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The Cerebellum

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Highlights

THE CEREBELLUM CONSTITUTES ONLY 10% of the total volume of the brain but contains more than one-half of its neurons. The cerebellar cortex comprises a series of highly regular, repeating units, each of which contains the same basic microcircuit. Different regions of the cerebellum receive projections from distinct brain and spinal structures and then project back to the brain. The similarity of the architecture and physiology in all regions of the cerebellum implies that different regions of the cerebellum perform similar computational operations on different inputs.

The symptoms of cerebellar damage in humans and experimental animals provide compelling evidence that the cerebellum participates in the control of movement. The symptoms, in addition to being diagnostic for clinicians, thus help define the possible roles of the cerebellum in controlling behavior.

Several fundamental principles define our understanding of the physiological function of the cerebellum. First, the cerebellum acts in advance of sensory feedback arising from movement, thus providing feed-forward control of muscular contractions. Second, to achieve such control, the cerebellum relies on internal models of the body to process and compare sensory inputs with copies of motor commands. Third, the cerebellum plays a special role in motor and perceptual timing. Fourth, the cerebellum is critical for adapting

and learning motor skills. Finally, the primate cerebellum has extensive connectivity to nonmotor areas of the cerebral cortex, suggesting it performs similar functions in the performance and learning of motor and nonmotor behaviors.

Damage of the Cerebellum Causes Distinctive Symptoms and Signs

Damage Results in Characteristic Abnormalities of Movement and Posture

Disorders that involve the cerebellum typically disrupt normal movement patterns, demonstrating the cerebellum's critical role in movement. Patients describe a loss of the automatic, unconscious nature of most movements. In the early 20th century, Gordon Holmes recorded the self-report of a man with a lesion of his right cerebellar hemisphere: "movements of my left arm are done subconsciously, but I have to think out each movement of the right arm. I come to a dead stop in turning and have to think before I start again."

This has been interpreted as an interruption in the automatic level of processing by cerebellar inputs and outputs. With a malfunctioning cerebellum, it seems that the cerebral cortex needs to play a more active role in programming the details of motor actions. Importantly, individuals with cerebellar damage do not experience the paralysis that can be associated with cerebral cortical damage. Instead, they show characteristic abnormalities in voluntary movement, walking, and posture that have provided important clues about cerebellar function.

The most prominent symptom of cerebellar disorders is *ataxia*, or lack of coordination of movement. Ataxia is a generic term used to describe the collective motor features associated with cerebellar damage. People with cerebellar disorders make movements that qualitatively appear jerky, irregular, and highly variable. *Limb ataxia* during reaching is characterized by curved hand paths that are *dysmetric* in that they over- or undershoot the intended target and oscillate (Figure 37–1A). Patients often break a movement down into components, presumably in an effort to simplify control of multi-joint movements (*decomposition of movement*). Yet this may not be effective. For example, patients often have difficulty holding the shoulder steady while moving the elbow, a deficit thought to be due to poor predictions of how the movement at the elbow mechanically affects the shoulder (Figure 37–1B). If prediction fails, then patients are forced to try to steady the shoulder using time-delayed feedback, which is less effective.

At the end of reaching movements, there can be marked oscillation as the hand approaches the target. This *action* (or *intention*) *tremor* is the result of a series of erroneous, overshooting attempts to correct the movement. It largely disappears when the eyes are shut, suggesting that it is driven by time-delayed visual feedback of the movement. Finally, patients show abnormalities in the rate and regularity of repeated movements, a sign referred to as *dysdiadochokinesia* (Greek, impaired alternating movement) that can be readily demonstrated when a patient attempts to perform rapid alternating movements (Figure 37–1C).

People with cerebellar damage also exhibit *gait ataxia* and poor balance. When walking, they take steps that are irregularly timed and placed. They have difficulty shifting their weight from one foot to the other, which can lead to falling. The trunk oscillates when they are unsupported in sitting, standing, and during walking, particularly as they start, stop, or turn. A wide stepping pattern with feet spread apart is common and is thought to be a compensatory measure to improve stability.

Other signs that are commonly observed with cerebellar dysfunction can also occur with damage to other brain regions. People with cerebellar damage often have slurred speech with irregular timing (dysarthria); repetitive to-and-fro movements of the eyes with a slow and fast phase (nystagmus); and reduced resistance to passive limb displacements (hypotonia), which is thought to be related to so-called "pendular reflexes" often observed in cerebellar patients. In patients with cerebellar disease, the leg may oscillate like a pendulum many times after a knee jerk produced by a tap on the patellar tendon with a reflex hammer, instead of coming to rest immediately.

Damage Affects Specific Sensory and Cognitive Abilities

It is now known that cerebellar damage affects proprioceptive abilities (the sense of limb position and movement), but only during active movement. Proprioceptive acuity—the sense of the position and movement of the limbs—is normally more precise for active movements than for passive movements. Cerebellar patients show normal proprioceptive acuity when they have to judge which of two passive movements is larger. However, their proprioceptive acuity is worse than that of healthy individuals when they move a limb actively. One interpretation of these findings is that the cerebellum normally helps to predict how active movements will unfold, which would be important for movement coordination and for perceiving where the limbs are during active movements.

Damage to the cerebellum also affects cognitive processes, although these deficits are less obvious compared to the pronounced disturbances of sensory-motor function. Some of the earliest studies implicating the cerebellum in a range of cognitive tasks involved functional imaging to study the brain activity during behavior in healthy individuals. For example, in a study using positron emission tomography to image the brain activity of subjects during silent reading, reading aloud, and speech, areas of the cerebellum involved in the control of mouth movements were more active when subjects read aloud than when they read silently. Surprisingly, however, cerebellar activation was more pronounced in a task with greater cognitive

load, when subjects were asked to name a verb associated with a noun; a subject might respond with "bark" if he or she saw the word "dog." Compared with simply reading aloud, the word-association task produced a pronounced increase in activity within the right lateral cerebellum. Consistent with this finding, a patient with damage in the right cerebellum could not learn a word-association task.

By now, many studies have revealed clear deficits in executive function, visual spatial cognition, language, and emotional processing after cerebellar damage. There appears to be some regional specificity within the cerebellum for different types of cognitive function. Damage to the midline cerebellum or *vermis* seems to be related to emotional or affective dysregulation, likely due to its interconnectivity with limbic structures. Damage to the right cerebellar hemisphere is related to language and verbal dysfunction, presumably because this hemisphere is interconnected with the left cerebral cortical hemisphere. Likewise, damage to the left cerebellar hemisphere is related to visuospatial dysfunction, probably because this hemisphere is interconnected with the right cerebral cortical hemisphere. Additionally, studies that examine cognitive dysfunction produce variable results; patients perform normally in one study but not another. Some studies show that cognitive deficits are most pronounced when patients are tested shortly after damage to the cerebellum and that compensations at the level of cerebral cortex might gradually make up for

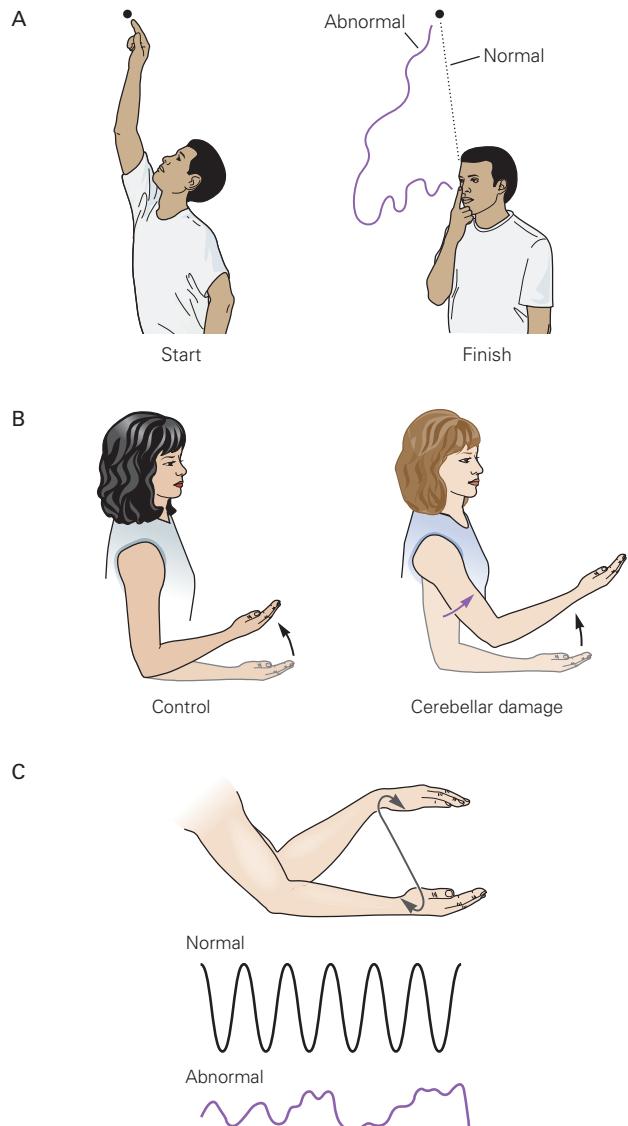


Figure 37-1 (Left) Typical defects observed in cerebellar diseases.

A. A cerebellar patient moving his arm from a raised position to touch the tip of his nose exhibits inaccuracy in range and direction (dysmetria) and moves his shoulder and elbow separately (decomposition of movement). Tremor increases as the finger approaches the nose.

B. Failure of compensation for interaction torques can account for cerebellar ataxia. Subjects flex their elbows while keeping their shoulder stable. In both the control subject and the cerebellar patient, the net elbow torque is large because the elbow is moved. In the control subject, there is relatively little net shoulder torque because the interaction torques are automatically cancelled by muscle torques. In the cerebellar patient, this compensation fails; the muscle torques are present but are inappropriate to cancel the interaction torques. As a result, the patient cannot flex her elbow without causing a large perturbation of her shoulder position. (Adapted, with permission, from Bastian, Zackowski, and Thach 2000.)

C. A subject was asked to alternately pronate and supinate the forearm while flexing and extending at the elbow as rapidly as possible. Position traces of the hand and forearm show the normal pattern of alternating movements and the irregular pattern (dysdiadochokinesia) typical of cerebellar disorder.

cerebellar loss of function. However, cognitive deficits may be more robust and long lasting when cerebellar damage is acquired in childhood.

Thus, cognitive deficits arising from cerebellar damage sometimes can be difficult to characterize. What is clear is that the motor dysfunction after cerebellar loss is more obvious than cognitive dysfunction. It may be that cortical regions of motor control are less able to compensate for losses of cerebellar motor control compared to cortical compensation for impairment of cerebellar computations involved in cognitive processes.

The Cerebellum Indirectly Controls Movement Through Other Brain Structures

Understanding the anatomy of the cerebellum and how it interacts with different brain structures is vital to understanding its function. In this section, we consider the general anatomy of the cerebellum as well as its inputs and outputs.

The Cerebellum Is a Large Subcortical Brain Structure

The cerebellum occupies most of the posterior cranial fossa. It is composed of an outer mantle of gray matter (the cerebellar cortex), internal white matter, and three pairs of deep nuclei: the fastigial nucleus, the interposed nucleus (itself composed of the emboliform and globose nuclei), and the dentate nucleus (Figure 37–2A). The surface of the cerebellum is highly convoluted, with many parallel folds or folia (Latin, leaves).

Two deep transverse fissures divide the cerebellum into three lobes. The primary fissure on the dorsal surface separates the anterior and posterior lobes, which together form the body of the cerebellum (Figure 37–2A). The posterolateral fissure on the ventral surface separates the body of the cerebellum from the smaller flocculonodular lobe (Figure 37–2B). Each lobe extends across the cerebellum from the midline to the most lateral tip. In the orthogonal, anterior-posterior direction, two longitudinal furrows separate three regions: the midline vermis (Latin, worm) and the two cerebellar hemispheres, each split into intermediate and lateral regions (Figure 37–2D).

The cerebellum is connected to the dorsal aspect of the brain stem by three symmetrical pairs of peduncles: the inferior cerebellar peduncle (also called the restiform body), the middle cerebellar peduncle (or brachium pontis), and the superior cerebellar peduncle (or brachium conjunctivum). Most of the output axons

of the cerebellum arise from the deep nuclei and project through the superior cerebellar peduncle to other brain areas. The main exception is a group of Purkinje cells in the flocculonodular lobe that project to vestibular nuclei in the brain stem.

The Cerebellum Connects With the Cerebral Cortex Through Recurrent Loops

Many parts of the cerebellum form recurrent loops with the cerebral cortex. The cerebral cortex projects to the lateral cerebellum through relays in the pontine nuclei. In turn, the lateral cerebellum projects back to the cerebral cortex through relays in the thalamus. Peter Strick and his colleagues used viruses for transneuronal tracing in nonhuman primates to show that this recurrent circuit is organized as a series of parallel closed loops, where a given part of the cerebellum connects reciprocally with a specific part of the cerebral cortex (Figure 37–3A). Through these reciprocal connections, the cerebellum interacts with vast regions of the neocortex, including substantial connections to motor, prefrontal, and posterior parietal regions. More recently, Strick's group also demonstrated disynaptic connections between the cerebellum and basal ganglia in nonhuman primates.

The resting state connectivity between the cerebellum and cerebral cortex in humans was studied using fMRI scans of 1,000 subjects. Correlations in activity in different regions of the brain were assessed at low frequencies, measured by blood flow while subjects were at rest. They found that different regions of the cerebellum are functionally connected with cerebral cortical regions across the entire cerebral cortex (Figure 37–3C). Taken together, these studies demonstrate the vast impact the cerebellum could have on many aspects of brain function.

Different Movements Are Controlled by Functional Longitudinal Zones

The cerebellum can be broadly divided into three areas that have distinctive roles in different kinds of movements: the vestibulocerebellum, spinocerebellum, and cerebrocerebellum (Figure 37–4).

The *vestibulocerebellum* consists of the flocculonodular lobe and is the most primitive part of the cerebellum. It receives vestibular and visual inputs, projects to the vestibular nuclei in the brain stem, and participates in balance, other vestibular reflexes, and eye movements. It receives information from the semicircular canals and the otolith organs, which sense the head's motion and its position relative to gravity. Most of this

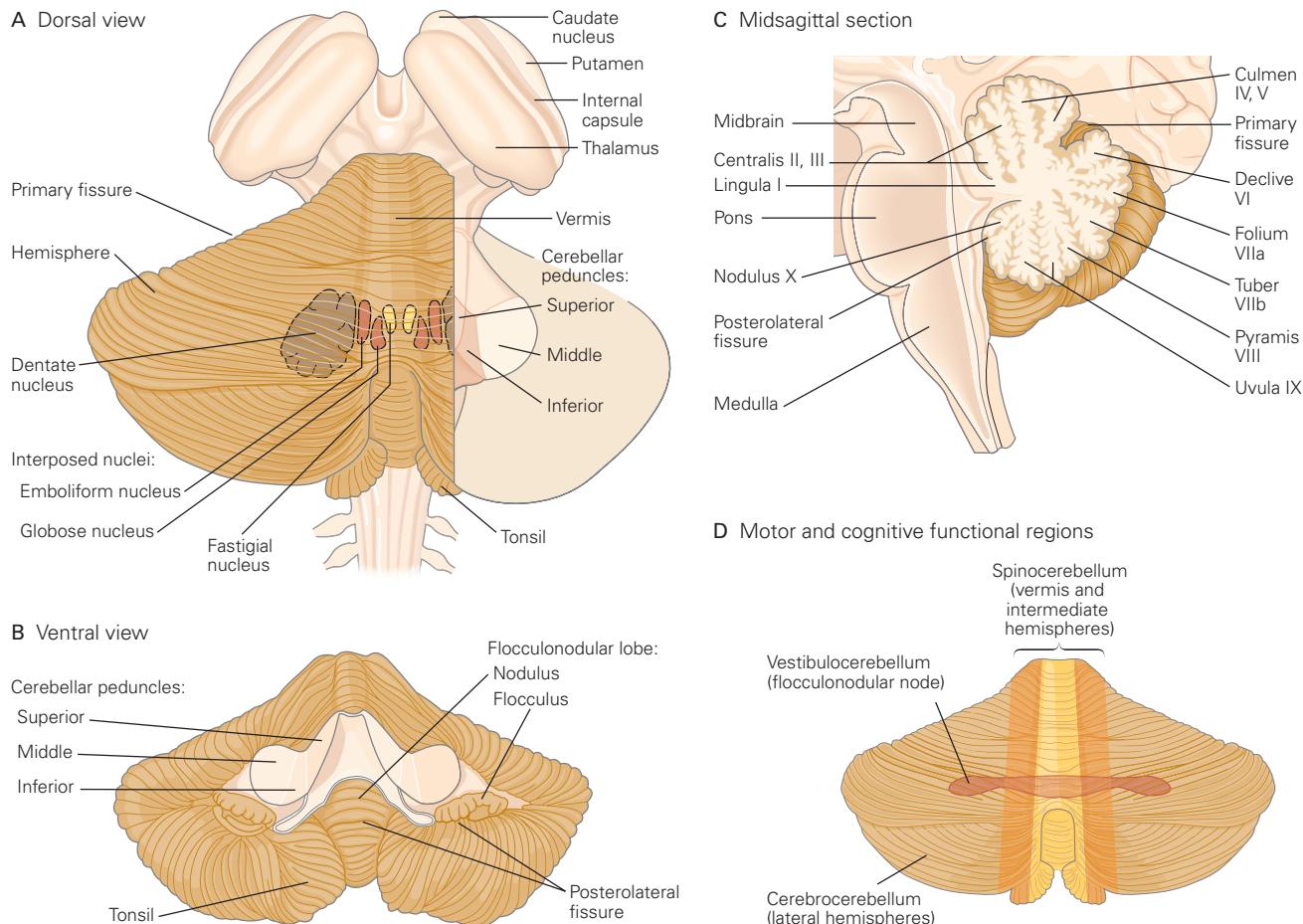


Figure 37-2 Gross features of the cerebellum. (Adapted, with permission, from Nieuwenhuys, Voogd, and van Huijzen 1988.)

- A. Part of the right hemisphere has been cut away to reveal the underlying cerebellar peduncles.
- B. The cerebellum is shown detached from the brain stem.

vestibular input arises from the vestibular nuclei in the brain stem. The vestibulocerebellum also receives visual input, from both the pretectal nuclei that lie deep in the midbrain beneath the superior colliculus and the primary and secondary visual cortex through the pontine and pretectal nuclei.

The vestibulocerebellum is unique in that its output bypasses the deep cerebellar nuclei and proceeds directly to the vestibular nuclei in the brain stem. Purkinje cells in the midline parts of the vestibulocerebellum project to the lateral vestibular nucleus to modulate the lateral and medial vestibulospinal tracts, which predominantly control axial muscles and limb extensors to assure balance

during stance and gait (Figure 37-5A). Disruption of these projections through lesions or disease impairs equilibrium.

The most striking deficits following lesions of the lateral vestibulocerebellum are in smooth-pursuit eye movement toward the side of the lesion. A patient with a lesion of the left lateral vestibulocerebellum can smoothly track a target that is moving to the right, but only poorly tracks motion to the left, using saccades predominantly (Figure 37-6A). These patients can have normal vestibulo-ocular reflex responses to head rotations but cannot suppress the reflex by fixating an object that rotates with the head (Figure 37-6B). These deficits occur commonly if the lateral

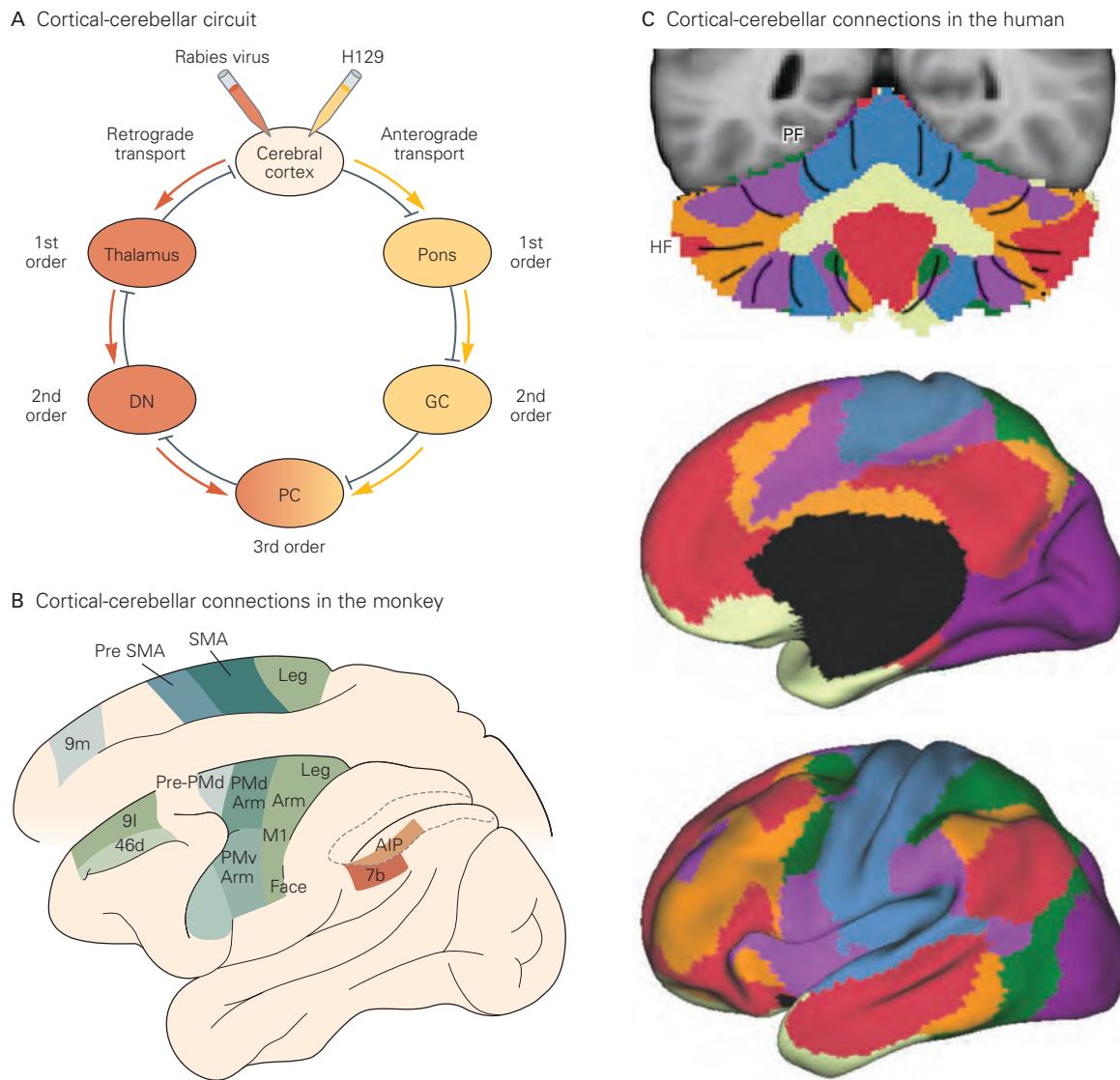


Figure 37–3 The cerebellum connects to many areas of cerebral cortex. (Parts A and B adapted, with permission, from Bostan, Dum, and Strick 2013. Copyright © 2013 Elsevier Ltd. part C adapted, with permission, from Buckner et al. 2011. Copyright © 2011 American Physiological Society.)

A. The cortical-cerebellar circuit in monkeys was traced with fluorescence-labeled transsynaptic viruses that can move in an anterograde or retrograde direction. Injection into the cerebral cortex of a retrograde virus, such as rabies virus, will label neurons that project to it and, by crossing synapses, can label second- and possibly higher-order neurons in a pathway. These are shown here in **red** as first-order (thalamus), second-order (deep nucleus), and third-order neurons (Purkinje cells). Injection into the cerebral cortex of an anterograde virus, such as the H129 strain of herpes simplex virus, will label neurons that are targets of the cerebral cortex. These are shown here in **yellow** as first-order (pons), second-order (granule cells), and third-order neurons (Purkinje cells). (Abbreviations: **DN**, dentate

nuclei; **GC**, granule cell; **H129**, strain of herpes simplex virus; **PC**, Purkinje cell rabies virus.)

B. Areas of the cerebral cortex connected to the cerebellum. The numbers refer to cytoarchitectonic areas. (Abbreviations: **AIP**, anterior intraparietal area; **M1**, face, arm, and leg areas of the primary motor cortex; **PMd** arm, arm area of the dorsal premotor area; **PMv** arm, arm area of the ventral premotor area; **PrePMd**, predorsal premotor area; **PreSMA**, presupplementary motor area; **SMA** arm, arm area of the supplementary motor area.)

C. Color-coded coronal section of the human cerebellum (**top**) and lateral and medial views of the human cerebral cortex (**bottom**) created from resting state functional connectivity maps (based on functional magnetic resonance imaging scans of 1,000 subjects). Colors correspond to cerebellar and cerebral areas that are connected. Note that the cerebellum is functionally connected with nearly all cerebral areas. (Abbreviations: **HF**, horizontal fissure; **PF**, primary fissure.)

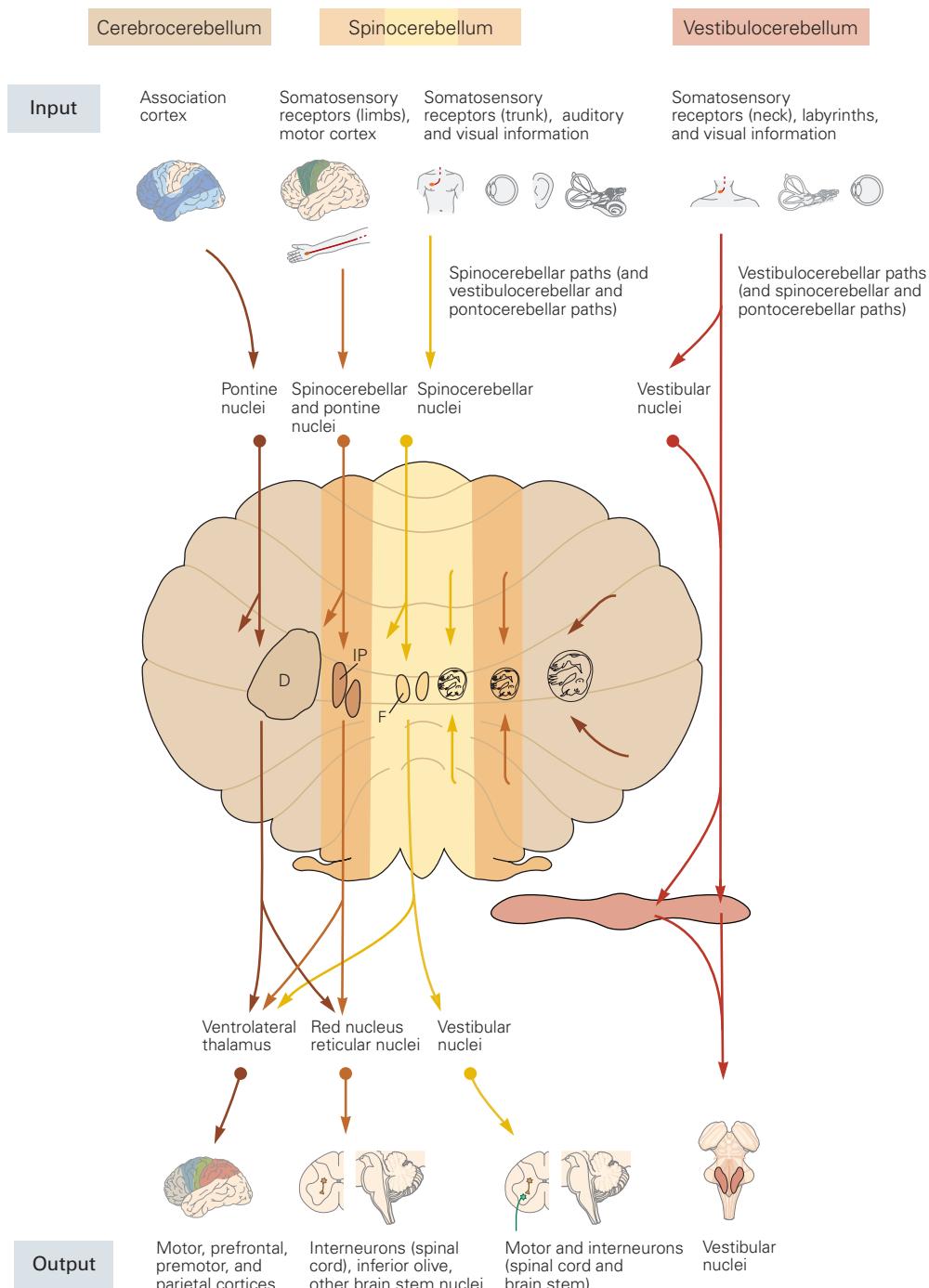


Figure 37–4 The three functional regions of the cerebellum have different inputs and different output targets. The cerebellum is shown unfolded, and arrows indicate the inputs and outputs of the different functional areas. The body maps in

the deep nuclei are based on anatomical tracing and single-cell recordings in nonhuman primates. (Abbreviations: D, dentate nucleus; F, fastigial nucleus; IP, interposed nucleus.) (Adapted, with permission, from Brooks and Thach 1981).

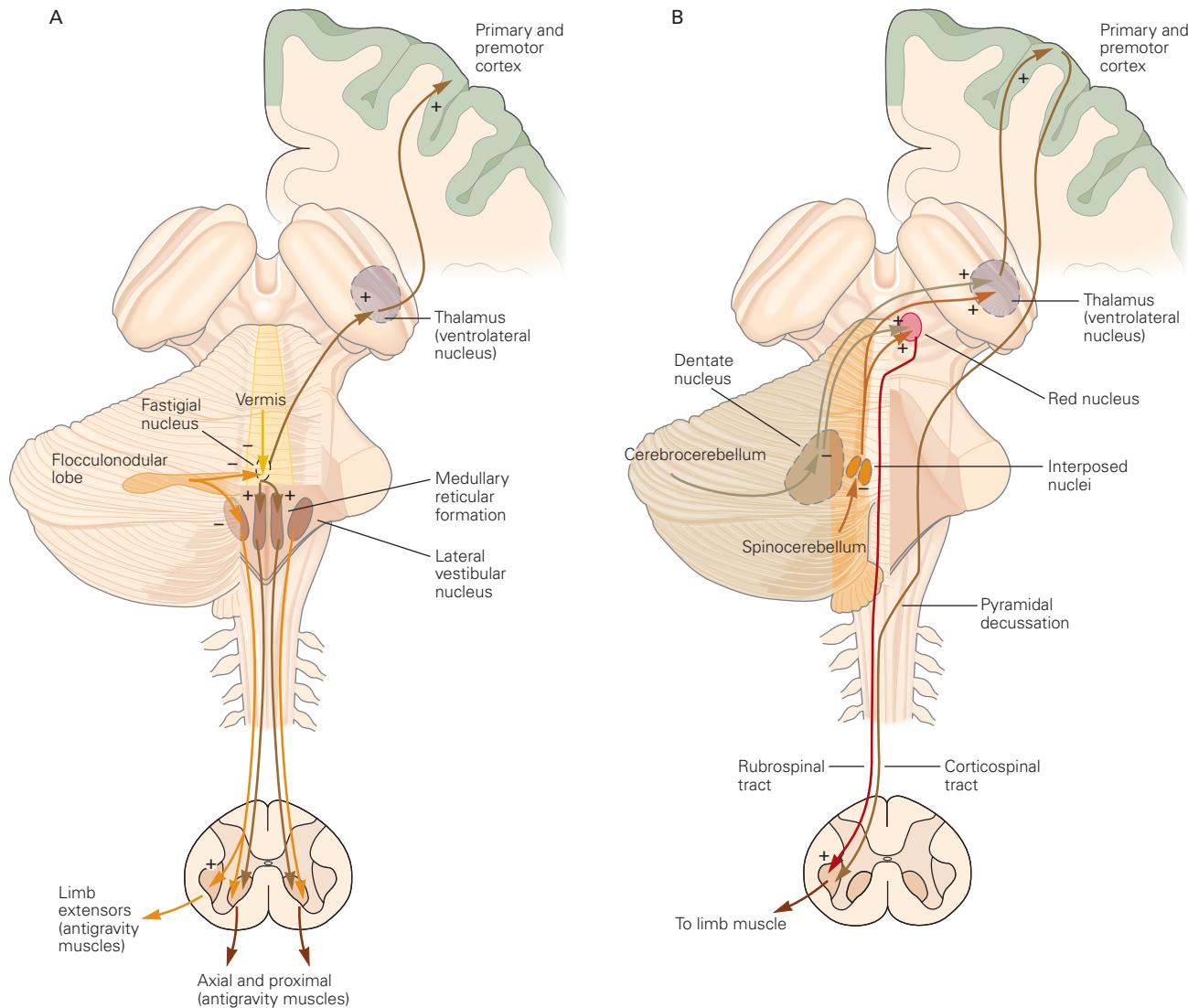


Figure 37-5 Input and output pathways of the cerebellum.

A. Nuclei in the vestibulocerebellum and the vermis control proximal muscles and limb extensors. The vestibulocerebellum (flocculonodular lobe) receives input from the vestibular labyrinth and projects directly to the vestibular nuclei. The vermis receives input from the neck and trunk, the vestibular labyrinth, and retinal and extraocular muscles. Its output is focused on the ventromedial descending systems of the brain stem, mainly the reticulospinal and vestibulospinal tracts and the corticospinal fibers acting on medial motor neurons. The

oculomotor connections of the vestibular nuclei have been omitted for clarity.

B. Nuclei in the intermediate and lateral parts of the cerebellar hemispheres control limb and axial muscles. The intermediate part of each hemisphere (spinocerebellum) receives sensory information from the limbs and controls the dorsolateral descending systems (rubrospinal and corticospinal tracts) acting on the ipsilateral limbs. The lateral area of each hemisphere (cerebrocerebellum) receives cortical input via the pontine nuclei and influences the motor and premotor cortices via the ventrolateral nucleus of the thalamus, and directly influences the red nucleus.

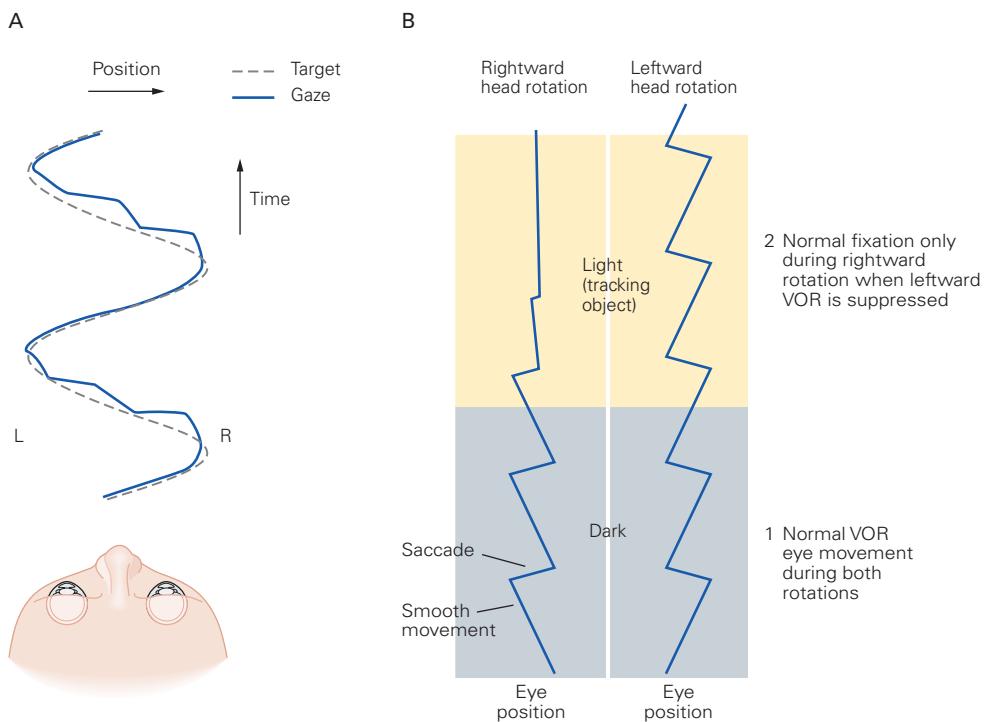


Figure 37-6 Lesions in the vestibulocerebellum have large effects on smooth-pursuit eye movements.

A. Sinusoidal target motion is tracked with smooth-pursuit eye movements as the target moves from left (L) to right (R). With a lesion of the left vestibulocerebellum, smooth pursuit is punctuated by saccades when the target moves from right to left.

B. In the same patient, responses to vestibular stimulation are normal, whereas object fixation is disrupted during leftward rotation. The traces on the left and right show the eye movements evoked by rightward and leftward head rotation experienced in separate sessions. In each session the patient sat in a

chair that rotated continuously in one direction, first in the dark then in the light while fixating on a target that moves along with him. (1) In the dark, the eyes show a normal vestibulo-ocular reflex (VOR) during rotation in both directions: The eyes move smoothly in the direction opposite to the head's rotation, then reset with saccades in the direction of head rotation. (2) In the light, the eye position during rightward head rotation is normal: Fixation on the target is excellent and the vestibulo-ocular reflex is suppressed. During leftward head rotation, however, the subject is unable to fixate on the object and the vestibulo-ocular reflex cannot be suppressed.

vestibulocerebellum is compressed by an acoustic neuroma, a benign tumor that grows on the eighth cranial nerve as it courses directly beneath the lateral vestibulocerebellum.

The *spinocerebellum* is composed of the vermis and intermediate parts of the cerebellar hemispheres (Figure 37-4). It is so named because it receives extensive input from the spinal cord via the dorsal and ventral spinocerebellar tracts. These pathways convey information about touch, pressure, and limb position as well as the spiking activity of spinal interneurons. Thus, these inputs provide the cerebellum with varied information about the changing state of the organism and its environment.

The vermis receives visual, auditory, and vestibular input as well as somatic sensory input from the head and proximal parts of the body. It projects by way of the fastigial nucleus to cortical and brain stem

regions that give rise to the medial descending systems controlling proximal muscles of the body and limbs (Figure 37-5A). The vermis governs posture and locomotion as well as eye movements. For example, lesions of the oculomotor region of the vermis cause saccadic eye movements that overshoot their target, much as patients with cerebellar damage make arm movements that overshoot their target.

The adjacent intermediate parts of the hemispheres also receive somatosensory input from the limbs. Neurons here project to the interposed nucleus, which provides inputs to lateral corticospinal and rubrospinal systems on the contralateral side of the brain and controls the more distal muscles of the limbs and digits (Figure 37-5B). Because corticospinal and rubrospinal systems cross the midline as they descend to the spinal cord, cerebellar lesions disrupt ipsilateral limb movements.

The *cererocerebellum* comprises the lateral parts of the hemispheres (Figure 37–4). These areas are phylogenetically the most recent and are much larger relative to the rest of the cerebellum in humans and apes than in monkeys and cats. Almost all of the inputs to and outputs from this region involve connections with the cerebral cortex. The output is transmitted through the dentate nucleus, which projects via the thalamus to contralateral motor, premotor, parietal, and prefrontal cortices. The dentate nucleus also projects to the contralateral red nucleus. The lateral hemispheres have many functions but seem to participate most extensively in planning and executing movement. They also have a role in cognitive functions unconnected with motor planning, such as visuospatial and language processes. There is now some correlative evidence implicating the cerebellar hemispheres in aspects of schizophrenia (Chapter 60), dystonia (Chapter 38), and autism (Chapter 62).

Two important principles of cerebellar function have emerged from recordings of the action potentials of single neurons in the cerebellar cortex and deep cerebellar nuclei during arm movements, along with controlled, temporary inactivation of specific cerebellar regions.

First, neurons in these areas discharge vigorously in relation to voluntary movements. Cerebellar output is related to the direction and speed of movement. The deep nuclei are organized into somatotopic maps of different limbs and joints, as in the motor cortex, although the organization of the cerebellar cortex has been characterized as “fractured somatotopy” with multiple disconnected and partial maps. Moreover, the interval between the onset of modulation of the firing of cerebellar neurons and movement is remarkably similar to that for neurons in the motor cortex. This result emphasizes the cerebellum’s participation in recurrent circuits that operate synchronously with the cerebral cortex.

Second, the cerebellum provides feedforward control of muscle contractions to regulate the timing of movements. Rather than awaiting sensory feedback, cerebellar output anticipates the muscular contractions that will be needed to bring a movement smoothly, accurately, and quickly to its desired endpoint. Failure of these mechanisms causes the intention tremor of cerebellar disorders. For example, a rapid single-joint movement is initiated by the contraction of an agonist muscle and terminated by an appropriately timed contraction of the antagonist. The contraction of the antagonist starts early in the movement, well before there has been time for sensory feedback to reach the brain, and therefore must be programmed as part of

the movement. When the dentate and interposed nuclei are experimentally inactivated, however, contraction of the antagonist muscle is delayed until the limb has overshot its target. The programmed anticipatory contraction of the antagonist in normal movements is replaced by a correction driven by sensory feedback. This correction is itself dysmetric and results in another error, necessitating a new adjustment (Figure 37–7).

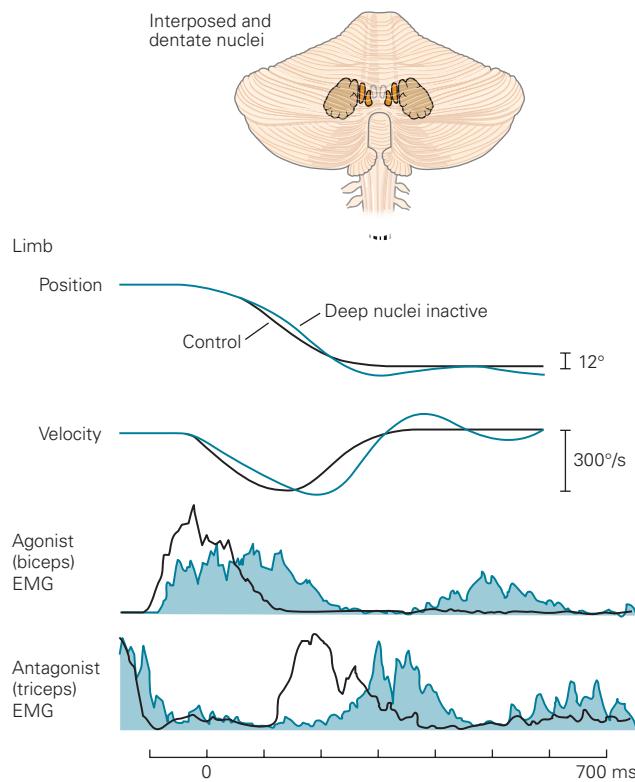


Figure 37–7 The interposed and dentate nuclei are involved in the precise timing of agonist and antagonist activation during rapid movements. The interposed (medial) and dentate (lateral) nuclei are highlighted in the drawing of the cerebellum. The records of limb movement show how a monkey normally makes a rapid elbow flexion limb movement and attempts to make the same movement when the interposed and dentate nuclei are inactivated by cooling. The electromyographic (EMG) traces show limb position and velocity and EMG responses of the biceps and triceps muscles. When the deep nuclei are inactivated, activation of the agonist (biceps) becomes slower and more prolonged. Activation of the antagonist (triceps), which is needed to stop the movement at the correct location, is likewise delayed and protracted so that the initial movement overshoots its appropriate extent. Delays in successive phases of the movement produce oscillations similar to the terminal tremor seen in patients with cerebellar damage.

The Cerebellar Cortex Comprises Repeating Functional Units Having the Same Basic Microcircuit

The cellular organization of the microcircuit in the cerebellar cortex is striking, and one of the premises of cerebellar research has been that the details of the microcircuit are an important clue to how the cerebellum works. In this section, we describe three major features of the microcircuit.

The Cerebellar Cortex Is Organized Into Three Functionally Specialized Layers

The three layers of the cerebellar cortex contain distinct kinds of neurons and are functionally specialized (Figure 37–8).

The deepest, or *granular layer*, is the input layer. It contains a vast number of granule cells, estimated at 100 billion, which appear in histological sections as small, densely packed, darkly stained nuclei. The granular layer also contains a few larger Golgi cells and, in some cerebellar regions, a smattering of other neurons such as cells of Lugaro, unipolar brush cells, and chandelier cells. The mossy fibers, one of the two principal afferent inputs to the cerebellum, terminate in this layer. The bulbous terminals of the mossy fibers excite granule cells and Golgi neurons in synaptic complexes called *cerebellar glomeruli* (Figure 37–8). As we will see later when discussing recurrent circuits in the cerebellum, Golgi cells inhibit granule cells.

The middle or *Purkinje cell layer* is the output layer of the cerebellar cortex. This layer consists of a single sheet of Purkinje cell bodies, each 50 to 80 μm in diameter. The fan-like dendritic trees of Purkinje cells extend upward into the molecular layer where they receive inputs from the second major type of afferent to the cerebellum, the climbing fibers, as well as from granule cells and inhibitory interneurons. Purkinje cell axons conduct the entire output of the cerebellar cortex, projecting to the deep nuclei in the underlying white matter or to the vestibular nuclei in the brain stem, where they release the inhibitory transmitter GABA (γ -aminobutyric acid).

The outermost or *molecular layer* contains the spatially polarized dendrites of Purkinje cells, which extend approximately 1 to 3 mm in the anterior-posterior direction but occupy only a very narrow territory in the medial-lateral direction. The molecular layer contains the cell bodies and dendrites of two types of “molecular layer interneurons,” the stellate and basket cells, both of which inhibit Purkinje cells. It also contains the axons of the granule cells, called the *parallel*

fibers because they run parallel to the long axis of the folia (Figure 37–8). Parallel fibers run perpendicular to the dendritic trees of the Purkinje cells and thus have the potential to form a few synapses with each of a large number of Purkinje cells.

The Climbing-Fiber and Mossy-Fiber Afferent Systems Encode and Process Information Differently

The two main types of afferent fibers in the cerebellum, the mossy fibers and climbing fibers, probably mediate different functions. Both form excitatory synapses with neurons in the deep cerebellar nuclei and in the cerebellar cortex. However, they terminate in different layers of the cerebellar cortex, affect Purkinje cells through very different patterns of synaptic convergence and divergence, and produce different electrical events in the Purkinje cells.

Climbing fibers originate in the inferior olive nucleus in the brain stem and convey sensory information to the cerebellum from both the periphery and the cerebral cortex. The climbing fiber is so named because each one wraps around the proximal dendrites of a Purkinje neuron like a vine on a tree, making numerous synaptic contacts (Figure 37–9). Each Purkinje neuron receives synaptic input from only a single climbing fiber, but each climbing fiber contacts 1 to 10 Purkinje cells that are arranged topographically along a parasagittal strip in the cerebellar cortex. Indeed, the axons from clusters of related olivary neurons terminate in thin parasagittal strips that extend across several folia, and the Purkinje cells from one strip converge on a common group of neurons in the deep nuclei.

Climbing fibers have an unusually powerful influence on the electrical activity of Purkinje cells. Each action potential in a climbing fiber generates a protracted, voltage-gated Ca^{2+} conductance in the soma and dendrites of the postsynaptic Purkinje cell. This results in prolonged depolarization that produces an electrical event called a “complex spike”: an initial large-amplitude action potential followed by a high-frequency burst of smaller-amplitude action potentials (Figure 37–9). Whether these smaller spikes are transmitted down the Purkinje cell’s axon is not clear. In awake animals, complex spikes occur spontaneously at low rates, usually around one per second. Specific sensory or motor events cause one or two complex spikes that occur at precise times in relation to those events.

Mossy fibers originate from cell bodies in the spinal cord and brain stem. They carry sensory information from the periphery as well as both sensory information and corollary discharges that report the current movement command (Chapter 30) from the cerebral cortex

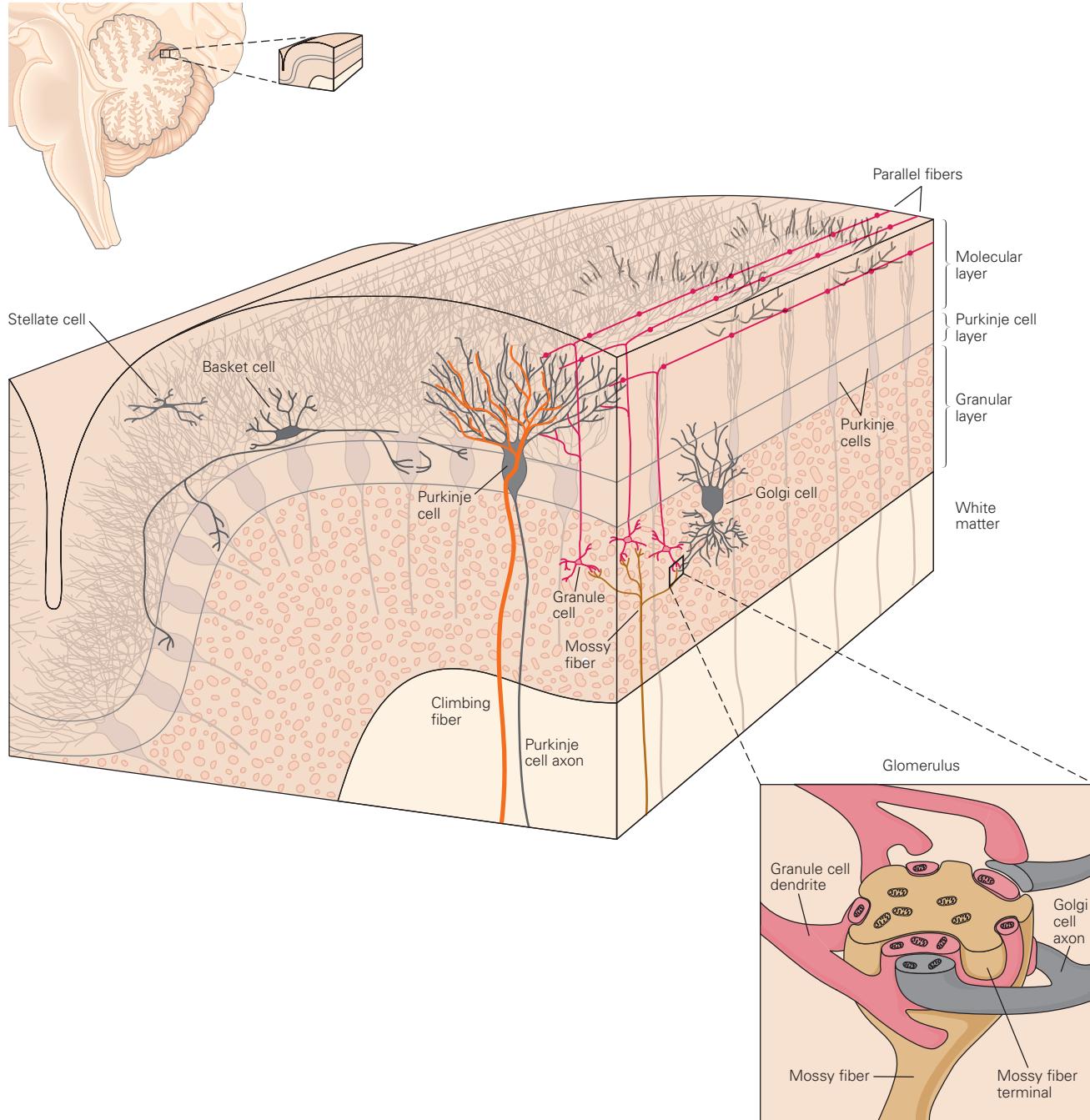


Figure 37–8 The cerebellar cortex contains five main types of neurons organized into three layers. A vertical section of a single cerebellar folium illustrates the general organization of the cerebellar cortex. The detail of a cerebellar glomerulus in the granular layer is also shown. A

glomerulus is the synaptic complex formed by the bulbous axon terminal of a mossy fiber and the dendrites of several Golgi and granule cells. Mitochondria are present in all of the structures in the glomerulus, consistent with their high metabolic activity.

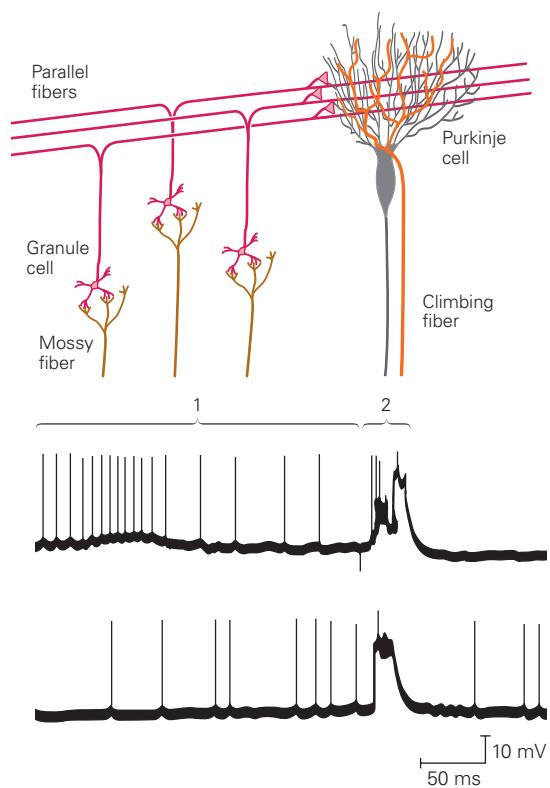


Figure 37-9 Simple and complex spikes recorded intracellularly from a cerebellar Purkinje cell. Simple spikes are produced by mossy-fiber input (1), whereas complex spikes are evoked by climbing-fiber synapses (2). (Reproduced, with permission, from Martinez, Crill, and Kennedy 1971.)

via the pontine nuclei. Mossy fibers affect Purkinje cells via multisynaptic pathways that have intriguing patterns of convergence and divergence. Individual mossy fibers, acting through granule cells and parallel fibers, have a tiny influence on Purkinje cell output, but collectively, the whole population of mossy fibers has massive effects on cerebellar output.

Mossy fibers form excitatory synapses on the dendrites of granule cells in the granular layer (Figure 37-8). Each granule cell has three to five short dendrites, and each dendrite receives contacts from a single mossy fiber. Due to this paucity of inputs, the spatial integration by a granule cell of its different mossy fiber synapses is not extensive; however, the cell can be the site of convergence of mossy fibers from multiple sensory modalities and motor corollary discharge. The next synaptic relay, between the granule cell axons and Purkinje cells, distributes information with very wide divergence and convergence. The parallel fibers allow each mossy fiber to influence a large number

of Purkinje cells, and each Purkinje cell is contacted potentially by axons from somewhere between 200,000 and 1 million granule cells. Importantly, in response to changing conditions there seems to be tremendous potential for adaptation of cerebellar output at the synapses between parallel fibers and Purkinje cells. It appears that only a small fraction of these synapses are active at any given time.

Parallel fibers produce brief, small excitatory potentials in Purkinje cells (Figure 37-9). These potentials converge in the cell body and spread to the initial segment of the axon where they generate conventional action potentials called “simple spikes” that propagate down the axon. In awake animals, Purkinje cells emit a steady stream of simple spikes, with spontaneous firing rates as high as 100 per second even when an animal is sitting quietly. Purkinje cells fire at rates as high as several hundred spikes per second during active eye, arm, and face movements.

The climbing-fiber and mossy-fiber/parallel-fiber systems seem to be specialized for transmission of different kinds of information. Climbing fibers cause complex spikes that seem specialized for event detection. Although complex spikes occur only infrequently, synchronous firing in multiple climbing fibers enables them to signal important events. Synchrony seems to arise partly because signaling between many neurons in the inferior olive nucleus occurs electrotonically (at gap-junction channels). In contrast, the high firing rates of the simple spikes in Purkinje cells can be modulated up or down in a graded way by mossy-fiber inputs, and thereby encode the magnitude and duration of peripheral stimuli or centrally generated behaviors.

The Cerebellar Microcircuit Architecture Suggests a Canonical Computation

The cerebellar microcircuit is replicated many times across the surface of the cerebellar cortex. This repeating architecture and pattern of convergence and divergence has led to the suggestion that since every such module has the same architecture and pattern of convergence and divergence, the cerebellar cortex performs the same basic “canonical” computation on all of its inputs, and that it potentially transforms cerebellar inputs in a similar way for all cerebellar output systems. Inspection of a diagram of the cerebellar microcircuit (Figure 37-10) reveals a number of different computational components. One general feature is the existence of parallel excitatory and inhibitory pathways to the Purkinje cells or deep cerebellar nuclei. The other general feature is the prevalence of recurrent loops.

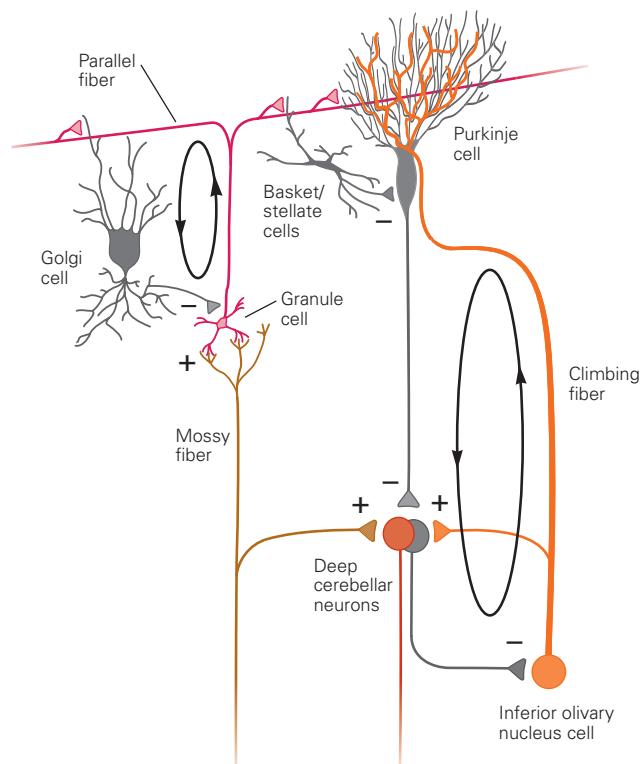


Figure 37–10 Synaptic organization of the cerebellar microcircuit. Excitation and inhibition converge both in the cerebellar cortex and in the deep nuclei. Recurrent loops involve Golgi cells within the cerebellar cortex and the inferior olive outside the cerebellum. (Adapted, with permission, from Raymond, Lisberger, and Mauk 1996. Copyright © 1996 AAAS.)

Parallel Feedforward Excitatory and Inhibitory Pathways

The excitatory inputs relayed from mossy fibers to granule cells to Purkinje cells work in parallel with feedforward inhibitory inputs through the two molecular layer interneurons, the stellate and basket cells. Both of these interneurons receive inputs from parallel fibers and inhibit Purkinje cells, but they have quite different architectures.

The short axons of stellate cells contact the nearby dendrites of Purkinje cells. Thus, a stellate cell acts locally in the sense that it and the Purkinje cell it inhibits are excited by the same parallel fibers. In contrast, a basket cell acts more widely. Its axon runs perpendicular to the parallel fibers (Figure 37–8) and creates flanks of inhibition on Purkinje cells that receive input from parallel fibers other than those that excite the basket cell. Stellate cells affect Purkinje cells via synapses that are on distal dendrites, whereas basket cells make powerful synapses on the cell body of Purkinje cells and seem to be positioned for a powerful influence on

Purkinje cell simple spiking. Remarkably, even 60 years after the architecture of the cerebellar microcircuit was described, the functional role of molecular layer interneurons remains a mystery.

Convergence of excitatory and inhibitory pathways is a predominant feature also in the deep cerebellar nuclei. Here, inhibitory inputs from Purkinje cells converge with excitatory inputs from axon collaterals of mossy and climbing fibers (Figure 37–10). Thus, a mossy fiber affects target neurons in the deep nuclei in two ways: directly by excitatory synapses and indirectly by pathways through the cerebellar cortex and the inhibitory Purkinje cells. Neurons of the deep cerebellar nuclei are active spontaneously even in the absence of synaptic inputs, so the inhibitory output of the Purkinje cells both modulates this intrinsic activity and sculpts the excitatory signals transmitted from mossy fibers to the deep nuclei. In almost all parts of the cerebellum, collaterals from climbing fibers to the deep cerebellar nuclei create the opportunity for a similar interaction of excitatory and inhibitory inputs.

Recurrent Loops

An important recurrent loop is contained entirely within the cerebellar cortex and employs Golgi cells to sculpt the activity of the granule cells, the input elements in the cerebellar cortex. Golgi cells receive a few large excitatory inputs from mossy fibers, many smaller excitatory inputs from parallel fibers, and inhibitory inputs from neighboring Golgi cells. The GABAergic terminals from Golgi cells inhibit granule cells (Figure 37–10) and thereby regulate the activity of granule cells and the signals conveyed by the parallel fibers. This loop is evidence that important processing may occur within the granular layer. It may shorten the duration of bursts in granule cells, limiting the magnitude of the excitatory response of granule cells to their mossy fiber inputs, or could ensure that the granule cells respond only when a certain number of their mossy fiber inputs are active.

A second recurrent loop provides Purkinje cells with a way to regulate their own climbing fiber inputs (Figure 37–10). Purkinje cells inhibit GABAergic inhibitory neurons in the deep cerebellar nuclei that project to the inferior olive. When the simple-spike firing of a group of Purkinje cells decreases, the activity of these inhibitory interneurons increases, leading to decreases in the excitability of neurons in the inferior olive. The decreased excitability of the inferior olive reduces both the probability of action potentials in climbing fibers that project to the original group of Purkinje cells and the duration of each burst of climbing fiber action

potentials. In the section on cerebellar learning, we will see how this recurrent loop could allow the cerebellar cortex to control the inputs that cause adaptive changes in the synapses on its Purkinje cells.

The Cerebellum Is Hypothesized to Perform Several General Computational Functions

We know that the cerebellum is important for motor control and some nonmotor functions. Even though we do not yet know how the cerebellar circuit controls these functions, we are able to identify aspects of the control that seem to be particularly “cerebellar.” These include reliable feedforward control, internal control of timing, integration of sensory inputs with corollary discharge, and state estimation through internal models.

The Cerebellum Contributes to Feedforward Sensorimotor Control

Sensory feedback is by its nature delayed. Therefore, when a movement is initiated there is a period of time before any useful sensory feedback is received about the movement. We saw earlier that cerebellar damage causes movement disorders that appear to result from out-of-date sensory feedback. If so, it is reasonable to assume that the cerebellum regulates and coordinates movement by preprogramming and coordinating commands for muscular contraction prior to the arrival of useful sensory feedback. The cerebellar output anticipates the muscular contractions that will be needed to bring a movement smoothly, accurately, and quickly to the desired endpoint, and uses sensory feedback mainly to monitor and improve its own performance.

Like neurons in the motor cortex, cerebellar neurons are activated before movement. Still, lesion studies and the symptoms in human motor disorders imply that the cerebellum and motor cortex play very different roles in movement. Lesions of the cerebellum disrupt the accuracy and coordination of voluntary movement, while lesions of the cerebral cortex largely prevent movement.

In addition, the pattern of cerebellar activity, not simply the rate of activity, conveys information for movement control. This is illustrated in mouse models of cerebellar disease. Deletion of certain ion channels produces excessive variability of Purkinje cell simple-spike firing patterns, which seems to lead to ataxia. This suggests that the regularity of cerebellar activity must be closely regulated to achieve normal movement.

The Cerebellum Incorporates an Internal Model of the Motor Apparatus

To program the correct muscle contractions for a smooth, accurate arm movement, the cerebellum needs to have some information about the physical configuration of the arm. Thus, it needs to create and maintain what are called “internal models” of the motor apparatus (Chapter 30). Internal models allow the cerebellum to perform a computation that helps the brain make good estimates of the exact muscle forces needed to move an arm in a desired manner.

An accurate *inverse dynamic* model of the arm, for example, can process sensory data about the current posture of the arm and automatically generate a sequence of properly timed and scaled commands to move the hand to a new desired position. An accurate *forward dynamic* model does the opposite: It processes a copy of a motor command and makes a prediction about the upcoming kinematics (ie, position and speed) of the arm movement. Recordings of the output of the cerebellum have provided evidence compatible with the idea that the cerebellum contains both types of models and that they are used to program both arm and eye movements.

One reason that the cerebellum may need these types of models for motor control is because of the complexities associated with moving linked segments of the body. Consider the mechanics of making a simple arm movement. Because of the mechanics of the arm and the momentum it develops when moving, movement of the forearm alone causes inertial forces that passively move the upper arm. If a subject wants to flex or extend the elbow without simultaneously moving the shoulder, then muscles acting at the shoulder must contract to prevent its movement. These stabilizing contractions of the shoulder joint occur almost perfectly in healthy subjects but not in patients with cerebellar damage, who experience difficulty controlling the inertial interactions among multiple segments of a limb (Figure 37–1B). As a result, patients exhibit greater inaccuracy of multi-joint versus single-joint movements.

In conclusion, the cerebellum uses internal models to allow it to preprogram a sequence of muscle contractions that will generate smooth, accurate movement. It also anticipates the forces that result from the mechanical properties of a moving limb. We do not yet know what these internal models look like in terms of the activity of cerebellar neurons, the circuits that operate as internal models, or how the cerebellar output is transformed into muscle forces. However, given that the properties of the limbs change throughout life, we can be confident that the cerebellum’s learning capabilities

are involved in adapting these internal models to help generate the most proficient movements.

The Cerebellum Integrates Sensory Inputs and Corollary Discharge

Sensory signals converge in the cerebellum with motor signals that are called a corollary discharge (or efference copy) because they report commands that are being sent to motor nerves at the same time. For example, some neurons in the dorsal spinocerebellar tract relay inputs from sensory afferents in the spinal cord and transmit sensory signals to the cerebellum. In contrast, the neurons in the spinal cord that give rise to the axons in the ventral spinocerebellar tract receive the same afferent and descending inputs as do spinal motor neurons, and they transmit the final motor command back to the cerebellum. The interaction of sensory signals and corollary discharge allows comparison of the plans for a movement with the sensory consequences. This comparison occurs to some degree at Purkinje cells, but we now know that at least some granule cells receive converging sensory and corollary discharge inputs and could perform the comparison.

Internal models and corollary discharge together provide one possible explanation of the role of the cerebellum in movement. To be able to program accurate movements the cerebellum must be able to estimate the state of the motor system through sensory feedback and knowledge of prior motor activity. Next, it must combine information on the state of the motor system with the goals of the next movement and use internal models of the effector to help create commands for muscle forces that will generate an accurate and efficient movement. During the movement, the cerebellum must monitor movement performance through sensory feedback. Current thinking is that much of this is done by an internal model that converts corollary discharge into predictions of the sensory feedback. The cerebellum then compares real and predicted sensory feedback to determine a sensory prediction error and uses the sensory prediction error to guide corrective movements and learning.

Using a paradigm that required monkeys to ignore the sensory signals caused by their own movement, Kathy Cullen and colleagues have identified a neural correlate of a sensory prediction error in the deep cerebellar nuclei. Specifically, they studied the vestibular sensory signals that result from an animal's active head movements. They showed that the brain attenuates or even eliminates the vestibular sensory signals caused by one's own active head movement in order to better detect unpredictable vestibular signals due to the

environment. However, when the head is effectively made heavier by adding resistance via a mechanical device, the vestibular sensory signals no longer match the predicted sensory signals that normally would attenuate the vestibular input. They showed that the cerebellum adjusts its predictions of the vestibular input to account for the changes in head movement caused by resistance due to the mechanical device. After some practice, the predicted and actual self-generated sensory inputs again match, and neurons in the deep cerebellar nucleus return to being unresponsive to vestibular inputs. Cerebellum-dependent learning is described in detail later in this chapter.

The Cerebellum Contributes to Timing Control

The cerebellum seems to have a role in movement timing that goes well beyond its role in regulating the timing of contractions in different muscles (Figure 37–7). When patients with cerebellar lesions attempt to make regular tapping movements with their hands or fingers, the rhythm is irregular and the motions vary in duration and force.

Based on a theoretical model of how tapping movements are generated, Richard Ivry and Steven Keele inferred that medial cerebellar lesions interfere only with accurate execution of the response, whereas lateral cerebellar lesions interfere with the timing of serial events. Such timing defects are not limited to motor events. They also affect the patient's ability to judge elapsed time in purely mental or cognitive tasks, as in the ability to distinguish whether one tone is longer or shorter than another or whether the speed of one moving object is greater or less than that of another. We will see in our discussion of motor learning that the cerebellum is critical for learning the timing of motor acts.

The Cerebellum Participates in Motor Skill Learning

In the early 1970s, on the basis of mathematical modeling of cerebellar function and the cerebellar microcircuit, David Marr and James Albus independently suggested that the cerebellum might be involved in learning motor skills. Along with Masao Ito, they proposed that the climbing-fiber input to Purkinje cells causes changes at the synapses that relay mossy fiber input signals from parallel fibers to Purkinje cells. According to their theory, the synaptic plasticity would lead to changes in simple-spike firing, and these changes would cause behavioral learning. Subsequent experimental evidence has supported and extended this theory of cerebellar motor learning.

Climbing-Fiber Activity Changes the Synaptic Efficacy of Parallel Fibers

Climbing fibers can selectively induce *long-term depression* in the synapses between parallel fibers and Purkinje cells that are activated concurrently with the climbing fibers. Many studies in brain slices and cultured Purkinje cells have found that concurrent stimulation of climbing fibers and parallel fibers depresses the Purkinje cell responses to subsequent stimulation of the same parallel fibers. The depression is selective for the parallel fibers that were activated in conjunction with the climbing-fiber input

and does not appear in synapses from parallel fibers that had not been stimulated along with climbing fibers (Figure 37–11A). The resulting depression can last for minutes to hours.

Many studies in a variety of motor learning systems have recorded activity in Purkinje cells that is consistent with the predictions of the cerebellar learning theory. For example, if an unexpected resistance is applied to a well-practiced arm movement, extra muscle tension will be required to move. Climbing fiber activity can signal error until the unexpected resistance is learned. They presumably depress the synaptic

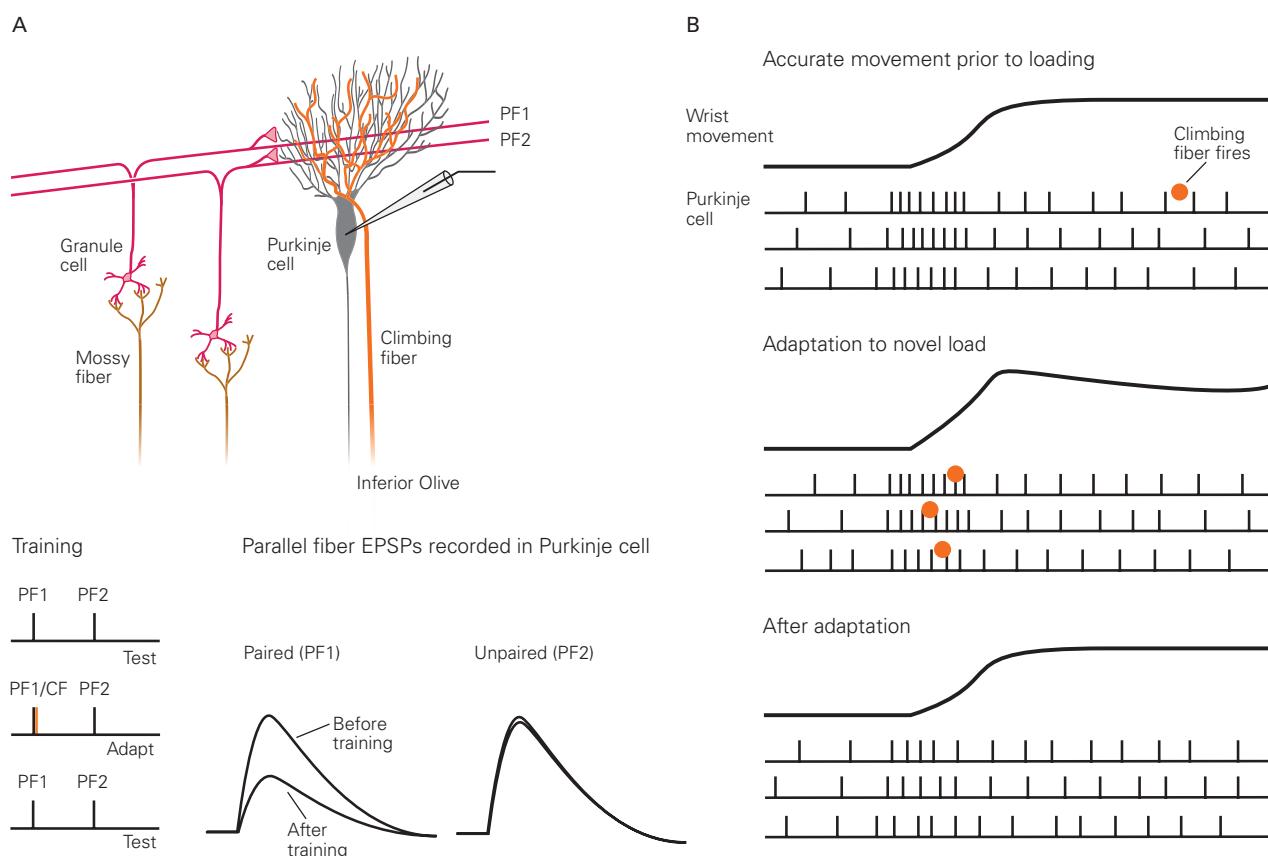


Figure 37–11 Long-term depression of the synaptic input from parallel fibers to Purkinje cells is one plausible mechanism for cerebellar learning.

A. Two different groups of parallel fibers and the presynaptic climbing fibers are electrically stimulated *in vitro*. Repeated stimulation of one set of parallel fibers (PF1) at the same time as the climbing fibers produces a long-term reduction in the responses of those parallel fibers to later stimulation. The responses of a second set of parallel fibers (PF2) are not depressed because they are not stimulated simultaneously with the presynaptic climbing fibers. (Abbreviations: CF, climbing fiber; EPSP, excitatory postsynaptic potential.) (Adapted from Ito et al. 1982.)

B. Top: An accurate wrist movement by a monkey is accompanied by a burst of simple spikes in a Purkinje cell, followed later by discharge of a single climbing fiber in one trial. Middle: When the monkey must make the same movement against a novel resistance (adaptation), climbing-fiber activity occurs during movement in every trial and the movement itself overshoots the target. Bottom: After adaptation, the frequency of simple spikes during movement is quite attenuated, and the climbing fiber is not active during movement or later. This is the sequence of events expected if long-term depression in the cerebellar cortex plays a role in learning. Climbing fiber activity is usually low (1/s) but increases during adaptation to a novel load. (Adapted, with permission, from Gilbert and Thach 1977.)

strength of parallel fibers involved in generating those errors, namely those that drove Purkinje simple-spike firing at the time of the climbing-fiber activity (Figure 37–11B). With successive movements, the parallel-fiber inputs conveying the flawed central command are increasingly suppressed, a more appropriate pattern of simple-spike activity emerges, and eventually movement errors disappear, along with the climbing-fiber error signal. Although this kind of result is consistent with the theory of cerebellar learning, it stops short of proving that the neural and behavioral learning was caused by long-term depression of the synapses from parallel fibers onto Purkinje cells.

The Cerebellum Is Necessary for Motor Learning in Several Different Movement Systems

The cerebellum is involved in learning a wide variety of movements, ranging from limb and eye movements to walking. In each movement system, motor learning operates to improve the feedforward control of movement. Errors render motor control transiently dependent on sensory feedback, and motor learning restores the ideal situation where performance is accurate without relying on sensory feedback.

Adaptation of limb movements that rely on eye-hand coordination can be demonstrated by having people wear prisms that deflect the light path sideways. When a person plays darts while wearing prism goggles that displace the entire visual field to the left, the initial dart throw lands to the left side of the target by an amount proportional to the strength of the prisms. The subject gradually adapts to the distortion through practice; within 10 to 30 throws, the darts land on target (Figure 37–12). When the prisms are removed, the adaptation persists, and the darts hit to the right of the target by roughly the same distance as the initial prism-induced error. Patients with a damaged cerebellar cortex or inferior olive are severely impaired or unable to adapt at all in this test.

Classical conditioning of the eye-blink response also depends on an intact cerebellum. In this form of associative learning, a puff of air is directed at the cornea, causing the eye to blink at the end of a neutral stimulus such as a tone. If the tone and the puff are paired repeatedly with a fixed duration of the tone, then the brain learns the tone's predictive power and the tone alone is sufficient to cause a blink. Michael Mauk and his colleagues have shown that the brain also can learn about the timing of the stimulus so that the eye blink occurs at the right time. It is even possible to learn to blink at different times in response to tones of different frequencies.

All forms of conjugate eye movement require the cerebellum for correct performance, and each form is subject to motor learning that involves the cerebellum. For example, the vestibulo-ocular reflex normally keeps the eyes fixed on a target when the head is rotated (Chapter 27). Motion of the head in one direction is sensed by the vestibular labyrinth, which initiates eye movements in the opposite direction to prevent visual images from slipping across the retina. When humans and experimental animals wear glasses that change the size of a visual scene, the vestibulo-ocular reflex initially fails to keep images stable on the retina because the amplitude of the reflex is inappropriate to the new conditions. After the glasses have been worn continuously for several days, however, the size of the reflex becomes progressively reduced (for miniaturizing glasses) or increased (for magnifying glasses) (Figure 37–13A). These changes are required to prevent images from slipping across the retina because magnified (or miniaturized) images also move faster (or slower). The performance of the baseline vestibulo-ocular reflex does not depend heavily on the cerebellum, but its adaptation does and can be blocked in experimental animals by lesions of the lateral part of the vestibulocerebellum called the floccular complex.

Saccadic eye movements also depend on the integrity of Purkinje cells in the oculomotor vermis in lobules V, VI, and VII of the vermis (Figure 37–2C). These cells discharge prior to and during saccades, and lesions of the vermis cause saccades to become hypermetric, much as we see in the arm movements of cerebellar patients. The outputs from neurons of the vermis concerned with saccades are transmitted through a very small region of the caudal fastigial nucleus to the saccade generator in the reticular formation.

The same Purkinje cells participate in a form of motor learning called saccadic adaptation. This adaptation is demonstrated by having a monkey fixate on a target straight ahead and then displaying a new target at an eccentric location. During the saccade to the new target, the experimenter moves the new target to a more eccentric location. Initially, the subject needs to make a second saccade to fixate on the target. Gradually, over several hundred trials, the first saccade grows in amplitude so that it brings the eye directly to the final location of the target (Figure 37–13B). Recordings during saccadic adaptation have revealed that climbing fiber inputs to the Purkinje cells in the oculomotor vermis signal saccadic errors during learning, and the simple-spike firing rate of the same cells adapts gradually along with the monkey's eye movements. Thus, the oculomotor vermis is a likely site for motor learning of the amplitude of saccadic eye movements. The story

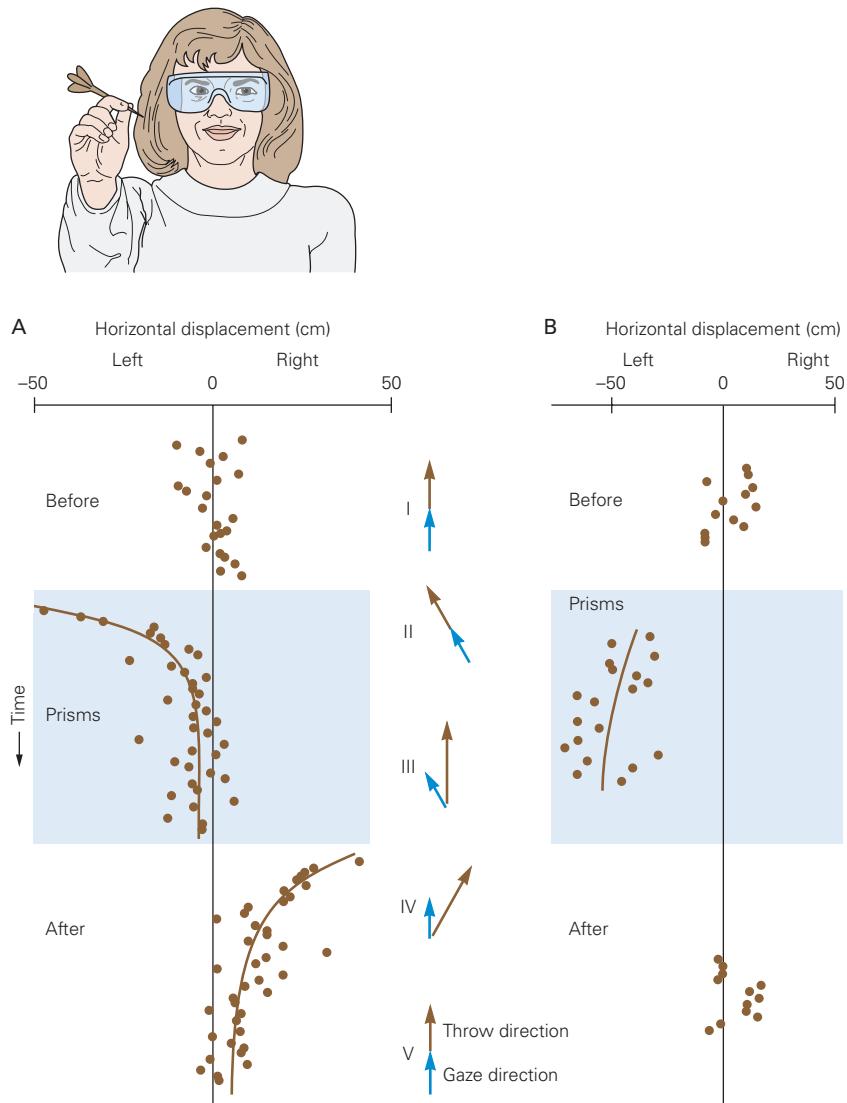


Figure 37-12 Adjustment of eye-hand coordination to a change in optical conditions. The subject wears prism goggles that bend the optic path to her right. She must look to her left along the bent light path to see the target directly ahead. (Adapted, with permission, from Martin et al. 1996).

A. Without prisms, the subject throws with good accuracy (I). The first hit after the prisms have been put in place is displaced left of center because the hand throws where the eyes are directed. Thereafter, hits trend rightward toward the target, away from where the eyes are looking (II). After removal of the prisms, the subject fixes her gaze in the center of the target; the first throw hits to the right of center, away from where the eyes are directed. Thereafter, hits trend toward the target (III).

Immediately after removing the prisms, the subject directs her gaze toward the target; her adapted throw is to the right of the direction of gaze and to the right of the target (IV). After recovery from adaptation, she again looks at and throws toward the target (V). Data during and after prism use have been fit with exponential curves. Gaze and throw directions are indicated by the blue and brown arrows, respectively, on the right. The inferred gaze direction assumes that the subject is fixating the target.

B. Adaptation fails in a patient with unilateral infarctions in the territory of the posterior inferior cerebellar artery that affect the inferior cerebellar peduncle and inferior lateral posterior cerebellar cortex.

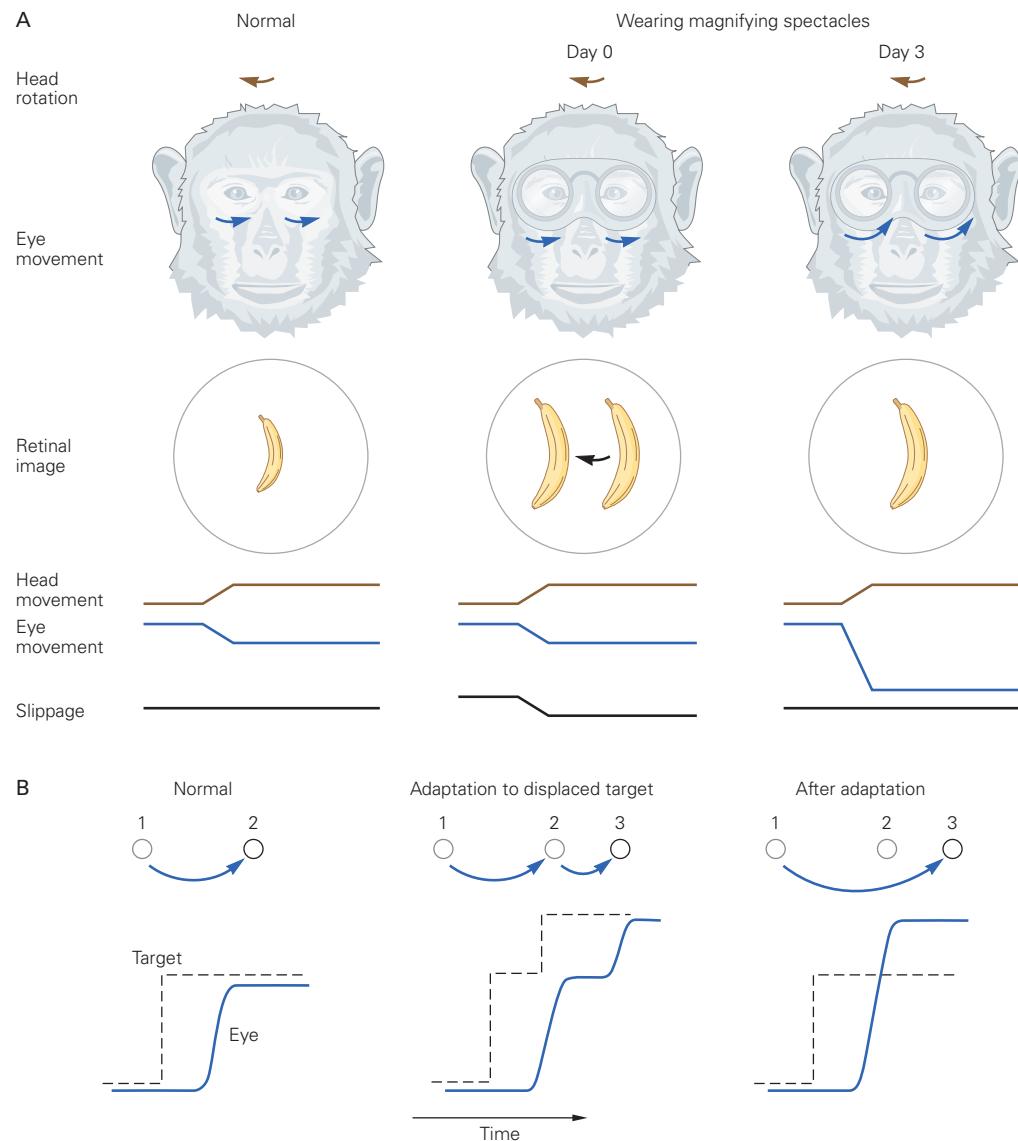


Figure 37-13 Cerebellar learning in the vestibulo-ocular reflex and in saccadic eye movements.

A. Motor learning in the vestibulo-ocular reflex of a monkey wearing magnifying spectacles. The columns show normal conditions before learning, the situation when the monkey first dons the spectacles (day 0), and after complete adaptation (day 3). Eye movements are normally equal and opposite to head turns, and the banana stays stable in the retina during head turns. With the spectacles on, the banana appears larger; when the head turns, the vestibulo-ocular reflex is too small and the banana's image slips across the retina. After adaptation, the eye movements are large enough that the image of the banana

again remains stable on the retina during head turns. (Adapted, with permission, from Lisberger 1988.)

B. Motor learning in saccadic eye movements. The columns show saccades under normal conditions, on the first adaptation trial, and after full adaptation. Normally, the saccade responds to a change in target position by bringing the eye almost perfectly to the new target position. During adaptation, the target moves to a new position during the initial saccade, requiring a second saccade to bring the eye to the new, final target position. After adaptation, the original target position evokes a larger saccade that is appropriate to bring the eye to the new target position, even though the target does not move.

is very similar for smooth-pursuit eye movements, except that the relevant part of the cerebellum is the floccular complex, using the same Purkinje cells that participate in adaptation of the vestibulo-ocular reflex.

Finally, learning of new walking patterns has been studied in cerebellar patients using a split-belt treadmill that requires one leg to move faster than the other. Cerebellar damage does not impair the ability to use feedback to immediately change the walking pattern when the two belt speeds differ: Patients can lengthen the time that they stand on the slower treadmill belt and shorten the time that they stand on the faster treadmill belt. However, cerebellar patients cannot learn over hundreds of steps to make their walking pattern symmetric, whereas healthy individuals can (see Figure 30–14).

Learning Occurs at Several Sites in the Cerebellum

We know now that there are many sites of synaptic and cellular plasticity in the cerebellar microcircuit. Almost every synapse that has been studied undergoes either potentiation or depression, and the theory of cerebellar learning has been broadened accordingly. Detailed analyses of the role of cerebellar circuits in motor learning have been conducted in several motor systems: adaptation of multiple kinds of eye movements, classical conditioning of the eye blink, and motor learning in arm movements.

In today's broadened theory of cerebellar learning, learning occurs not only in the cerebellar cortex, as postulated by Marr, Albus, and Ito, but also in the deep cerebellar nuclei (Figure 37–14). Our understanding of learning in the cerebellar cortex is based partly on long-term depression of the synapses from parallel fibers to Purkinje cells, but many other synapses are characterized by plasticity, and they also probably participate. Available evidence is still compatible with the long-standing idea that inputs from climbing fibers provide the primary instructive signals that lead to changes in synaptic strength within the cerebellar cortex, but now there is room for the possibility of other instructive signals as well. Learning probably results from coordinated synaptic plasticity at multiple sites rather than from changes at a single site.

Studies of classical conditioning of the eye blink and adaptation of the vestibulo-ocular reflex provide strong evidence that learning occurs in both the cerebellar cortex and the deep cerebellar nuclei. Further, considerable evidence suggests that learning may occur first in the cerebellar cortex and then be transferred to the deep cerebellar nuclei. At least for eye

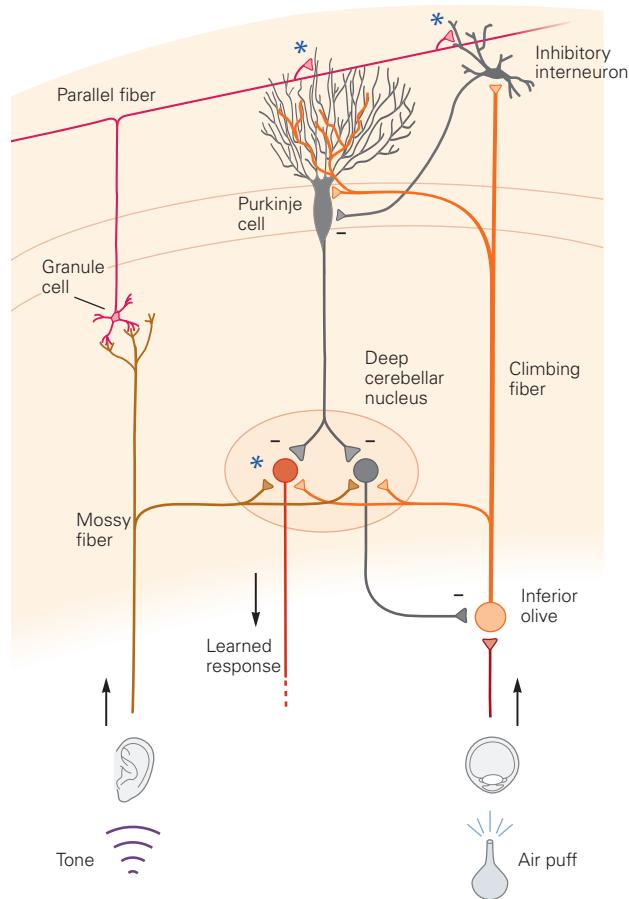


Figure 37–14 Learning in the cerebellar microcircuit can occur in the cerebellar cortex and the deep cerebellar nuclei. The diagram is based on classical conditioning of blinking, which is driven by pairing a tone (so-called conditioned stimulus carried by mossy fibers) and an air puff (the unconditioned stimulus carried by climbing fibers). Learning occurs at the parallel fiber–Purkinje cell synapses when the climbing fiber and parallel fibers are active together. Learning also occurs at the mossy-fiber synapse onto the deep cerebellar nuclei. (Sites of learning are denoted by asterisks.) While this example diagrams a classical conditioning paradigm, plasticity occurs at the same sites during adaptation of the vestibulo-ocular reflex when head turns are associated with image motion on the retina (Chapter 27). (Adapted, with permission, from Carey and Lisberger 2002.)

blink conditioning, the cerebellar cortex may play a special role in learning timing.

As discussed earlier, the cerebellum makes use of internal models to ensure smooth and accurate movement in advance of any guidance by sensory feedback. Synaptic changes that lead to circuit learning could be the mechanisms that create and maintain accurate internal models. One important function of learning in the cerebellum may be the continuous tuning of

internal models. Cerebellar internal models may use sensory feedback to adjust synaptic and cellular function so that motor commands produce movements that are rapid, accurate, and smooth. Thus, the cerebellum appears to be the learning machine envisioned by the earliest investigators, but its learning capabilities may be greater and more widely dispersed than originally imagined and may affect all cerebellar contributions to behavior.

Highlights

1. The cerebellum plays a critical role in movement. Damage to the cerebellum leads to profound movement incoordination called ataxia, which affects all movements ranging from eye and limb movements to balance and walking. Cerebellar damage also leads to some sensory deficits but only during active movement.
2. The cerebellum also plays a role in cognitive and emotional behavior. Deficits in these domains are less immediately obvious after cerebellar damage but appear with formalized testing. There is probably a common mechanism for deficits across both motor and nonmotor domains, but the mechanism is not yet understood.
3. The cerebellum acts through its connections to other brain structures. Its inputs come indirectly from wide regions of the cerebral cortex, as well as from the brainstem and spinal cord. Cerebellar outputs project to the vestibular nuclei, the brainstem reticular formation, and the red nucleus and via the thalamus to wide regions of the cerebral cortex.
4. Reciprocal connections between the cerebellum and the cerebral cortex include sensory and motor cortices as well as wide regions of the parietal and prefrontal cortices. Cerebrocerebellar connections are organized as a series of parallel, closed, recurrent loops, where a given region of the cerebral cortex makes both efferent and afferent connections with a given part of the cerebellum.
5. The circuit of the cerebellar cortex is highly stereotyped, suggesting a common computational mechanism for its interactions with other brain regions. It includes an input granular layer where mossy fibers synapse on granule cells and Golgi cells provide inhibitory feedback; an inhibitory Purkinje cell layer, with the sole output neurons of the cerebellar cortex; and a molecular layer where Purkinje cell dendrites and inhibitory interneurons receive inputs from the parallel fibers that emerge from the axons of granule cells.
6. The climbing-fiber and mossy-fiber inputs to the cerebellum are very different anatomically. Each Purkinje cell receives many synaptic contacts from a single climbing fiber but can be influenced via granule cells by a huge number of mossy fibers. Climbing fibers fire at very low frequencies and cause unitary “complex spikes” in Purkinje cells. Mossy fibers cause “simple spikes” that can discharge at very high rates. It is thought that the interplay between these inputs is essential for learning.
7. Theories of cerebellar motor control emphasize several general principles. The cerebellum is important for generating reliable feedforward action before there has been time for useful sensory feedback to occur. It plays a key role in the internal control of timing. The cerebellum relies on computations that combine sensory inputs with corollary discharge reporting the movement that was commanded. Internal models of the motor effector organs and the world allow the cerebellum to estimate the state of the motor system and guide accurate feedforward actions.
8. Learning and adaptation of movement are fundamental functions of the cerebellum. Cerebellar learning requires feedback about movement errors and updates movement on a trial-by-trial basis. There are many sites of synaptic plasticity in the cerebellum, and current evidence for motor learning systems supports at least two sites of learning in the cerebellum. One site involves long-term depression of the synapses from parallel fibers to Purkinje cells, guided by errors signaled by climbing-fiber inputs. The other site is in the deep cerebellar nuclei. It is likely that the same learning mechanism is used for cognitive and emotional processing.

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