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

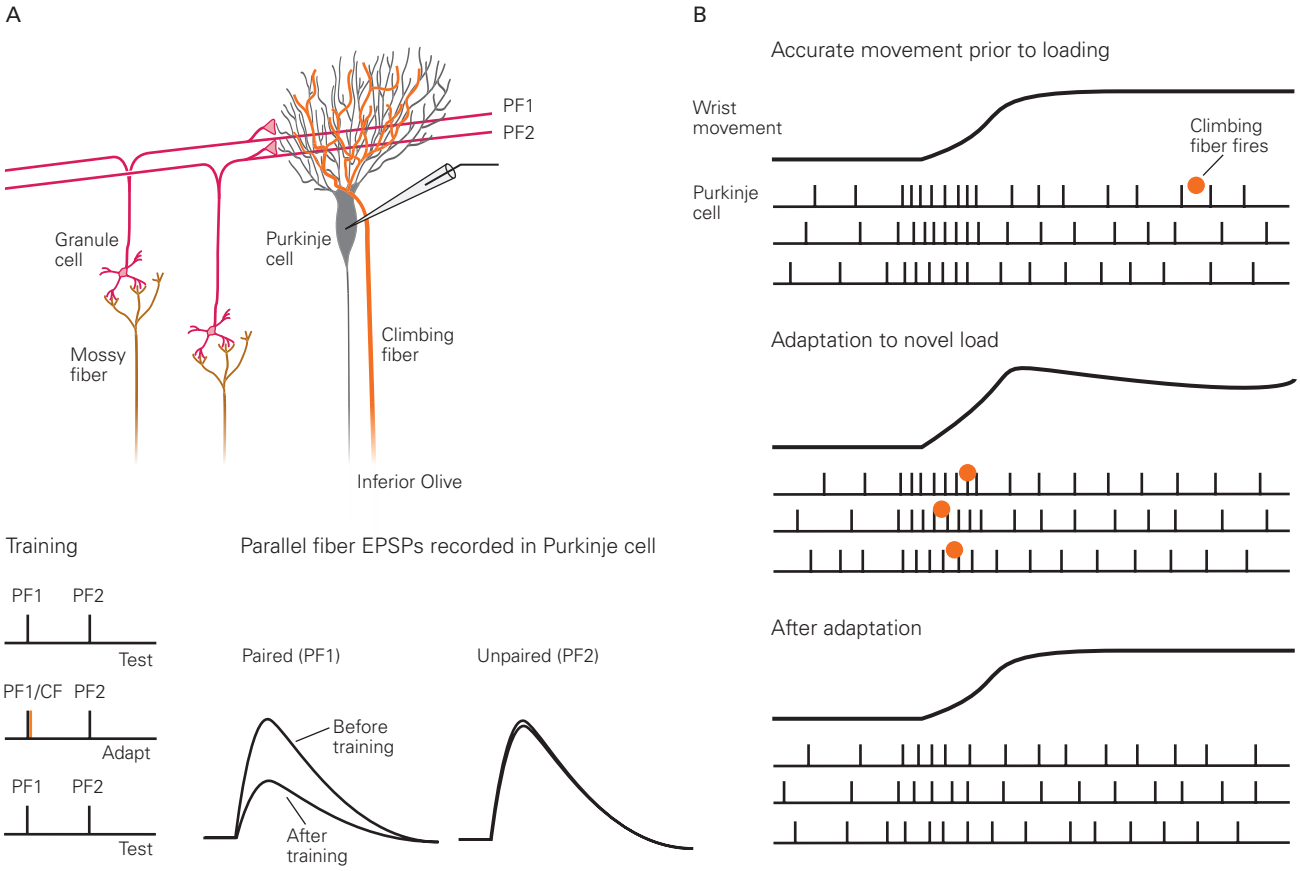

Figure 37–11 Long-term depression of the synaptic input from parallel fibers to Purkinje cells is one plausible mechanism for cerebellar learning.

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

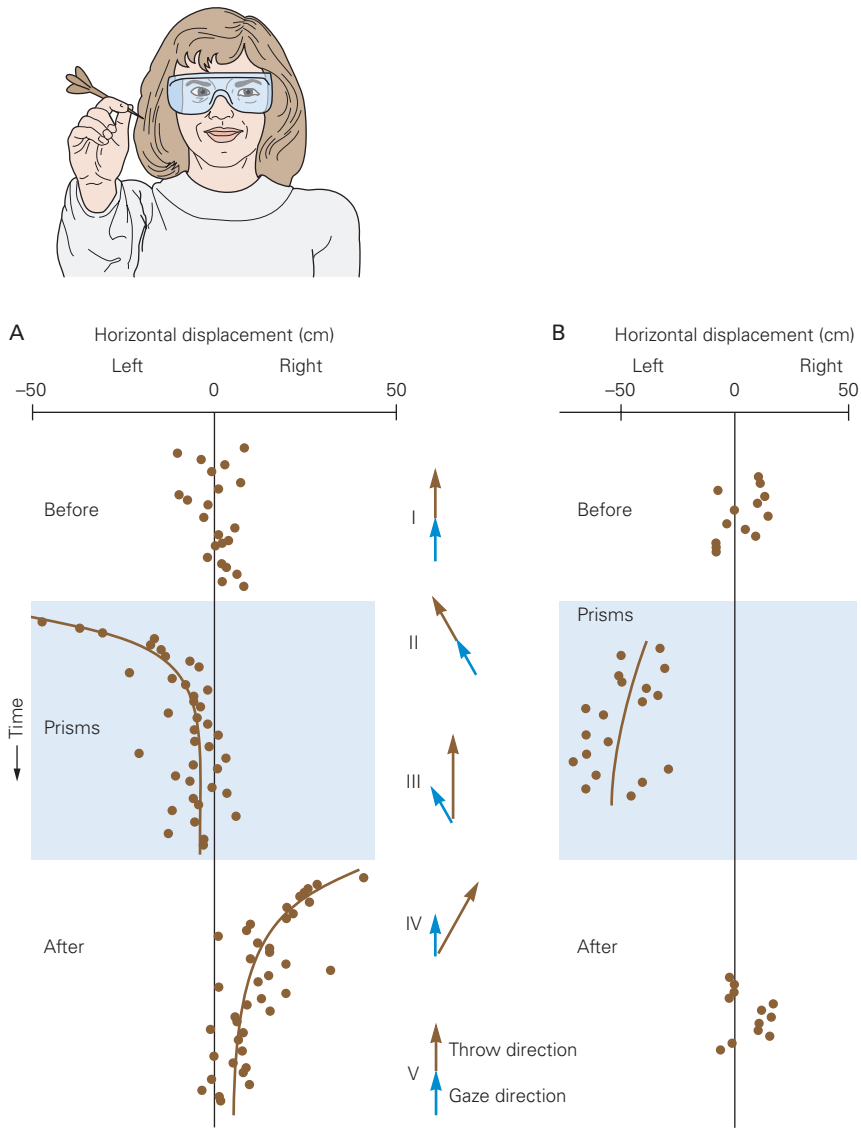

Figure 37–12 Adjustment of eye–hand coordination to a change in optical conditions. The subject wears prism goggles that bend the optic path to her right. She must look to her left along the bent light path to see the target directly ahead. (Adapted, with permission, from Martin et al. 1996).

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.

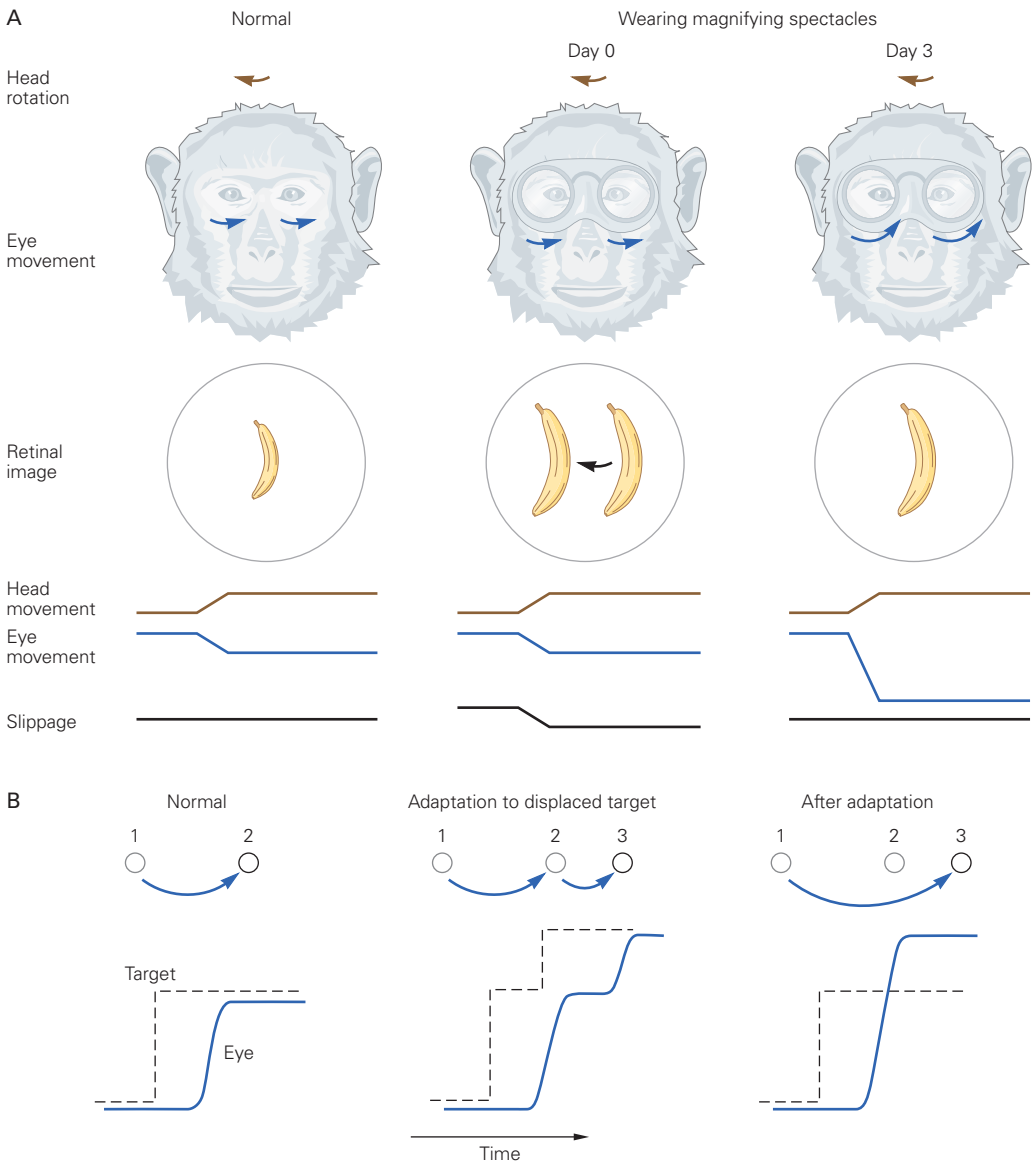

Figure 37–13 Cerebellar learning in the vestibulo-ocular reflex and in saccadic eye movements.

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

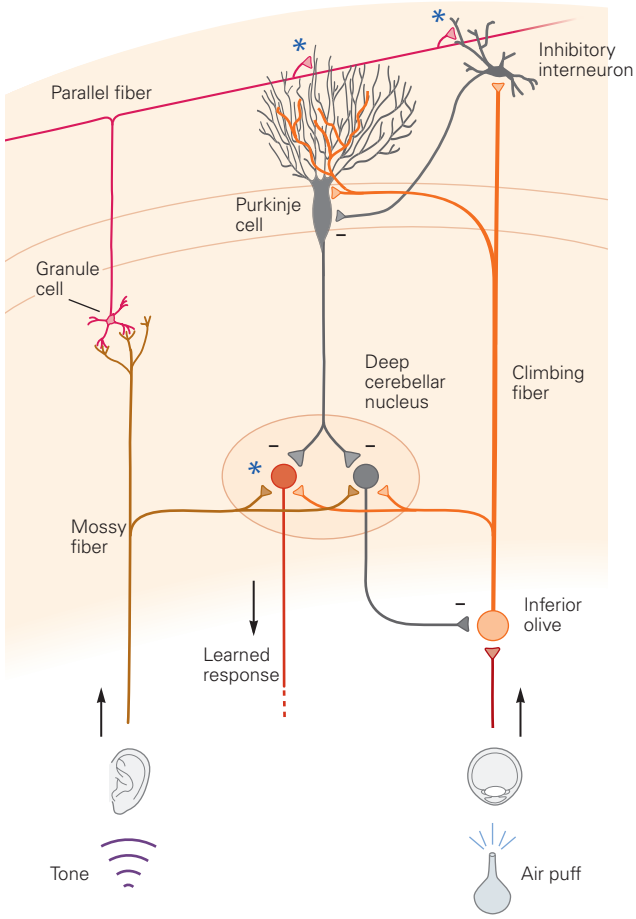

Figure 37–14 Learning in the cerebellar microcircuit can occur in the cerebellar cortex and the deep cerebellar nuclei. The diagram is based on classical conditioning of blinking, which is driven by pairing a tone (so-called conditioned stimulus carried by mossy fibers) and an air puff (the unconditioned 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.)

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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The Basal Ganglia