

The anatomy of the cerebellum

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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 neurons of the cerebellar cortex and in the prominence of their afferent, intrinsic and efferent connections.

The cerebellar cortex is built from four main types of neurones: granule cells, Purkinje cells and two types of inhibitory interneurons, the Golgi cells and the stellate/basket cells¹⁻⁵ (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 interneurons (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 fibre⁶ (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 cells⁷ (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 cortex⁸ 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 interneurons of the molecular layer into stellate and basket cells in birds and mammals⁴.

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 cartilaginous fish² (Fig. 1G). The granular eminences and their caudal interconnection are closely related to the nuclei of the vestibulo-lateral line system. Rostrally, the cerebellum of bony fish protrudes as the valvula cerebelli under the mid-brain tectum (Fig. 2A). In Mormyridae, electroreceptive teleosts, the valvula is huge and has 'pushed' the tectum aside to cover the entire surface of the brain¹³ (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 system¹⁴.

The folial pattern of mammals is more complicated¹⁵ (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

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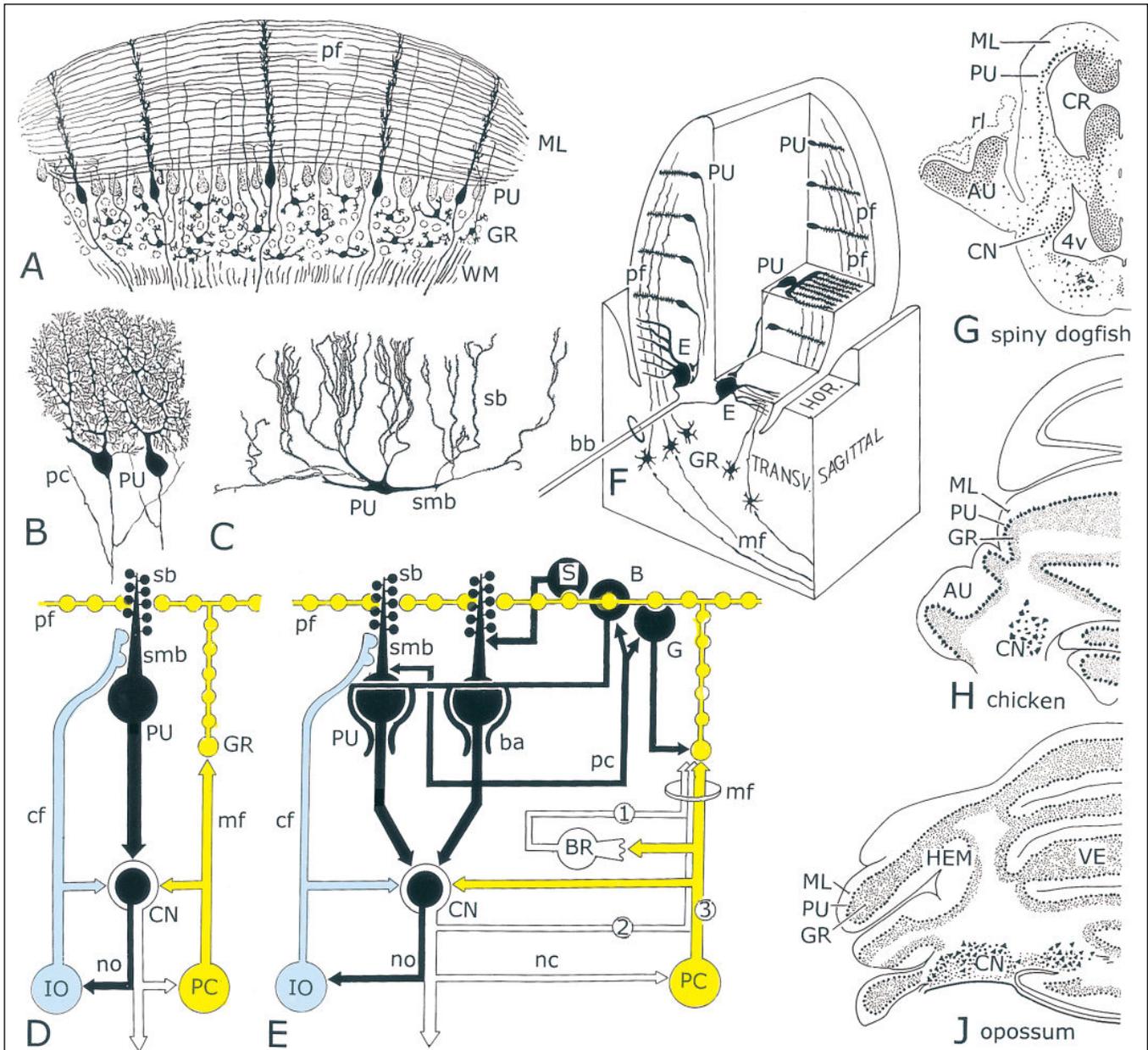
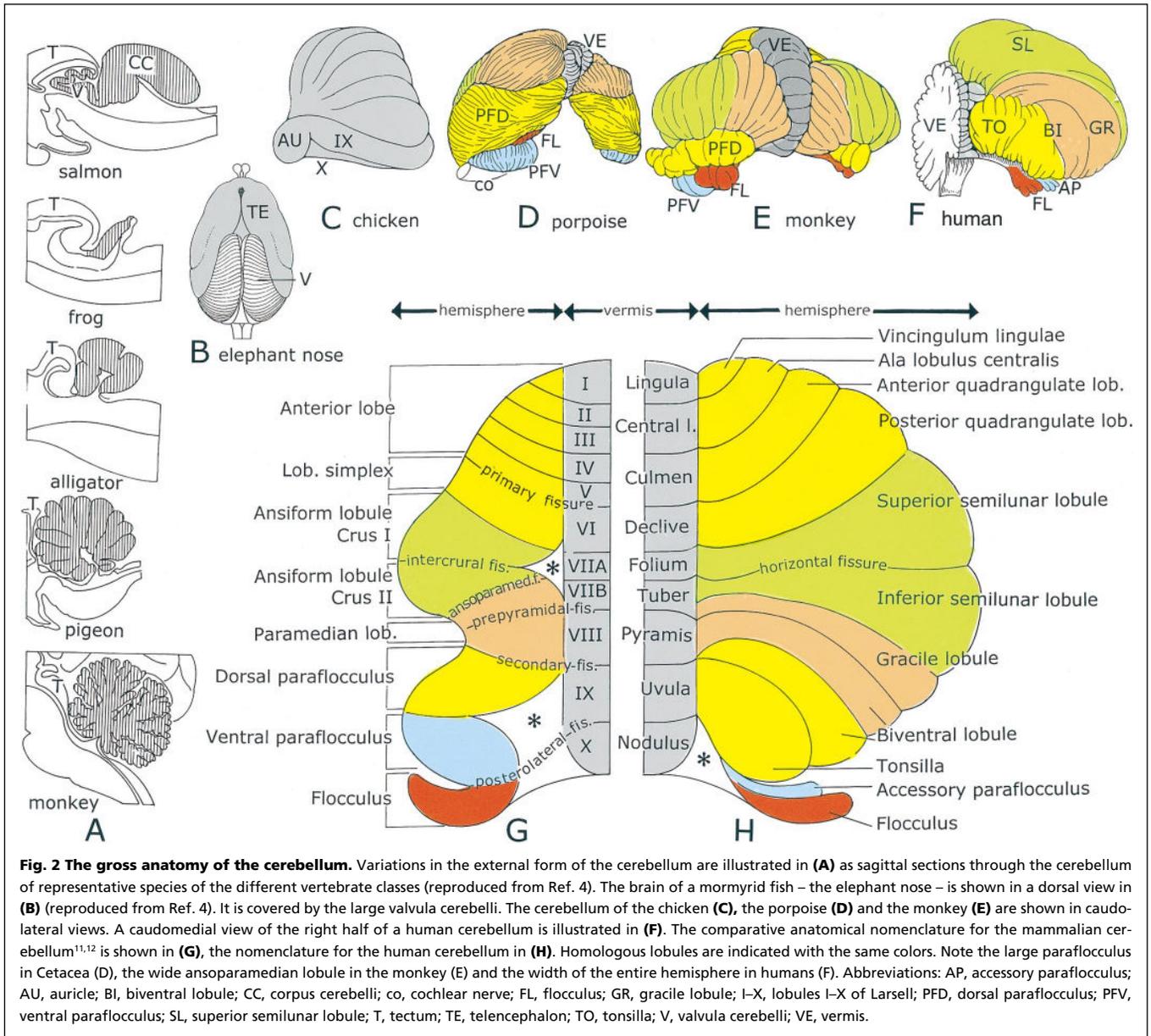


Fig. 1 The cerebellar cortex. (A) Classical drawing by Ramón y Cajal of a transverse, Golgi-stained section through the cerebellar cortex shows the molecular (ML), Purkinje-cell (PU) and granule-cell (GR) layers on top of the white matter (WM). Note the medio-lateral constriction of the Purkinje-cell 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 interneurons 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 nuclei³ (2) and axons of brush cells³ (BR) located in the granular layer of certain lobules (1). In the 3-D 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; AU, auricle; B, basket cell; ba, basket terminal; bb, efferent basal bundle; BR, brush cell; G, Golgi cell; GR, granule cell (layer); HEM, hemisphere; IO, inferior olive; mf, mossy fibre; ML, molecular layer; nc, collateral of nuclear relay cell; no, nucleo-olivary pathway; pc, Purkinje-cell axon collateral; pf, parallel fibre; PU, Purkinje cell (layer); rl, lateral recess; S, stellate cell; sb, spiny branchlets of the Purkinje-cell dendritic tree; smb, smooth branches Purkinje cell dendritic tree; VE, vermis.

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 asterisk). Within the folial chains the cortical lattice always maintains its orientation with respect to the long axis of the chain.



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}. Larsell¹², 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 caudalmost 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.

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 nucleus¹⁷ (Fig. 3A). Collaterals of these olivocerebellar fibres innervate the corresponding target nucleus²³. 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 mammals¹⁵.

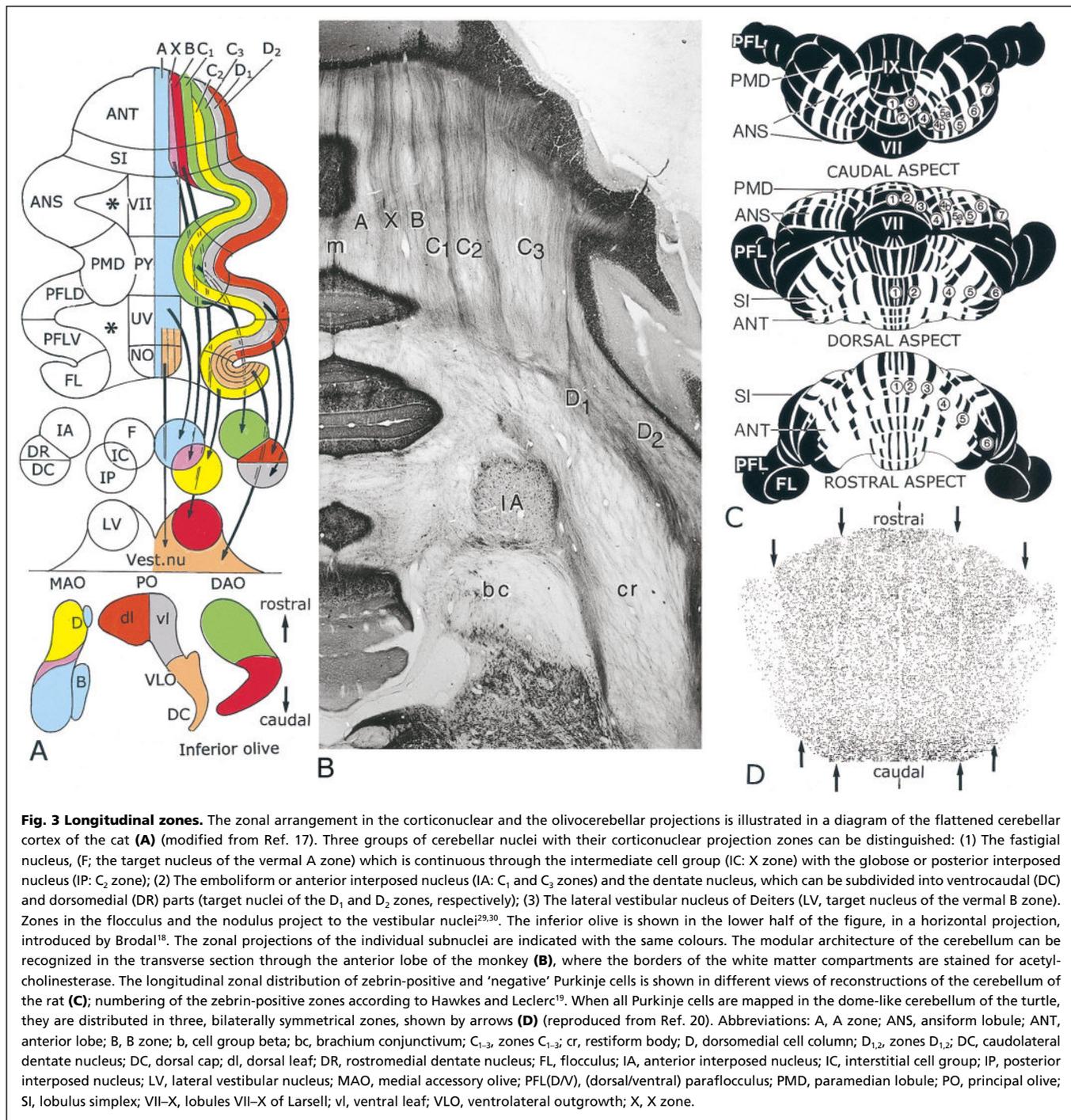


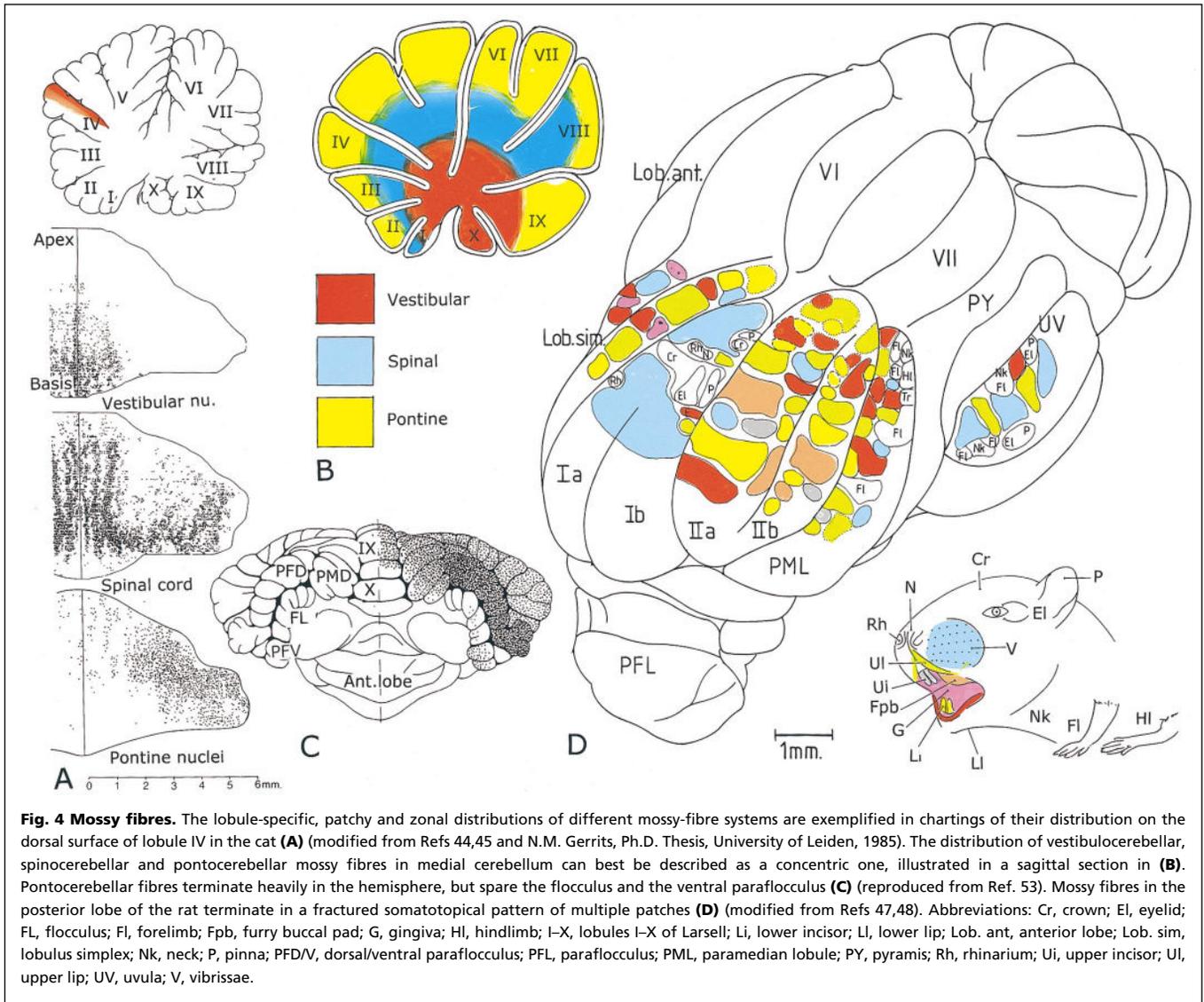
Fig. 3 Longitudinal zones. The zonal arrangement in the corticonuclear and the olivocerebellar projections is illustrated in a diagram of the flattened cerebellar cortex of the cat (A) (modified from Ref. 17). Three groups of cerebellar nuclei with their corticonuclear projection zones can be distinguished: (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: C₂ zone); (2) The emboliform or anterior interposed nucleus (IA: C₁ and C₃ zones) and the dentate nucleus, which can be subdivided into ventrocaudal (DC) and dorsomedial (DR) parts (target nuclei of the D₁ and D₂ 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 Brodal¹⁸. 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 zebren-positive and 'negative' Purkinje cells is shown in different views of reconstructions of the cerebellum of the rat (C); numbering of the zebren-positive zones according to Hawkes and Leclerc¹⁹. 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; C₁₋₃, zones C₁₋₃; cr, restiform body; D, dorsomedial cell column; D_{1,2}, zones D_{1,2}; DC, caudolateral dentate nucleus; DR, 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.

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 nuclei²⁸⁻³⁰. 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 C₂ zone³³. 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 of the entire hemisphere in humans³⁴ (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 paraflocculus³⁵. Additional zones are present in certain species, such as the rat³⁶.



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 Leclerc¹⁹ 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 one⁴⁰.

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 mammals⁴³. In so-called lower vertebrates Purkinje-cell maps reveal longitudinally distrib-

uted differences in density which corresponded to differences in projection to the cerebellar and certain brainstem nuclei²⁰ (Fig. 3D). Cerebellar nuclei have been identified in species of all vertebrate classes⁴ (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 fissures²⁸, 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 pons⁵³ (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 lobes⁵⁴. The fine grain in the somatotopical localization of the face was studied by Welker⁴⁷ 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 maintained²⁴.

Acknowledgements

We thank Edith Klink for her secretarial assistance and Eddy Dalm for the photography.

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Cerebellar learning in the vestibulo-ocular reflex

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The vestibulo-ocular reflex, because of its close relationship with the cerebellum and its marked adaptiveness, has become a model system for studying the functions of the cerebellum. It has been hypothesized that an evolutionarily old part of the cerebellum, the flocculus, forms a modifiable accessory pathway for the vestibulo-ocular reflex arc for adaptive control, and that the modification is due to the synaptic plasticity induced by retinal errors conveyed by a unique structure of the cerebellum, the climbing fibers. The flocculus hypothesis has been supported by several lines of evidence, including lesioning or functionally impairing the flocculus and recording the activity of flocculus Purkinje cells, and, more recently, from pharmacologically or genetically inhibited synaptic plasticity, which produces long-term depression. There has also been debate on a possible site for memory retention in vestibulo-ocular-reflex adaptation, and about the signal content in flocculus Purkinje cells. This article reviews recent studies on the learning mechanisms of the cerebellum that underlie the adaptation of the vestibulo-ocular reflex.

The vestibulo-ocular reflex, commonly termed the VOR, evokes eye movements in the direction opposite to head movement, thus serving to stabilize vision automatically relative to space. Around 1930, the VOR attracted the attention of anatomists and physiologists (including Magnus¹, Lorente de No² and Szentágothai³) as a simple neural system mediated by a three-neuron arc and displaying a distinct function. In recent years, the VOR has

been re-examined because of its close relationship with the cerebellum.

The VOR arc is associated with the flocculus, an evolutionarily old part of the cerebellum, and therefore provides a simple model system for studying the functions of the cerebellum. The flocculus has been proposed to be a center of learning in VOR gain⁴ (Box 1). Another evolutionarily old part of the cerebellum, consisting of the nodulus and

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