Cerebellum: Anatomy and Function

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Abstract

The cerebellum is the largest motor structure in the CNS and, in humans, contains more neurons than the whole of the cerebral cortex. It occupies about one tenth of the skull cavity, sitting astride the brain stem beneath the occipital cortex (Fig. 1). A great deal is now known about its circuitry and microphysiology. It contains only six main cell types and is one of the most regularly organized structures in the CNS, having a repeated, almost crystalline form. Thus, input signals to each point on the cerebellar cortex that arise from other parts of the CNS are likely to be processed in the same way and are then output from the cerebellum to specific targets. The cerebellum is performing similar processes on different signals. The cerebellum has also been conserved across vertebrate evolution. There must be good reasons for maintaining such a massive parallel neural structure, but despite

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its prominent architecture and some clear symptoms of its malfunction, the exact role of the cerebellum is still far from clear. This challenge has attracted a great number of scientists to study it, and the cerebellum is also remarkable for the number of theories put forward to account for its function.

An Overview

The cerebellum is the largest motor structure in the CNS and, in humans, contains more neurons than the whole of the cerebral cortex. It occupies about one tenth of the skull cavity, sitting astride the brain stem beneath the occipital cortex (Fig. 1). A great deal is now known about its circuitry and microphysiology. It contains only six main cell types and is one of the most regularly organized structures in the CNS, having a repeated, almost crystalline form. Thus, input signals to each point on the

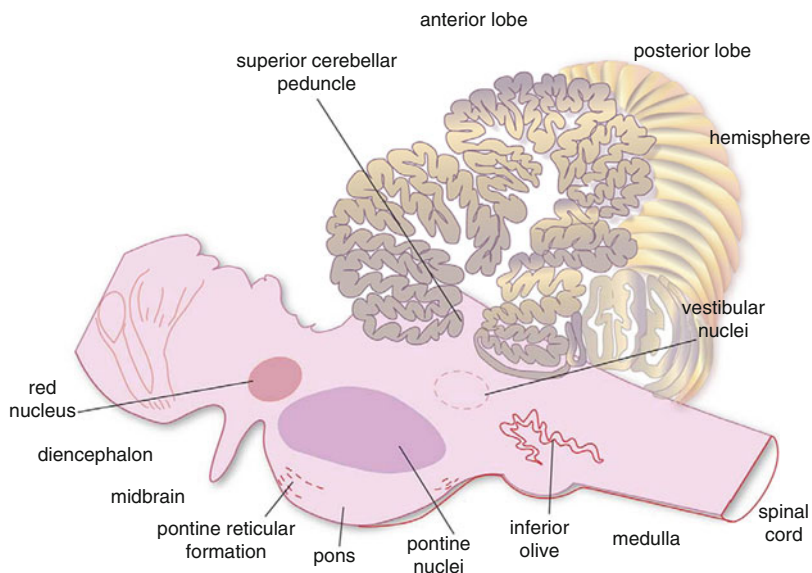
Fig. 1 A parasagittal view of the human cerebellum and brain stem, indicating some of the principle sites of input and output connections. The middle and inferior peduncles lie out of the plain of the section, just below the superior peduncle

cerebellar cortex that arise from other parts of the CNS are likely to be processed in the same way and are then output from the cerebellum to specific targets. The cerebellum is performing similar processes on different signals. The cerebellum has also been conserved across vertebrate evolution. There must be good reasons for maintaining such a massive parallel neural structure, but despite its prominent architecture and some clear symptoms of its malfunction, the exact role of the cerebellum is still far from clear. This challenge has attracted a great number of scientists to study it, and the cerebellum is also remarkable for the number of theories put forward to account for its function.

Structure of the cerebellum. The cerebellar cortex consists of an extensive three-layered sheet (Fig. 2) wrapped around three pairs of nuclei (called the deep cerebellar nuclei, although there are no shallow ones). It connects to the brainstem via three large paired roots: the *superior*, *middle*, and *inferior peduncles*. These are also termed the brachium conjunctivum, brachium pontis, and restiform body. The cortical sheet is divided along the rostro-caudal axis into three lobes; a small anterior and much larger posterior lobe are separated by the primary fissure, and the tiny flocculonodular lobe, tucked beneath the posterior lobe, is separated by the postero-lateral fissure. The anterior and posterior lobes are further folded into a number of lobules, themselves folded into a series of folia. This transverse organization is then divided at right angles into five longitudinal bands. The central band of the posterior
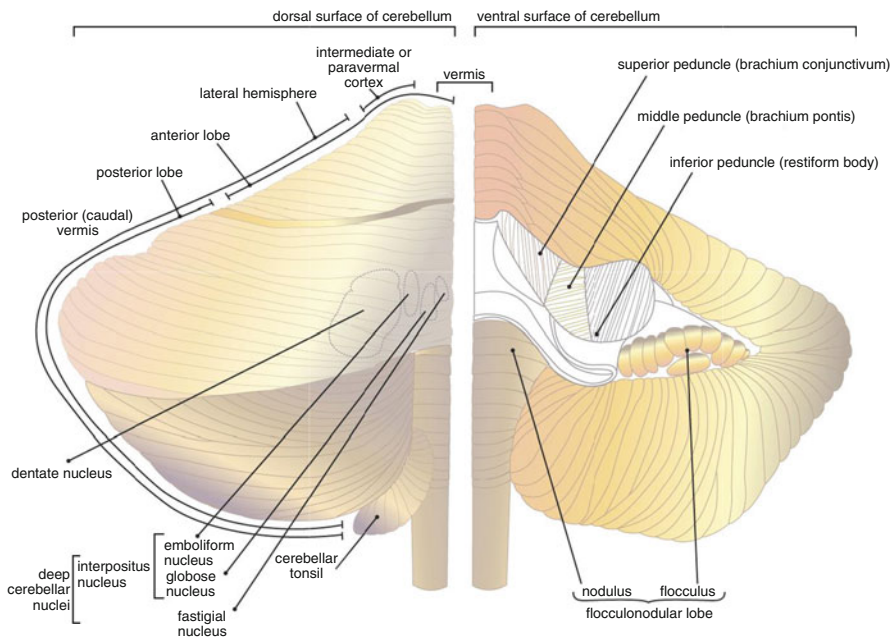

Fig. 2 The gross anatomy of the human cerebellum, shown in dorsal view on the *left* and ventrally on the *right*. The cerebellar cortex is heavily folded into a series of transverse lobes, lobules, and folia surrounding the deep cerebellar nuclei. It connects with the brainstem via three paired roots

lobe is most obvious externally and is named the *vermis* for its wormlike appearance. On either side of the vermis is the *paravermal* or *intermediate* cortex which merges into the *lateral hemispheres*.

Deep nuclei of the cerebellum. Each cortical zone projects in a systematic manner to the underlying deep nuclei, which give rise to the only output fibers from the cerebellum. The lateral hemisphere projects predominantly to the *dentate nucleus*; the paravermis projects mainly to the *interpositus nucleus*, which is divided in humans into the *globose* and *emboliform* nuclei, and the vermis projects mainly to the *fastigial* nucleus. The flocculonodular cortex projects to the lateral vestibular nucleus – Deiter's nucleus – but this is best thought of functionally as a displaced deep cerebellar nucleus.

Lateral organization. This lateral organization is also mirrored phylogenetically. The oldest part, the *archi-* or *vestibulo-cerebellum*, is retained as the flocculonodulus. It is the only part of the cerebellum that receives a significant direct sensory input, from hair cells in the semicircular canals, and as mentioned above, it projects in part directly back to the vestibular nuclei. It is therefore closely connected with the vestibular system and predominantly involved in balance. The next part, the paleo- or *spino-cerebellum* corresponds to the anterior vermis, pyramid, uvula, and paraflocculus and is concerned with balance, posture, and also orientation. The spino-cerebellum receives spinal proprioceptive inputs as well as auditory and visual input and projects back to the spinal cord via the red nucleus. The spino-cerebellum is highly developed in fish and bats; fish use their lateral line organs for detecting vibration in the water, and electric fish have further developed this system to allow sampling of the surrounding environment with electric pulses generated by modified muscle cells. In an analogous fashion, bats orientate to their external surroundings using auditory echo detection. The neocerebellum (caudal vermis, paravermis, and lateral hemispheres) has developed in terrestrial animals with the need for independent control of the limbs, and in mammals it has expanded further in concert with the development of fine control of the distal musculature. Diving mammals such as whales and dolphins also have quite large hemispheres, relative to their body mass. It has been suggested that this is in response to echolocation or navigation within the three-dimensional ocean environment. In primates, the lateral hemispheres (the *ponto-* or *cerebro-cerebellum*) have expanded dramatically and are involved in skilled actions, in motor learning, and predictive motor control. 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 Cortex of the Cerebellum Is Geometrically Organized

The gross anatomical 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 *Purkinje cell*, which has its soma in the middle cortical layer, the Purkinje or

ganglionic layer, and a large flattened dendritic tree lying fan-like in the sagittal plane of the upper layer, the molecular layer. Neighboring Purkinje cells line up to form overlapping stacks along the course of the folium (Fig. 3). The Purkinje cell provides the only output from the cerebellar cortex, sending an inhibitory axon down to one of the cerebellar nuclei. The most numerous cell types, the *granule cells*, are the main excitatory interneurons within the cortex (Table 1). Each granule cell has its soma and a sparse dendritic arbor within the granular layer and then sends a fine unmyelinated axon up to the molecular layer. Here, the axon bifurcates into two *parallel fibers* running transversely along the folia, passing through, and making synapses onto the dendritic trees of many Purkinje cells (Fig. 3). Each parallel fiber extends up to 2–4 mm across the cortex, with more superficial fibers traveling furthest. The perpendicular arrangement of these cells means that each Purkinje cell intercepts a beam of parallel fibers (Fig. 3). Each parallel fiber makes excitatory synaptic contact with the dendrites of perhaps a few hundred Purkinje cells, while each Purkinje cell receives 200,000 parallel fiber synapses. Parallel fibers activity can evoke in the Purkinje cell a series of "simple spikes" whose frequency reflects the strength of the input. Parallel fibers also make excitatory synaptic contact with
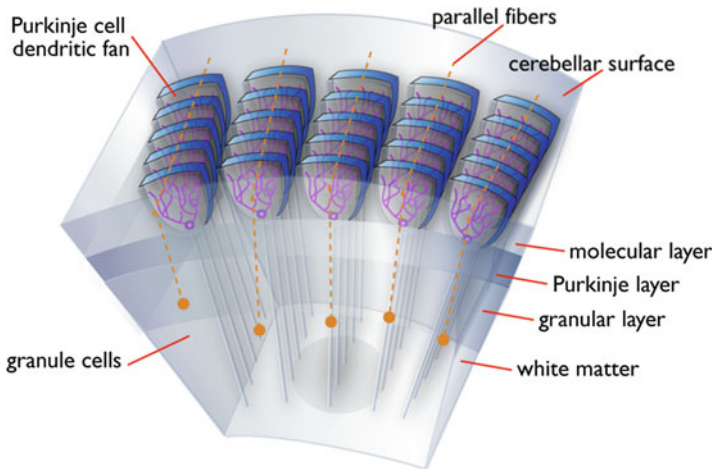

Fig. 3 A sketch of the layout of the cerebellar cortex. The Purkinje cell dendritic fans form dense stacks in the uppermost layer, pierced by huge numbers of parallel fibers

Table 1 Cell types in the cerebellar cortex

Cell	Estimated numbers in adult human	Action
Granule cell (parallel fibers)	10–100,000,000,000	Excitatory (glutamate)
Stellate cells	250,000,000	Inhibitory (GABA)
Basket cells	90,000,000	Inhibitory (GABA)
Golgi cell	20–40,000,000	Inhibitory (GABA)
Purkinje cell	15,000,000	Inhibitory (GABA)
Unipolar brush cells	Unknown	Excitatory (glutamate)

the other three inhibitory cells types of the cortex: the *Golgi, stellate*, and *basket cells*. This basic cerebellar microcircuit (Fig. 4) is found at all points of the cortex; within some known constraints, the connections between cells in any one part of the cerebellar cortex are the same as at any other: it is a uniform structure. The Golgi

Fig. 4 Cell types in the cerebellar cortex. Purkinje cells have very flattened dendritic arbors, lying in a sagittal plane. Parallel fiber axons run in the transverse direction, whereas Golgi cells occupy a more cylindrical volume. The dendritic trees of stellate and basket cells are smaller and less flattened than Purkinje cells

dorsal (to cortical surface)

transverse (along folium)

saggital (across folium)

500 μm

numbers of cells in human cerebellum

Purkinje cells — 1.5 million (1.5×10^7)

sagittal

parallel fibers

granule cells — 10–100 billion (10^{10}–100^{11})

transverse

golgi cells — 20–40 million (2.4×10^7)

stellate cells — 250 million (2.5×10^8)

sagittal

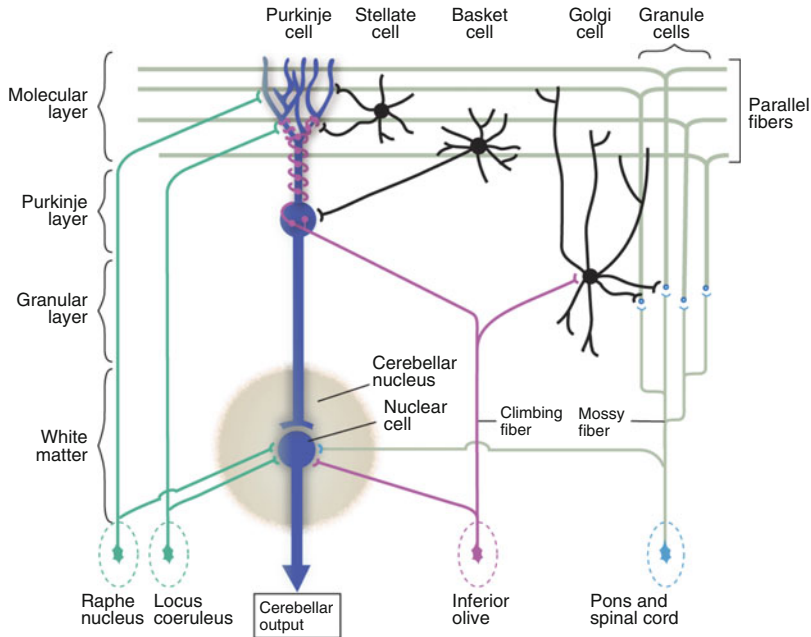basket cells — 90 million (9×10^7)

sagittal
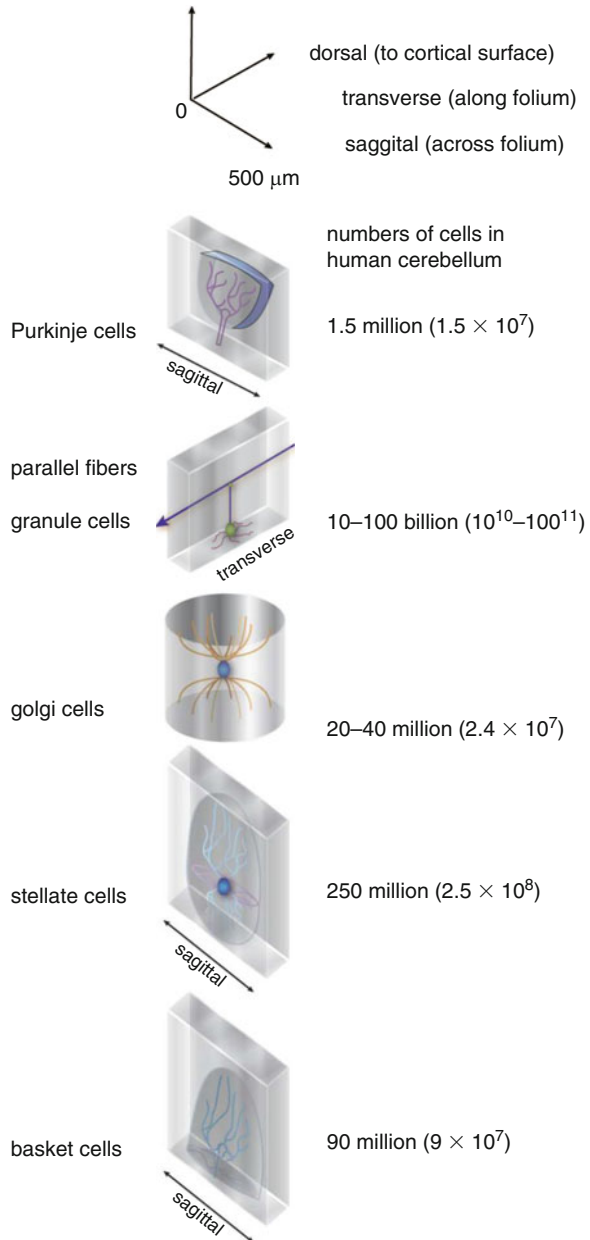
Fig. 5 The cerebellar circuit. The main inputs are the mossy and climbing fibers shown in blue. These cells transmit aspartate or glutamate. The granule cells (*black*) transmit glutamate, while all other interneurons are GABAergic (*red*). Purkinje cells form the only output fibers from the cortex. The *arrows* indicate the direction of transmission across each synapse. Some pathways have been omitted for the sake of clarity

cells have a roughly cylindrical dendritic arbor; the stellate and basket cells have a sagittally flattened or elliptic arbor (Fig. 5). 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 narrow beam of active Purkinje cells is created, bordered by inhibited cells. Another excitatory cell, the unipolar brush cell, also lies within the granular layer and makes local connections between mossy fiber inputs arriving into the granular layer (see below) and granule cells.

Two Cell Types Provide the Major Inputs to the Cerebellum

Mossy fiber 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. All mossy fibers also send collaterals to the cerebellar nuclei so that cerebellar inputs reach the cerebellar output nuclei directly and via a cortical loop through the granule cell-Purkinje cells (Fig. 4). Mossy fibers also excite the Golgi cells.

The *climbing fibers* arise solely from the inferior olive within the brain stem. The olive receives inputs from many areas, including vestibular, spinal, cranial, and much cortical descending information. Its cells therefore can have quite complex properties but a rather precise topographical arrangement. They appear to be particularly responsive to unexpected somatosensory events such as when the foot hits an obstacle during its forward swing. They are also activated by noxious stimuli. There is intense discussion about what information is carried by the climbing fibers. Each climbing fiber projects to contralateral parasagittal strips of cortex, branching to reach about 10 Purkinje cells. They also send collateral connections to the corresponding deep cerebellar nucleus, as well as exciting basket, stellate, and Golgi cells. The terminals of the climbing fiber form an extensive complex of up to 300 synapses that climb like ivy up around the soma and primary dendrites of the Purkinje cell. Climbing fibers fire at very low rates, with an apparently random baseline rate of about 1 spike per second, and a maximum of only 5–10 spikes per second, but this massive excitatory input reliably causes a "complex" spike or "climbing fiber" response in each Purkinje cell that receives it.

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 roles of these minor inputs are not yet clear, and they thought to be neuromodulatory.

There Are Three Main Divisions of the Cerebellar Cortex

Vestibulo-cerebellum. The vestibulo-cerebellar cortex receives some mossy fibers which arise directly from the vestibular apparatus and others which are derived from the vestibular nuclei, as well as climbing fibers from parts of the inferior olive related to the vestibular nuclei. It also receives mossy fiber inputs carrying visual information from the 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 (Fig. 6). The vestibular nuclei also project via the medial longitudinal fasciculus to the oculomotor nuclei III, IV, and VI. The flocculonodular lobe's action is therefore mainly on axial muscles and on eye movement, controlling balance and coordinating head-eye movement.

Spino-cerebellum. Most ascending somatosensory and proprioceptive inputs reach the vermis and paravermis to form topographic maps on both the anterior and posterior lobes. 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
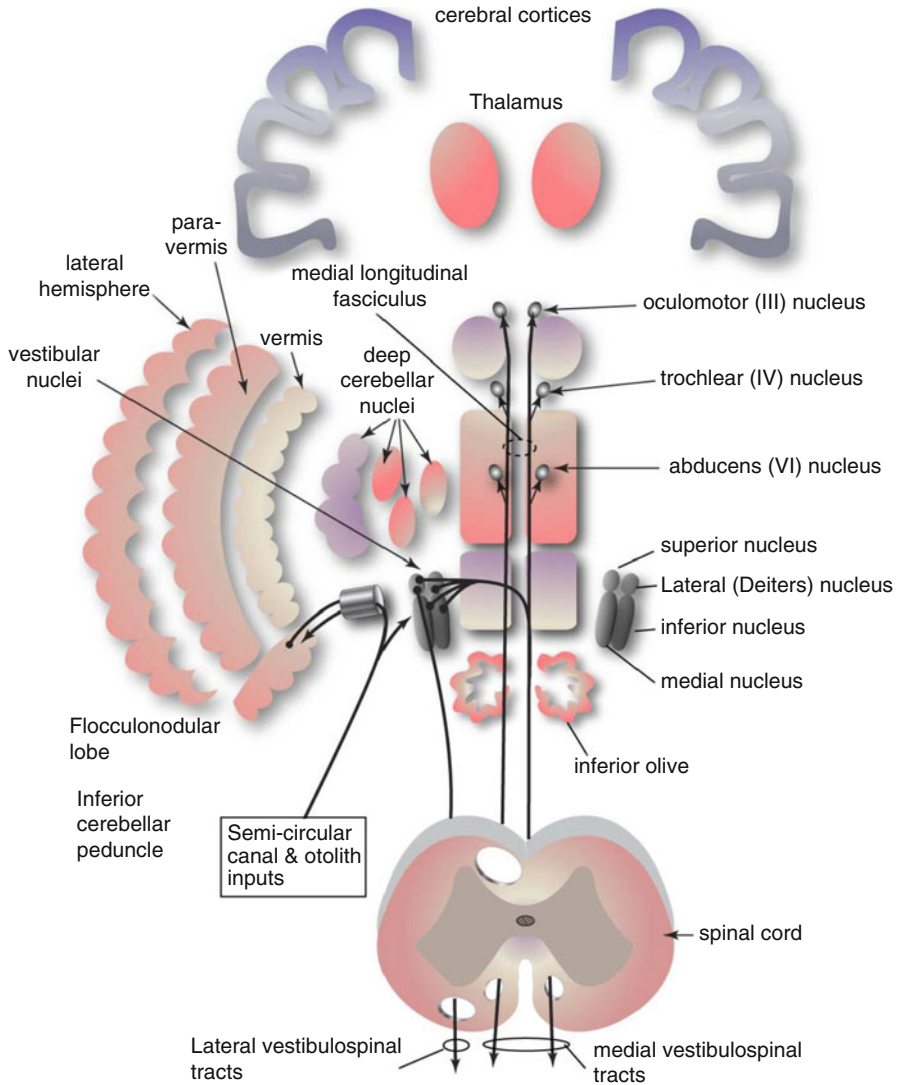
Fig. 6 Major connections of the vestibulo-cerebellum. Inputs from the vestibular system are indicated in *red*, reaching the flocculonodular lobe and the vestibular nuclei. The cerebellar outputs are shown in *blue*, projecting to the vestibular nuclei, and on to the medial descending pathways modulating posture and balance. For simplicity, climbing fiber connections from the inferior olive are not shown

granule cells forming a mosaic or "fractured somatotopic map." Quite distant body parts can therefore be mapped onto adjacent patches some 50–100 μm wide. This precise map is then "blurred" because the granule cells project their parallel fibers to Purkinje cells over several millimeters across the folium.

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 rostral spinocerebellar 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 rather precise proprioceptive feedback, the VSCT integrates descending, spinal, and proprioceptive signals to provide feedback of the motor commands, reaching the motoneurons. If proprioceptive input is eliminated by cutting the dorsal roots, the cerebellar input from DSCT is interrupted while 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 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 to the brainstem reticular formation (Fig. 7). 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 which mediate postural control.

The paravermal cortex projects to the interposed nucleus and then on to the magnocellular red nucleus, with additional outputs to LRN, and to the motor cortex via the ventrolateral thalamus (Fig. 8). 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 (Fig. 9). 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 which 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 patterns of cerebellar activity. These might be involved in timing or in generating 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 to the cerebellum as climbing fibers.

Cerebro-cerebellar 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 sensory cortices, especially extrastriate visual areas, premotor and motor cortical areas, and a large projection from the posterior parietal cortex. The cerebro-cerebellum receives little somatosensory input from the spinal cord. While earlier reports suggested that cerebral inputs were almost exclusively from sensory-motor areas, it is now thought that most cerebral regions, including frontal and temporal cortical areas also connect
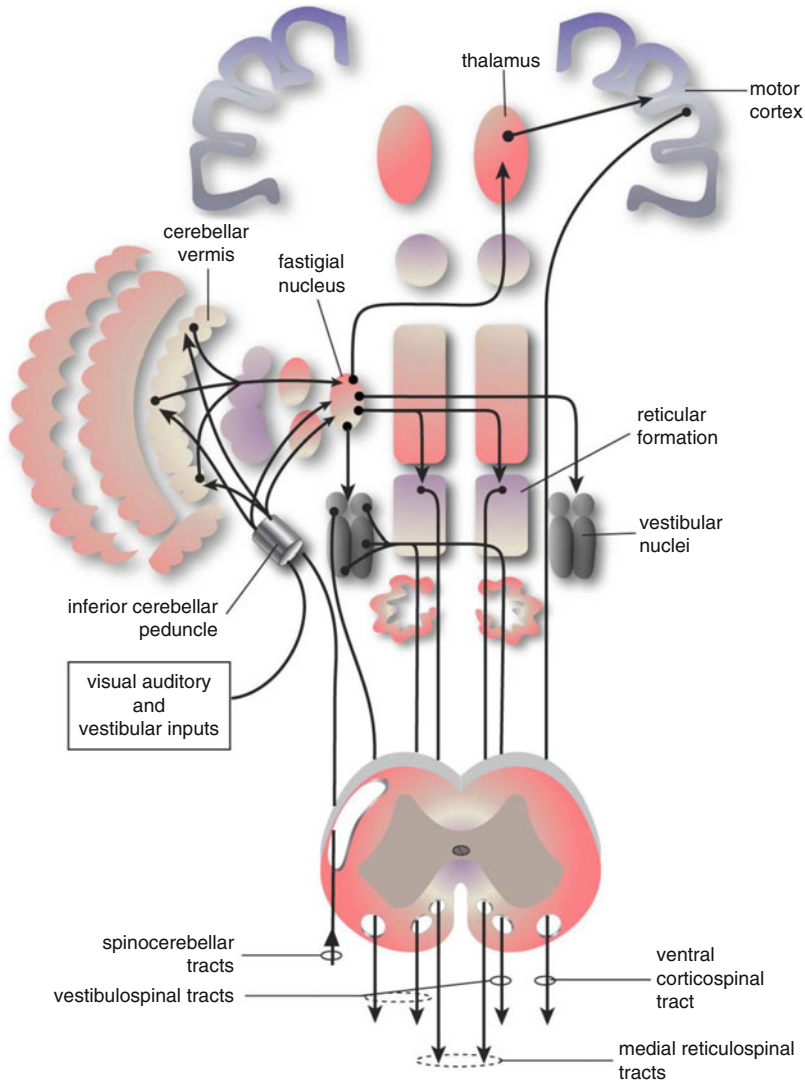
Fig. 7 Major connections of the vermal spino-cerebellum. The spinal tracts provide detailed somatosensory inputs, auditory, vestibular, and visual inputs also project to the central portion of the vermis. The outputs modulate the descending pathways directly and also via the motor cortex

with the cerebellum via the pons. The pontine inputs then 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 cerebral cortex. While there is a heavy return projection to premotor and motor cortices (Fig. 10), there is good evidence that each area that projects to the cerebellum also receives back from it, in a series of "closed loops."
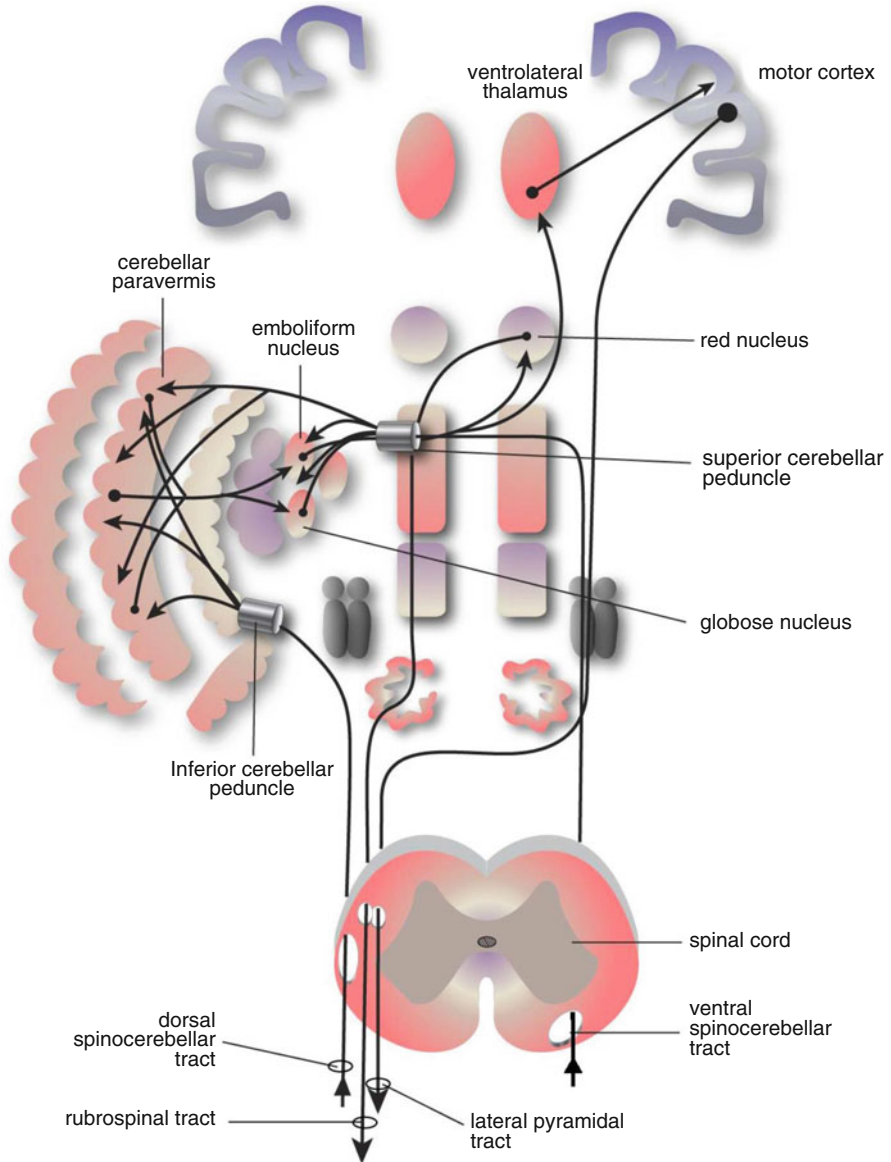
Fig. 8 Major connections of the paravermal spino-cerebellum. The inputs are similar to those of the vermis, but the major output modulates the rubrospinal tract

Some output also projects to the parvocellular red nucleus and hence to the inferior olive.

Because of its connections, cerebro-cerebellar function is therefore related more to the preplanning and refinement of motor programs being developed
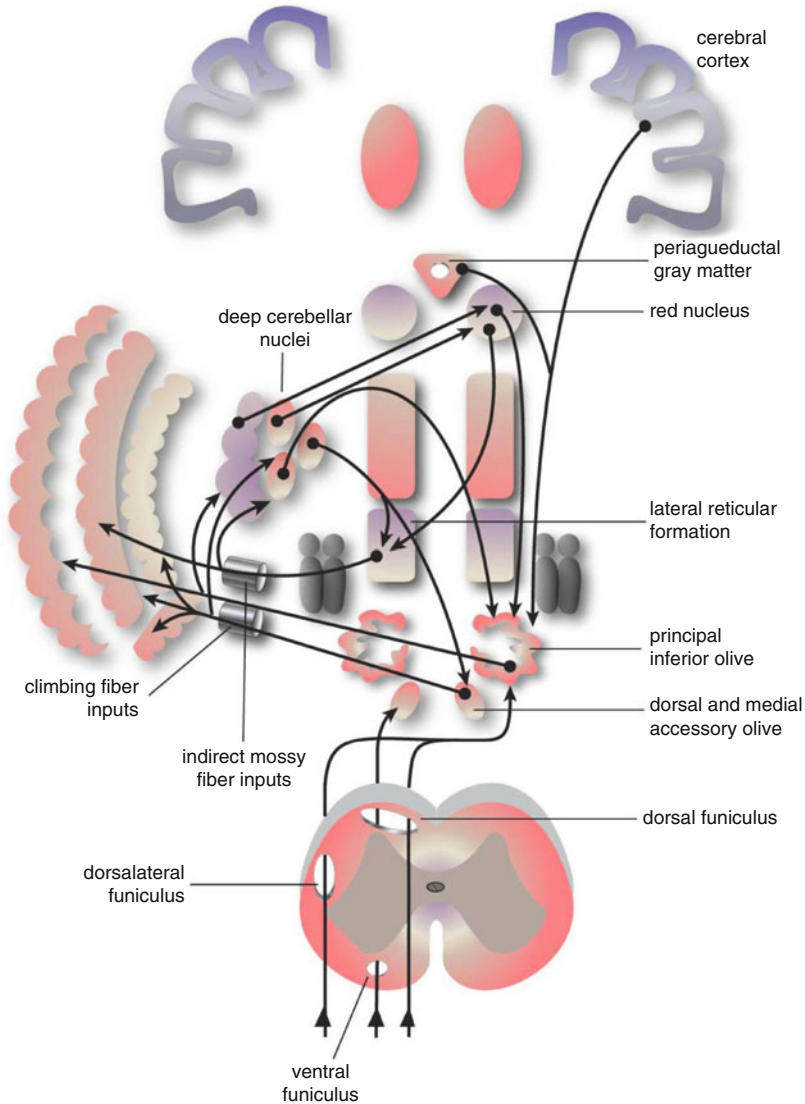
Fig. 9 Indirect pathways to the cerebellum. The inferior olive and the LRN receive inputs from wide areas of the cerebral cortex, brainstem, and spinal cord. Both also form closed loops to the cerebellum

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. It may have cognitive roles in addition to its motor functions, although evidence for these in patients is surprisingly sparse.
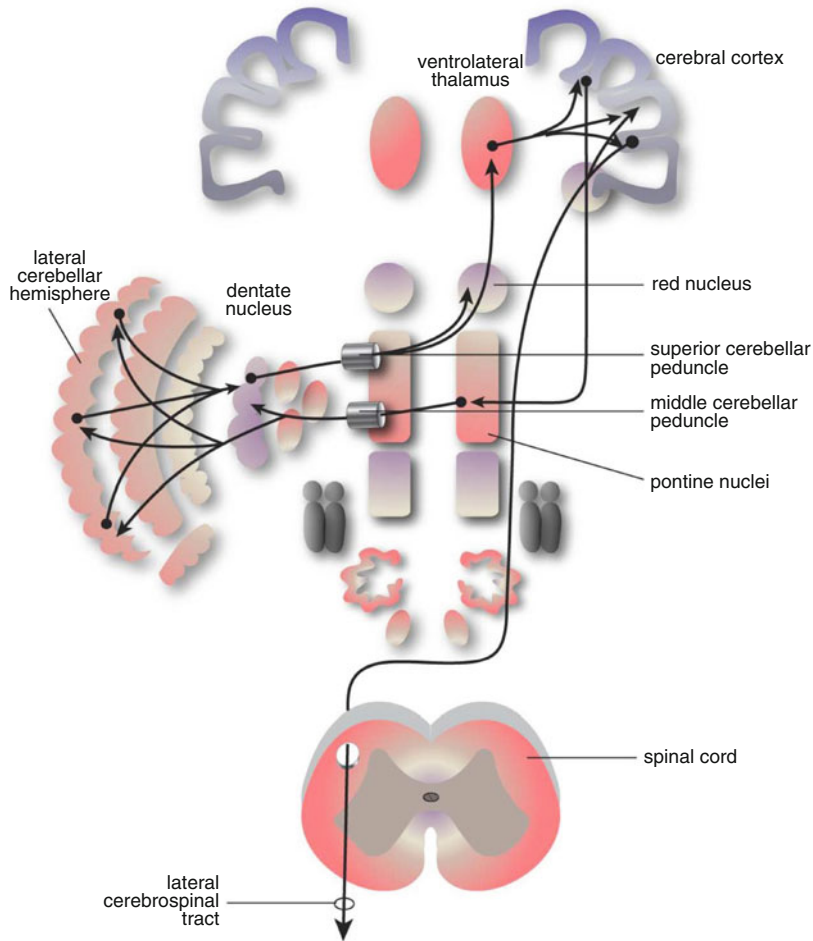
Fig. 10 Major connections of the cerebro-cerebellum. Diverse cortical areas project to the cerebellum via the pontine nuclei, and the principle output returns to the motor and premotor cortices

Cerebellar Dysfunction

The cerebellum can be affected by direct mechanical trauma, vascular damage (stroke), degenerative diseases such as multiple sclerosis, and by long-term alcohol abuse. The exposed cerebellar tonsils can be damaged mechanically by violent accelerative forces of the sort experienced in traffic accidents and also by tumors or fluid buildup which force the brainstem backward. This is most dangerous if pressure in the spinal fluid is suddenly reduced by a lumbar puncture and can result in the brain stem and cerebellar tonsils herniating through the foramen magnum.

The cerebellum is also affected by a large number of genetic disorders known as spinocerebellar ataxias (SCAs). There are about 30 of these identified, and all cause symptoms that have some similarity to those caused by direct damage to the cerebellum. However, most SCAs also involve some degeneration of extracerebellar structures. There are also some rare episodic ataxias that result in repeated onset and recovery of cerebellar symptoms. These are also genetic disorders, often know as channelopathies, because of their links to specific potassium, calcium, or glycine ion channel dysfunctions. Episodic ataxias are often induced by stress, including heat or exercise.

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 often been said to have very little effect, although the evidence for these claims is dubious. In adulthood, the effects of lesions or damage are profound, but the symptoms of smaller lesions reduce greatly over time.

An important and influential clinical analysis of the cerebellum was performed by Gordon Holmes in years following World War I, in studies of gunshot wounded soldiers, at the sage in history when guns were powerful enough to penetrate the skull, but not so powerful as to frequently kill the victim. Holmes described three classic symptoms: ataxia, intention tremor, and hypotonia.

Ataxia

Ataxia refers to the imperfect coordination of movements, with poor timing, clumsiness, and unsteadiness. Cerebellar patients tend to overshoot when pointing at targets, and hence, their movements are *hypermetric* (Fig. 11a). They also have increased reaction times, disturbed temporal patterns of EMG activity, abnormal patterns of joint acceleration and braking, and difficulties in performing rapid alternating movements (*dysdiadochokinesia*).

Intention Tremor

Intention tremor is a tremor of the hand or arm when performing voluntary actions and may result from continual hypermetric corrections of position. Unlike the tremor associated with Parkinson's disease, intention tremor is not seen when the patient is at rest.

Hypotonia

Hypotonia is a loss of muscle tone and is associated with rapid fatigue of the muscles. It results from the loss of facilitating drive from the cerebellar nuclei to gamma motoneurons in the spinal cord. If the hemispheres are affected, the

Fig. 11 A cartoon of cerebellar motor dysfunctions. (**a**) Visually guided movements of the limbs are hypermetric, and intention tremor leads to oscillations about the desired target. (**b**) Nystagmus is evident as a sawtooth motion of the eyes, with a slow drift phase and rapid corrective phase
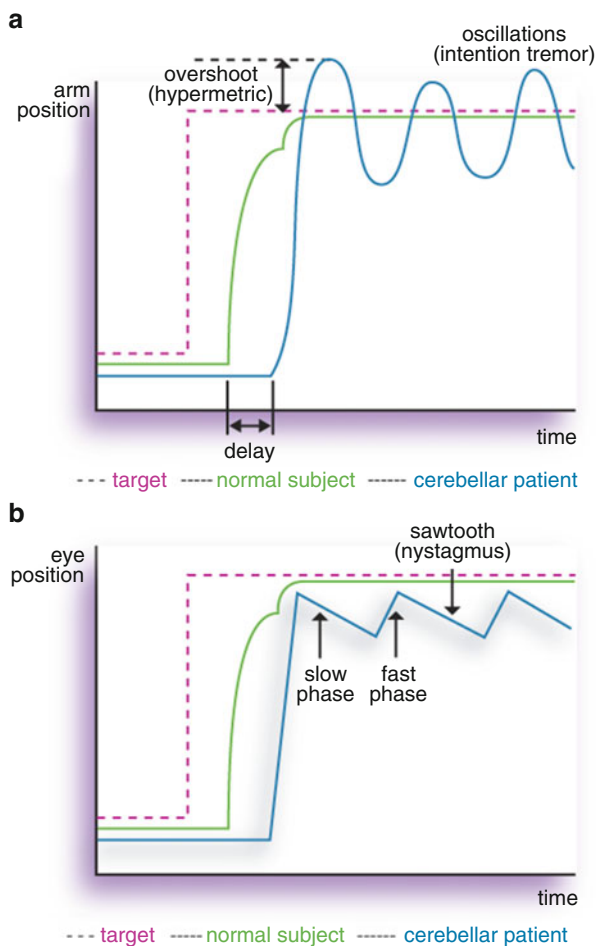
ipsilateral limbs are affected, whereas postural deficit follows damage to the vermis. Hypotonia is particularly found with lesions of the posterior lobe. It is evident as a "pendular" knee jerk in which the leg continues to swing because of the reduced braking action of the muscles (Fig. 11a). In alcoholic cerebellar damage, and in patients with lesions of the anterior lobe, *hypertonia* may result instead, through disinhibition of Deiter's nucleus, and hence excitation of alpha motoneurons.

Charcot's Triad

Cerebellar symptoms are also known by Charcot's triad: nystagmus, intention tremor, and staccato or scanning speech. *Nystagmus* is a regular off-target drift of the eyes which must be corrected by rapid eye movements (saccades), leading to a

sawtooth movement of the eye (Fig. 11b). *Scanning speech* is the breakdown of the normal continuous flow of words into a series of separate utterances.

What Does the Cerebellum Do?

Many theories of cerebellar function have been proposed. These are either based mainly on clinical evidence or on the extensive anatomical and physiological information. No one theory yet manages to fully account for all three!

Comparator. An early suggestion was that the cerebellum formed a comparator in a "servo-control loop," involved in a comparison of the desired plans and the actual movement. Difference between these signals is an error that should be corrected, bringing the movement closer and closer in line with the plan. This theory was supported by the many loops formed by connections to or within the cerebellum which could provide the necessary pathways for a servo-loop as well as by clinical evidence of motor performance. Cerebellar patients exhibit behavior similar to that of malfunctioning servo-controlled devices, most noticeably in the overshoot and intention tremor of their limbs (Fig. 11a). However, this theory does not account for the complexities of cellular physiology of the cerebellum, for its complex anatomy, nor for more recent evidence of learning within the cerebellum.

Timing theories. The cerebellum could provide a mechanism to time sensory-motor control signals. In one theory, 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 receive a more and more delayed version of the information. Cerebellar patients do have problems in the timing of their voluntary movements. However, the time delays caused by even the longest parallel fibers are far too short to explain these problems. If the cerebellum is involved in timing motor action, it is not as straightforward as originally thought, and recent theories propose that the timing function is achieved by recurrent patterns activity set up in loops between the cerebellar cortical neurons (Purkinje, Golgi, and granule cells) or by the neurons complex biophysical membrane properties.

Parameter control. An alternative proposal is that the cerebellum indirectly affects motor performance by setting control parameters such as the gain of reflex loops. Evidence for this theory can be found in the hypo- and hypertonia that results 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 powerful reflex responsible for the steady gaze position of the eyes; it generates eye movements that compensate for motion of the head detected by the vestibular apparatus and thus allows steady fixation of visual targets despite head movement. The reflex is plastic and adapts to the changed 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). If the glasses magnify the visual image by a factor of two, for example, then only half the eye movement is needed to compensate for head movement. When the glasses are removed after adaptation, the VOR reflex gain must adapt back to its normal level. There is no

direct feedback pathway between the vestibular and visual systems to set the strength of this reflex and the vestibulo-cerebellum forms this link. Lesion experiments have shown the flocculonodular Purkinje cells to be necessary for VOR adaptation. The VOR must also be suppressed to allow moving targets to be followed, and flocculonodular Purkinje cells are most active during and necessary for VOR suppression.

Of course, we have not evolved the cerebellum just to deal with reading glasses. The VOR is tuned in all mammals through experience, rather than being hard wired, and is probably important to compensate for changes in sensitivity of the vestibular system, especially in old age, and for changes in the power of the ocular muscles.

Learning machine. The remaining theories can all be grouped within the idea of the cerebellum as a learning machine. There is now good evidence for changes in the strength 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 so modifies Purkinje cell inhibition of the cerebellar nuclei. The climbing fibers may therefore provide an error signal to modulate or "instruct" the Purkinje cells. Indeed, the climbing fibers are most active in situations when changes in motor behavior are required, for example, in learning new motor skills or adapting reflex behaviors. This basic learning mechanism could then support a wide variety of cerebellar functions, including adjusting the strength of the VOR reflex described above.

The very divergent mossy fiber projections and rather specific climbing fiber inputs are also suggestive of an *associative learning* role, as 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 now available from studies of the nictating 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 ideas are that the cerebellum is involved in learning motor programs, in learning voluntary coordinated actions, or in forming predictive internal models. Here, the proposal is that LTD modulates the strength of the connections from many hundreds or thousands of parallel fibers projections to Purkinje cells that project via the deep cerebellar nuclei or motor areas of the cerebral cortex or the spine. Over many repetitions, driven by climbing fibers that inform the cerebellum about the outcome of each movement (assuming this signal reports motor errors), the cerebellar output is adjusted until the movements are performed without error. Recent computational theories suggest that the overall function of the cerebellum is to act as a predictor, and these predictions about how the body responds to sensory stimuli and to motor commands are then are used by other areas of the CNS to better control actions. Prediction is particularly important in the control of complex, fast, and coordinated actions, just those that are most sensitive to cerebellar damage.

Outlook

A precise answer to the question "What does the cerebellum do?" is still not possible. What seems clear is that the answer should combine some aspects of all these theories. Its role as a predictive system may be able to fit most easily with most 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.

However, there is a big gap between these theories and the details of the neural mechanisms. Hence, we cannot yet give precise answer to the question of why the cortex is organized with massive parallel fiber projections along one dimension nor why the climbing fibers that fire so slowly and irregularly are so important. Advances in recoding and imaging over recent years have shown that activity in the massive dendritic branches of the Purkinje cells is controlled by local active calcium signaling, suggesting our understanding must move down to a further level of detail, within each dendritic tree.

Synaptic modification at the synapse between parallel fibers and Purkinje cells is now well documented and provides a mechanism to support the learning theories. However, there is growing evidence for synaptic plasticity at other points in the cerebellar circuit (Fig. 5), especially at the synapse between the Purkinje cells and nuclear cells, and the mechanism, function, and control of learning at these different sites is still being studied.

At the other end of the spectrum, there are many laboratories studying the human cerebellum with brain scanning methods, and we know that different parts of the cerebellum are active in almost every task that has been studied. This raises the challenge of extending theories of the cerebellar role from sensory-motor control to many other cognitive and even autonomic realms. But the nearly uniform structure of the cerebellar cortex implies that we should look for one neural operation that is involved in all these different processes.

References

Holmes G (1939) The cerebellum of man. Brain 62:1–30

Ito M (1984) The cerebellum and neural control. Raven, New York

Manto M, Marmolino D (2009) Cerebellar ataxias. Curr Opin Neurol 22:419–429

Miall RC, Weir DJ, Wolpert DM, Stein JF (1993) Is the cerebellum a Smith Predictor? J Motor Behav 25:203–216

Ohyama T, Nores WL, Murphy M, Mauk MD (2003) What the cerebellum computes. Trends Neurosci 26:222–227

Schmahmann JD (ed) (1997) The cerebellum and cognition. Academic, San Diego