MEDICAL SCHOOL COMPANION

7

CEREBELLUM

Objectives

Define the organization and function of the three strips of the cerebellum and their roles in controlling planned, volitional movements.

Describe the afferent (mossy and climbing fibers) and efferent pathways of the cerebellum and how they relate to cerebellar function.

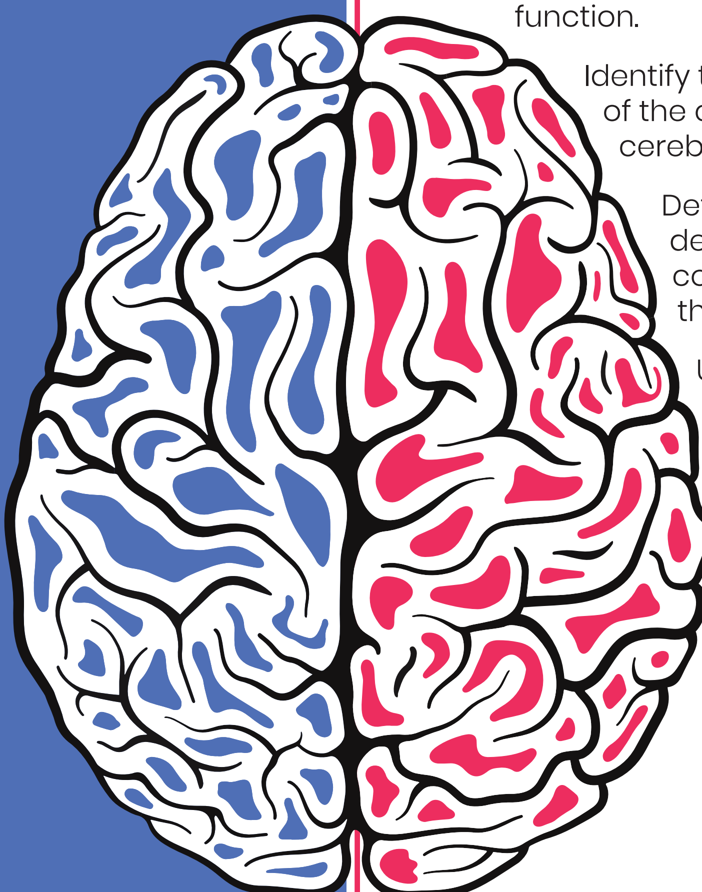
Identify the neurotransmitters (GABA and glutamate) of the cerebellum and their role in the circuits of the cerebellum.

Define the outer cortex of gray matter and the deeper white matter and describe the cellular components in the cortex and the deep nuclei in the white matter.

Understand the roll of Purkinje and granule cells.

Explain why lesions of the cerebellum present with ipsilateral signs.

Describe the clinical presentation of lateral hemisphere and vermis lesions.



CEREBELLUM

General Introduction

The cerebellum (little brain) plays a critical role in the smooth execution and planning of ongoing, volitional movements of skeletal muscles.

1. The cerebellum receives and integrates massive amounts of **sensory information** from most areas of the central nervous system (CNS) including the spinal cord, all lobes of the cortex, brainstem, and the visual, auditory, and vestibular systems.
2. The cerebellum constantly monitors this sensory input to coordinate and smooth out planned limb movements, to maintain muscle tone, and to maintain balance and equilibrium. It is also monitors and corrects any errors of ongoing planned movement.
3. The different afferent inputs to the cerebellum project directly or indirectly to the **Purkinje cells** of the cerebellar cortex (gray matter). The axons of the Purkinje cells then project to the deep cerebellar nuclei located in the white matter. The axons of the deep nuclei form the efferent, motor output of the cerebellum that relays via the thalamus to the upper motor neurons (UMN) of the cortex and brainstem, providing control of movement.
4. The cerebellum has **no direct** connections with the lower motor neurons (LMN) but exerts its motor effects via inputs onto **upper motor neuron** (UMN) systems in the **cortex** and **brainstem**.
5. Cerebellum develops from **metencephalon** with the pons.
6. Cerebellar lesions result in uncoordinated movements (ataxia) of limbs and eyes, affects balance disturbances, and reduced muscle tone. However, lesions do not affect sensory perception or muscle strength.
7. Norepinephrine from the locus ceruleus and serotonin from the raphe nuclei project to the cerebellum.

Functions of Cerebellum

1. Pre plans the timing, distance, and force of the skilled limb movements before the movements begin.
2. Coordinates, smooths out, and fine tunes ongoing movements. It is also involved with the maintenance of muscle tone.
3. Plays an important role in learning motor skills
4. Compares ongoing movements with the intended, planned movements, and corrects for any errors of movement.
5. Involved with the maintenance of balance and equilibrium, eye movements, and muscle tone (flocculonodular lobe).
6. Each hemisphere controls muscles on the same (ipsilateral) side of the body.

Macroscopic Structure of the Cerebellum

The cerebellum is located in the posterior cranial fossa along with the brainstem. It is attached via three cerebellar peduncles to the dorsal surface of the brainstem. It forms the roof of the fourth ventricle.

1. **Surface features:** The surface of the cerebellum exhibits many folds called **folia** separated by fissures. The folia increase the surface area of the cerebellum similar to the gyri of the cerebral cortex.
2. **Layers:** The **cortex** (gray matter) is the outer layer of the cerebellum containing a massive density of cells. The underlying **white matter** forms the deeper layer of the cerebellum and contains paired sets of **deep cerebellar nuclei**.
3. **Cerebellar Peduncles:** Three pairs of cerebellar peduncles containing different combinations of afferent or efferent fibers connect the cerebellum to the brainstem.
   a. The **inferior cerebellar peduncles** (restiform body) connect the cerebellum to the upper medulla and contain primarily **afferent**, input fibers from the upper medulla and spinal cord to the cerebellum.
   b. The **middle cerebellar peduncles** are the largest and it's fibers connect the cerebellum to the contralateral pons. They contain only **afferent** fibers from the pons to the cerebellum (pontocerebellar fibers). These fibers to the pons come from Betz cells of the cerebral cortex (corticopontine fibers). This is the major route from cortex to cerebellum for motor planning.
   c. The **superior cerebellar peduncles** connect the cerebellum to the midbrain and contain primarily output or **efferent** fibers from the cerebellum to the thalamus and spinal cord.

Organization of cerebellum is shown in Figure 7.1 and described below.

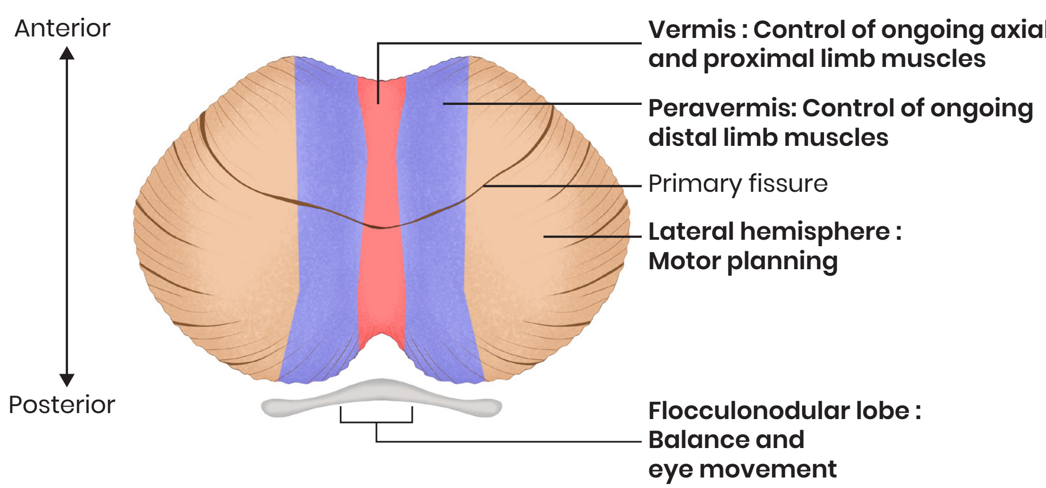


FIGURE 7.1 Organization of Cerebellum

4. **Anatomical Divisions.** The cerebellum can be divided into lobes (anterior, posterior, and flocculonodular lobe) or into vertical strips (vermis, paravermis, and lateral hemispheres), The latter is the most efficient way to describe the circuits and functions of the cerebellum (see Table 7.1).

a. The **vermis** is the median strip that is involved in the motor control and execution of ongoing movements of the axial muscles of the **trunk** and the **proximal limb**. The main sensory input to the vermis is derived from the muscle spindles and Golgi tendon organs of the trunk and limb muscles via the **dorsal spinocerebellar** and the **cuneocerebellar tracts** of the spinal cord.

b. The **paravermis** (**intermediate strip**) is involved in motor control and execution of ongoing movements of the **distal limb** muscles. The main sensory input to the paravermis is also via the dorsal spinocerebellar and the cuneocerebellar tracts of the spinal cord.

c. The two **lateral hemispheres** form the largest part of the cerebellum and are involved in the planning of the sequence, distance, force, and timing of voluntary movements. The lateral hemispheres also are involved in error correction and learning motor skills. The primary sensory input to the hemispheres is via from two main sources:

   1. The most abundant sensory input to the lateral hemispheres comes from all areas of the **contralateral** cortex via a massive number of **corticopontine** fibers. These fibers derive primarily from the frontal lobe (frontopontine fibers). The cortical fibers descend through the anterior part of the internal capsule, the cerebral peduncle, and the midbrain to reach the pons where they synapse with pontine nuclei. These nuclei send massive numbers of **pontocerebellar** axons that cross the pons horizontally and enter the contralateral middle cerebellar peduncle to reach the lateral hemispheres.

   2. The **inferior olivary nucleus** of the upper medulla also sends fibers **(olivocerebellar tract)** to the contralateral lateral hemisphere. It is suggested that these projections from the inferior olivary nucleus are utilized in error correction and learning new motor skills.

d. The **flocculonodular** lobe projects to the vestibular system of the brainstem. These fibers function in balance and eye movements.

Table 7.1: General Organization and Functions of the Regions of the Cerebellum

Regions	Functions	Primary Sensory Inputs	Motor Circuits Affected
A Vermis and paravermis (Spinocerebellum)	Coordination of ongoing movements of trunk, proximal and distal limb muscles	Dorsal spinocerebellar and cuneocerebellar tracts of spinal cord (unconscious proprioception)	Corticospinal, vestibulospinal tract
B Lateral hemispheres (Cerebrocerebellum)	Motor planning for extremities; Error correction and motor learning	Cortex and inferior olivary nucleus: Corticopontine and olivocerebellar tracts	Corticospinal tract
C Flocculonodular lobe (Vestibulocerebellum)	Balance and eye movement (VOR)	Vestibular apparatus and CN VIII nuclei	Vestibulospinal tract

Cerebellar Afferent Pathways

The afferent inputs to the cerebellum enter primarily through the inferior and middle peduncles with a few afferents coursing in the superior peduncle. The inputs are classified as **mossy fibers** or **climbing fibers**, based on their histological structure. Both of these sets of afferent fibers are excitatory, using **glutamate** as their neurotransmitter and either directly or indirectly project to Purkinje neurons.

The major afferent fibers to the cerebellum are summarized in Table 7.2.

Table 7.2: Major Cerebellar Afferent Circuits

Tracts and Origin	Target	Function	Peduncle
A. Climbing Fibers 1. Olivocerebellar from inferior olivary nucleus	**Directy to purkinje cells** of cerebellar cortex and deep nuclei	Motor learning; Error correction	Inferior
B. Mossy Fibers 1. Cuneocerebellar from upper limb and upper trunk	First to granule cells and then to purkinje cells of vermis and paravermis	Unconscious proprioception	Inferior
2. Dorsal spinocerebellar from lower limb and lower trunk	First to granule cells and then to purkinje cells of vermis and paravermis	Unconscious proprioception	Inferior
3. Corticopontocerebellar from most parts of the cerebral cortex via pons	First to granule cells and then to purkinje cells of lateral hemisphere	Input for motor planning	Middle
4. Vestibulocerebellar from vestiblar nuclei and apparatus	Purkinje cells of flocculodular lobe	Balance and eye movement	Inferior

Climbing Fibers

Climbing input fibers derive exclusively from the neurons in the contralateral **inferior olivary nucleus** (olivocerebellar tracts) of the upper medulla and enter the cerebellum via the contralateral inferior cerebellar peduncle.

1. The climbing fibers are the **only afferents** that synapse directly on the **Purkinje cells.**
2. A single climbing axon will synapse on only 5-10 Purkinje cells in the cortex. Thus, they exert a powerful **excitatory** (glutamate) influence on the Purkinje cells resulting in a direct, powerful and sustained prolonged action potential spikes.
3. Climbing fibers also provide collaterals that synapse on and are **excitatory** to the deep cerebellar nuclei in the white matter.

Mossy Fibers

Mossy input fibers derive from numerous regions of the nervous system including:

a. All areas of the cerebral cortex (corticopontine)

b. Sensory input from vestibular, visual, and auditory systems

c. Brainstem

d. Spinal cord

1. Mossy axons ascend through the white matter of the cerebellum, enter the cerebellar cortex, and branch making excitatory synapses (glutamate) with numerous **granule cells** in the cerebellar cortex. Examples of mossy fibers are cuneocerebellar, dorsal spinocerebellar and corticopontine fibers.
2. The granule cell axons ascend to the surface of the cerebellar cortex (molecular layer) where they turn 90 degrees to form **parallel fibers** that synapse on the dendritic trees of numerous **Purkinje cells**.
3. Mossy fibers have a continuous weak excitatory influence on Purkinje cells.
4. Mossy fibers also provide collateral branches that synapse on and are **excitatory** to the deep cerebellar nuclei in the white matter.

Microscopic Structure of the Cerebellum

The internal structure of the cerebellum is divided into an outer **cortex** (**gray matter**) and an inner layer of white matter. This structure of cerebellum is described and illustrated below (Fig. 7.2).

A. Cortex

The outer cortical gray matter contains **five cell types** (Purkinje, granule, Golgi, stellate, and basket cells). The **Purkinje** and **granule** cells are the two major cell types in the cortex. Granule cells are the only excitatory neuron (glutamate) in the cerebellar cortex. The other four cortical neurons are inhibitory (GABA). These cells are located within three layers of the cortex: **molecular, Purkinje**, and **granule cell** layers.

Table 7.3 Neurons Of Cerebellar Cortex

Cell	Project To	Neurotransmitter
Purkinje	Deep cerebellar nuclei	Inhibitory (GABA)
Granule	Purkinje cell	Excitatory (glutamate)
Basket	Purkinje cell	Inhibitory (GABA)
Stellate	Purkinje cell	Inhibitory (GABA)
Golgi	Granule cell	Inhibitory (GABA)

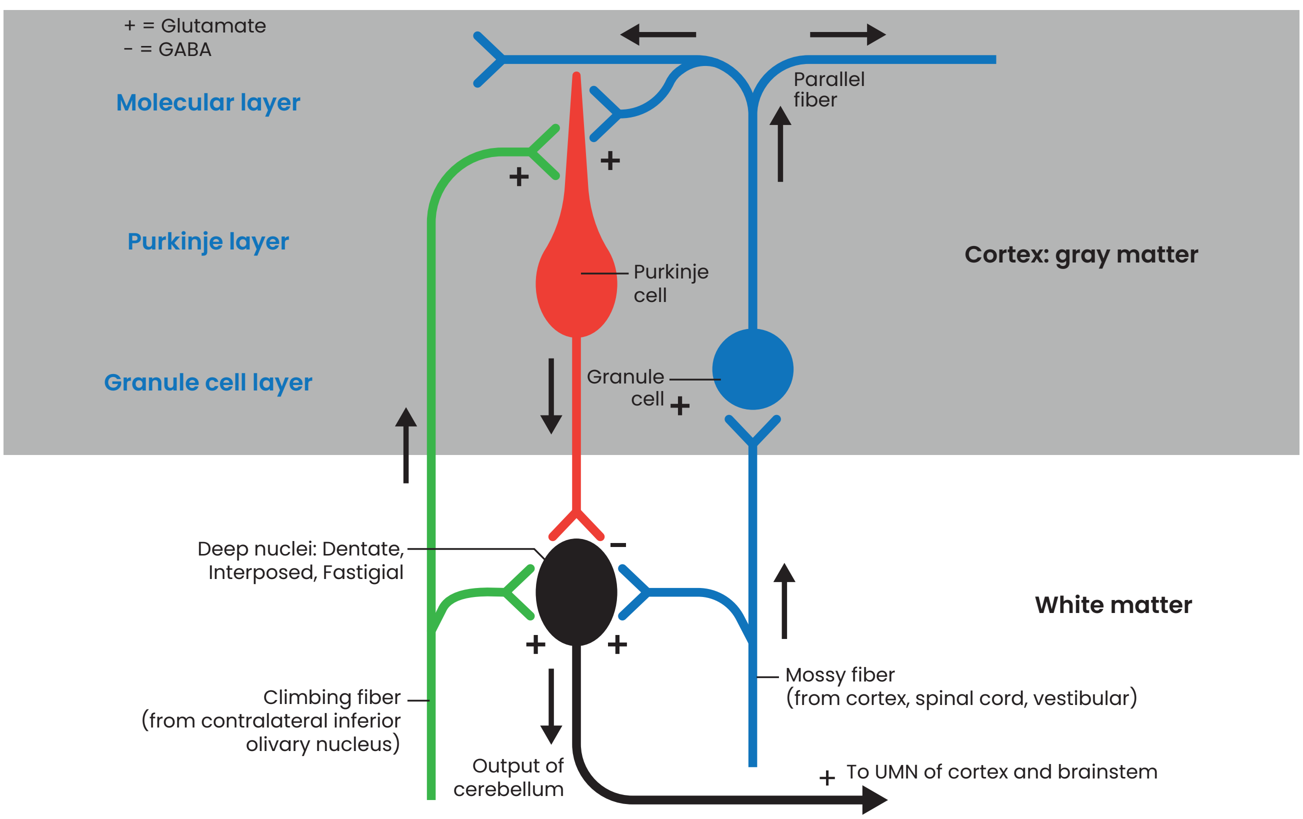


FIGURE 7.2 Histology of Cerebellum

1. **Granule cell layer**. The granule cell layer forms the innermost layer of the cortex. It contains billions of excitatory (glutamate) **granule cells.**

   a. The granule cell receives massive numbers of mossy fiber inputs from most areas of the central nervous system **except** from the inferior olivary nucleus.

   b. The axons of granule cells ascend into the molecular layer where they form **parallel fibers** described below.

   c. Golgi cells (GABA) are also found in this layer. These cells function as support cells for the granule cells.

2. **Purkinje cell layer**. This layer forms the middle layer of the cortex and consists of millions of large Purkinje cells.

   a. The cell bodies of the **Purkinje cells** are located in this layer, but most of the very elaborate and highly branched dendritic trees of the Purkinje cells extends up into the molecular layer.

   b. The Purkinje cells receive **direct inputs** from **climbing fibers** coming from the **contralateral** inferior olivary nucleus.

   c. The Purkinje cells also receive **indirect input** from **mossy fibers**. Mossy fibers first synapse on the granule cells in the granule cell layer, and then the granule cell axons (parallel fibers) synapse on the Purkinje cells in the molecular layer.

   d. Purkinje cells are **inhibitory** (**GABA**), and their axons are the only ones that **project** from the **cortex** to the ipsilateral **deep nuclei** in the **white matter**. Thus, the excitatory output of the deep nuclei is regulated by the inhibitory output of the cortical Purkinje axons.

3. **Molecular Layer**. The molecular layer is the outermost layer of the cortex located immediately deep to the surface of the cerebellum.

   a. The molecular layer consists primarily of the elaborate, branched dendritic trees of the **Purkinje cells.**

   b. This layer also contains the **parallel fibers** which are the continuations of the axons of the granule cells. These axons bifurcate forming t-shaped divisions that run extended courses deep to and parallel to the folia at the surface of the cerebellum.

   c. The parallel fibers pass through the Purkinje cell dendritic trees where collaterals of the parallel fibers provide **excitatory activation** (glutamate) to numerous Purkinje cell dendrites.

   d. Two additional types of inhibitory cells (GABA) are found in the molecular layer: basket and stellate cells. These function as support cells for the Purkinje neurons.

B. White matter

The white matter contain two bilateral sets of deep nuclei. From medial to lateral they are the **fastigial nucleus, interposed nuclei** (**consisting** of the **globose** and **emboliform nuclei**), and the **dentate nucleus (Fig. 7.3).** These nuclei provide the **excitatory motor output** of the cerebellum to the upper motor neurons. Excitatory efferents (glutamate) from the deep nuclei exit primarily via the superior cerebellar peduncle.

1. These deep nuclei receive input from two main sources:

   a. A continuous **excitatory** drive via the **collaterals** of **climbing** and **mossy fibers** described earlier.

   b. The **inhibitory** (GABA) projections from the **axons** of the **Purkinje cells** to the white matter that regulate and control the excitatory motor output of the deep nuclei.

   c. Thus, deep nuclei receive excitatory and inhibitory inputs. The firing of the deep nuclei results from the balance between these two types of input on the nuclei.

2. There are specific patterns of projections from the Purkinje cells to the three cerebellar strips to these deep nuclei as described and illustrated below:

   a. Purkinje cells of the flocculonodular lobe and vermis project bilaterally to the **fastigial nucleus.** This circuit controls bilateral axial and proximal limb muscles and is involved in balance and walking.

   b. Purkinje cells of the paravermis project to the **interposed nuclei** and function in control of distal limb muscles.

   c. Purkinje cells of the lateral hemispheres project to the **dentate nuclei** and are involved in motor planning, error correction, and motor learning. Firing in this circuit **precedes** the initiation of movement by the motor cortex by milliseconds.

3. Collaterals of both the climbing and mossy fibers provide continuous excitatory activation of the deep nuclei.

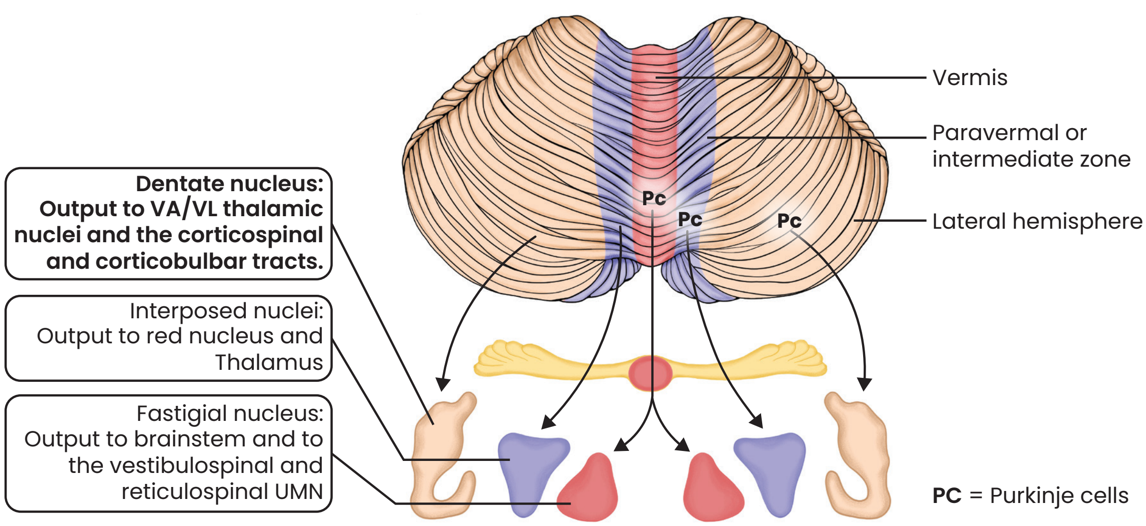


FIGURE 7.3 Nuclei of White Matter

Cerebellar Efferent Pathways

The excitatory (glutamate) projections of the deep nuclei represent the major motor output of the cerebellum. These efferent pathways primarily use the superior cerebellar peduncle to exit the cerebellum. This motor output projects to the UMNs of the **contralateral** cortex and brainstem. Deep nuclei have no direct projections to the LMNs.

1. Of the different patterns of efferent projections from the cerebellum illustrated in the figure on page 9, one should focus primarily on the pattern of efferents from the Purkinje cells of the lateral hemispheres to the **dentate nucleus** as outlined in the flow chart below.

2. Notice in the flow chart below that the projection of the Purkinje cells to the lateral hemispheres decussate in the midbrain, relay in the thalamus, and project to the contralateral upper motor neurons in the motor cortex. Then the UMNs (corticospinal tract) descend and decussate in the lower medulla to the provide innervation to the contralateral lower motor neurons (double crossing) of the spinal cord. Because of the specific arrangement of this circuit, each side of the cerebellum will coordinate and control **ipsilateral limb muscles.** Note this is opposite of cerebral cortex and internal capsule that influence the contralateral side of the body,

Pattern of hemisphere Purkinje axon projection to distal limbs: Ipsilateral control.

1 Purkinje cells of hemisphere → 2 Dentate nucleus → 3 SCP → 4 **First Decussation in midbrain** → 5 Contralateral thalamus (VA, VL) →
6 Corticospinal UMN in motor cortex → 7 **Second Decussation (CST) in lower medulla** → 8 LMN of **contralateral** limbs

The cerebellar efferent pathways are summarized in Table 7.4.

Table 7.4: Cerebellar Efferent Pathways

Cerebellar Areas	Deep Nuclei	Outputs to
1. Spinocerebellum (paravermis)	Interpositus nucleus (active during movement)	Contralateral red nucleus reticular formation
2. Pontocerebellum (Lateral himspheres)	Dentate nucleus (active before movement begins)	Contralateral thalamus (VA, VL) and cortex
3. Vestibulocerebellum (flocculonodular lobe)	Fatstigal nucleus	Bilateral Vestibular nucleus

Blood Supply Of The Cerebellum

1. The paired **posterior inferior cerebellar arteries** (PICA) are branches of the vertebral arteries and supply the lateral medulla and the inferior aspect of the cerebellum and inferior vermis.

2. The paired **anterior inferior cerebellar arteries** (AICA) are branches of the lower basilar artery and supply the lower lateral pons and the middle cerebellar peduncle and the central part of the cerebellum.

3. The paired **superior cerebellar arteries** (SCA) are branches of the upper basilar artery and supply the lateral mid and upper pons, the superior cerebellar peduncle, the upper half of the cerebral hemisphere, deep cerebellar nuclei, and part of the vermis.

Clinical Application

Clinical disorders of the cerebellum are usually divided into lesions of the **lateral hemisphere** or lesions of the **vermis**

Lesions of the lateral hemisphere

Lesions of the right or left lateral hemisphere commonly involve the cortex, deep nuclei of white matter, and peduncles. These lesions are severe and result in the lack of coordination of voluntary movements with alteration of reflexes and reduced muscle tone of the **distal** limb muscles. These lesions can result from vascular accidents (more common in the SCA), trauma, degenerative diseases, or tumors.

Note that lesions of the lateral hemispheres occur **without paralysis,** loss of muscle strength or loss of **sensory functions.** Cerebellar deficits present in the **ipsilateral limbs** as described above.

The major presenting signs and symptoms of lateral hemisphere lesions are described below :

1. **Ipsilateral dysfunction.**

2. **Ataxia**. Ataxia (without order) is the loss of coordination of voluntary movements and is most pronounced in the limbs. Ataxia presents as awkward and clumsy movements of the limbs. There are disturbances in the timing, range, force, and the sequence of the limb movements due to the **defective planning of movements** in the hemispheres. The normal smooth execution of movement does not occur. In the lower limb, ataxia results in an uncoordinated gait, and the individual will fall and stumble **to the side of cerebellar lesion when walking.**

3. **Intention tremor.** When an attempt is made to produce planned movements, an **intention tremor** develops with the limbs which sway back-and-forth. The intensity of the tremor increases as the individual tries to reach an object. At rest, there is no tremor. Intention tremor seen with cerebellar disease is in contrast to the resting tremor seen in Parkinson’s and other basal ganglia diseases.

4. **Dysmetria**. Lateral hemisphere lesions result in the inability to judge distances and the inability to stop movements at a target, resulting in overshooting or undershooting when trying to reach an object. A common test for this is to see if the individual can touch their nose with the finger of each hand or touch the leg with the opposite foot.

5. **Dysdiadochokinesia**. This refers to the inability to repeat rapid alternating movements. Common test for this is to see if the individual can rapidly pronate and supinate each forearm and the heel to the opposite leg movement in the lower limb.

6. **Nausea, vomiting, vertigo**, **headaches**, and cerebellar swelling causing hydrocephalus are common.

7. **Hypotonia** and **reduced deep tendon reflexes.** Widespread decreases in deep tendon reflexes occur more commonly when deep nuclei are affected. Note that hypotonia and decreased reflexes resemble LMN lesions.

8. Disorders of **eye movement** and **dysarthria.** These usually are present with **flocculonodular lesions.** There are disruptions of normal eye movements with suppression of the vestibulo-ocular reflex (VOR). The normal rhythm of speech is disrupted, and the individual will break the words into separate syllables (scanning speech).

Lesions of the Vermis

The vermal circuits function in the control and coordination of the muscles of the **trunk.** Lesions of the vermis affect **bilateral** trunk muscles and result in disturbances of posture, balance, and gait. Note that vermal lesions usually do not affect distal limb movements. Vermal lesions are divided into **anterior** and **posterior vermis lesions**.

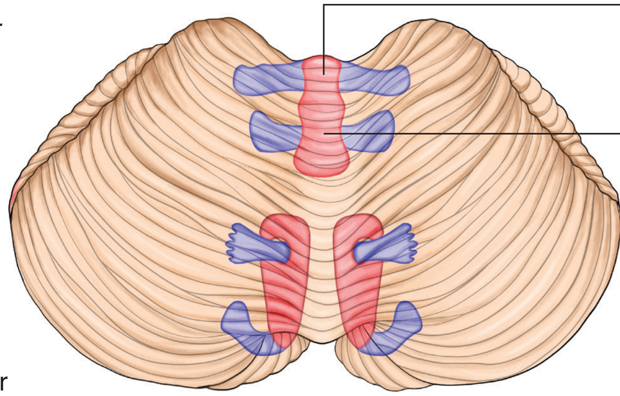


FIGURE 7.4 Somato Topic Maps of Cerebellum

Anterior Vermis

The **anterior vermis** (Fig. 7.4) is functionally related to the coordination of the muscles of the lower trunk and lower limbs. Lesions of the anterior vermis often result from malnutrition that occurs with long-term alcoholics. There is degeneration of the neurons of the anterior vermis, and the individual will lose coordination of the lower limbs. They have a staggering, unstable gait with clumsy lower limb movements that appears as if they are drunk (**gait ataxia**).

Posterior Vermis

The **posterior vermis** (Fig. 7.4) functions in the coordination of the trunk muscles with lesions resulting in problems with balance and postural instability due to the loss of coordination of the trunk muscles. Lesions of the posterior vermis are commonly seen in children with medulloblastomas at the roof of the fourth ventricle. These tumors grow quickly and cause headache, vomiting, and increased intracranial pressures.

In posterior lesions there is loss of control of the axial muscles of the trunk resulting in disturbances of equilibrium. This is results in a wide-based gait, swaying-back-and forth (**trunk ataxia**), and a tendency to fall over with feet pulled together.

The **Romberg test** can be used to differentiate between a cerebellar vermis lesion and a dorsal column lesion of the spinal cord. Because vermis lesions cause a great deal of instability of the trunk, an individual with a vermis lesion will begin to fall over when the feet are pulled together with the eyes open (**motor ataxia**). With a dorsal column lesion, the individual will fall with the eyes closed (**sensory ataxia**).