37

The Cerebellum

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 feedforward 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

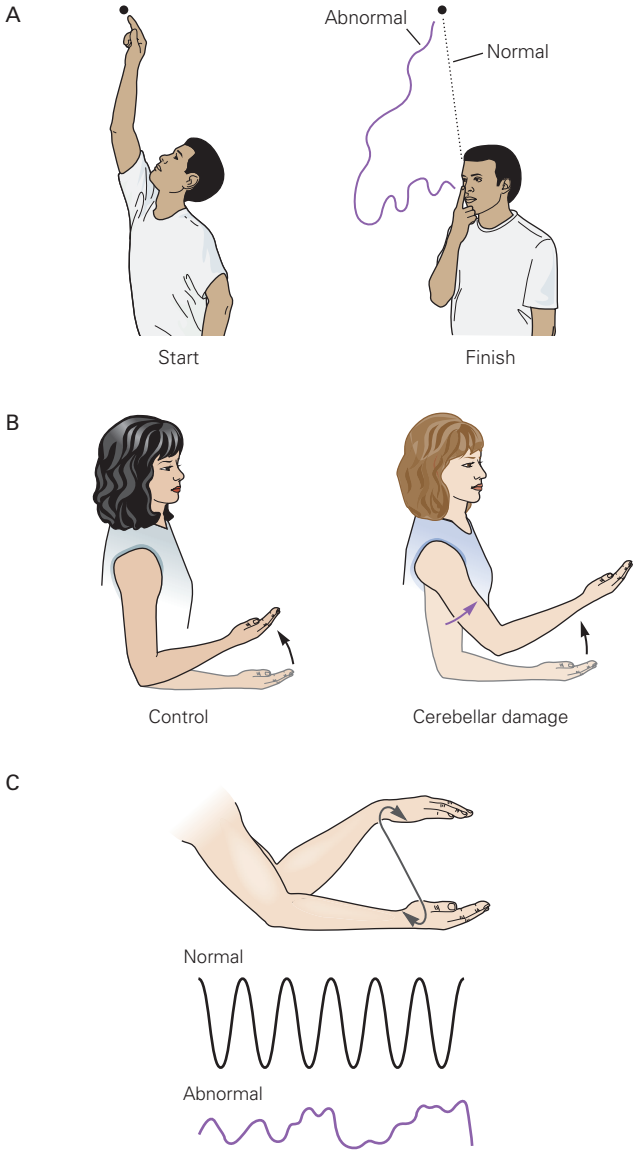

Figure 37–1 (Left) Typical defects observed in cerebellar diseases.

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

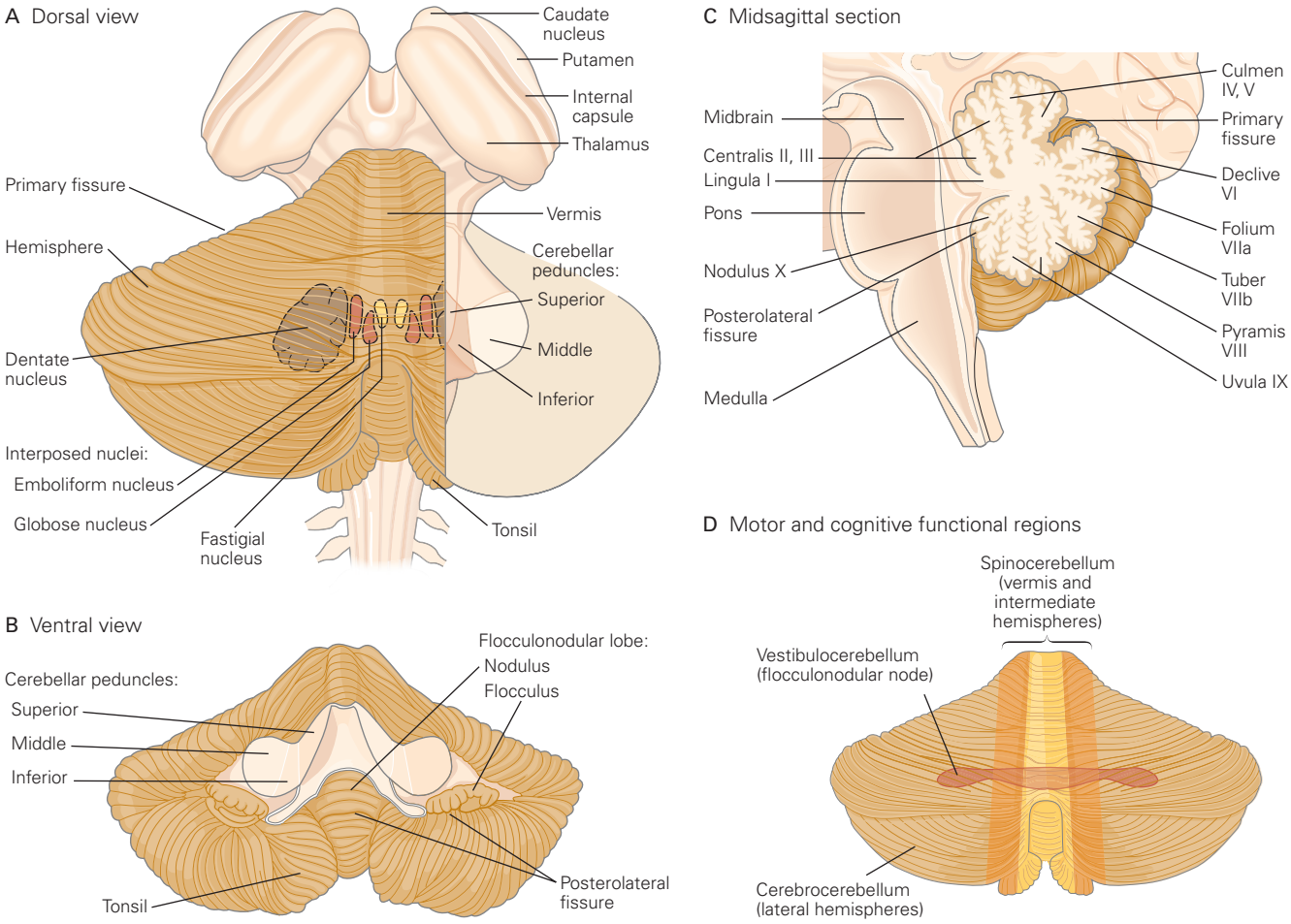

Figure 37–2 Gross features of the cerebellum. (Adapted, with permission, from Nieuwenhuys, Voogd, and van Huijzen 1988.)

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.

C. A midsagittal section through the brain stem and cerebellum shows the branching structure of the cerebellum. The cerebellar lobules are labeled with their Latin names and Larsell's Roman numeral designations. (Reproduced, with permission, from Larsell and Jansen 1972.)

D. Functional regions of the cerebellum.

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

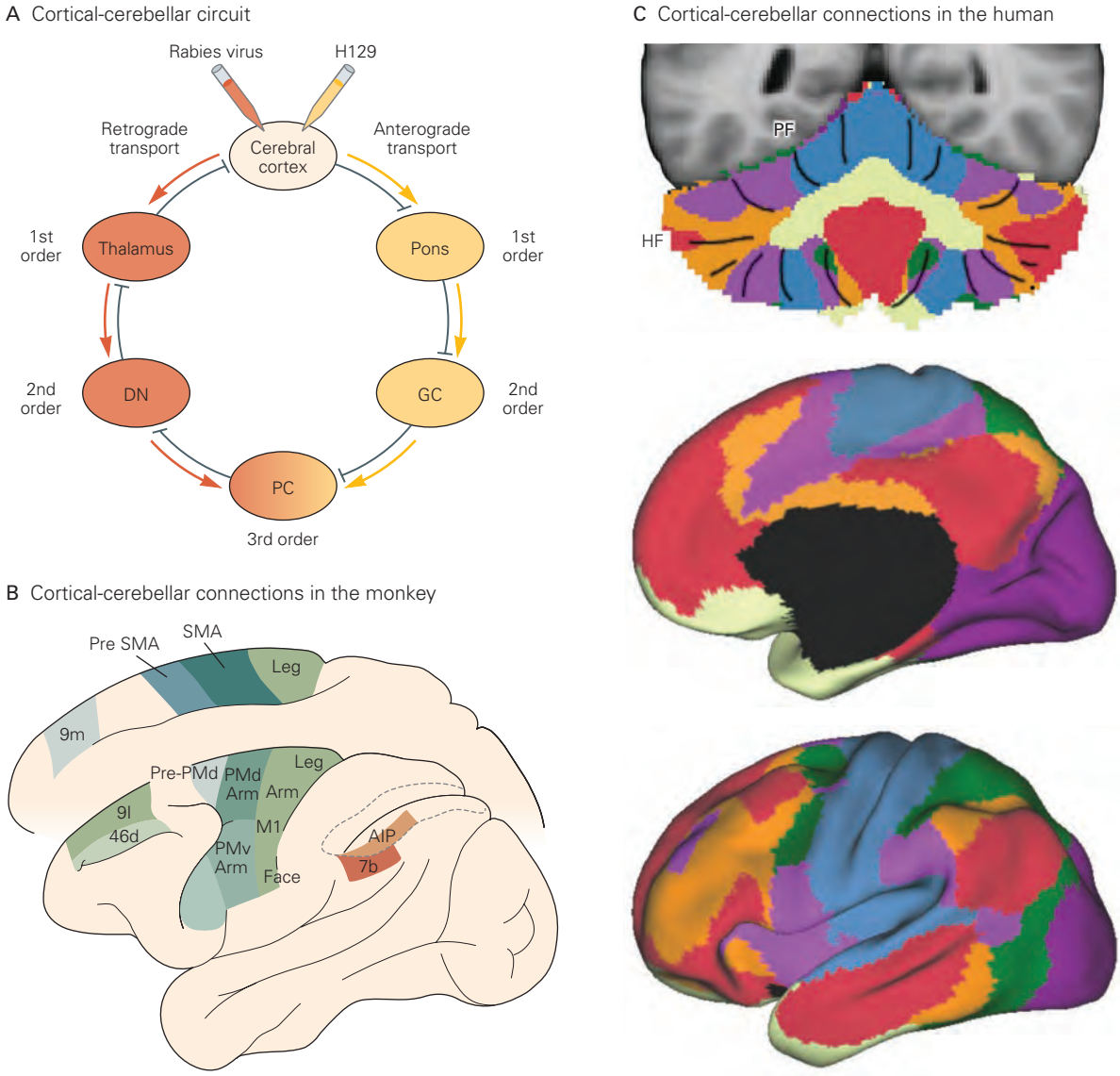

Figure 37–3 **The cerebellum connects to many areas of cerebral cortex.** (Parts A and B adapted, with permission, from Bostan, Dum, and Strick 2013. Copyright © 2013 Elsevier Ltd. part C adapted, with permission, from Buckner et al. 2011. Copyright © 2011 American Physiological Society.)

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.)

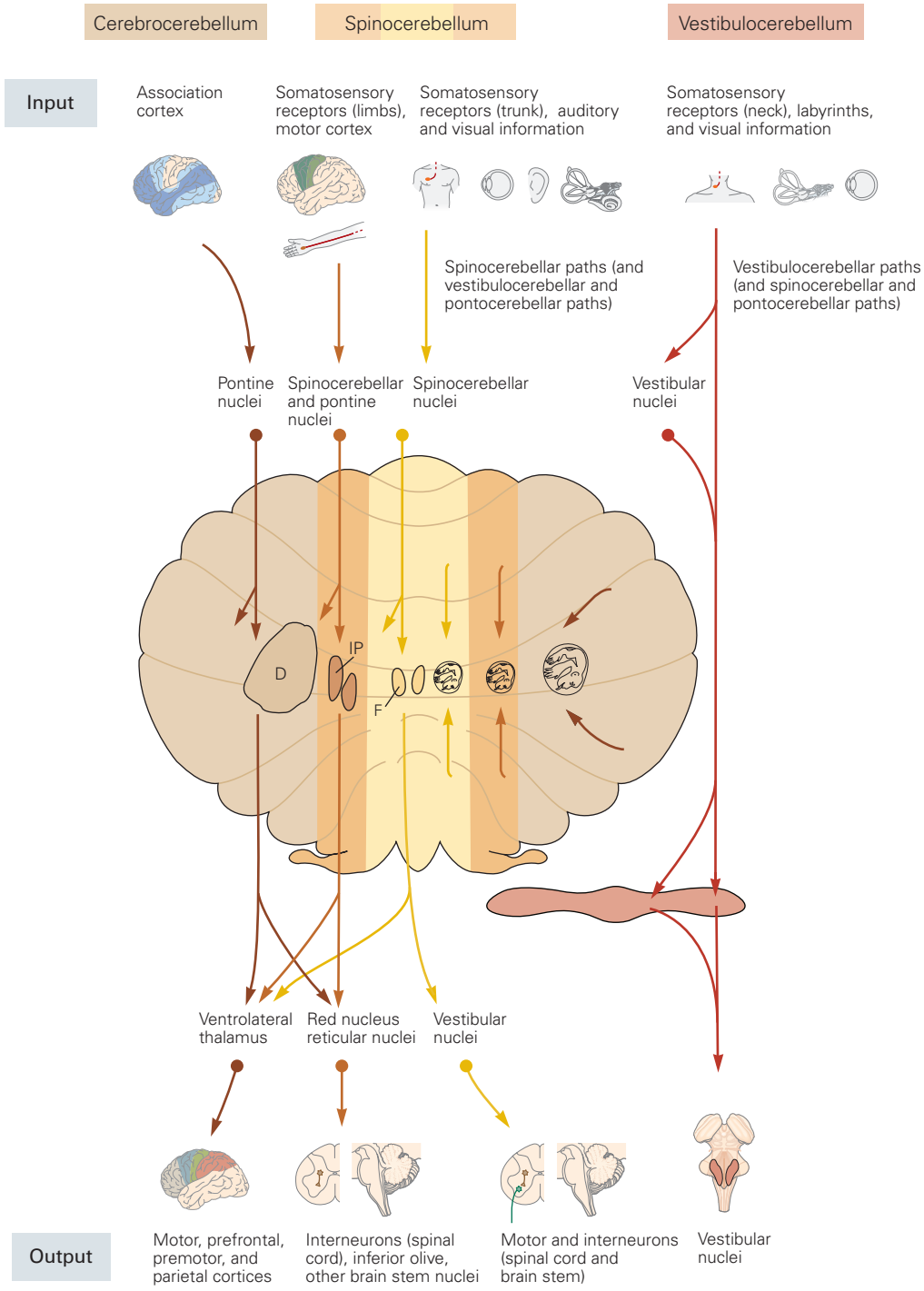

Figure 37–4 **The three functional regions of the cerebellum have different inputs and different output targets.** The cerebellum is shown unfolded, and **arrows** indicate the inputs and outputs of the different functional areas. The body maps in the deep nuclei are based on anatomical tracing and single-cell recordings in nonhuman primates. (Abbreviations: **D**, dentate nucleus; **F**, fastigial nucleus; **IP**, interposed nucleus.) (Adapted, with permission, from Brooks and Thach 1981).

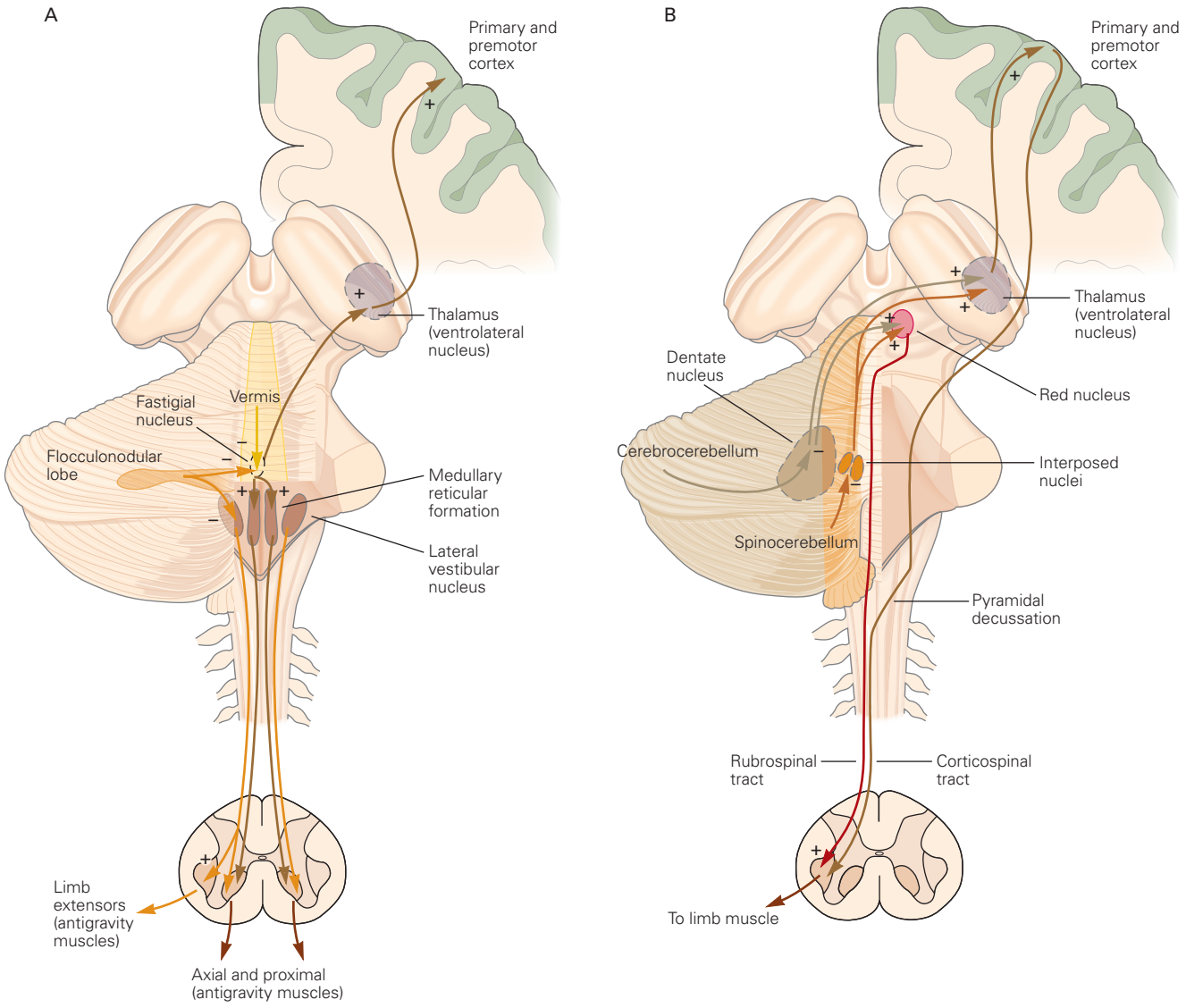

Figure 37–5 Input and output pathways of the cerebellum.

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.

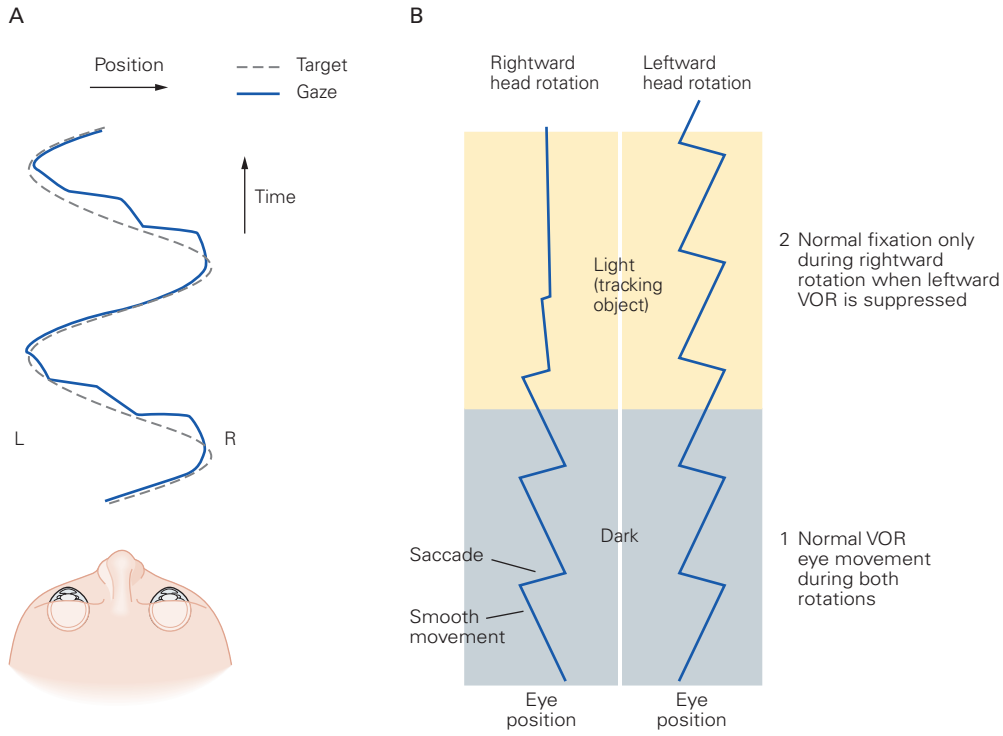

Figure 37–6 Lesions in the vestibulocerebellum have large effects on smooth-pursuit eye movements.

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.