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Cerebellum

THE HUMAN CEREBELLUM ("little brain") is a significant part of the central nervous system both in size and in neural structure. It occupies approximately one-tenth of the cranial cavity, sitting astride the brainstem, beneath the occipital cortex, and contains more neurons than the whole of the cerebral cortex. It consists of an extensive cortical sheet, densely folded around three pairs of nuclei. The cortex contains only five main neural cell types and is one of the most regular and uniform structures in the central nervous system (CNS), with an orthogonal "crystalline" organization. Major connections are made to and from the spinal cord, brainstem, and sensorimotor areas of the cerebral cortex.

The most common causes of damage to the cerebellum are stroke, tumors, or multiple sclerosis. These result in prominent movement disorders, the principal symptoms being ataxia, tremor, and hypotonia. Affective, cognitive, and autonomic symptoms are also common. Childhood cancers, developmental disorders, and ion channel disorders also affect the cerebellum.

Despite its remarkable structure and well-understood physiology, the role of the cerebellum is far from clear. This challenge has attracted many scientists and the cerebellum is also remarkable for the number of conflicting theories put forward to account for it.

HISTORY

The early anatomists recognized the distinct nature of the cerebellum. Accurate drawings of its gross structure originate from Vieussens in 1684, the first book devoted solely to the cerebellum was published in 1776 by M. V. G. Malacarne, and the principal cell type was named by Jan Purkyne (Purkinje) in 1837. At approximately the same time, Marie-Jean-Pierre Flourens (1824) described the results of experimental ablation of the cerebellum on the coordination of movements. In 1900, Charles Sherrington stated that the cerebellum is the "head ganglion" of the proprioceptive system, neatly encapsulating the notion that the cerebellum strongly influences spinal sensorimotor functions.

GROSS ANATOMY

Cortex

The cerebellar cortex is an extensive three-layered sheet with a surface approximately 15 cm laterally and 180 cm rostrocaudally but densely folded around three pairs of nuclei. The cortex is divided into three transverse lobes: Anterior and posterior lobes are separated by the primary fissure, and the smaller flocculonodular lobe is separated by the posterolateral fissure (Fig. 1). The anterior and posterior lobes are folded into a number of lobules and further folded into a series of folia. This transverse organization is then divided at right angles into broad longitudinal regions. The central vermis, named for its worm-like appearance, is most obvious in the posterior lobe. On either side is the paravermal or intermediate cortex, which merges into the lateral hemispheres.

Deep Nuclei of the Cerebellum

Each cerebellar cortical region projects in a systematic manner to the underlying deep nuclei, which provide the output fibers from the cerebellum. The lateral hemisphere projects predominantly to the dentate nucleus; the paravermis projects to the interpositus nucleus, which in man is divided into globose and emboliform nuclei; and the vermis projects to the fastigial nucleus. The flocculonodular

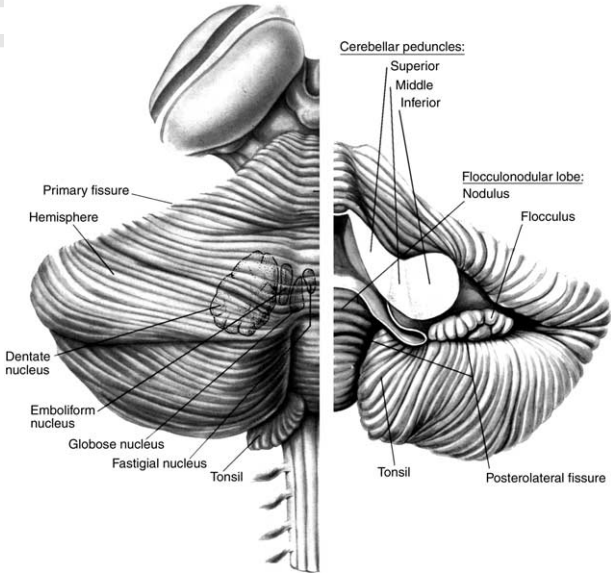

Figure 1
The gross anatomy of the human cerebellum, shown in dorsal view on the left and ventrally on the right (modified with permission from Kandel and Schwartz, *Principles of Neural Science*, Elsevier, New York, 1985).

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cortex projects to the lateral vestibular nucleus (Dieter's nucleus)—functionally a displaced deep cerebellar nucleus. AU:1

Gross organization is mirrored phylogenetically. The oldest part, the archi- or vestibulocerebellum, is retained as the flocculonodulus. It is closely connected with the vestibular system and predominantly involved in balance. The paleo- or spinocerebellum corresponds to the anterior vermis, pyramid, uvula, and paraflocculus and is concerned with balance, posture, and orientation. It receives spinal proprioceptive inputs as well as auditory and visual input, and it projects back to the spinal cord via the red nucleus. The neocerebellum (caudal vermis, paravermis, and lateral hemispheres) has developed in terrestrial animals for independent control of the limbs and in mammals has expanded further in concert with the development of fine control of the distal musculature. The paravermis and lateral hemispheres affect ipsilateral muscles, and their dysfunction results in movement deficits of the limb on the same side as the lesion. The vermis and flocculonodulus influence muscles of the trunk and the eyes, and therefore lesions can have bilateral effects.

The gross anatomy of the cerebellum varies across vertebrate species in line with their sensorimotor specialization. Fish use a sensory "lateral line organ" for detecting vibration in the water, and electroreceptive mormyrid fish have further developed this system to allow sampling of the surrounding environment with electric pulses. The valvula cerebelli (a medial region of the anterior cerebellum) in these species is enormous. Certain bats also have large cerebellar volumes perhaps related to their use of auditory echo location. In cetaceans (whales and dolphins) the dorsal paraflocculus is greatly expanded. In primates, the lateral hemispheres (the ponto- or cerebrocerebellum) have expanded dramatically approximately in proportion to the expanse of the neocortex.

CYTOARCHITECTURE

The perpendicular arrangement of transverse and longitudinal axes is maintained in the cellular organization of the cortex. The most prominent cell type of the cortex is the GABAergic Purkinje cell (P cell; Fig. 2), which has its soma in the middle cortical layer (the Purkinje or ganglionic layer) and a large

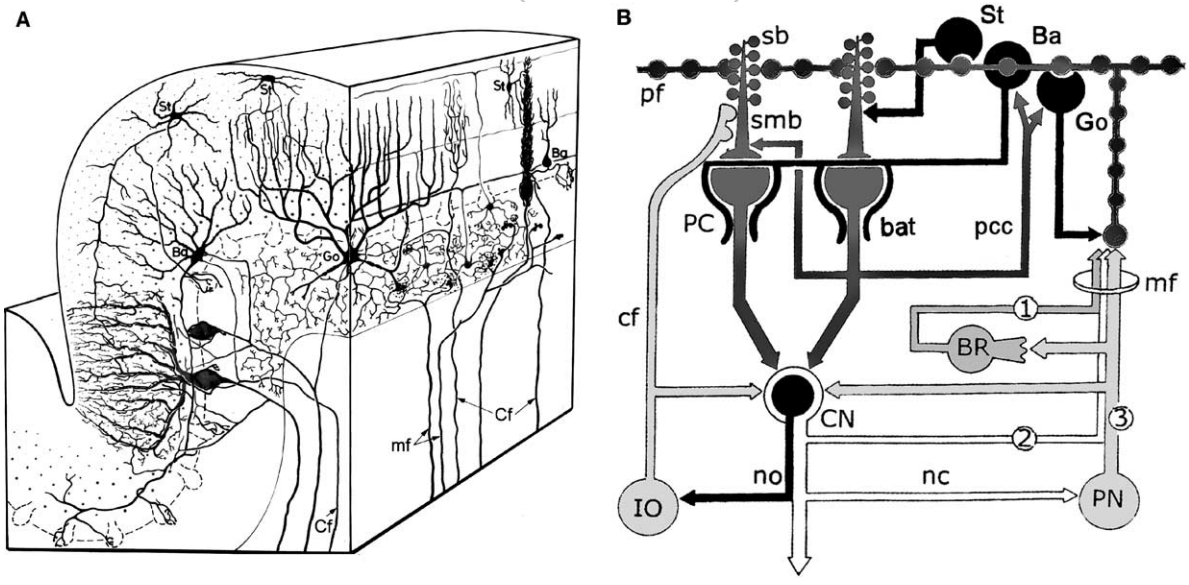

Figure 2
(A) The cerebellar cortex. Inputs are shown in blue, output (Purkinje cells) in red. Inhibitory interneurones are black; granule cells are green (reproduced with permission from Eccles *et al*., *The Cerebellum as a Neuronal Machine*, Springer-Verlag, Berlin, 1967). (B) The cerebellar circuit. Arrows indicate the direction of transmission across each synapse; color coding is as in Fig. 2A (modified with permission from Voogd and Glickstein, *TICS* **2**, 307–313, 1998). 1–3, Sources of mossy fibers; Ba, basket cell; BR, brush cell; cf, climbing fiber; CN, cerebellar nuclei; Go, Golgi cell; IO, inferior olive; mf, mossy fiber; pf, parallel fibers; PN, pontine nuclei; sb and smb, spiny and smooth branches of P cell dendrites, respectively; St, stellate cell; PC, Purkinje cell; bat, basket cell terminal; pcc, P cell collateral; no, nucleo-olivary pathway; nc, collateral of nuclear relay cell.

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flattened dendritic tree lying fan-like in the sagittal plane of the upper layer (the molecular layer). P cells form the only output from the cortex, sending inhibitory axons to the cerebellar nuclei. The glutamatergic granule cells, the most numerous cell type, have their soma and a sparse dendritic arbor within the granular layer and then send single axons to the molecular layer. Here, the axons bifurcate into two unmyelinated parallel fibers running transversely along the folia, passing through the dendritic trees of the P cells. Each parallel fiber extends 2–4 mm across the cortex, with more superficial fibers traveling furthest. P cell dendritic trees lie across a beam of parallel fibers. Each parallel fiber makes excitatory synaptic contact with the dendrites of perhaps 200 Purkinje cells along this beam, whereas each P cell receives 200,000 parallel fiber synapses. Parallel fiber activity can evoke in the P cell a series of "simple spikes" whose frequency reflects the strength of the input. Parallel fibers also make excitatory synaptic contact with the other three GABAergic cell types of the cortex, all with cell bodies within the molecular layer: the Golgi, stellate, and basket cells (Fig. 2). The Golgi cells have an approximately cylindrical dendritic arbor, whereas the stellate and basket cells have a sagittally flattened or elliptic arbor. The Golgi cells inhibit neighboring granule cells and therefore help to limit the activity within the parallel fibers. The basket cells and stellate cells send axons across the folium at right angles to the parallel fibers, inhibiting neighboring Purkinje cells. Together these interneurons sharpen the zone of activation caused by the granule cells so that a beam of active Purkinje cells is created, bordered by inhibited cells. Two less well-documented and less numerous cell types, the unipolar brush cells and Lugano cells, lie below the Purkinje cell layer: The first is an excitatory interneuron feeding onto granule cells and the latter an inhibitory cell feeding back from P cell collaterals onto stellate and basket cells.

INPUTS

Mossy and Climbing Fibers

The two major inputs to the cortex are the mossy fibers and climbing fibers. Mossy fibers originate from many extracerebellar sites and branch repeatedly to reach one or more narrow sagittal strips of cortex, where they make excitatory contact with the dendrites of the granule cells. The complex of mossy fiber terminal and granule cell dendrites is called a synaptic glomerulus. Mossy fibers also send collaterals to the cerebellar nuclei so that inputs reach these nuclei directly via a cortical loop involving granule cells and Purkinje cells (Fig. 2B). Mossy fibers reaching the intermediate cerebellar cortex and the fastigial and interposed nuclei carry visual, somatic, auditory, and vestibular information as well as outputs from the sensory motor cortex. Mossy fibers reaching the lateral cortex and the dentate nucleus carry information from prefrontal, premotor, parietal, and occipital cortex.

Climbing fibers arise solely from the inferior olive. The inferior olive receives inputs from many areas, carrying vestibular, spinal, cranial, and much cortical descending information. Its cells can have quite complex properties, but they have a precise topographical arrangement (Fig. 3). Each climbing fiber projects to one or more contralateral parasagittal strips of cerebellar cortex, branching to reach approximately 10 P cells. They also send collateral connections to the corresponding deep cerebellar nucleus. The terminals of the climbing fiber on the Purkinje cell form an extensive complex of up to 300 synapses around its soma and primary dendrites. Climbing fibers typically fire at low rates of only 1–10 spikes per second and often with low probability to a particular stimulus, but each climbing fiber action potential reliably causes a complex spike in the Purkinje cell. They are particularly responsive to unexpected sensory stimuli, such as gentle touch of the skin for somatosensory cells or motion of the visual image on the retina for visual cells. Many are nociceptive. However, sensitivity is strongly modulated during motor activity so that stimulation during active movement can fail to trigger responses. This very low firing rate signal has proven difficult to decode, and there are many different opinions about what information is carried by the climbing fibers.

The cortex also receives diffuse projections of noradrenergic fibers from locus coeruleus, serotonergic fibers from the Raphe complex, and a small dopaminergic input from the mesencephalic tegmentum. The role of these inputs is not clear.

CONNECTIVITY

The cerebellum connects to the brainstem via three large paired roots—the superior, middle, and inferior peduncles (brachium conjunctivum, brachium pontis, and restiform body, respectively; Fig. 1).

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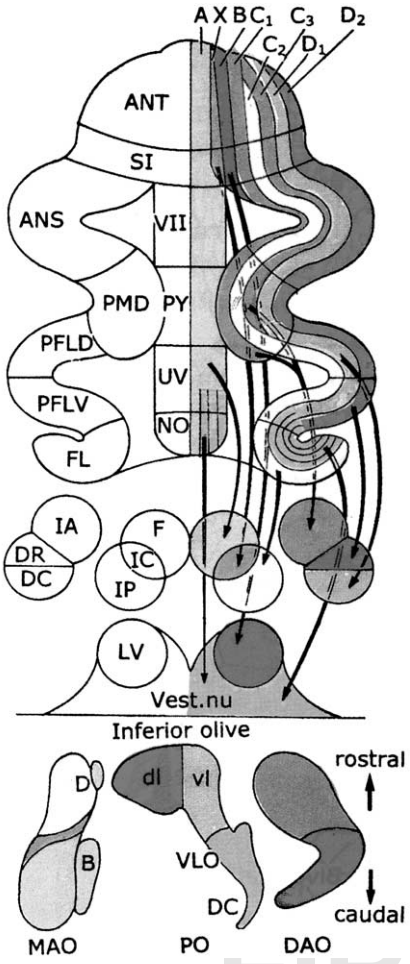

Figure 3
Olivocerebellar and corticonuclear projections. Climbing fiber projection from regions of the contralateral inferior olive (bottom) to the cerebellar cortex (top) are color coded. Sagittal olivocerebellar zones (A, X, B, etc.) are labeled at top right. Cerebellar output nuclei are shown in the middle. DAO and MAO, dorsal and medial accessory olive, respectively; PO, principal olive; IA and IP, anterior and posterior interposed nucleus, respectively; DC and DR, caudal and rostral dentate nuclei, respectively; F, fastigial nucleus (reproduced with permission from Voogd and Glickstein, *TICS* **2**, 307–313, 1998).

Vestibulocerebellum

The vestibulocerebellar cortex receives some mossy fibers that arise directly from the vestibular apparatus and others that are derived from the vestibular nuclei as well as climbing fibers from parts of the inferior olive related to the vestibular nuclei (Fig. 3). It also receives mossy fiber inputs carrying visual information from lateral geniculate nucleus and superior colliculus. The flocculonodular cortex projects back mostly to the lateral vestibular nucleus and hence to the medial descending spinal pathways. The vestibular nuclei also project via the medial longitudinal fasciculus to the ocular motor nuclei III, IV, and VI. Its action is therefore mainly on axial muscles and on eye movement, controlling balance and coordinating head–eye movement.

Spinocerebellum

Most ascending somatosensory and proprioceptive inputs reach the vermis and paravermis to form topographic maps on both the anterior and posterior lobes (Fig. 4A). There are also considerable vestibular, visual, and auditory inputs, the latter two reaching mainly the posterior lobe. The maps drawn on the cerebellar cortex have been gradually refined with improved recording techniques, and it is now known that mossy fiber input actually reaches discrete patches of granule cells forming a mosaic or "fractured somatotopic map" (Fig. 4B). Quite distant body parts can therefore be mapped onto adjacent patches approximately 50–100 μm wide. This map is then blurred by the granule cells projecting their parallel fibers over several millimeters.

Two pairs of spinocerebellar tracts arise directly from the spinal cord: the dorsal and ventral spinocerebellar tracts, which carry information from the hindlimbs and lower trunk, and the cuneo- and rostrospinocerebellar tracts carrying corresponding information from the forelimbs and upper trunk. The dorsal spinocerebellar tract (DSCT) arises from Clarke's nucleus and provides rapidly adapting cutaneous and muscle mechanoreceptor information to the cerebellum via the inferior peduncle. The ventral spinocerebellar tract (VSCT) arises from more lateral ("border") cells of the spinal gray matter and carries muscle spindle, cutaneous, and particularly Golgi tendon organ inputs via the superior cerebellar peduncle, but the cells have extensive connections in the cord. It has been suggested that whereas the DSCT carries precise proprioceptive feedback, the VSCT integrates descending, spinal, and proprioceptive signals to provide feedback of the motor commands reaching the motor neurons. If proprioceptive input is eliminated by cutting the dorsal roots, the cerebellar input from DSCT is interrupted, whereas that from VSCT is maintained.

There is also indirect mossy fiber input from the lateral reticular nucleus (LRN), again via the inferior cerebellar peduncle. Like the inferior olive, the LRN receives input from spinal cord, cranial nuclei, and

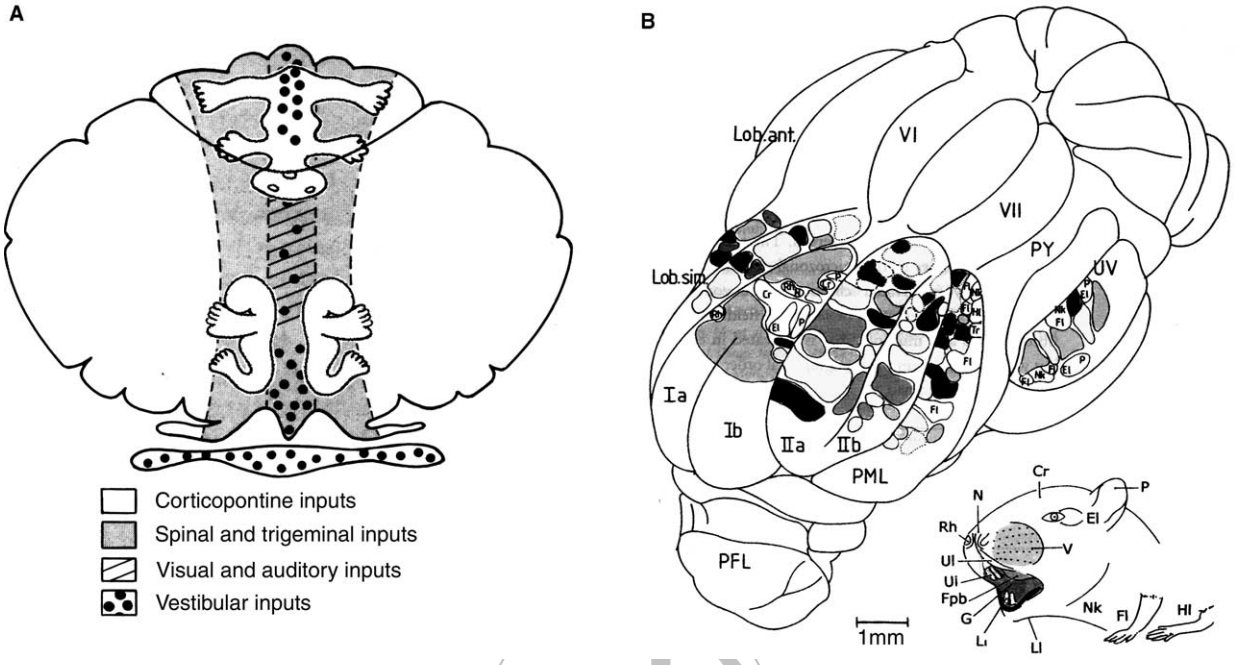

Figure 4
Representation of sensory information in the cerebellar cortex. (A) Two somatotopic maps are found in the anterior and posterior lobes, with exteroceptive and vestibular information distributed in between (modified with permission from Kandel and Schwartz, *Principles of Neural Science*, Elsevier, New York, 1985). (B) These maps are fractured in detail, forming a mosaic over the cortex (reproduced with permission from Voogd and Glickstein, *TICS* **2**, 307–313, 1998). Tactile inputs to the rat cerebellum were mapped by W. Welker onto the cerebellar cortex by recordings from individual granule cells. The rat cerebellum has massive facial inputs and very small limb and trunk input.

cerebral cortex, but unlike the inferior olive, its cells have large multimodal receptive fields.

The anterior and posterior vermis project to the fastigial nucleus, the lateral vestibular nuclei, and the brainstem reticular formation. Some outputs also relay via the thalamus to the motor cortex. The outflow therefore affects the medial descending systems of the brainstem and cortex, modulating the descending signals to axial muscles that mediate postural control.

The paravermal cortex projects to the interpositus nucleus and then on to the magnocellular red nucleus with additional outputs to LRN and to the motor cortex via the ventrolateral thalamus. The paravermal outflow therefore indirectly modulates rubrospinal and lateral corticospinal descending systems. Its major influence is on ipsilateral distal limb musculature.

Cerebellar connections form a number of closed loops. One is from the interpositus nucleus to LRN (either directly or via the red nucleus) and back to the intermediate cortex as mossy fibers. Another loop is formed by mossy fibers that project directly from the deep cerebellar nuclei back to the cortex. Although the function of these loops is not clear, one suggestion is that they provide reverberating circuits to generate prolonged motor control signals. A second class of closed loops is formed by indirect projections from the cerebellar cortex to the inferior olive, projecting back as climbing fibers.

Cerebrocerebellar Connections

Wide areas of the cerebral cortex project to the cerebellar hemispheres via the contralateral pontine nuclei, and these provide quantitatively the largest input to the human cerebellum. These include secondary sensory cortices, especially visual but also premotor and motor cortical areas, and a large projection from the posterior parietal cortex. The cerebrocerebellum receives little somatosensory input from the spinal cord. The pontine inputs reach the contralateral cerebellar cortex via the middle cerebellar peduncle. The output from the hemispheres projects to the dentate nucleus and from there to the ventrolateral thalamus and hence back to the premotor and motor cortices. Some output also projects to the parvocellular red nucleus and hence to

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the inferior olive. Recent evidence of projection to cortical regions other than senorimotor has emerged, and it seems likely that the closed loops between sensorimotor cerebral areas and the cerebellum are matched by closed loops with frontal, cingulate, parahippocampal, and occipitotemporal prestriate areas. Certain cerebral areas do not project to cerebellum, including primary sensory cortices and orbitofrontal and inferior temporal areas; these also appear not to receive cerebellar outputs.

The cerebrocerebellar function is thought to relate more to the preplanning and refinement of motor programs being developed by the cerebral cortex than with the control of ongoing movements. Inputs to the hemispheres are particularly important in visually guided movements and precede any motor activity.

DEVELOPMENT

Studies of the development of the cerebellum have rapidly advanced with the identification of genes important for its growth and cellular organization. Proteins expressed in the embryonic mes- and metencephalon are crucial for its gross structure. Other genes are crucial for Purkinje cell development and migration, granule cell development, and neuron–glial interactions.

The cerebellum arises from the dorsal alar plate of the neural tube, with neural cells derived from at least two germinal zones. The neuroepithelial ventricular zone gives rise to cells that form the cerebellar nuclei. Soon after, the Purkinje cells emerge, forming a sheet-like layer. Later, Golgi cells also form from the same germinal zone. A secondary germinal matrix, the external granular layer (EGL), comes from the rhombic lip and the EGL cells migrate over the cerebellar surface to provide the abundant granule cells as well as stellate and basket cells. Granule cell neuroblasts migrate inwards past the Purkinje cells, and this is a crucial process for the final organization of the Purkinje cell layer and their dendritic arbors.

A number of knockout mutations have been found in the mouse that illuminate some of these stages. Knockout of *En-1* or *Wnt-1*, expressed at the junction of the mesencephalon and metencephalon, leads to near total agenesis of the cerebellum. Development and regulation of the different cerebellar neural populations is still unclear but seems closely bound to the fate of Purkinje cells. In mutant mice such as meander tail or weaver, P cell development and migration are impaired, which leads to either reduced production of granule cells or their subsequent death. Weaver, staggerer, and several other mutations affect P cell survival through ion channel function.

The compartmental organization of the cerebellar cortex is complex. Several proteins (e.g., zebrin) are expressed in narrow sagittal stripes, closely related to but probably independent of the olivocerebellar zones (Fig. 3). The developmental rules for the organization of the climbing fiber input from the olive are unclear.

CLINICAL

Motor

The cerebellum can be affected by neoplasms or paraneoplastic disorders, vascular damage (stroke), inflammatory diseases such as multiple sclerosis, and long-term alcohol abuse or other toxic substances. The exposed cerebellar tonsils can be damaged mechanically by violent acceleration and also by tumors or fluid buildup that force the brainstem backwards. This is most dangerous if pressure in the spinal fluid is suddenly reduced by a lumbar puncture, and it can result in the brainstem and cerebellar tonsils herniating through the foramen magnum. Because different parts of the cerebellum are involved in the control of vestibular, postural, and distal muscles, lesions of the cerebellum will variously affect primarily balance, posture, or the skilled control of the limbs. Congenital deformation (or even absence) of the cerebellum has much less effect than acute damage, but even in adulthood the effects of lesions are reduced greatly over time.

Purkinje cells and granule cells are both sensitive to toxic substances. P cells are very sensitive to ischemia, bilirubin, ethanol, and diphenylhydantoin. Granule cells appear sensitive to methyl halides, thiophene, methyl mercury, 2-chloropropionic acid, and trichlorfon. Both are sensitive to excitotoxic chemicals. Acute effects of cannabinoids are dependent on the G protein-coupled cannabinoid receptor CB1, which is found at high densities in the cerebellum.

An important clinical analysis of the cerebellum was performed in the years following World War I by Gordon Holmes, who studied gunshot-wounded soldiers. He described three classic symptoms: ataxia, intention tremor, and hypotonia. AU:2

Ataxia refers to the imperfect coordination of movements, with poor timing, clumsiness, and unsteadiness. Cerebellar patients tend to overshoot when pointing at targets (hypermetric movements). They also have increased reaction times, disturbed temporal patterns of EMG activity and hence abnormal patterns of joint accelerations, and difficulties in performing rapid alternating movements (dysdiadochokinesia).

Intention tremor probably results from continual hypermetric corrections of position. Unlike tremor associated with Parkinson's disease, intention tremor is not seen when the limb is at rest.

Hypotonia is a loss of muscle tone and it is associated with rapid fatigue of the muscles. It results from the loss of facilitating drive from the cerebellar nuclei to gamma motor neurons. If the hemispheres are affected, the ipsilateral limbs are affected, whereas postural deficit follows damage to the vermis. Hypotonia is found particularly with lesions of the posterior lobe. It is evident as a "pendular" knee-jerk in which the leg continues to swing because of the reduced braking action of the muscles. In alcoholic cerebellar damage, and in patients with lesions of the anterior lobe, hypertonia may result through disinhibition of Deiter's nucleus and hence excitation of alpha motor neurons. Other cerebellar symptoms are nystagmus and dysarthria.

Hereditary Ataxias

A mixed group of inherited disorders related to degeneration of the cerebellum and its afferent or efferent connections and characterized by progressive ataxia have been identified and linked to approximately 10 different genes. They can be categorized as autosomal recessive or dominant ataxias.

Friedreich's ataxia is the most common of the recessive ataxias and is caused by mutation causing GAA trinucleotide repeats in a gene on chromosome 9. Onset is in childhood or early adulthood, marked by degeneration of large fibers in the spinocerebellar, posterior columns, and pyramidal tracts with later mild cerebellar degeneration.

The autosomal dominant cerebellar ataxias [ADCAs or spinocerebellar ataxias (SCA)] are designated by different clinical signs (SCA-1, -2, -3, -6, and -7) but all appear to be caused by inheritance of unstable CAG trinucleotide repeat sequences, albeit in different chromosomes, leading to dysfunction within the Purkinje cell nuclei. Pathological changes are also found outside the cerebellum, including in the basal ganglia, brainstem, spinal cord, and peripheral nervous system.

Variants of the autosomal dominant disorders, episodic ataxia types EA-1 and -2 and SCA-6, lead to brief episodes of ataxia, often triggered by stress, exercise, or fatigue and with near-normal symptoms during remission. These disorders are thought to be due by mutations affecting ion channel function—K^+ channels in granule cells in the case of EA-1 and voltage-gated Ca^{2+} channels on Purkinje cells for EA-2 and SCA-6—and can often be clinically treated accordingly.

Nonmotor

In the past few years, there has been a change in opinion about the extent of cerebellar function. Early awareness of its involvement in autonomic, vasomotor, and affective processes was largely ignored as research concentrated on aspects of motor control. However, it is now accepted that it has roles in many cognitive functions: language processing, classical conditioning, problem solving and planning, working memory, attention shifting, and others. There is reported volume loss in the vermis of a proportion of schizophrenic patients and children with attentional deficit hyperactive disorder as well as more widespread depletion with autism. Clinical stimulation of the vermis can reduce fear and aggression in emotionally disturbed patients. Tumor resection in children can lead to behavioral and linguistic problems, especially for midline tumors. Anterior lobe lesions seem to lead to few cognitive symptoms, whereas symptoms are more frequently seen following posterior lobe damage. The term cerebellar cognitive affective syndrome covers signs of deficient executive function, impaired spatial cognition, personality changes with flattening of affect, and language deficits, leading to a net reduction in intellectual function.

SYNAPTIC PLASTICITY

There is good evidence for long-term changes in the efficacy of synapses between the parallel fibers and Purkinje cells. If the climbing fiber is active during parallel fiber input, the strength of the synapse from parallel fiber to Purkinje cell is reduced by a process called long-term depression (LTD). This changes the relationship between mossy fiber input to the cortex and Purkinje cell output and thus modifies P cell inhibition of the cerebellar nuclei. The climbing fibers may therefore provide an error signal to

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modulate or "instruct" the Purkinje cells. Indeed, the climbing fibers are most active in situations in which changes in motor behavior are required, for example, in learning new motor skills or adapting reflex behaviors. Synaptic plasticity is suspected at other sites in the cerebellum. Evidence from studies of the modification of the vestibulo-ocular reflex indicates that a change at the level of the cerebellar targets (the deep cerebellar nuclei or vestibular nuclei) is required, but the mechanism for this plasticity in unknown. There is also evidence for long-term potentiation at the synapse between mossy fiber and granule cells and perhaps onto stellate and basket cells as well. There seems to be important structural plasticity between climbing fibers and Purkinje cells.

Parallel Fiber/Purkinje Cell LTD

The molecular basis of long-term change at the excitatory synapse between parallel fibers and Purkinje cells is reasonable well understood. It is dependent on phosphorylation of postsynaptic ionotropic AMPA glutamate receptors and thus a reduction in synaptic efficacy. There are two ways to induce plasticity. In one, a use-dependent homosynaptic form, plasticity is triggered by powerful parallel fiber input sufficient to depolarize the postsynaptic P cell dendrites and induce calcium entry via voltage-sensitive channels. The second form is heterosynaptic, requiring the conjoint excitation of the P cell by parallel fiber activity and by climbing fiber input. The complex spike depolarization of the P cell dendritic tree produced by the climbing fiber input again causes Ca^{2+} influx. Then, there is a second messenger cascade of events involving protein kinase C that links AMPA receptor and G –protein-coupled metabotropic mGluR1 activation, Ca^{2+} entry or release from intracellular stores, and AMPA receptor phosphorylation. This process is also linked to nitric oxide (NO) production, although not from P cells but perhaps from adjacent parallel fibers or glia. NO is highly diffusable and may be an important messenger to induce synaptic changes in adjacent cells.

LTD has been well studied in culture and slice preparations, and pharmacological manipulations *in vivo* during adaptation of motor reflexes and studies of knockout mutations (e.g., the mGluR1 receptor) are largely consistent. It is generally recognized to be the key process by which the cerebellum could show experience-dependent changes to underpin its role in motor learning.

THEORIES OF CEREBELLAR FUNCTION

Many theories of cerebellar function have been proposed based mainly on clinical evidence or on extensive anatomical and physiological information. No one theory manages to fully account for all reported aspects of cerebellar function.

Comparator

An early suggestion was that the cerebellum formed a comparator in a servo-loop involved in a comparison of the actual movement with a desired plan. This theory is supported by the many loops formed by connections to or within the cerebellum that could provide the necessary pathways for a servo-loop and also by clinical evidence. Cerebellar patients exhibit behavior similar to that of malfunctioning servo-controlled devices, most noticeably in the overshoot and intention tremor of their limbs. However, this theory does not account for the complexities of cellular physiology of the cerebellum or for evidence of learning within the cerebellum.

Timing Theories

The cerebellum could provide a mechanism for timing: Mossy fiber inputs are delayed by the slow conduction of action potentials along the unmyelinated parallel fibers, and so Purkinje cells lying along a parallel fiber beam could read off delayed versions of the information. Cerebellar patients do have problems in the timing of their voluntary movements and in temporal estimation or discrimination. However, the time delays caused by even the longest parallel fibers are too short to explain these problems. If the cerebellum is involved in timing motor action, it is not as straightforward as originally thought.

Parameter Control

An alternative proposal is that the cerebellum indirectly affects motor performance by setting parameters such as the gain of reflex loops. Evidence for this theory can be found in the hypo- and hypertonia that result from cerebellar lesions, due to its influence on the balance of alpha and gamma drive to the motoneurons, and in the control of the vestibulo-ocular reflex (VOR).

The VOR is responsible for the steady gaze position of the eyes; it generates eye movements that compensate for motion of the head and thus allows fixation of visual targets during movement. The reflex is plastic and readily adapts to the changed

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visual input induced by wearing, for example, strong reading glasses (or even inverting glasses so that the eyes must move in the opposite direction to maintain gaze). When the glasses are removed after adaptation, the VOR reflex gain returns to its normal level. Lesion experiments have shown the flocculonodulus to be necessary for VOR adaptation. Climbing fibers carry retinal slip signals to the flocculus, which is thought to represent the "motor error" in the VOR; mossy fibers carry vestibular and eye velocity signals; and output from the flocculus projects via the vestibular nuclei to oculomotor neurons. The VOR must also be suppressed to allow moving targets to be followed, and flocculonodular Purkinje cells are necessary for and most active during VOR suppression.

Learning Machine

The remaining theories can all be grouped within the idea of the cerebellum as a learning machine, based on synaptic plasticity in the cerebellar cortex. This basic learning mechanism could then support a wide variety of cerebellar functions, including the VOR reflex described previously. The very divergent mossy fiber projections and specific climbing fiber inputs are also suggestive of an associative learning role because they could provide the mechanism to allow Purkinje cells to pair specific unconditional stimuli carried by the climbing fibers with conditional sensory stimuli carried by the mossy fibers. Detailed support for this proposal is available from studies of the nictitating membrane eye-blink reflex in rabbits. Lesions of topographically related parts of the pons, cerebellar cortex, interpositus nucleus, and inferior olive can affect the acquisition and retention of this reflex.

Related proposals are that the cerebellum is involved in learning motor programs, in coordinate transformations, or in forming predictive internal models. Computational theories based on forward and inverse internal models of the motor system have been advanced to cover several areas of cerebellar operation and are proving useful in guiding interpretation of electrophysiological data.

A precise answer to the question, What does the cerebellum do? is not possible. What seems clear is that the answer should combine parts of all these theories. Its role as a predictive model seems to fit most easily with much of the data. Such a predictive internal model would involve both learning and timing mechanisms, could be involved in setting motor parameters, and if damaged could lead to the impaired motor performance seen clinically.

—R. C. Miall

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