The anatomy of the cerebellum

Jan Voogd and Mitchell Glickstein

Vertebrate cerebella occupy a position in the rostral roof of the 4th ventricle and share a common pattern in the structure of their cortex. They differ greatly in their external form, the disposition of the neurones of the cerebellar cortex and in the prominence of their afferent, intrinsic and efferent connections.

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THE CEREBELLAR CORTEX is built from four main types of neurones: granule cells; Purkinje cells and two types of inhibitory interneurones, the Golgi cells and the stellate/basket cells[1–5] (Fig. 1). The cortex receives three kinds of extra cerebellar afferents: the mossy fibres, the climbing fibres, both of which are excitatory, and the diffusely organized mono-aminergic and cholinergic afferents.

Granule cells are small, glutamatergic neurones. They are by far the most numerous elements in the cerebellar cortex and in the brain as a whole. Mossy-fibre terminals (rosettes) contact the short, claw-like dendrites of several granule cells in complex synapses (glomeruli). Axons of granule cells are unmyelinated and ascend towards the superficial, cell-poor molecular layer of the cerebellar cortex, where they typically bifurcate and terminate on dendrites of Purkinje cells and interneurones (Fig. 1A,D,E).

Purkinje cells are large, GABAergic neurones, which serve as the sole output of the cerebellar cortex. Their myelinated axons terminate on neurones of the cerebellar nuclei and certain brainstem nuclei. The initial ramifications of the Purkinje-cell dendritic tree are relatively smooth; their distal branchlets are closely covered with spines. Parallel fibres terminate on the spines of these spiny branchlets. The proximal, smooth branches are innervated by multiple synapses from a single climbing fibre[6] (Fig. 1B–E).

Golgi cells provide feed-backward inhibition to granule cells. The co-localization of GABA and glycine and the differences in their localization, morphology and neurochemical characteristics, distinguish the Golgi cells from the stellate/basket cells, which are purely GABAergic neurones located in the molecular layer, which provide feed-forward inhibition to the Purkinje cells[7] (Fig. 1E).

Purkinje cells typically are located in a single row at the border of the granular and the molecular layer. Their dendritic trees are flattened and oriented perpendicular to the parallel fibres. The 'lattice structure' of the cerebellar cortex[8] is enhanced by the orientation of dendrites and axons of stellate/basket cells and the collateral plexus of the Purkinje-cell axons, which share the orientation of the Purkinje-cell dendritic tree (Fig. 1A–C,F).

Pallisades of Bergmann glia extend into the molecular layer, between the dendrites of Purkinje cells. Their cell bodies are located among the Purkinje cells. Bergmann glia are developmentally related to the radial glia, which guide the Purkinje cells and the granule cells from their origin in the ventricular matrix and the external granular layer, respectively, to their definite position in the cerebellar cortex[9,10].

Although the basic plan of the cortex is similar among vertebrates, there are differences in the distribution of granule and Purkinje cells (Fig. 1G), the topology of smooth and spiny branchlets of the Purkinje cells (Fig. 1B,C) and their climbing-fibre afferents, the presence of target cells of the Purkinje-cell axons (eurodendroid cells, Fig. 1F) within the cerebellar cortex of teleost fish, and the differentiation of the inhibitory interneurones of the molecular layer into stellate and basket cells in birds and mammals[4].

Variations in the external form of cerebella

The gross anatomy of the cerebellum varies from that of a single leaf or dome-like structure, as in amphibians and reptiles, to the more complicated shapes in fish, birds and mammals (Fig. 2A). In fish the cerebellum consists of a central mass, the corpus cerebelli, and two lateral granular eminences, also known as the auricles in cartilagenous fish[2] (Fig. 1G). The granular eminences and their caudal interconnection are closely related to the nuclei of the vestibulo–lateral line systems. Rostrally, the cerebellum of bony fish protrudes as the valvula cerebelli under the midbrain tectum (Fig. 2A). In Mormyridae, electroreceptive teleosts, the valvula is huge and has 'pushed' the tectum aside to cover the entire surface of the brain[13] (Fig. 2B).

In birds and mammals the cerebellum is foliated. In birds the folia radiate from a common centre as the pages of a book. The cortex of the two caudal-most folia is continuous as the so-called auricle, around the lateral extremity of the intervening posterolateral fissure (Fig. 2C). The auricle and the caudal-most folium of the avian cerebellum are closely related to the vestibular system[14].

The folial pattern of mammals is more complicated[15] (Fig. 2D–F). In the anterior region transverse fissures extend uninterruptedly to the lateral margin of the cerebellum. This anterior region can be subdivided into the anterior lobe and the lobulus simplex by the deep primary fissure. In the caudal cerebellum there are three folial chains extending from a region behind the lobulus simplex; a central vermis and two hemispheres. Although the distinction between vermis and hemisphere is not obvious in the anterior region of the cerebellum, a division by a shallow groove, which contains the paravermal vein, can be present. The cortex of the folial chains of the caudal vermis and the hemisphere is continuous in the depth of the transverse fissures. Between vermis and hemisphere the cortex, that is, the communication through the parallel fibres, can be interrupted (Fig. 2G,H asterisks). Within the folial chains the cortical lattice always maintains its orientation with respect to the long axis of the chain.

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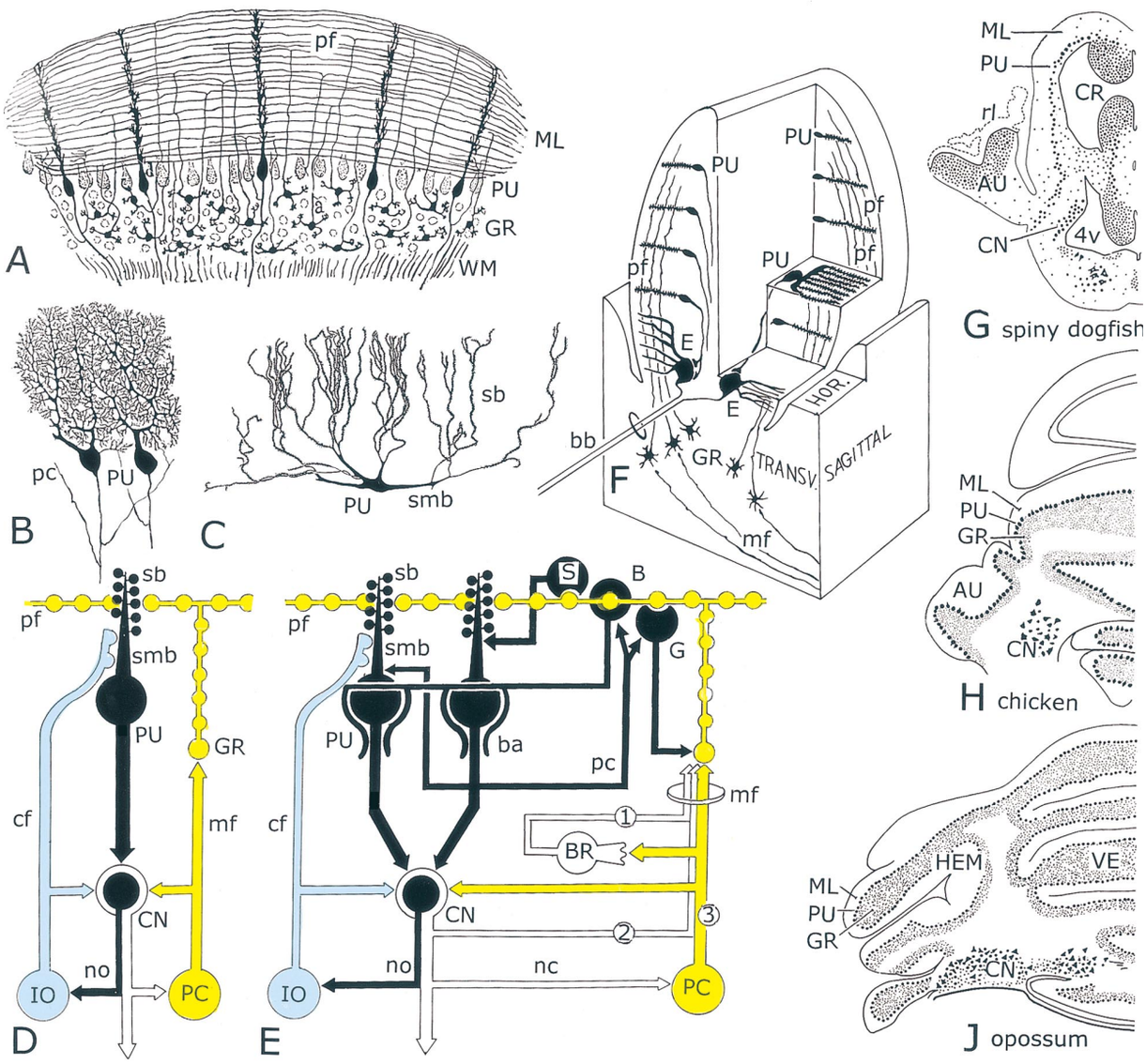

Fig. 1. ***The cerebellar cortex.*** **(A)** *Classical drawing by Ramón y Cajal of a transverse, Golgi-stained section through the cerebellar cortex shows the molecular (ML), Purkinje-cell (PU) and granule-cell (GR) layers on top of the white matter (WM). Note the medio–lateral constriction of the Purkinje-cell dendritic trees and the transverse orientation of the parallel fibres (pf).* Reproduced from Ref. 1. *Profiles of Purkinje cells of mammals and cartilaginous fish, shown in* **(B** *and* **C)** (reproduced from Refs 1 and 2, respectively) *are virtually identical. However, in fish (and other non-mammalian species) the proximal smooth branches (smb) of the dendritic tree ramify close to the layer of Purkinje-cell somata and their spiny branchlets (sb) extend as spikes into the molecular layer. In mammals, smooth branches extend up to the meningeal surface of the cortex. As a consequence, climbing fibres in non-mammalian forms are confined to the bottom of the molecular layer, whereas they terminate over the entire width of the molecular layer in mammals. The main cerebellar circuit is illustrated in* **(D)** *and the wiring of interneurones and collateral projections are added in* **(E)**. *Inhibitory neurones are indicated in black. Three types of mossy fibres (mf) can be distinguished: those of extracerebellar origin (3); collaterals of relay cells of the cerebellar nuclei (2) and axons of brush cells*[3] *(BR) located in the granular layer of certain lobules (1). In the three-dimensional representation* **(F)** (redrawn from Ref. 4) *of the main circuit in a ridge of the valvula (see Fig. 2A,B) of a Mormyrid fish, the granule cells are located at the base of the ridge. Unbranched parallel fibres ascend in the ridge, where they synapse with the Purkinje cells. Purkinje-cell axons terminate on eurodendroid cells* (E), *comparable to cerebellar nuclear cells in mammals, located at the bottom of the ridge. Granule cells in fish, reproduced from Ref. 2 in panel* **(G)**, *are often segregated from the Purkinje cells in lateral auricles (AU) or granular cristae (CR). In birds and mammals* **(H,J)** *a regular three-layered cortex is found. Abbreviations: 4v, 4th ventricle; B, basket cell; ba, basket terminal; bb, efferent basal bundle; cf, climbing fibre; CN, cerebellar nuclei; G, Golgi cell; HEM, hemisphere; IO, inferior olive; nc, collateral of nuclear relay cell; no, nucleo–olivary pathway; pc, Purkinje-cell axon collateral; pf, parallel fibre; rl, lateral recess; S, stellate cell; VE, vermis.*

In all mammals the caudal vermis is divisible into four or five lobules, which derive their names from human anatomy (Fig. 2H). The folial chain of the hemisphere can be subdivided into the ansiform and paramedian lobules, the paraflocculus and the flocculus on the basis of sudden changes in the direction of the chain[11,16]. Larsell[12], who considered the lobules of the hemisphere as mere lateral extensions of the lobules of the vermis, distinguished ten lobules in the vermis, shown by the roman numerals I–X and indicated the corresponding lobules of the hemisphere with the prefix H. Some of these relationships, however, are still disputed. The caudal-most lobules of vermis and hemisphere, the nodulus and flocculus, are closely related to the vestibular system. However, the vestibulocerebellum is not confined to the region bordered by the posterolateral fissure, but extends for some distance on the uvula and the ventral paraflocculus[7,28]. Measured over the surface the folial chains of vermis and hemisphere are extremely long and relatively narrow.

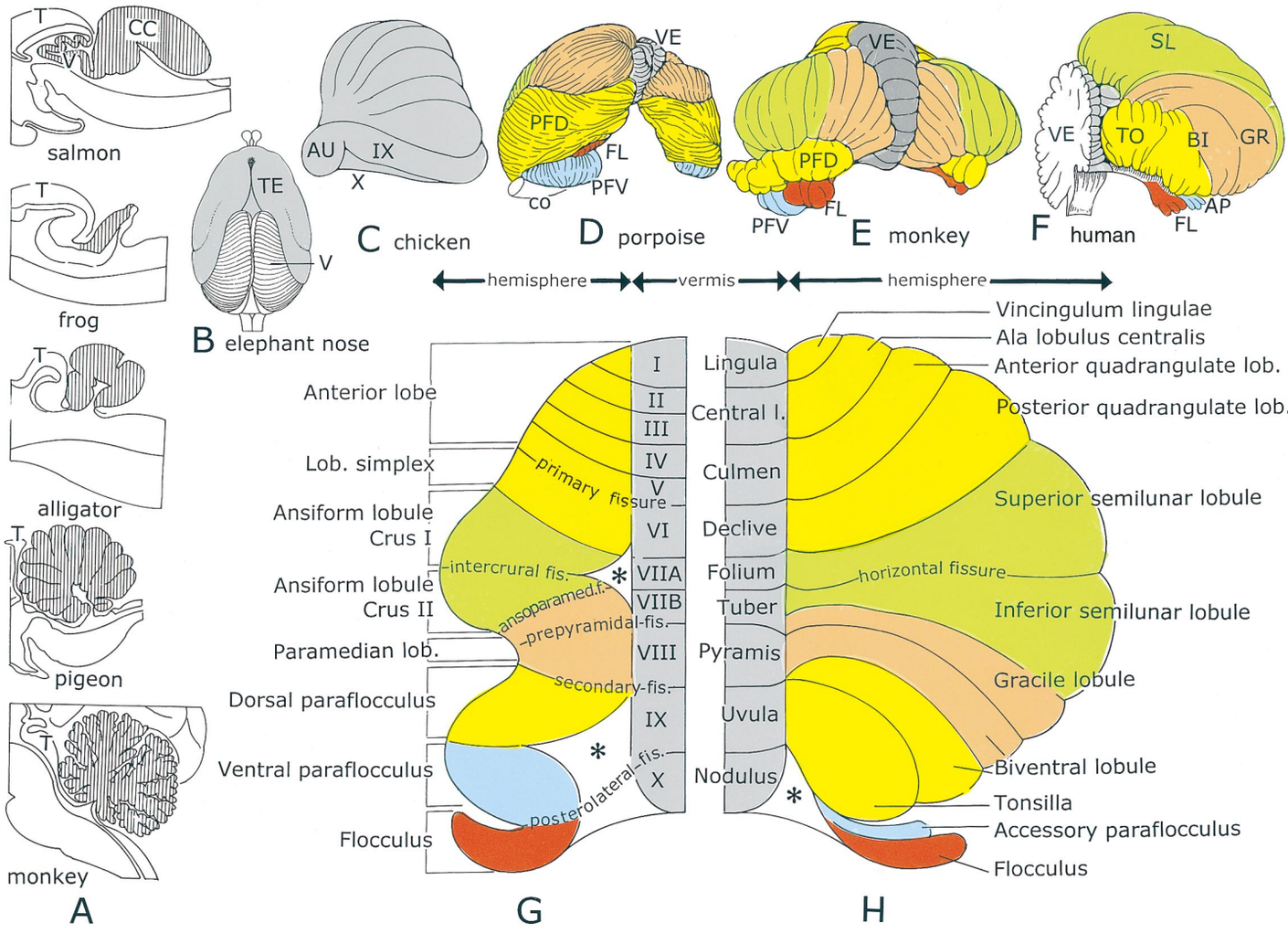

Fig. 2. ***The gross anatomy of the cerebellum.*** *Variations in the external form of the cerebellum are illustrated in* **(A)** *as sagittal sections through the cerebellum of representative species of the different vertebrate classes.* Reproduced from Ref. 4. *The brain of a mormyrid fish – the elephant nose – is shown in a dorsal view in* **(B)**. Reproduced from Ref. 4. *It is covered by the large valvula cerebelli. The cerebellum of the pigeon* **(C)**, *the porpoise* **(D)** *and the monkey* **(E)** *are shown in caudolateral views. A caudomedial view of the right half of a human cerebellum is illustrated in* **(F)**. *The comparative anatomical nomenclature for the mammalian cerebellum*[11,12] *is shown in* **(G)**, *the nomenclature for the human cerebellum in* **(H)**. *Homologous lobules are indicated with the same colours. Note the large paraflocculus in Cetacea* (D), *the wide ansoparamedian lobule in the monkey* (E) *and the width of the entire hemisphere in humans* (F). *Abbreviations: AP, accessory paraflocculus; AU, auricle; BI, biventral lobule; CC, corpus cerebelli; co, cochlear nerve; FL, flocculus; GR, gracile lobule; I–X, lobules I–X of Larsell; PFD, dorsal paraflocculus; PFV, ventral paraflocculus; SL, superior semilunar lobule; T, tectum; TE, telencephalon; TO, tonsilla; V, valvula cerebelli; VE, vermis.*

The modular organization of the output of the cerebellar cortex

In mammals and birds the output of the cerebellar cortex is organized in a pattern of parallel longitudinal zones (Fig. 3A). Purkinje cells of a zone, or a pair of non-contiguous zones, project to a particular cerebellar or vestibular target nucleus. Zones can extend across one or more lobules, some span the entire rostro–caudal length of the cerebellum. Within vermis and hemispheres the zones remain oriented parallel to the long axis of the folial chains[21,22].

The olivocerebellar projection is arranged according to the same principle: subnuclei of the inferior olive project to a single Purkinje-cell zone or to a pair of zones which share the same target nucleus[17] (Fig. 3A). Collaterals of these olivocerebellar fibres innervate the corresponding target nucleus[23]. Climbing fibres in zones that receive an input from the periphery through the inferior olive terminate in a regular somatotopical pattern of 'microzones'[24,25].

The zonal pattern in the corticonuclear and olivocerebellar projections is very similar in all mammals[15]. Consequently, the subdivision of the cerebellar nuclei which emerges from these studies, is similar in all species (Fig. 3A). Relay cells of the cerebellar nuclei project to thalamic and brainstem nuclei, involved in the control of movement. In addition to these excitatory connections there is a precise, reciprocal projection of the target nuclei to the corresponding subnuclei of the inferior olive, provided by a subset of small, GABAergic neurones[26,27] (Fig. 1D,E). The output of the cerebellar cortex, therefore, is organized as a series of discrete modules, each provided with its private connections with the inferior olive.

A modular organization is also present in the flocculus and nodulus, with Purkinje-cell zones projecting to discrete cell groups in the vestibular nuclei[28–30]. The presence of collateral projections of olivocerebellar fibres to these cell groups and the reciprocity of the GABAergic vestibulo–olivary projections is still disputed[31,32].

The width of the zones varies greatly among mammals. In Cetacea the huge size of the paraflocculus (Fig. 2D) is caused by an extremely wide C_2 zone[33]. In primates, wide D zones, projecting to a large dentate nucleus, are responsible for the width of the ansoparamedian lobules in non-human primates (Fig. 2E) and

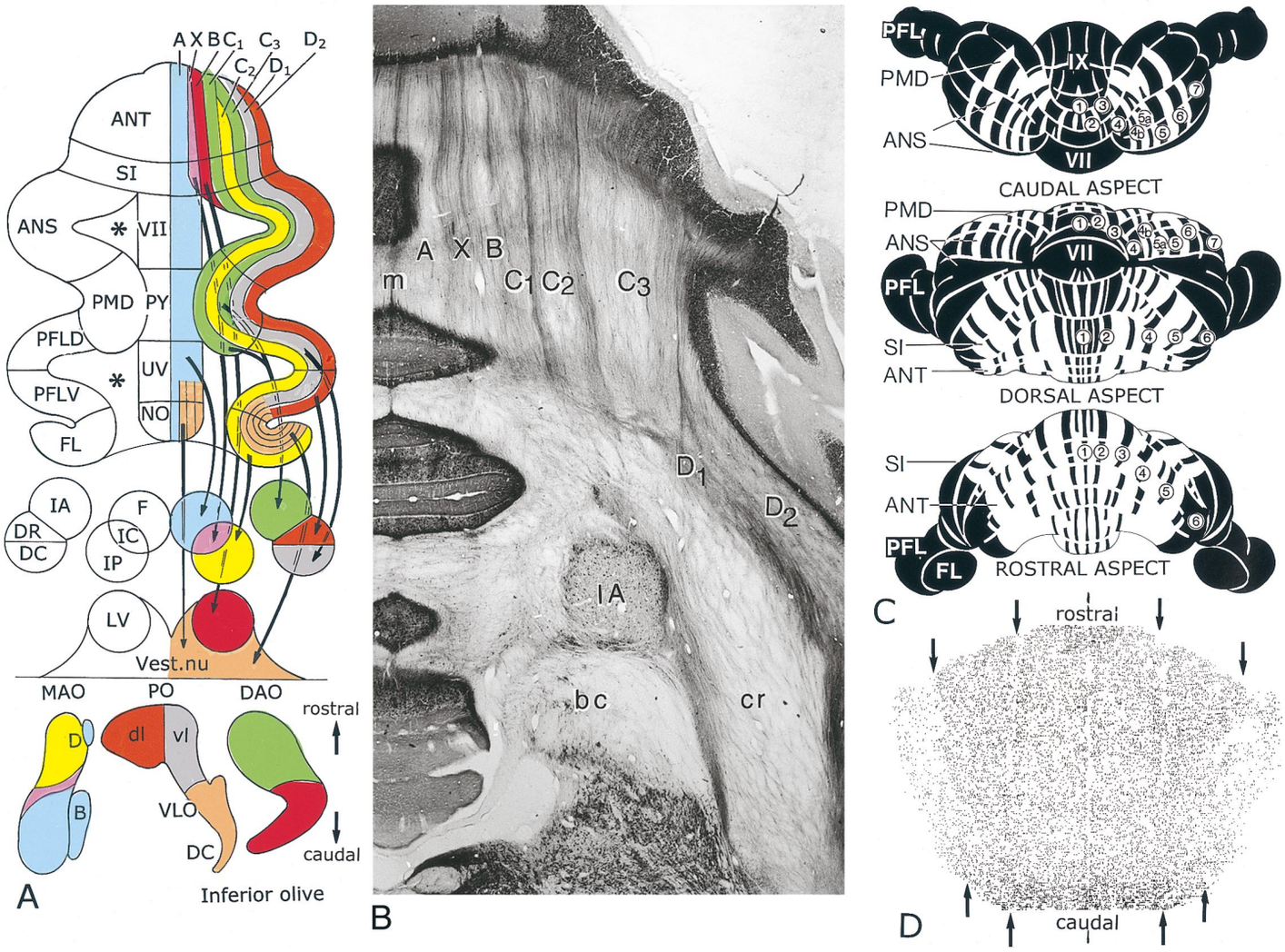

Fig. 3. ***Longitudinal zones.*** *The zonal arrangement in the corticonuclear and the olivocerebellar projections is illustrated in a diagram of the flattened cerebellar cortex of the cat* **(A)**. Modified from Ref. 17. *Three groups of cerebellar nuclei with their corticonuclear projection zones can be distinguished: (1) The fastigial nucleus (F; the target nucleus of the vermal A zone), which is continuous through the intermediate cell group (IC: X zone) with the globose or posterior interposed nucleus (IP: C_2 zone); (2) The emboliform or anterior interposed nucleus (IA: C_1 and C_3 zones) and the dentate nucleus, which can be subdivided into ventrocaudal (DC) and dorsomedial (DR) parts (target nuclei of the D_1 and D_2 zones, respectively); (3) The lateral vestibular nucleus of Deiters (LV, target nucleus of the vermal B zone). Zones in the flocculus and the nodulus project to the vestibular nuclei*[29,30]*. The inferior olive is shown in the lower half of the figure, in a horizontal projection, introduced by Brodal*[18]*. The zonal projections of the individual subnuclei are indicated with the same colours. The modular architecture of the cerebellum can be recognized in the transverse section through the anterior lobe of the monkey* **(B)**, *where the borders of the white matter compartments are stained for acetylcholinesterase. The longitudinal zonal distribution of zebrin-positive and 'negative' Purkinje cells is shown in different views of reconstructions of the cerebellum of the rat* **(C)**; *numbering of the zebrin-positive zones according to Hawkes and Leclerc*[19]*. When all Purkinje cells are mapped in the dome-like cerebellum of the turtle, they are distributed in three, bilaterally symmetrical zones, shown by arrows* **(D)** Reproduced from Ref. 20. *Abbreviations: A, A zone; ANS, ansiform lobule; ANT, anterior lobe; B, B zone; b, cell group beta; bc, brachium conjunctivum; C_{1-3}, zones C_{1-3}; cr, restiform body; D, dorsomedial cell column; $D_{1,2}$, zones $D_{1,2}$; DC, dorsal cap; dl, dorsal leaf; DR, rostromedial dentate nucleus; FL, flocculus; IA, anterior interposed nucleus; IC, interstitial cell group; IP, posterior interposed nucleus; LV, lateral vestibular nucleus; MAO, medial accessory olive; PFL(D/V), (dorsal/ventral) paraflocculus; PMD, paramedian lobule; PO, principal olive; SI, lobulus simplex; VII–X, lobules VII–X of Larsell; vl, ventral leaf; VLO, ventrolateral outgrowth; X, X zone.*

of the entire hemisphere in humans[34] (Fig. 2F). The rostro–caudal extent of the zones also varies. Floccular zones usually extend into the adjacent folia of the paraflocculus, but in non-human primates they occupy the entire ventral paraflocculus[35]. Additional zones are present in certain species, such as the rat[36].

The structure of the adult cerebellar cortex appears to be uniform and does not betray the presence of the longitudinal zones. However, a system of compartments in the white matter, which contain the axons of Purkinje cells and the climbing-fibre afferents of the zones and their target nuclei can be visualized with appropriate staining methods[37,38] (Fig. 3B). A strong heterogeneity has been found in the expression of certain proteins by sub-populations of Purkinje cells, distributed in alternating longitudinal zones (Fig. 3C). This pattern, which was first described by Hawkes and Leclerc[19] for the 'zebrin' epitope in the rat, is shared by the expression of several other proteins in Purkinje cells or in the Bergmann glia, or in both[7,39]. There is a certain correspondence between the chemoarchitecture of zebrin and the modular organization of the efferent connections of the Purkinje cells, but the relation between both patterns is not a strict one[40].

Both chemoarchitectonic and morphological studies suggest that the zonal patterns in the distribution of the Purkinje cells date from early stages in cerebellar development[41,42]. Great similarities are present in the modular organization of the cerebella of birds and mammals[43]. In so-called lower vertebrates Purkinje-cell

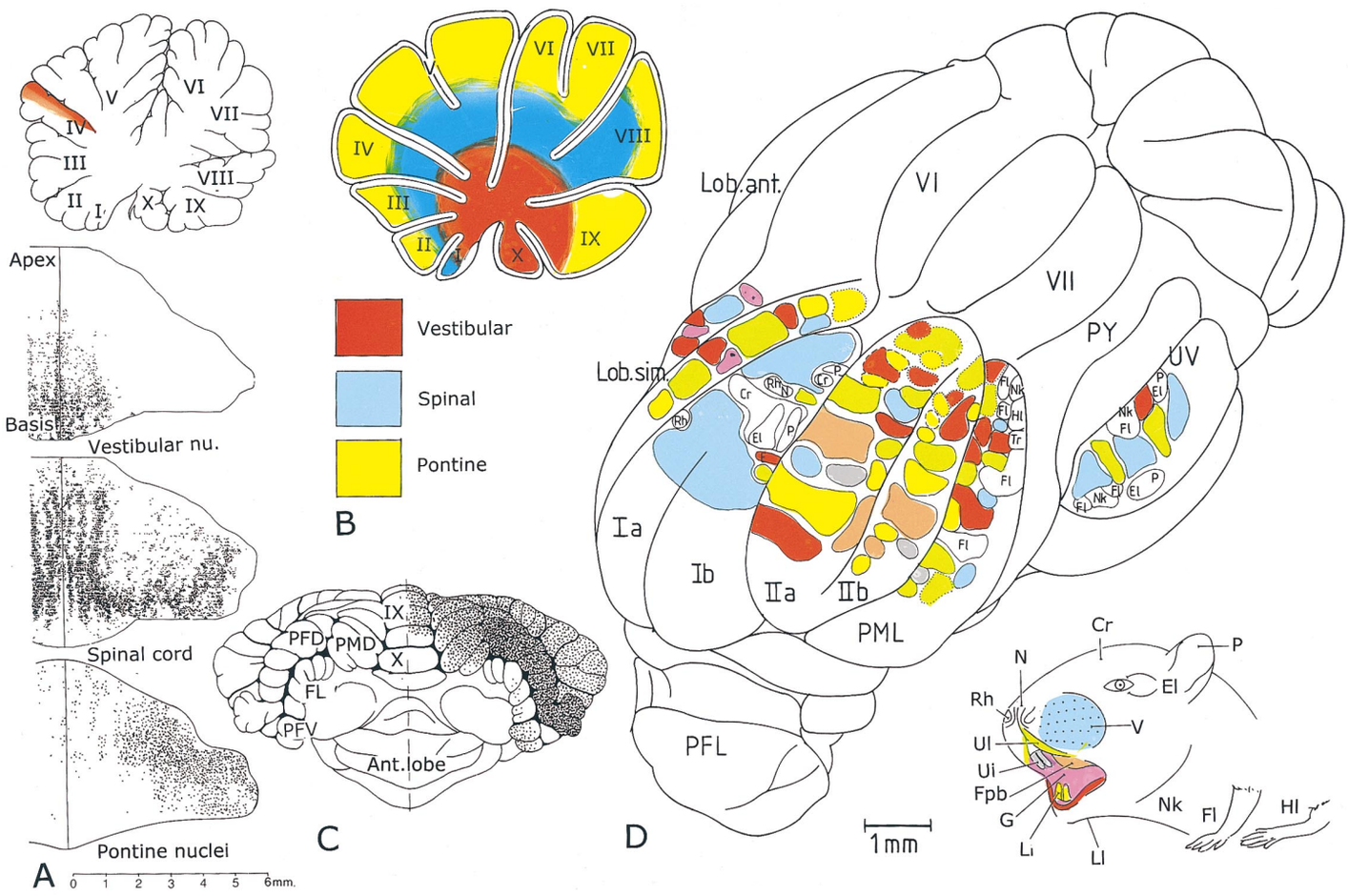

Fig. 4. ***Mossy fibres.*** *The lobule-specific, patchy and zonal distributions of different mossy-fibre systems are exemplified in chartings of their distribution on the dorsal surface of lobule IV in the cat* **(A)**, modified from Refs 44,45 and N.M. Gerrits, Ph.D. Thesis, University of Leiden, 1985. *The distribution of vestibulocerebellar, spinocerebellar and pontocerebellar mossy fibres in medial cerebellum can best be described as a concentric one, illustrated in a sagittal section in* **(B)**. *Pontocerebellar fibres terminate heavily in the hemisphere, but spare the flocculus and the ventral paraflocculus* **(C)**, reproduced from Ref. 53. *Mossy fibres in the posterior lobe of the rat terminate in a fractured somatotopical pattern of multiple patches* **(D)**, modified from Refs 47,48. *Abbreviations: Cr, crown; El, eyelid; FL, flocculus; Fl, forelimb; Fpb, furry buccal pad; G, gingiva; Hl, hindlimb; I–X, lobules I–X of Larsell; Li, lower incisor; Ll, lower lip; Lob. ant., anterior lobe; Lob. sim., lobulus simplex; Nk, neck; P, pinna; PFD/V, dorsal/ventral paraflocculus; PFL, paraflocculus; PML, paramedian lobule; PY, pyramis; Rh, rhinarium; Ui, upper incisor; Ul, upper lip; UV, uvula; V, vibrissae.*

maps reveal longitudinally distributed differences in density which corresponded to differences in projection to the cerebellar and certain brainstem nuclei[20] (Fig. 3D). Cerebellar nuclei have been identified in species of all vertebrate classes[4] (Fig. 1G,H).

Mossy fibres identify the lobules of the cerebellum

Mossy fibres arise from many different sources in the brainstem and the spinal cord. They enter the cerebellum rostrally; many of them cross the midline in the cerebellar commissure and distribute bilaterally. Mossy fibres terminate in lobule-specific patterns of ill-defined patches or zones, but these zones usually are discontinuous at the apex or the base of a lobule[44,45,49] (Fig. 4A). Some reticular and spinal mossy fibre systems emit collaterals to the cerebellar nuclei[46,50–52]. In the central region of the cerebellum the distribution of the main mossy-fibre systems is concentric, with vestibular fibres terminating ventrally and centrally in the base of the fissures[28], pontocerebellar fibres in the apex of the lobules (see Ref. 7) and spinocerebellar fibres occupying an intermediate position (Fig. 4B). The lateral parts of the cerebellum, with the exception of the flocculus, which receives secondary vestibular and reticular projections, receive an overwhelming input from the pons[53] (Fig. 4C).

A rough somatotopical pattern, with the hindlimb represented ventrally and the forelimb and the face more dorsally, is present both in the anterior and the posterior lobes[54]. The fine grain in the somatotopical localization of the face was studied by Welker[47] with electrophysiological mapping of mossy-fibre responses in the posterior lobe of the rat and other species (Fig. 4D). They found a mosaic-like pattern with multiple representations of the same receptive fields. In this type of 'fractured somatotopy', the precise topographical relations between adjacent receptive fields, do not appear to be preserved. The relation of these mossy-fibre patches to the microzonal organization in the somatosensory innervated climbing fibre zones is not known. The representation of receptive fields in climbing fibre zones is also multiple, that is, repeated in each zone, but within these zones the topographical order of the receptive fields is maintained[24].

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The cells and molecules that make a cerebellum

Dan Goldowitz and Kristin Hamre

The molecular underpinnings of cerebellar development are being established through the identification of naturally occurring mutated genes and the knockout of other genes. Sets of genes expressed in the regions of the mes- and metencephalon have been shown to play a crucial role in specifying the cerebellar anlage. Other genes have been shown to be crucial to early granule-cell development, migration of Purkinje and granule cells, and neuron–glia interactions. However, the process of development will ultimately be understood in terms of cellular interactions and the roles that each cell type plays in the assembly of cerebellar structure. One of the most important interactions is between granule and Purkinje cells. This relationship has been shown to be crucial for the control of cell number, migration of neuroblasts and cell differentiation.

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IT IS A DRAMATIC SHIFT in our view of cerebellar function to have an issue of *TINS* sister journal, *Trends in Cognitive Sciences*, devoted to the cerebellum. Equally dramatic insights have been gained in our understanding of the development of this region, stemming largely from the identification of genes crucial for cerebellar development through the study of natural or induced mutations. Thus it seems appropriate at this juncture to try to wed the well-documented cellular story with the emerging molecular picture of cerebellar development. First, a general overview of cerebellar development will be given to provide a framework for further discussions. This overview is largely derived from the seminal work of Miale and Sidman[1] and Altman and Bayer[2].

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