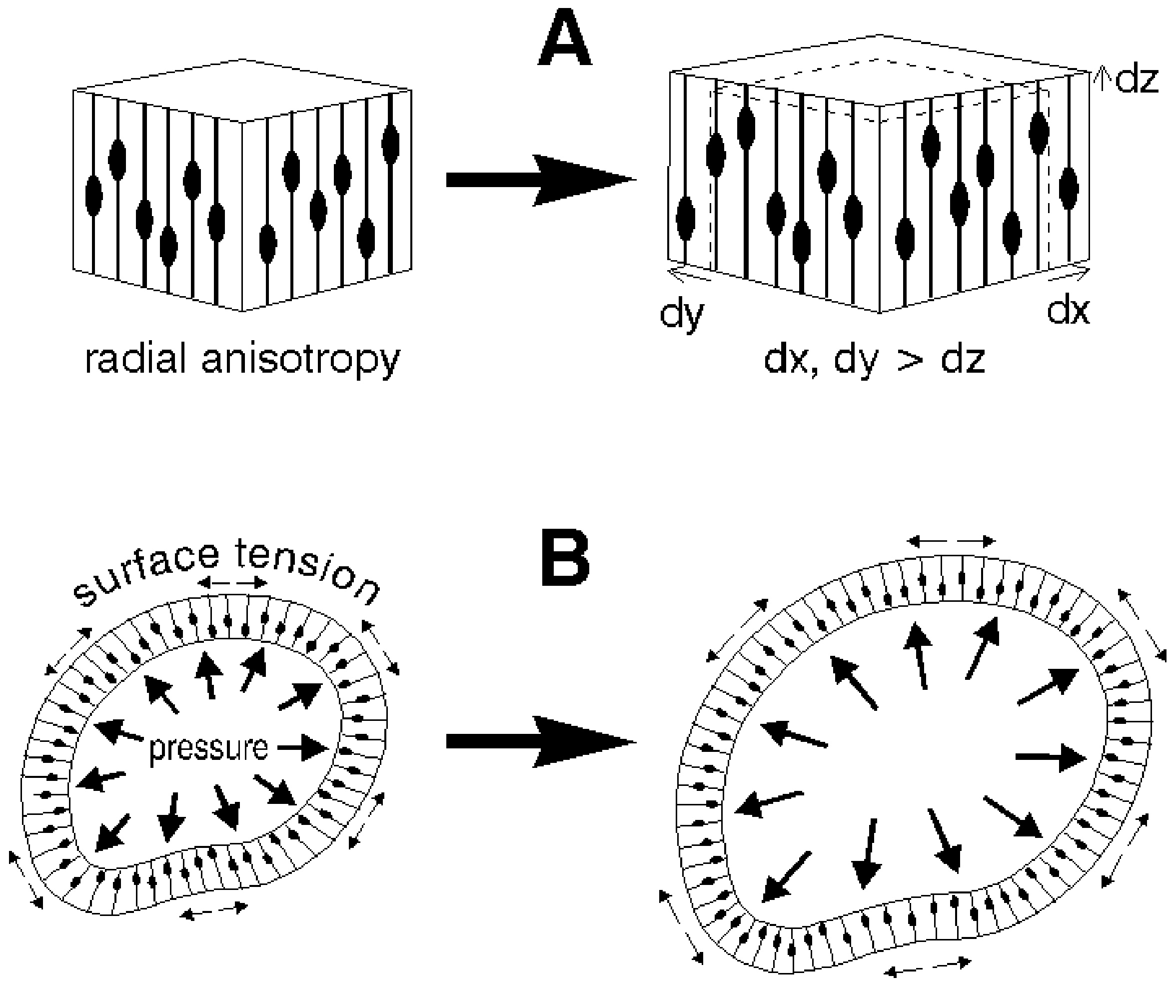
Figure 1.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radial anisotropy
dx, dy > dz
B
surface tension
pressure

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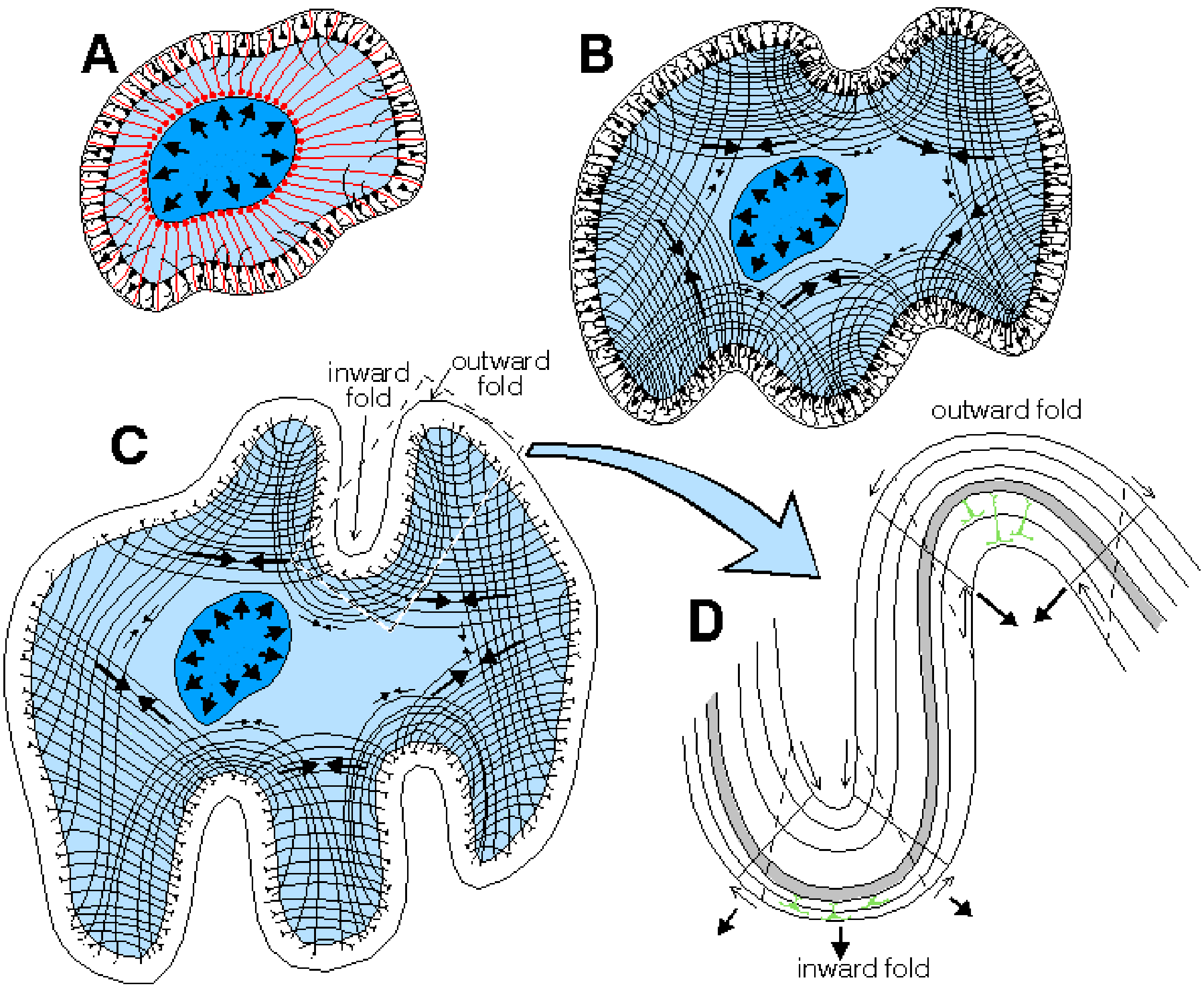

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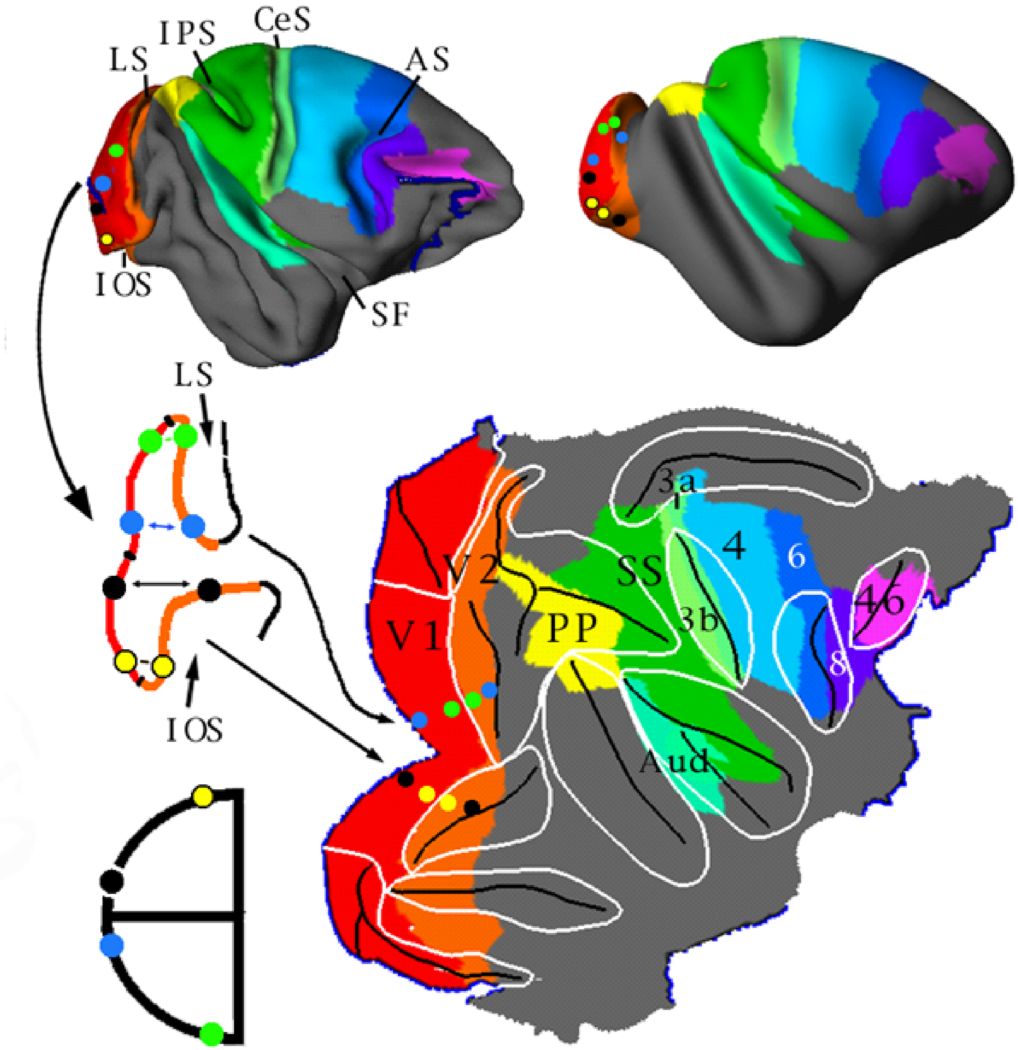

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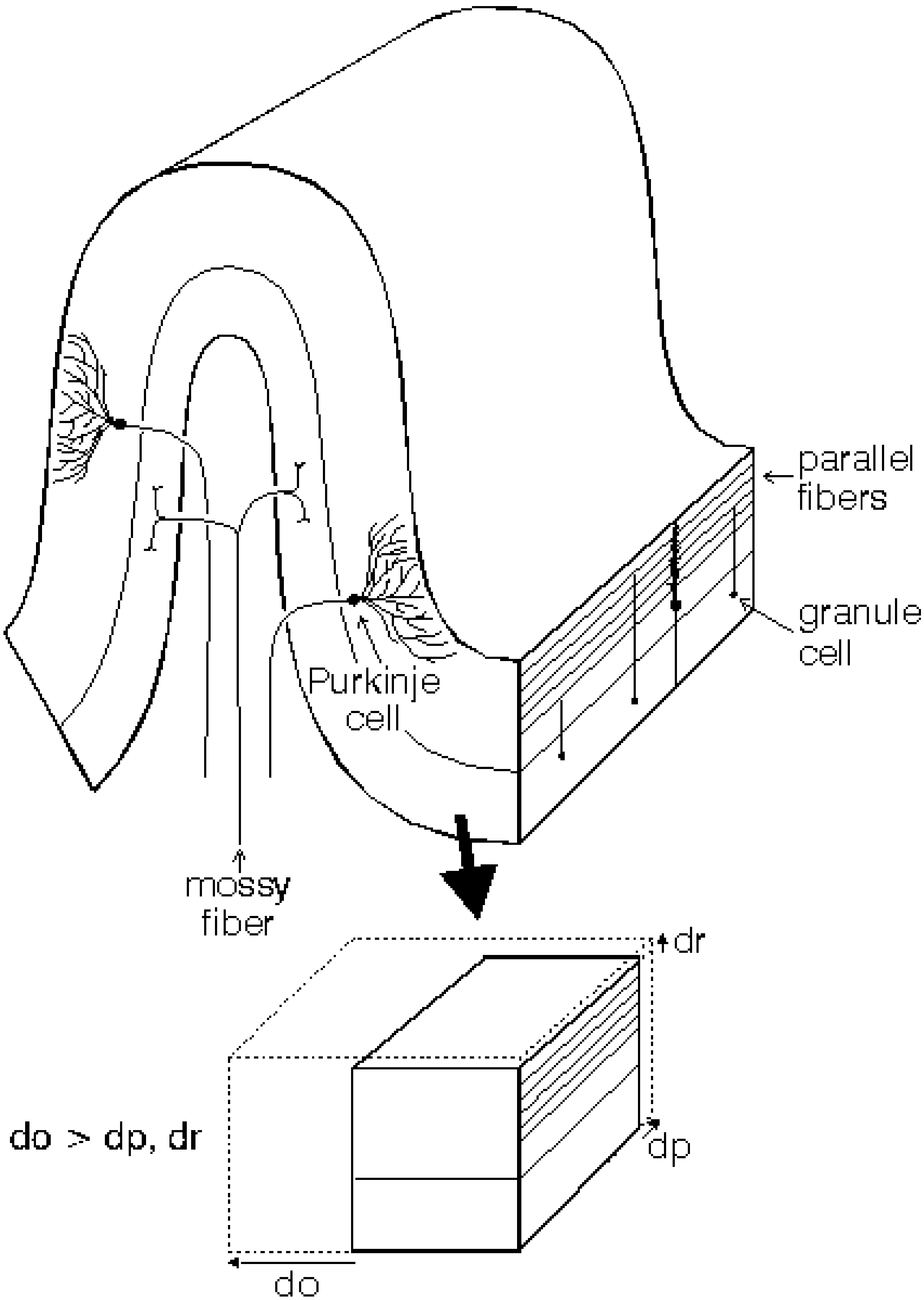
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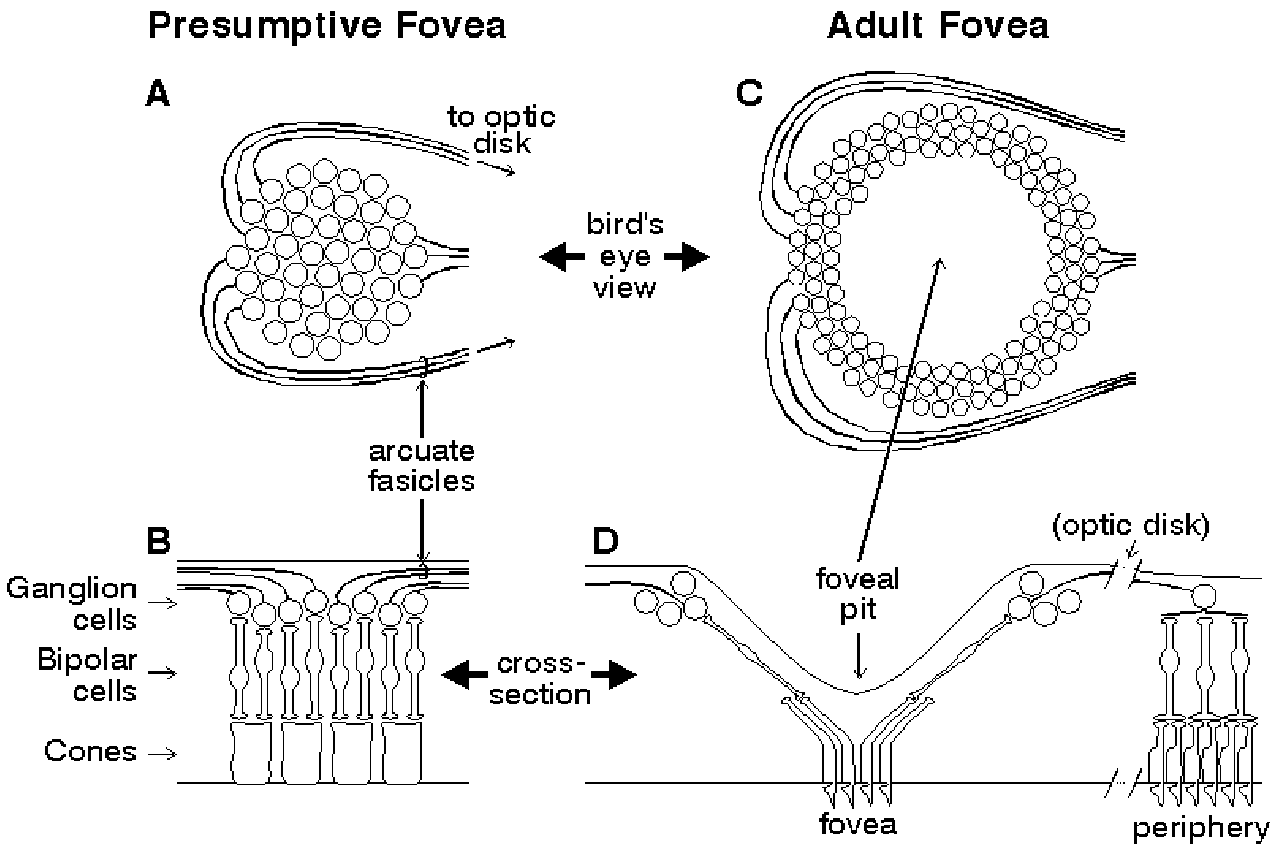
Figure 5.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