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THE SIGNIFICANCE OF FOLIATION AND FISSURATION OF CEREBELLAR CORTEX. THE CEREBELLAR FOLIUM AS A FUNDAMENTAL UNIT OF SENSORIMOTOR INTEGRATION

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INTRODUCTION

In this paper I would like to call attention to some obvious morphological features of cerebellar cortex that never appear to have been given much attention. In particular, I propose that each individual folium of cerebellar cortex is a distinct structural, connectional, and functional entity. The essence of this concept is that each cortical folium is an independent processing module which carries out integrative operations on a patterned assortment of afferent inputs that are unique for that folium. This view assumes that every cortical folium receives a special, individualized mosaic pattern of afferent inputs and delivers its outputs to a distinctive set of target neurons. If each folium has its own patterns of afferent and efferent connections which provide it with singular integrative functions, it follows that the number, length, height and size of folia, as well as the grouping of several adjacent cortical folia into lobules, will reflect the number, diversity and complexity of integrative operations embodied in different regions of the cerebellum. Moreover, species differences in folial and lobular number and complexity would be expected to reflect species differences in such functional attributes. I believe that there is sufficient evidence from developmental, anatomical, physiological and comparative data to lend credence to this general hypothesis. I will briefly review and discuss some of the relevant points.

I. DEVELOPMENTAL AND ANATOMICAL DATA.

1. Ontogenetic development of folia, lobules and lobes.

The special individuality of folia is best visualized by examining their growth and development. Early in ontogeny, the cerebellar cortex of all mammals develops from a small, simple, unfissured primordial plate overlying the developing metencephalon (5-8, 42, 49, 51, 58, 64, 67, 74, 106, 108). During subsequent embryological development, the cerebellar cortex foliates, fissures, lobulates and lobates into various taxon-specific morphological patterns of organization (9, 19, 58, 62-64,

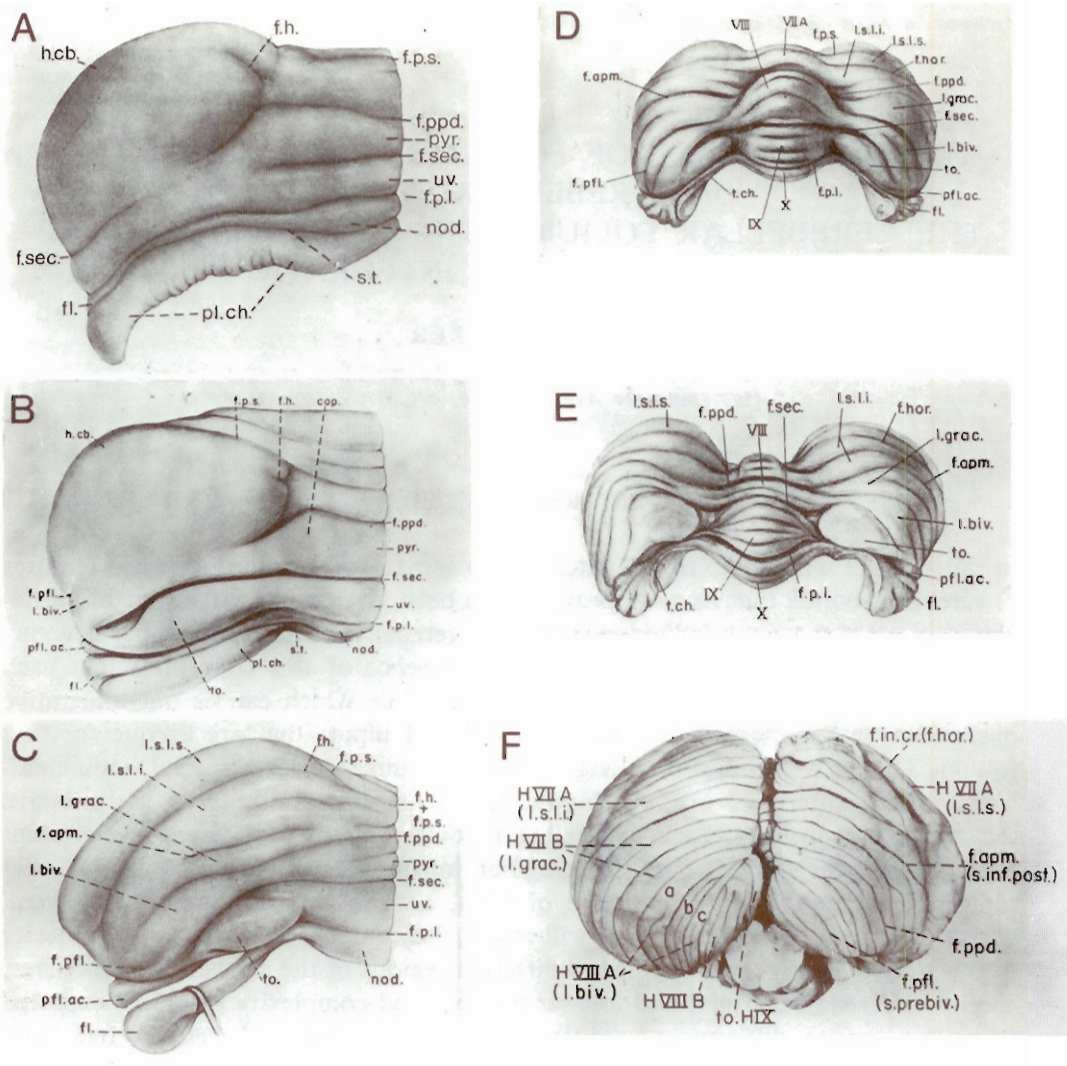


Fig. 1 – *Ontogenetic development of external morphology of human cerebellum.*

Note progressive development of lobules and folia showing differential enlargement of hemispheric lobules and folia and subdivision of lobes and lobules by primary fissures, and of folia by tertiary fissures. These figures show the progressive increase in number of folia as individual folia emerge out of the relatively larger smooth-surfaced cortical plates. The several drawings are differentially enlarged so as to have the same approximate size on the page. Reproduced with permission from Larsell and Jansen (ref. 64). A: right hemisphere reversed to appear as left; fetus of 105 mm crown-rump (CR) length (Fig. 30, p. 22). B. Left hemisphere; fetus of 130 mm CR length (Fig. 33A, p. 23). C. Left hemisphere; fetus of 150 mm CR length (Fig. 35, p. 24). D. Bilateral view; fetus of 175 mm CR length (Fig. 37, p. 25). E. Bilateral view; fetus of 180 mm CR length (Fig. 38, p. 25). F. Bilateral; 8-day old infant (Fig. 47, p. 33). Abbreviations: I-X, lobules of vermis; A-C, sublobules of vermis; a-f, folia of lobules; cop., copula pyramidis; f.apm, ansoparamedian fissure; (s.inf.post., posterior inferior sulcus); f.h. (f.hor.), horizontal fissure (f.in.cr., intercrural fissure); f.icul., intraculminate fissure; fl., flocculus; f.pc., preculminate fissure; f.pfl., parafloccular fissure (s.prebiv., prebiventral sulcus); f.p.l., posterolateral fissure; f.ppd., prepyramidal fissure; f.pr., primary fissure; f.prc., precentral fissure; f.p.s., posterior superior fissure; f.sec., secondary fissure; g.z., germinal zone; h.cb., cerebellar hemisphere; l.biv., lobulus biventer; l.grac., lobulus gracilis; lo.ant., anterior lobe (s.d., dorsal segment; s.v., ventral segment); lo.post., posterior lobe; l.s.l.i., inferior semilunar lobule; l.s.l.s., superior semilunar lobule; nod., nodulus; pfl.ac., accessory paraflocculus; pl.ch., choroid plexus; pyr., pyramis; s.dec., declival sulcus; s.ip., intrapyramidal sulcus; s.t., sulcus taeniae; s.v.m.a., sulcus of anterior medullary velum; t.ch., taenia choroidea; to., tonsilla; uv., uvula; v.m.a., anterior medullary velum.

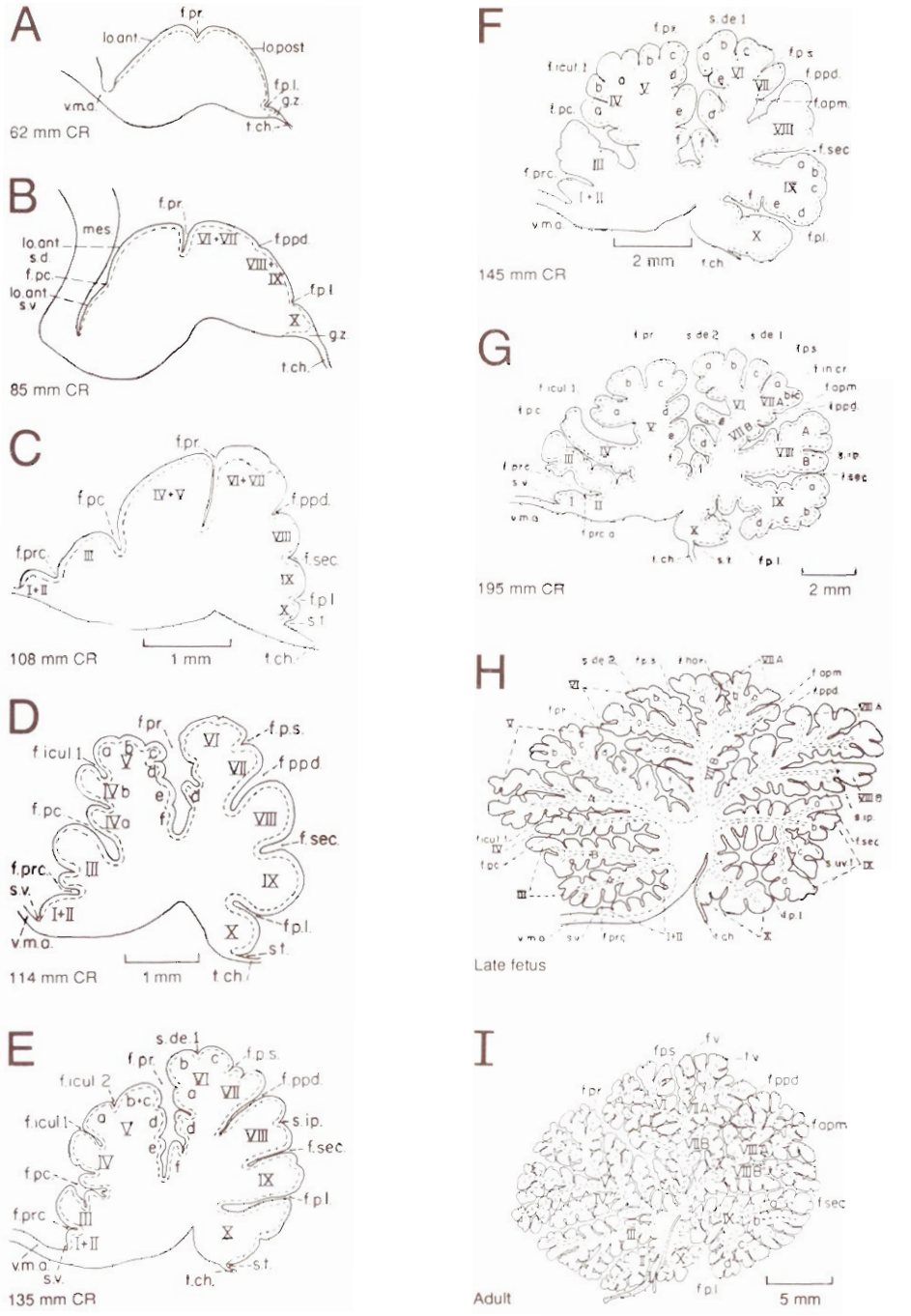


Fig. 2. – *Progressive folial development of human cerebellum as viewed in mid-sagittal section.*

These drawings depict progressive foliation, lobulation, lobation and fissuration of cerebellar cortex during ontogeny. Drawings are differentially enlarged so as to have the same approximate size on the page (note size scales on some drawings). A-H: fetuses of crown-rump (CR) lengths indicated at lower left of each drawing. I: Adult specimen. Reproduced with permission from Larsell and Jansen (ref. 64; A from Fig. 13B, p. 12; B: from Fig. 13B, p. 12; C from Fig. 16H, p. 13; D from Fig. 17A, p. 14; E from Fig. 19A, p. 15; F from Fig. 20A, p. 15; G from Fig. 23, p. 16; H from Fig. 24C, p. 17; I from Fig. 55B, p. 45). Abbreviations are listed in legend of Fig. 1.

67, 78, 83, 94). Figures 1 and 2 illustrate several successive stages in the development of the human cerebellum (64). It should be made clear at the outset that foliogenesis consists of several active developmental processes, as a result of which the cortex of folial crown grow, differentiate, expand and push outward to a greater degree than does cortex of folial walls and fundi. This fact was recognized by the earliest workers (61-64). Thus, it must be emphasized that the formation of fissures is *not* an infolding of cortex of fundi and walls. Rather, the cortex of folial walls and fundi grow, differentiate and are innervated to a lesser degree, and thus lag behind as the folial crowns push outward. Fissures themselves, although they may be useful identifying landmarks, are not cortical entities. Instead, they merely separate adjacent folia.

It is relevant to note that cerebellar cortex has a different developmental history than cerebral cortex. A major difference is that, in the formation of cerebral cortex, all cells in a vertical column arrive there from the same ependymal locus (87), whereas in cerebellar cortex, the different cell types in a particular cortical location arrive there by different migrational routes (1, 5, 48, 49, 87, 90, 91). Thus, in cerebellar cortex, granule cells and their processes (which eventually comprise the bulk of cerebellar cortex), have their origin in the primordial cells which spread out over the surface of the primordial plate fo form the external granule layer (EGL; 5, 90). Successive replications of EGL cells produce neurons which migrate radially inward past the Purkinje cells, and accumulate beneath them to form the internal granule cell (GC) layer (91). This layer consists primarily of GC bodies and dendrites (80). As these migrating cell bodies descend, their trailing axons bifurcate and extend to form the parallel fibers of the molecular layer (5, 80, 91). All the axons of all GCs travel in the same direction in a particular folium and, in doing so, may be a major determinant of folial orientation. Early on, the cells of the EGL appear (at least near the midline) to cluster into sagittal bands (58), but subsequently, as the definitive GC cell layer is formed, and as parallel fibers grow and the EGL becomes depleted, this sagittal alignment disappears (58).

To account for the cross-sectional appearance of foliated cortex (Fig. 3; see next section), I hypothesize that, during development, granule cells are produced in greater numbers, at a greater rate, and/or over a longer period of time at those locations which will become the folial crowns. Such a view implies that repeated cell division within the EGL of folial walls is relatively slow, late or shorter-lived, and is minimal in the bottoms (fundi) of the fissures. Moreover, during this period of granule cell production and maturation, Purkinje cell density becomes greater in folial crowns than in walls and fundi (Figs. 3 and 4). The fact that the enormous dendritic trees of these more densely packed Purkinje cells are oriented transversely across the folial crowns (80) may contribute to the bulkier character of cortex in folial crowns as seen in sections transverse to the major axis of a folium. In addition, arborization of afferent input and, I expect, enhanced synaptogenesis appear to be greater in folial crowns than in walls or fundi (Fig. 4). It also seems likely that the long thin alignment of each folium

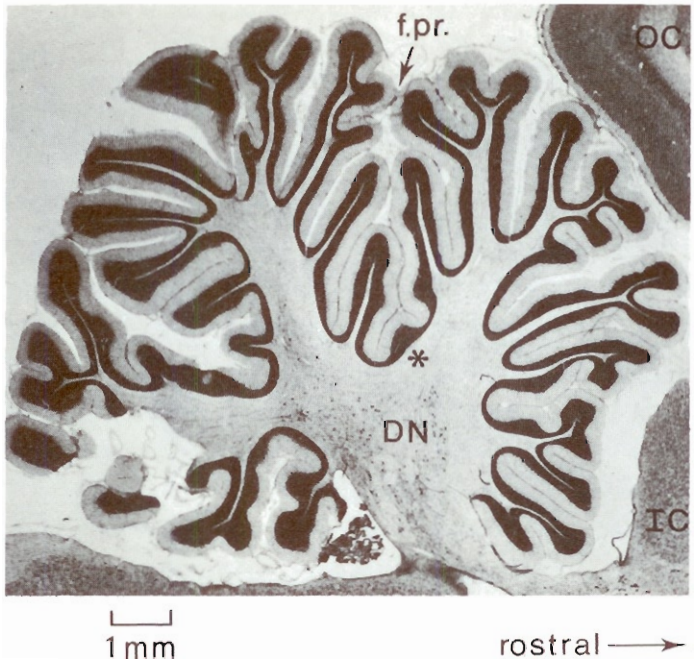


Fig. 3. – *Parasagittal section of cerebellum of domestic cat.*

Animal # 62-255, section # 788, thionin stain). Note that cortex of folial crowns always has a thicker granule cell (GC) layer than does cortex of walls or fundi, regardless of whether the crowns are at the cerebellar surface, emerge from the wall of a taller folial stalk, or bulge up from a fundus (indicated by asterisk). A lobule consists of several adjacent smaller folia on a common stalk. Note also that some folia are tall and slender and others are short and stubby. In addition, some folia appear as mere bulges in an otherwise smooth folial wall. The crowns of some folia are symmetrically broad and convex, whereas others are trapezoidal, triangular or skewed to one side. Regardless of their shape, width or height, the GC layer of all folia is thickest at the crown. DN, deep cerebellar nuclei; IC, inferior colliculus; F.pr., primary fissure; OC, occipital cerebral cortex.

is determined not only by the extensive growth of parallel fibers in the same direction as the folium, but by continued replication of EGL cells along the entire length of the folial crown. I hypothesize that all these differential developmental events in crowns, walls and fundi, particularly GC migration and pf growth, PC dendritic expansion, afferent innervation, and synaptogenesis, are the fundamental determinants of foliation of cerebellar cortex. They give folia their distinctive morphological appearance as viewed externally as well as in cross section.

Although most of the prominent features of cortical folia are probably determined by the *active developmental processes* mentioned above, the relative location, orientation of the long axis of a folium, and some minor aspects of surface curvature may also be influenced by certain *passive mechanical forces* which are secondary to the growth, development, and compression or protusion of other adjacent (and even distant) neural and non-neural (dura, skull, vasculature) structures during ontogeny. However, I emphasize that the major morphological features of folia

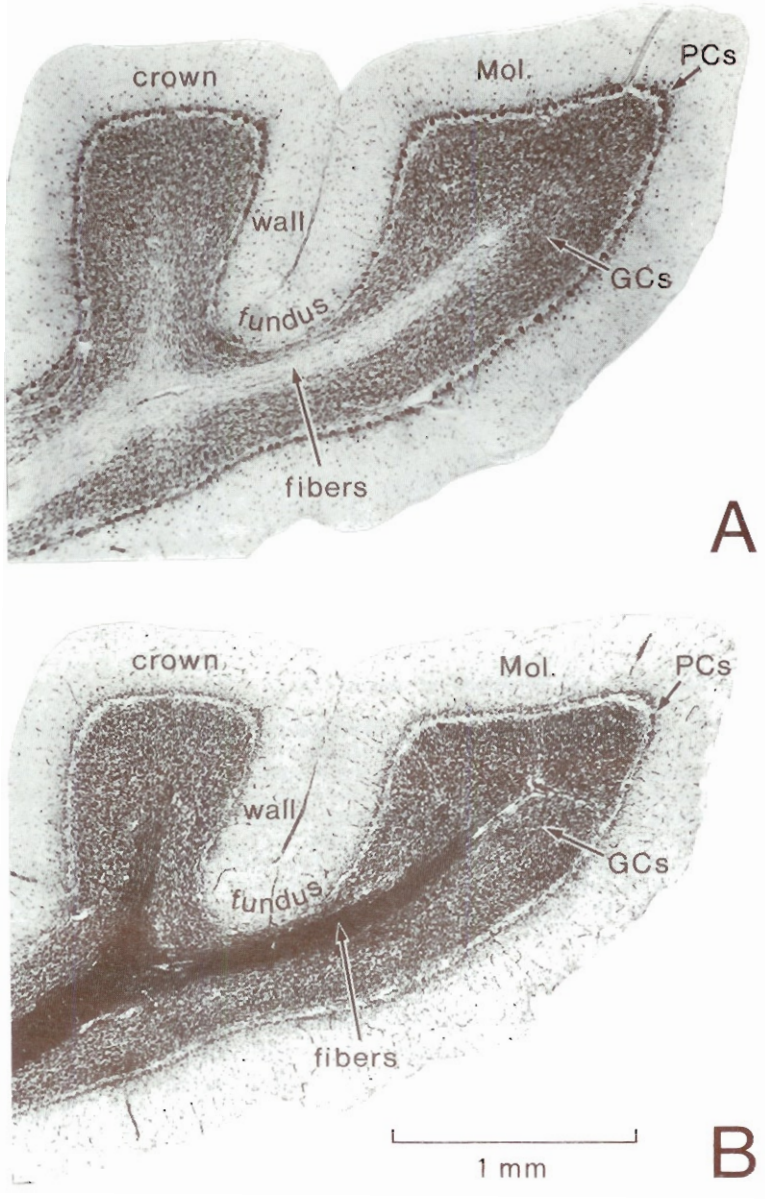


Fig. 4. – *Parasagittal section of two folia of cerebellar cortex of a Florida manatee* (Trichechus manatus).

Animal # 85-8. A. Cell stain; thionin; section # 946. B. Myelinated fiber stain; hematoxylin; section # 945. Note the thicker granule cell (GC) layer, more closely packed Purkinje cells (PCs) and the denser fiber innervation of folial crowns than of walls and fundi. PCs and GCs were stained by both thionin and hematoxylin stains. Note also that the PC layer is separated from the GC layer by a prominent infraganglionic plexiform layer.

(height, width, length) and of folial-fissural cortex itself (thickness, cell density, afferent innervation density) are probably determined by intrinsic growth processes and events.

Only a beginning has been made in identifying the relevant developmental processes and their timetables during foliation and lobulation of cerebellar cortex. Most of the early workers studied normal specimens at different developmental stages (1, 38, 60, 68, 70, 71, 77, 88, 98, 109, 116). More recently, experimental studies of details of generation, migration, differentiation and circuit formation have been carried out using autoradiographic (3-8), radiation (27, 30), nutritional (2, 65, 100), surgical (12, 13, 75, 101) and genetic (47, 87, 92, 93, 105), or other methods (10, 11, 41, 43, 70, 71, 72, 99, 115). These latter methods are currently the major source of information about many fine details of developmental events, their timetables, and their determinants. However, only the studies of Mares *et al.* (70, 71) have given attention to the differential developmental determinants of folial crowns, walls and fundi. There has been essentially no interest in determinants of the quantitative differences of different folia such as length, height, width, length and shape. Many types of factors which have been proposed to account for the formation of the convolutions of cerebral cortex (111) may also operate in the foliation of cerebellar cortex.

2. Cross sectional anatomy.

Consider the following morphological differences between the crowns, walls and fundi of folia as seen in sections at right angles to the long axis of any folium (Figs. 3 and 4): (1) The granule cell (GC) layer is thickest in folial crowns, thinner in the walls and thinnest in the fundi. (2) The Purkinje cells (PCs) are closer together in folial crowns and anguli than they are in folial walls, and they are least closely packed in the fundi (21). (3) The myelinated fiber bundles are more numerous and prominent beneath gyral crowns than they are in folial walls or fundi. All these features suggest that a folial crown is a structural entity that is differentially highly populated with neurons, by their afferents and efferents, and therefore also by local circuit connections and synapses.

These obvious differences in overall appearance of cerebellar cortex in folial crowns, walls and fundi might lead one to propose that these features are merely due to the mechanical folding of cortex which produces a bunching-up of folial crowns and the stretching-out of walls and fundi. Such mechanical folding and fissuring could be thought to be secondary to a "need" to increase the area of cerebellar cortex in larger and more complex cerebellae. This type of *post hoc* conjecture has been popular as an "explanation" of the convolutions and fissures of the cerebral cortex (28, 36, 45, 85). However, I believe that for both cortical sheets, the determinants of gyri, folia and fissures appear to consist of a variety of differential developmental events within those focalized zones of cortex which become the gyral or folial crowns.

There is another feature of folia that indicates that a folium is a distinct self-contained module. This is that the cortex of most folia is attenuated or truncated at its medial and/or lateral extremity. In such cases the three cortical layers become thin and terminate at the fiber stalk that serves the folium or the lobule of which the folium is a part. In other cases, such as at the margins of the hemisphere, the cortex curves back upon each folium laterally, ventrally and then medially. Such features signify the architectural containment of a folium as a specialized anatomical entity.

3. *Afferent and efferent connections.*

The earlier landmark experimental anatomical studies by Professors Brodal, Walberg and Jansen of afferent and efferent connections of the cerebellum utilized retrograde and anterograde degeneration methods following selective partial ablations of specific target or source nuclei and fiber tracts (23, 24, 25, 52, 62-64). These studies established the fundamental principles of cerebellar organization and connectivity (14, 23, 33, 48, 67). The methods used have been supplemented in recent years by more precise lesioning and intracellular and extracellular labelling of neurons and their processes. There are two major problems with lesioning and extracellular injecting and labelling techniques: (1) The lesions and labels are usually relatively large and cannot identify spatial details of projection patterns that are smaller than the lesion or injection site, and (2) they usually cannot be confined to functionally discrete neuronal assemblies. Intracellular injections are the only precise means to provide evidence regarding the fine-grained specificity of neuronal projections. A problem with this method is that sample size is limited by practical considerations. Nevertheless, several studies, particularly those of Per Brodal, which used small injection sites in both cerebral and cerebellar cortex, have demonstrated detailed patterns of projections which are multiply represented in the cerebro-ponto-cerebellar circuitry (25). His studies suggest that different portions of each cerebellar lobule must receive several different sets of information from different areas of cerebral cortex. These, and other studies of afferent projections provide additional evidence of a differentiated fine-grained mosaic patterns of multiple inputs to each folium and lobule (14, 37, 48, 55, 81, 84). Only a beginning has been made in defining these afferent projection patterns.

Mossy fiber afferents. A normal feature of mossy fiber (mf) afferents to cerebellar cortex is that they send several collaterals into two or more adjacent, or even distant, folia (33, 48, 84). When they enter cortex, individual mossy fibers branch locally rather profusely. Such observations led to the speculation that the mossy fiber systems project diffusely into cerebellar cortex (20, 33, 48). Physiological studies (see next section) now show that such collateralized projections, although dispersed, are not diffuse. Rather, they provide the same source-specific information to several different folia (see next section). Except for the studies mentioned in the previous sections, relatively few neuroanatomical studies have attempted

to explore the possibility that mf afferents from the several known sources project to cerebellar cortex in fine-grained patterns.

Climbing fiber afferents. In contrast to mossy fibers, individual climbing fibers (cfs), although collateralizing into several folia, when they reach cortex they terminate on one or only a few adjacent Purkinje cells (PCs; 33, 48). Any one PC receives only one cf. Cfs arise from the inferior olivary (IO) nuclear complex, and when that nucleus is injected or lesioned, cfs are deployed into cerebellar cortex as continuous sagittal strips or bands that align rostrocaudally throughtout the folia of the vermis and intermediate zone (14, 24, 33, 37, 55, 67). However, physiological studies of peripherally activated climbing fiber inputs (see section on Physiology) reveal a quite complex and detailed pattern of projections in which localized somatosensory projections are distributed, not as sagittal zones, but are deployed into multiple patchy mosaics which differ for each folium. Detailed studies of different functional olivary sources must be carried out with precision for each folium.

Efferent projections. Most studies of efferent projections have also used lesion or injection methods (23, 25, 33, 39, 40, 46). All these studies reveal a medial to lateral topographical plan of organization of efferents to the deep cerebellar nuclei. Such studies show that in the rostro-caudal direction, there is also a topographically orderly pattern of projections. Thus, PCs from each small region of cerebellar cortex project to a distinct subset of deep nuclear neurons (40, 46, 80, 81). In effect, PC efferents from different folia project to different deep nuclear cell populations. However, the fine-patterned details of projection from different small patches of Purkinje cells to deep nuclei have not been worked out. Haines (39) has evidence that corticonuclear fibers take origin from small mosaics or microzones.

4. *Intracortical connections.*

It had been assumed for some time that cerebellar cortex exhibits a strikingly uniform architecture and local circuit organization throughout its enormous extent (14, 20). As mentioned above, the two major types of afferents and efferents were found to be deployed in an array of remarkably sheet-like sagittally-oriented planes. This plane of projection was not only parallel to the plane of one type of cortical neural element (Purkinje cell dendrites), but also was strictly transverse to those of another (parallel fibers of granule cells). Moreover, the several different cell types within the cerebellar cortex were well defined and their intracortical dendritic and axonal territories were thought to be stereotypical for each cell type, many of which were orthogonal to those neural components of other cortical neurons. The basic local circuit organization that was conceived as a result of numerous careful anatomical and physiological studies, has come to be accepted as the fundamental groundplan of all cerebellar cortex (20, 22, 33, 48, 89, 107). The anatomical differences between the cortex in crowns, walls and fundi apparent-

ly have not been viewed as disruptions or alterations of the basic uniformity. More likely, they were conceived as mere folding artifacts.

In recent years, however, numerous variations in neuronal morphology, connectivity and chemistry have been disclosed in different localities of cerebellar cortex (14, 48, 55, 81). These data, together with the physiological data discussed in the next section, raise the spectre that local circuits within the enormous sheet of cerebellar cortex in mammals may have numerous local variations and specializations which are functionally important, and that each of these will have to be examined in fine detail. It even may be that different folia may exhibit different types of local circuit organization.

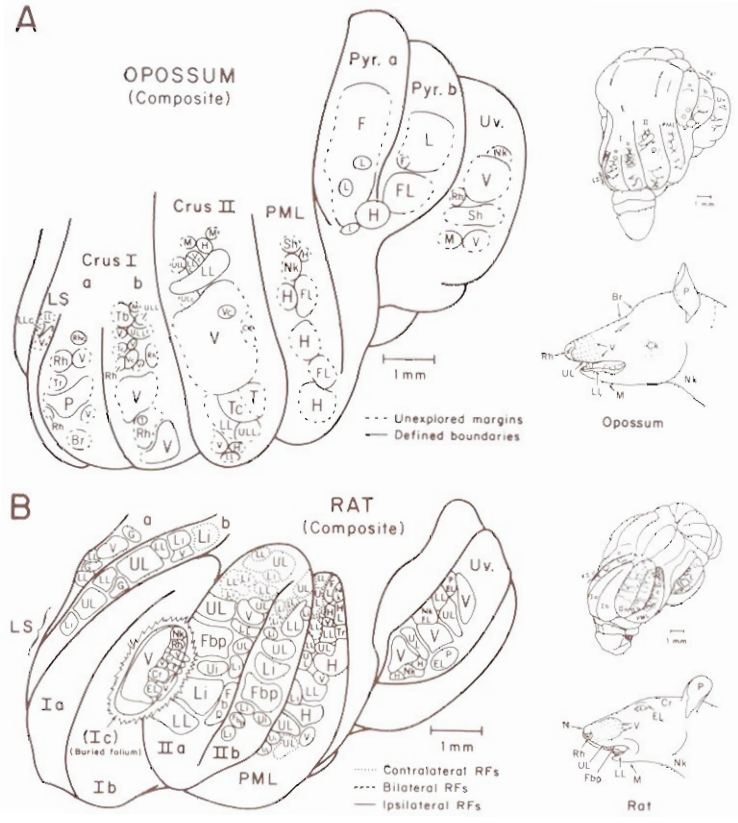
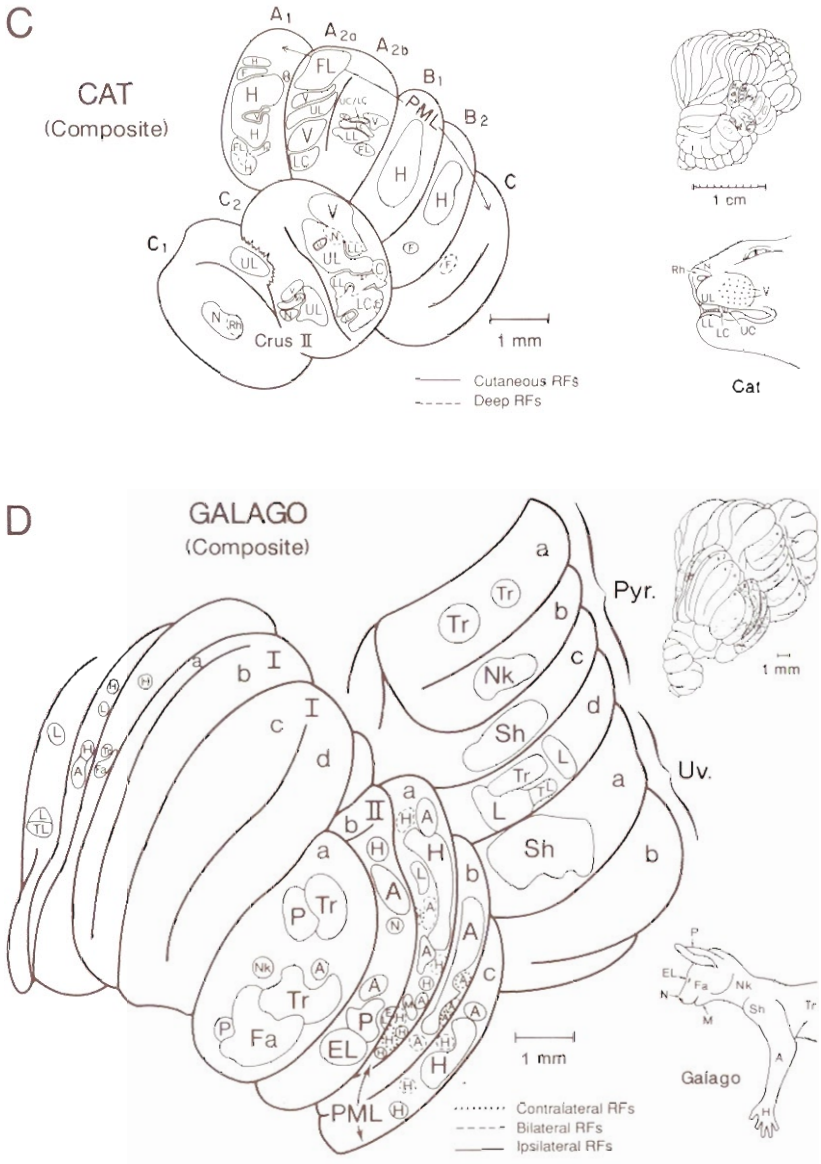


Fig. 5. – *Schematic diagrams of fractured patchy mosaical somatosensory projections to the granule cell (GC) layer showing species differences as well as folial differences in fractured projection patterns.*

Brain diagrams portray composite patchy mosaic projections to the GC layer for A North American opossum (*Didelphis virginiana*), B albino rat (*Rattus rattus*), C domestic cat (*Felis domesticus*) and D giant galago (*Galago crassicaudatus*). Note that opossum (A) has tactile projections to all posterior lobe hemispheric folia including those of Crus I, whereas in rat (B), two out of 3 Crus I folia do not have tactile projections. In cats (C), the folia of Crus I, and most folia of Crus II did not have tactile projections; and in galago (D), Crus I not only did not have somatosensory projections, but there are gaps between tactile projections in both of the Crus II lobules. Abbreviations of somatosensory projections: A, Arm; Br, brow; Ck, cheek; Cr, crown; C, upper and lower canines; El, eyelid; Fbp, furry buccal pad; F, foot; Fa, face; Fl, forelimb; G, gingiva; H, hand; HL, hindlimb; L, leg; LC, lower canine; Li, lower incisor;



LL, lower lip; LLc, contralateral lower lip; M, mandible; N, nose; Nk, neck; P, pinna; Rh, rhinarium; Rhc, contralateral rhinarium; Sh, shoulder; T, multiple teeth; Tc, contralateral multiple teeth; Tr, trunk; UC, upper canine; Ui, upper incisor; UL, upper lip; ULc, contralateral upper lip; V, mystacial vibrissae; Vc, contralateral vibrissae pad. Abbreviations of folia: A1, A2a, Al2b, B1, B2, C, folia of paramedian lobule (PLM) in cat; C1, C2, medial folia of Crus II in cat; Crus Ia, Ib, Ic, folia of Crus I; LSa, b, folia of lobulus simplex; PML, paramedian lobule or its homologue; Pyr, a, b, c, d, four folia of the pyramidal lobule; UV, uvula. Opossum composite (A) reproduced with permission from Welker and Shambes (ref. 113, Fig. 3). Rat composite (B) reproduced with permission from Shambes *et al.* (ref. 96, Fig. 6), Shambes *et al*, (ref. 97, Fig. 2), Joseph *et al*, (ref. 54, Fig. 4), and Bower and Woolston (ref. 16, Fig. 1). Cat composite (C) reproduced with permission from Kassel *et al.* (ref. 54a, Fig. 6). Galago composite (D) reproduced with permission from Welker *et al.* (ref. 114, Figs., 3, 5, 6, 7).

II. Physiological organization of somatosensory projections.

1. Afferents to the granule cell (GC) layer.

Until recently, very little attention had been given to studying projections to the granule cell (GC) layer using physiological methods. We found, quite fortuitously, that somatosensory projections to the uniform-appearing GC layer were deployed in highly detailed asomatotopic patchy mosaics (Fig. 5; 54, 96, 97, 110, 112). The precision, reproducibility, and unusually detailed pattern of these projections became apparent only if low-threshold cutaneous mechanosensory projections were defined using high-density-sample micromapping methods, in-depth recording methods, and gentle natural-stimulation of mechanoreceptors. These projection patterns were different in different folia, as well as in what were assumed to be homologous folia in different animal types (Fig. 5A, B, C, D). The mosaic patterns for a given folium also varied slightly from animal to animal within a given species (47, 59). This suggests one neuroanatomical source of individual differences in behavioral patterns. The somatopically organized projections from SI cerebral cortex (15), as well as from the roughly somatotopic tactile lamina of the superior colliculus (see 112), become rearranged in the cerebro-ponto-cerebellar, as well as the tecto-ponto-cerebellar, circuits to conform, in convergent homotopic patterns, to the somatotopically fractured patchy mosaic peripheral projections to the GC layer. Studies from our laboratory also revealed that short-latency simple-spike-activating, granule-cell-mediated somatosensory projections to the Purkinje (PC) layer exhibit patchy mosaic features that are congruent (in boundary, size, shape and receptive field properties) with the projections to the underlying GC layer (Fig. 6; 16).

2. Afferents to the Purkinje cell layer.

Several physiological studies, particularly those of Robertson and his colleagues (69, 95), have shown that climbing fibers, which carry somatosensory receptive field information, project to the PC layer in a series of complex patches arranged as asomatotopic mosaics on different folia of the anterior lobe. In our studies of the granule cell layer, we often encountered isolated climbing fiber (cf) complex spikes in the molecular layer as we approached the PC layer. The receptive fields (RFs) of these cf spikes were always from the same body locus as were the RFs that activated the underlying GC layer deeper in each vertical penetration. The RFs of these cfs were always much larger and of higher mechanical stimulus threshold than were the RFs of the subjacent GCs. Such topological correspondence of RFs of cf-PC responses with those of mf-GCs had been noted early by Eccles *et al.* (33).

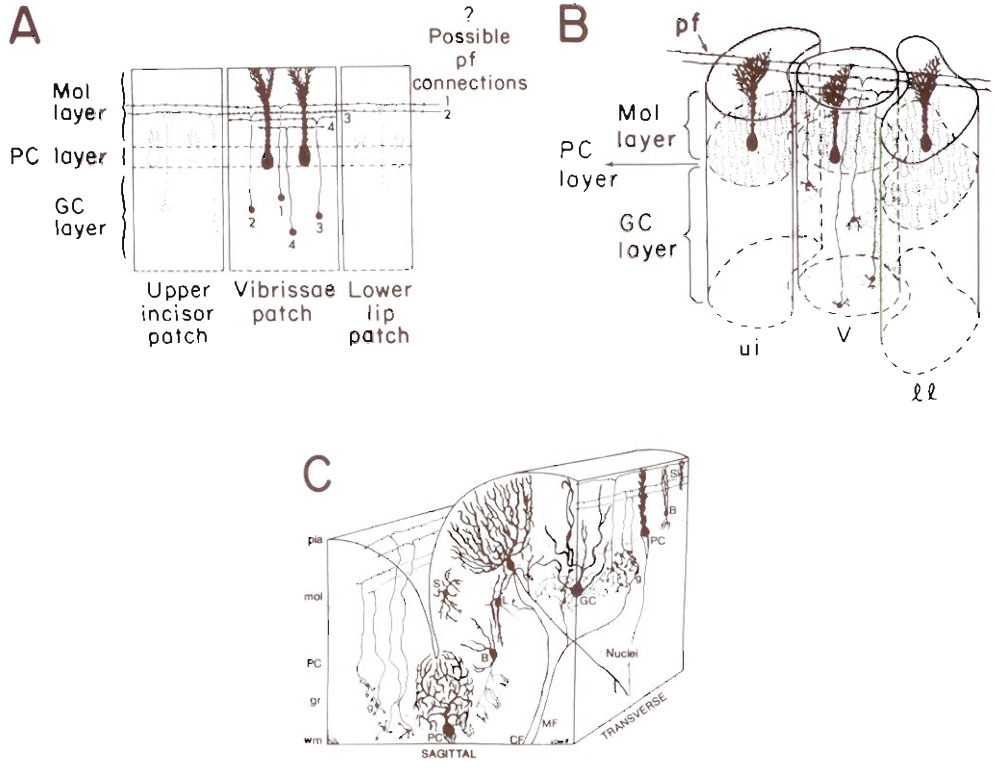


Fig. 6. – *Schematic conceptions of cerebellar cortical circuits.*

A. Diagram of three adjacent patches with different receptive fields (RFs). The four granule cells (GC) in the center (vibrissae) patch may have parallel fibers (pfs) that project different distances, or they may have different synaptic densities in different adjacent patches. B. Three-dimensional sketch of the same three patches depicted in A. This sketch portrays our patchy columnar module conception of short latency GC-PC projection. C. Three-dimensional classical depiction of basic skeleton of cerebellar cortical circuitry (reproduced with permission from Palay and Chan-Palay (ref. 80, Fig. 5).

III. Comparative morphology.

The cerebellar cortex in mammals exhibits a variety of complex configurations in different mammals (Fig. 7). The course of evolution of such diversity is poorly documented by paleoneurological studies (34, 35, 53, 86). Larger, or perceptually-behaviorally more complex mammals have a larger and more elaborately foliated cerebellar cortex than do smaller or less complex mammals (18, 19, 50, 62-64, 67, 78, 82, 83, 94, 102-104). There exist only a few broadly comparative studies of cerebellar morphology (17, 19, 62-64, 94, 102). The monumental works of Larsell and Jansen summarized earlier literature and established the basic nomenclature in use today (61-64). These studies used comparative embryological methods to identify what were thought to be fundamental homologies of folial arrangement

in different mammals. Whether or not such topographical similarities are connectionally and functionally homologous remains to be determined.

Although essentially alike early in embryological development, the cerebellar cortex of different adult mammals exhibits great diversity in the number, spatial orientation, height, width, and length of folia, as well as in lobular complexity of folial aggregates (Fig. 7; 18, 56, 78). With regard to overall folial and lobular arrangement, in many mammals, the long axes of cerebellar folia are aligned mediolaterally, but in others, differential development of different folial groups or lobules, results in more complexly configured folial patterns (Fig. 7). The stacks of mediolaterally oriented folia are usually aligned rostrocaudally on the vermis, which straddles the midline. The vermis is relatively large in some mammals. But, in others, it is relatively small, whereas the folia of the hemisphere have become more numerous and extensive. Thus, the hemispheres are differentially enlarged in different mammals. Folial orientation of the hemisphere is mediolateral like those of the vermis in most small cerebellae, and in some of the larger cerebellae as well (Fig. 7). In many of the larger cerebellae, however, the hemispheric folia are lobulated and contorted into diverse and complex morphological patterns (Fig. 7).

Identifying homologous folia in different mammals is often impossible. It is particularly difficult for the larger and more complexly foliated cerebellae (9, 32, 50, 57, 62-64, 78). The study of homologies in living mammals is a complex task and must be undertaken with care (26, 44, 79). Usually only topographical homologies have been suggested, and these are identified mainly on the basis of studies of normal cerebellar ontogeny (9, 32, 62-64). In a few cases, homologous connectivities have been roughly identified using lesion or injection methods. However, the vast expanse of cerebellar cortex remains to be explored in most major mammalian orders.

Electrophysiological studies initially held great promise for defining functional similarities and differences of different cerebellar folia and lobules in different mammals. The early work of Snider and others (see references in 33, 48, 67, 97, 112) demonstrated the feasibility and importance of using functional approaches. Yet, such early studies could not provide evidence of fine detail because they used macro-electrode, surface-recording, evoked-potential methods. However, several recent studies have now shown that micromapping methods can provide data that reveal the location of folia that appear to be homologous with respect to some physiological criteria. These methods also reveal the presence of differential enlargement, composition and specialization of afferent projection patterns to the cerebellar cortex in different folia and lobules. Nevertheless, only a few folia, and only the smaller, simpler cerebellae, have been examined so far by these methods. It is probable that many mammals have folia and lobules which have no homologs in other mammals. Study of the more complex and larger cerebellae will be an interesting but enormous challenge.

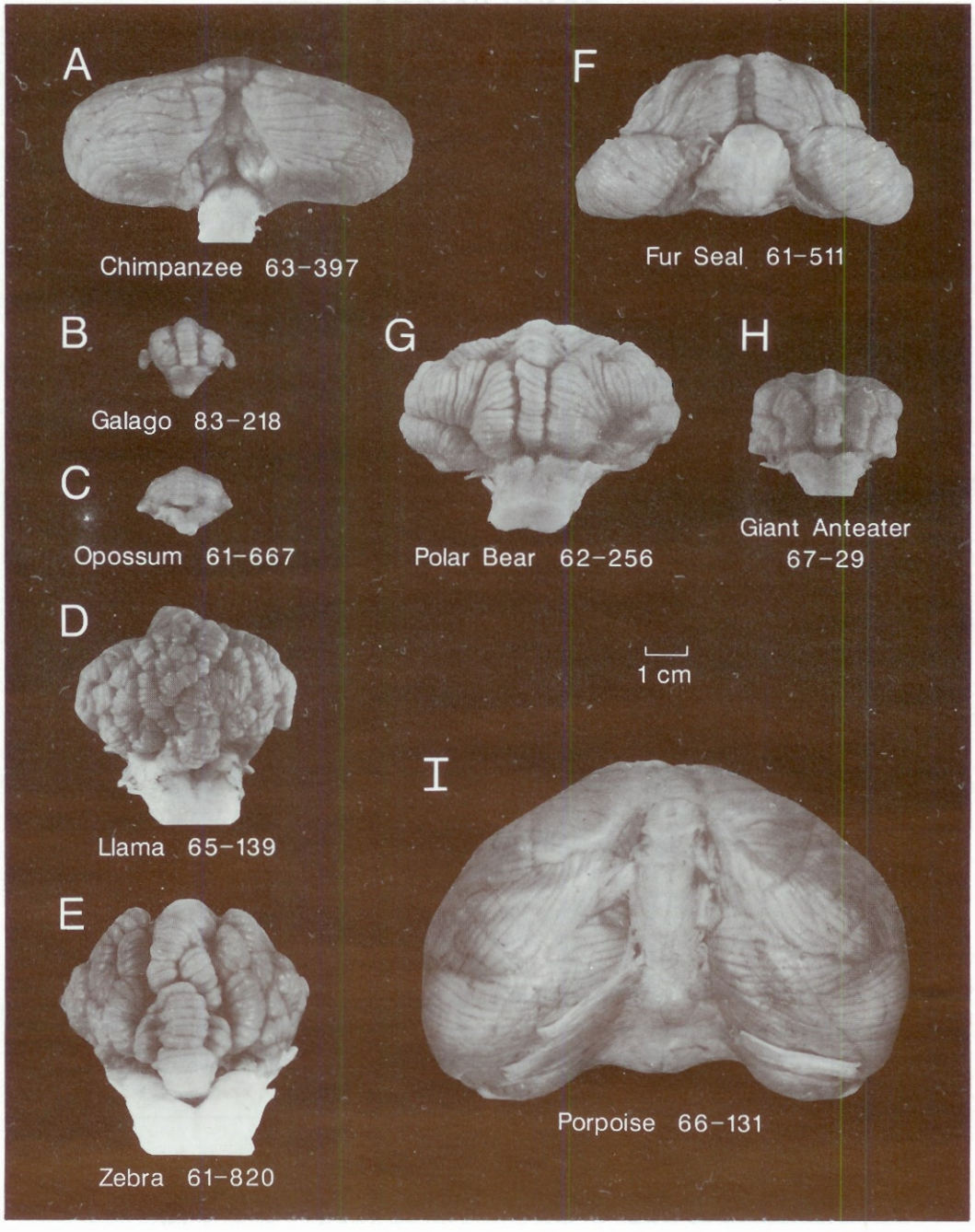


Fig. 7. – *Diverse species-specific variations in overall conformation, foliation, lobulation and lobation in several different mammals.*

All specimens are depicted from the caudal view and are all to the same scale. Two primates: A chimpanzee (*Pan paniscus*) and B giant galago (*Galago crassicaudatus* O). C: opossum (*Didelphis virginiana*). D: Llama

CONCLUSIONS

My goal in this paper has been to propose that foliation of cerebellar cortex reflects a fundamental principle of design in which each folium develops into a distinct structural and functional entity or module. In this view, every folium is uniquely constructed of a complex mosaic of afferents from several sources, numerous assemblies of local circuits, as well as a patterned arrangement of efferents. The afferents from each folium derive from many different sensory and sensorimotor sources throughout the spinal cord, medulla, midbrain and forebrain. The efferents project to several sets of deep nuclear and brainstem neurons, and these in turn project to other nuclei in the spinal cord, brainstem, and thalamocortical motor and motor-sensory circuits. Thus, the cerebellar cortex is disposed so as to deal with sensorimotor transactions.

There are many views regarding the functions of such cerebellar transactions (14, 20, 23, 29, 31, 33, 37, 46, 48, 55, 66, 73, 107). All of these views conceive cerebellar functions to involve some kind of sensorimotor integration. Since the organization of the afferents and efferents appears to be completely different for different folia, it seems appropriate to propose that each individual folium of cerebellar cortex is a fundamental unit of sensorimotor integration.

However, the subtleties and complexities of morphology, connectivity and function outlined in this paper must be identified and defined for each and every folium before operational principles of a specific folium can be understood, and before a general theory of cerebellar function can be judged to be valid. Only a start has been made in this direction of inquiry. Nevertheless, I believe that further detailed analysis of the input patterns, local-circuits assemblies and output patterns of each individual folium in different mammals will provide the new insights needed to clarify the integrative roles played by different cerebellar folia in the guidance, control, and learning of specific sensorimotor act sequences.

SUMMARY

I propose the general hypothesis that each individual folium in the cerebellum is an integrative module that is involved in unique sets of sensorimotor transactions. Although the basic types of operations carried out by cerebellar cortex

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(*Lama glama*). E: Zebra (*Equus burchelli*). F: Northern fur seal (*Callorhinus ursinus*). G: Polar bear (*Thalarctos maratimus*). H: giant anteater (*Myrmecophaga tridactyla*). G. Atlantic porpoise (*Tursiops truncatus*). Note that the vermis is relatively reduced in chimpanzee (A), fur seal (F) and porpoise (all of which have enlarged hemispheres), but is relatively large in llama (D) and zebra (E). Folia are arranged predominantly mediolaterally in chimpanzee, galago, opossum, fur seal and porpoise, but the hemispheric folia in porpoise and fur seal are arranged in different diagonal orientations in different lobules or lobes. The hemispheric folia of polar bear and giant anteater are lobulated into a laterally convex series of lobules. The hemispheric elaboration of lobules in llama and zebra are arranged into more complex irregular lobular patterns. In all cases, however, adjacent folia within a given lobule are parallel to one another despite displacement of their major axes from the transverse plane commonly seen in many mammals.

may be similar in all folia, the mosaic of afferent sources, intrinsic organization and efferent destinations appear to be unique for each folium. I believe that this conception is supported by: 1) comparative data which illustrate species-typical folial patterns, 2) neuroanatomical data which reveal not only different structural features of folial crowns and fundi, but differential afferent and efferent connectivity of different folia as well, 3) physiological data, which demonstrate unique patterns of afferent activity in different folia, and especially by 4) ontogenetic data which establish that each folial crown expands and differentiates into an architecturally distinct cortical entity. Taken together, all these lines of evidence suggest that the numbers and patterns of folia exhibited by the cerebellar cortex of different mammals are morphological indicators of differential organization of sensorimotor control functions in each animal. Even intraspecific individual variations in folial number, size and pattern may signify structural-functional determinants of some individual differences in sensorimotor transactions. Since so little research has addressed the many testable ideas embodied in these general hypotheses, it seems to me that neuroscientists have a long way to go to clarify how the many different folia and lobules of cerebellar cortex actually function in the common, everyday, orderly, dynamic and ongoing reflex, postural, learned and deliberate behavioral sequences that characterize the normal behavioral repertoires of different animals. The enormous advances in understanding brought forth by the extensive research and writings of Professor Brodal and his colleagues have expanded our horizons to avail us of an enormous range of new vistas into cerebellar functional morphology. It is now the task of neurobiologists to explore these diverse new domains in ever greater depth and detail.

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