CEREBELLUM

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Cerebellum

- Lies in the posterior cranial fossa, below the tentorium cerebelli.
- Co-ordinates posture while walking and running. Involved in executing complex, sequential movements. Controls trajectory, velocity, and acceleration of movements. Ensures smooth and accurate pursuit movements.
- Attached to the medulla, pons, and midbrain by cerebellar peduncles.
- Consists of two hemispheres and a midline vermis. Anterior and posterior lobes are separated by a primary fissure.

Cerebellum

- On the anterior surface, the postero-lateral fissure separates the flocculo-nodular lobe from the posterior lobe.
- Cerebellar tonsils on the inferior surface.
- The lateral hemispheres are involved in motor planning for the extremities, influence the lateral corticospinal tracts.
- The intermediate hemispheres are involved in distal limb cordination, influence the lateral corticospinal and rubrospinal tracts (lateral pathways).

Cerebellum

- The vestibulo-cerebellum contains the cortex of the vermis together with the fastigial nucleus in the white matter close to the nodule. Fastigial nucleus projects to the ventral lateral thalamus and tectum. Via the juxtarestiform body it projects to the vestibular nuclei.
- It has two way connections with the vestibular nucleus; it projects as well to the gaze centers of the brainstem. Co-ordinates with the medial longitudinal fasciculus. It involves the anterior corticospinal, tectospinal, vestibulospinal, and reticulospinal tracts (medial pathways).

Cerebellum

- The spino-cerebellum includes the paravermal cortex and the globose and emboliform nuclei (together, the interposed nucleus). Controls posture and gait (proximal limb and trunk co-ordination). Somatotopic.
- The inferior vermis and flocculo-nodular lobe connect with the vestibular nuclei (medial longitudinal fasciculus).
- Deep nuclei (from medial to lateral) are fastigial, globose, emboliform, and dentate.
- Intermediate cerebellar cortex projects to interposed nuclei; project to ventral lateral and red nucleus. Do not overlap dentate.

Cerebellum

- The ponto-cerebellum includes the dentate nucleus and conveys information from the nuclei pontis to the neocortex.
- The cortical structure is uniform throughout. The granular cell layer contains granular cells whose short dendrites receive mossy fibers (excitatory) from all sources except the inferior olive; collateral branches are given off to the central nuclei.
- Granular cell axons penetrate to the molecular layer where they run parallel to the axes of the folia. Excitatory to Purkinje cells in pyriform layer.

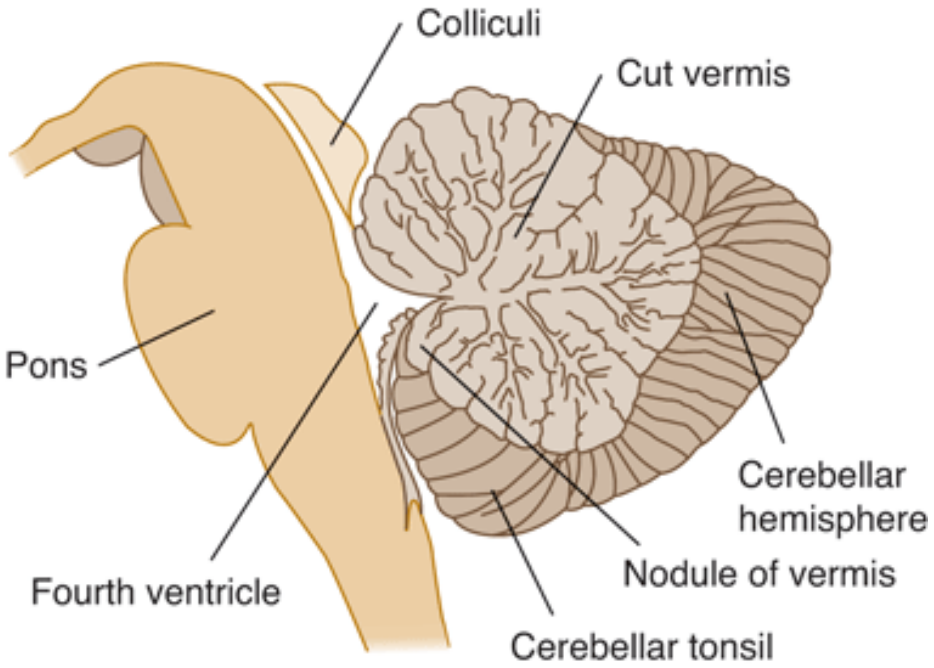
Cerebellum

- The granular layer also contains Golgi cells. The synaptic assembly that includes a mossy fiber terminal, granule cell dendrites, and Golgi cell boutons is called glomerulus.
- Purkinje cells are inhibitory. Theirs are the only axons to emerge from the cerebellar cortex. They are excited by a single climbing fiber from the contralateral inferior olivary nucleus (multiple contacts with dendritic trees of Purkinje cells).
- Stellate cells in the molecular layer synapse upon dendritic shafts; basket cells form a basket of contacts about Purkinje soma. Inhibitory.

Cerebellum

- Purkinje neurons in the lateral cerebellar cortex project to dentate nucleus; thence to superior cerebellar peduncle, and, either
- to contralateral ventrolateral thalamus to premotor and primary cortical motor areas, or
- to contralteral parvocellular red nucleus that then project back to the inferior olivary nuclues which in turn project back to contralateral cerebellum via climbing fibers (parvocellular nucleus also receives input from lateral premotor sensory areas).
- This loop may be involved with mental rehearsal (a cognitive function) or motor learning.

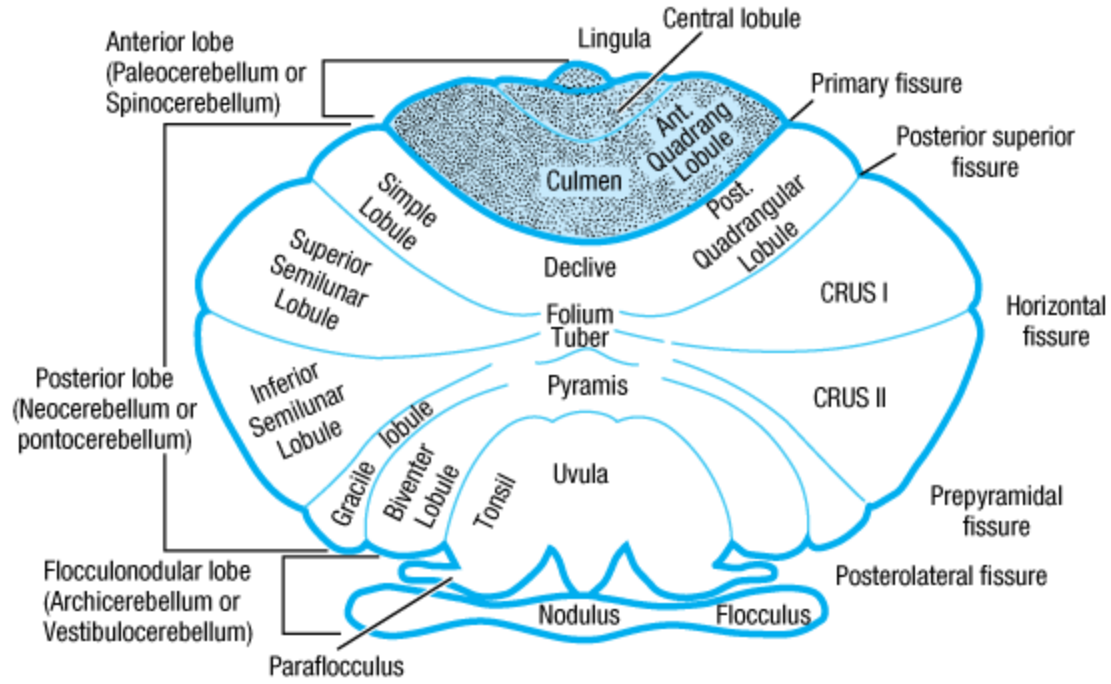
Cerebellum (sagittal view)



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*:
http://www.accessmedicine.com

Fig. 7-15 Accessed 07/01/2010

Cerebellum



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

Diagram of the cerebellum, illustrating the major fissures, lobes, and lobules and the major phylogenetic divisions (left labels).

Fig. 5-1 Accessed 07/01/2010

Cerebellum

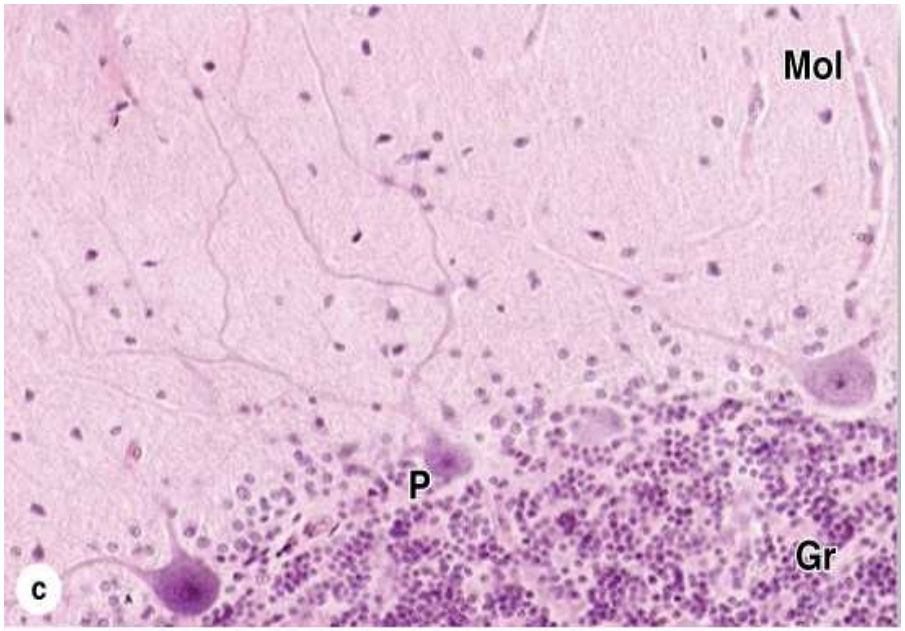
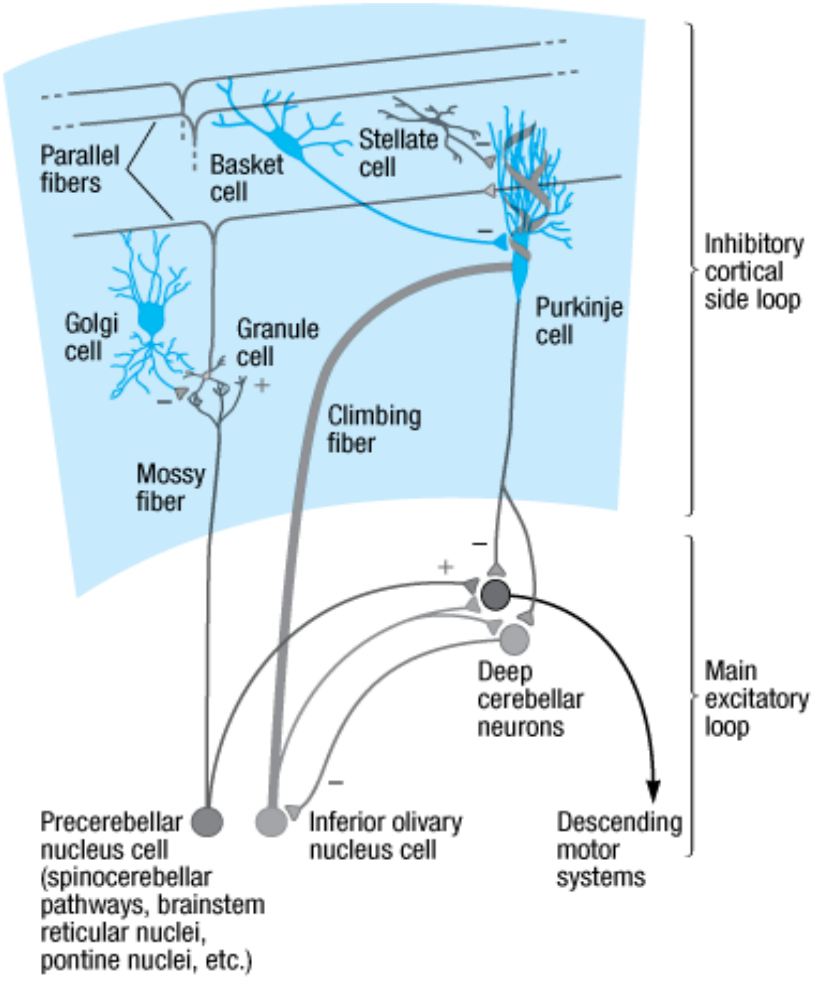


Fig. 9-16C Accessed 07/01/2010

The cerebellum is arranged in lobules. Each lobule contains a core of white matter and a cortex consisting of three layers—granular, Purkinje, and molecular—of gray matter. At the interface between the granular and molecular layers is a single layer with very large neuronal cell bodies of unique Purkinje cells (P), whose axons pass through the granular layer (Gr) to join tracts in the medulla and whose multiple branching dendrites ramify throughout the molecular layer (Mol). X40. H&E.

Internal cerebellar connections



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

The physiologic organization of cerebellar circuitry. The main output of the deep cerebellar nuclei is excitatory and is transmitted through mossy and climbing fibers. This "main loop" is modulated by an inhibitory cortical loop, which is effected by Purkinje cell output but indirectly includes the other main cell types through their connections with Purkinje cells. Recurrent pathways between the deep nuclei and cortical cells via mossy and climbing fibers complete the cerebellar servomechanism for motor control.

(Reproduced with permission from Kandel ER, Schwartz JH, Jessel TM: *Principles of Neural Science*, 4th ed. New York, McGraw-Hill, 2000.)

Fig. 5-5 Accessed 07/01/2010

Cerebellar structure

- A single **Purkinje cell** is innervated by only one climbing fiber; a single climbing fiber can innervate more that one Purkinje cell.
- Individual mossy fibers bifurcate: one branch innervates the deep nuclei and one innervates the cerebellar cortex (granule and Golgi cells). **Golgi cells** inhibit **granular cells** (excitatory). Granular cell axons course through molecular layer.
- **Basket cells** are inhibitory cells that have a large basket-like ending on Purkinje cells
- **Stellate cells** send inhibitory projections to Purkinje cell dendrites.

Cerebellum

- Mossy fibers originate from nuclei in the spinal cord and brain stem. Terminate as excitatory synapses on granule cell dendrites. Parallel fibers (axons of the granule cells) travel along the long axis of the cerebellar folia in the molecular layer, thus exciting large numbers of Purkinje neurons in the same plane.

Cerebellum

- Climbing fibers originate from the inferior olivary nucleus. They wrap around the cell bodies and proximal dendrites of Purkinje neurons. Each climbing fiber interacts with up to 10 Purkinje neurons but each Purkinje neuron only receives one climbing fiber. Climbing fiber terminals arranged topographically.
- Climbing fiber generates a prolonged voltage-gated Ca^{2+} conductance in the Purkinje cell (initial large amplitude spike followed by a high frequency burst of small amplitude action potentials).

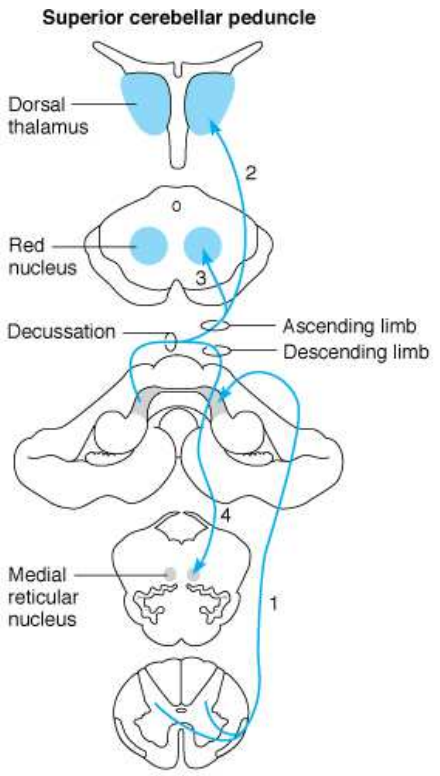
Cerebellum

- Parallel fibers produce a brief EPSP that generates a single action potential.
- Stellate cells contact nearby dendrites of Purkinje cells. Basket cell axons run perpendicular to parallel fibers and form synapses with Purkinje neurons anterior and posterior to parallel fiber bundles (beams). Arrangement resembles center-surround antagonism in visual and somatosensory pathways.

Cerebellum

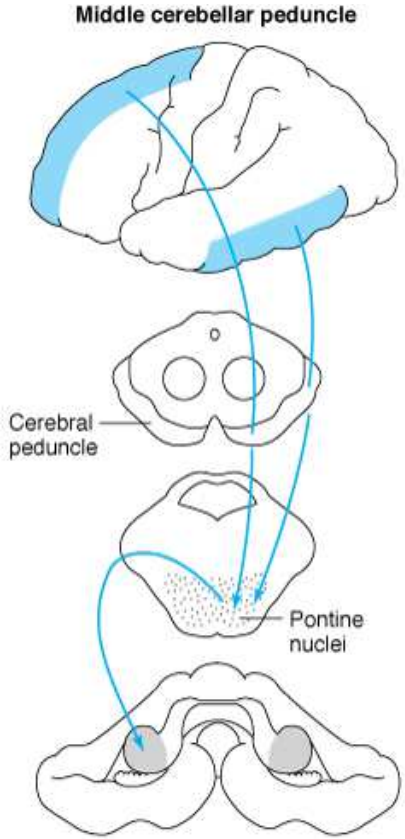
- Golgi cells have elaborate dendritic tree in the overlying molecular layer. Form axo-dendritic synapses with granule cells in the glomeruli. Firing initiated by parallel fibers suppresses mossy fiber excitation of granule cells and shortens duration of bursts in parallel fibers.

Cerebellar connections (overview)

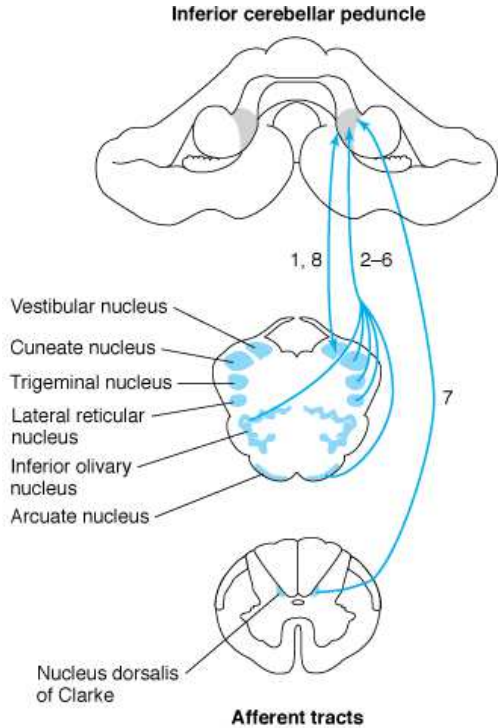


Afferent tract
1 Ventral spinocerebellar

Efferent tracts
2 Cerebellothalamic
3 Cerebellorubral
4 Cerebelloreticular



Afferent tract
Corticopontocerebellar



Afferent tracts
1 Vestibulocerebellar
2 Cuneocerebellar
3 Nucleocerebellar
4 Reticulocerebellar
5 Olivocerebellar
6 Arcuatocerebellar
7 Dorsal spinocerebellar

Efferent tract
8 Cerebellovestibular

Fig. 3-2 Accessed 07/01/2010

Cerebellar efferents

- Lateral cerebellar activity is greatest during speech (object naming).
- Affect may be flat if vermis involved.
- Diminished reasoning power, inattention, errors of grammar, poor spatial sense, patchy memory loss are associated with cerebellar damage.

Cerebellar afferents

- Mossy fibers are the most numerous afferent axon to the cerebellum. Excitatory.
- Arise from spinocerebellar tracts; the cuneocerebellar tract; the vestibulocerebellar tract; the pontocerebellar tract; the trigeminocerebellar tract; the tectocerebellar tract; and the reticular formation.
- From muscles and skin, afferent information travels in the posterior spinocerebellar and cuneocerebellar tracts and enter the ipsilateral inferior cerebellar peduncle.

Cerebellar afferents

- Comparable information from the area served by CN V enters all three cerebellar peduncles.
- Afferents from spinal reflex arcs run in the anterior spinocerebellar tract, which reaches the upper pons before looping into the superior cerebellar peduncle.
- Special sense afferents comprise tectocerebellar fibers entering the superior peduncle from the ipsilateral midbrain colliculi; vestibulocerebellar fibers enter from the ipsilateral vestibular nucleus.

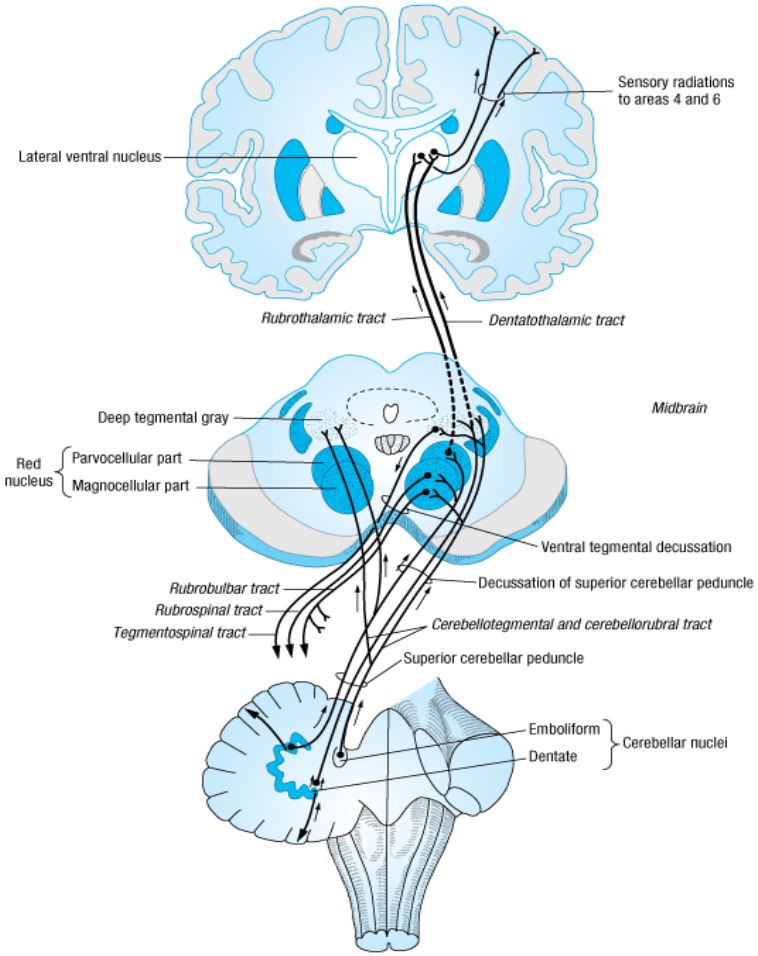
Cerebellar afferents

- The pontocerebellar tract enters the contralateral middle peduncle; the olivocerebellar tract enters through the contralateral inferior peduncle. somatotopic.
- Reticulocerebellar fibers enter the inferior peduncle from the paramedian and lateral reticular nuclei of the medulla.

Cerebellar efferents

- All of the fibers leaving the cerebellar cortex arise from Purkinje cells.
- Almost all of these axons end in the deep cerebellar nuclei (some to vestibular nuclei).
- Almost all axons leaving the cerebellum originate in the deep nuclei (some from Purkinje cells).
- The deep nuclei are from medial to lateral are the fastigal, interpositus (globose and emboliform), and the dentate.

Cerebellar connections



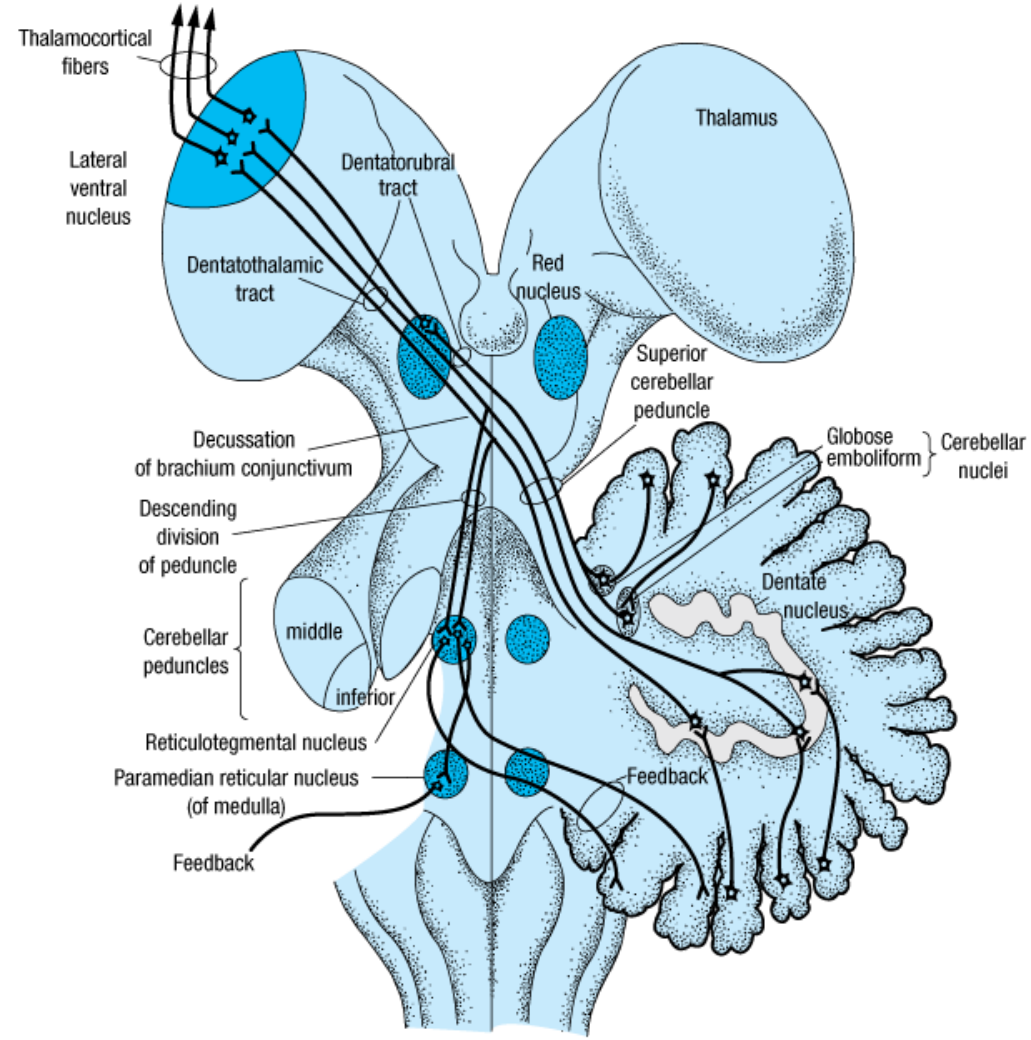
Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology* 9th *Edition*: http://www.accessmedicine.com

Cerebellar projections to the red nucleus, thalamus, and cerebral cortex.

(Adapted by permission from House EL et al: *A Systematic Approach to Neuroscience*, 3rd ed. New York, McGraw-Hill, 1979.)

Fig. 5-2 Accessed 07/01/2010

Cerebellar connections



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

Dentatothalamic and dentatorubrothalamic projections via the superior cerebellar peduncle. The "feedback" circuit via the reticular nuclei and reticulocerebellar fibers is also shown (Mollaret triangle).

Fig. 5-3 Accessed 07/01/2010

Somato-sensory input

- The cerebellum is required for precise control and coordinated movements. Functions to modify acts initiated by the motor cortex and basal nuclei.
- Vestibulo-cerebellar and spino-cerebellar output affect the descending motor system at the brainstem level (red nucleus, CN motor nuclei and vestibular nuclei); they affect the motor act while it is in progress.
- Cerebro-cerebellar inputs information about a command about to be executed so it can modulate motor command information before execution of the command.

Somato-sensory inputs

- Cortico-pontocerebellar tract.
- Arise from cortex, synapse in the pons. Pontocerebellar mossy fibers enter the cerebellum via the middle peduncle.
- Fibers cross in the pons and enter the cerebellum via the opposite middle cerebellar peduncle.
- Carry information from the motor, somatosensory, visual, auditory and association cortex to the pontine nuclei.

Somato-sensory inputs

- Dorsal spino-cerebellar tract (lower limb pathway)
- Primary afferents are large, myelinated axons carrying proprioception, touch and pressure inputs from lower limb and trunk. Synapse in the dorsal nucleus of Clark.
- Axons ascend ipsilaterally to enter the cerebellum in the inferior cerebellar peduncle.
- Cuneo-cerebellar tract (upper limb pathway)
- Afferents synapse in the ipsilateral accessory (external) cuneate nucleus. Enter the inferior cerebellar peduncle.
- The two tracts feedback movements of the limbs.

Somato-sensory inputs

- Ventral spino-cerebellar tract (lower limb pathway)
- Arise from spinal border cells in the intermediate zone of the spinal gray matter.
- Axons cross in the ventral white commissure of the spinal cord.
- Ascend in the contralateral ventral funiculus.
- Cross again in the superior cerebellar peduncle.
- Rostral spino-cerebellar tract (upper limb pathway)
- Enters the cerebellum in the inferior and superior cerebellar peduncles. Cross twice.

Somato-sensory inputs

- The inferior olive receives input from the ipsilateral parvocellular part of the red nucleus and the ipsilateral cortex, brain stem nuclei and cerebellum.
- Fibers that arise in the olive cross and enter the cerebellum in the contralateral inferior cerebellar peduncle.
- Climbing fibers distribute throughout the cerebellar cortex. Modulate Purkinje cells.

Somato-sensory inputs

- Some primary vestibular neurons in the vestibular (Scarpa's) ganglion project directly to the ipsilateral inferior cerebellar vermis and flocculondular lobe through the juxtarestiform body.
- Secondary vestibular axons arising in the vestibular nuclei also project to these areas.
- Vestibulo-cerebellar pathways are important for balance and equilibrium as well as vestibulo-ocular reflexes.

Outputs

- Purkinje cells of the lateral hemisphere project to the dentate nucleus.
- The dentate nucleus projects via the superior cerebellar peduncle to the contra-lateral red nucleus and ventral lateral nucleus of the thalamus.
- The ventral lateral nucleus of the thalamus projects to motor, pre-motor, and supplementary motor cortex.

Cerebellar Ataxia

- Cerebellar lesions are ipsilateral.
- Lesion of the anterior lobe of Cerebellum.
- Unable to stand with feet together. Lurch.
- May see to and fro movement of trunk. “Drunken” gait.
- Lesions of the vermis involve gait disturbance alone.
- Cerebellar hemispheric lesions are associated with limb ataxia and nystagmus.
- The shoulder is lower on the affected side. The patient falls to the side of the lesion.

Truncal Ataxia

- Lesions of the 4th Ventricle are associated with truncal ataxia. There is no motor incoordination but the inability to stand upright without support.
- It is difficult to separate vestibulo-cerebellar injury from injury to the nuclei.
- Spino-cerebellar and cerebro-cerebellar injury affect the most precise movements of the extremities.
- Asynergy, dysdiadochkinesia, dysmetria, decomposition of movement, hypotonia and pendular patellar tendon reflex are noted.

Freidrich's Ataxia

- Sensory ataxia
- Rare in those of non-Indo-European ancestry
- Autosomal-recessive
- GAA triplet expansion in FXN gene at 9q21.11
- Diminished production of frataxin
- Frataxin assists iron-sulfur synthesis in electron transport chain to produce ATP
- Degeneration particularly of sensory neurons in spinal cord

Freidrich's Ataxia

- Symptoms generally start between 5 -15 years of age (late onset, after 25 years of age)
- Gait and limb ataxia, dysarthria, loss of lower limb reflexes
- Hypertrophic cardiomyopathy very frequent in those with early onset disease
- Scoliosis in 60% of patients
- Increased prevalence of diabetes mellitus
- Omaveloxolone administration leads to long term symptom improvement

Charcot-Marie-Tooth (HMSN IA)

- Hereditary motor and sensory neuropathy with ataxia
- One of the most common inherited neurologic disorders
- Autosomal dominant
- Presents in early adolescence or adulthood
- Slowly progressive
- Weakness and atrophy of the muscles of the lower legs beginning in childhood
- Loss of fine motor skills (first, in toes)
- Later, hand weakness, distal sensory loss, and muscle atrophy.

Charcot-Marie-Tooth (HMSN IA)

- Foot drop and high stepped gait, claw toes
- “Inverted champagne bottle” appearance to lower legs as muscle bulk lost
- Duplication of PMP22 gene at 17p11.2 in 55% of cases
- Regulate Schwann cell growth and maturation

Charcot-Marie-Tooth (HMSN IA)

- Hereditary neuropathy with predisposition to pressure palsy (HNPP) is caused by a deletion of one of the PMP22 genes.
- Abnormally low levels of the PMP22 gene result in episodic, recurrent demyelinating neuropathy

HMSN IB

- CMT1B
- Myelin protein zero (MPZ) gene at 1p36.22 produces an identical clinical phenotype
- Adhesion molecule for myelin
- 9% of cases

Charcot-Marie-Tooth (HSN 1E)

- Progressive weakness of the feet and/or ankles; foot drop; atrophy of muscles below the knee; absent tendon reflexes of upper and lower extremities; and a decreased sensitivity to touch, heat, and cold in the feet and/or lower legs
- Cochlear earing loss associated with alanine to proline change at position 67 in PMP22 gene
- Autosomal dominant .

HMSN 1X

- CMT1X
- X-linked dominant form
- Secoond most common type
- 15% of cases
- GJB1 gene at Xq13.1 (gap junction or connexin-32 protein)
- Delayed transmission as gap covered by radial diffusion
- Demyelination

HMSN II

- CMT2A
- Autosomal dominant.
- Clinical presentation is as with classic Charcot-Marie-Tooth.
- Onset 5-25 years of age
- Loss of myelinated axons is prominent.
- Internodal demyelination is infrequent.
- Nerve conduction velocity impaired.
- Mutation involves the mitofusion protein 2, MFN2, at 1p36.22
- Prevents the mitochondrion from moving down the axon; synapse is inoperative.
- 4% of cases

HMSN II

- Some cases involve mutations in the KIF1B gene at 1p36.22, encoding the microtubular transport motor, kinesin, that transports synaptic vesicles (neurons) and mitochondria (other cells)
- GARS1 gene (glycyl tRNA synthetase) at 7p14.3
- Blocks glycine translation and attachment to cognate RNA
- Mutant protein product binds with neurolipin 1, leading to VEGF overexpression
- Associated with disease in hands.

HMSN II

- The constant cycle of demyelination and remyelination, which occurs in CMT, can lead to the formation of layers of myelin around some nerves, termed an "onion bulb".
- Muscles show fiber type grouping, a finding that indicates a cycle of denervation/reinnervation
- Generally milder than CMT I
- Some types of CMT2 may have vocal cord or phrenic nerve involvement, causing speech or breathing problems

Charcot-Marie-Tooth (HSN II)

- Another severe form of CMT2B is also associated with the formation of ulcers in the hands and feet.
- Onset in late childhood
- Four missense mutations in RAB7A gene at 3q21.3
- Alters autophagy

Charcot-Marie-Tooth (HSN II)

- CMT2F
- HSPBI gene at 7q11.23
- Chaperone function of heat shock protein altered by N-terminal change
- Autosomal dominant
- Onset in adolescence
- normal nerve conduction velocities
- upper limb amyotrophy, talipes equinovarus, steppage gait,

Charcot-Marie-Tooth (HSN II)

- MFN2-HMSN
- MFNP at 1p36.22
- Onset before 10 years of age
- Autosomal dominant (90%)
- Optic atrophy in 20% of those with autosomal recessive inheritance (7%, if autosomal dominant)
- Severe loss of sensation in the feet, lower legs, hands, and forearms; reduced tendon reflexes in the ankles; weakness in the lower limbs; muscle atrophy.

HMSN III, now HMSN IVF

- Dejerine-Sottas disease
- Can be inherited either dominantly or recessively
- Severe demyelinating neuropathy that begins in infancy.
- Involves both trunk and limb muscles
- Severe muscle atrophy and weakness, delayed motor skills development, sensory problems
- Progress to severe disability, loss of sensation, and curvature of the spine.

HMSN III, now HMSN IVF

- Caused by mutations in multiple genes
- PMP22, MPZ, and GJB1
- Protein degradation pathways (LITAF at 16p13.13)
- Mediate TNF-a
- Also in Type 1C
- Myelination induction (early growth response or EGR2 at 18q21.3)
- Transcription factor with three tandem C2H2 zinc fingers
- Also in Type 1D and 4E

Charcot-Marie-Tooth (HSN-IV)

- Rare in the U.S.
- Autosomal recessive.
- CMT4B2 SBF1 gene at 22q13.33
- Converts GDP to GTP
- Myoblast differentiation
- Pseudogenes found on chromosomes 1 and 8 as well
- Onset in childhood

  Poor fine motor control, leg weakness and distal upper limb weakness
- Myelin outfoldings in peripheral nerve sheath

Late onset ataxia

- RFC1 associated ataxia:
- This is the most common cause of late-onset ataxia.
- The ataxia symptoms are usually accompanied by dizziness, numbness or tingling in the body, and sometimes unexplained cough.
- Gene at 4p14 encodes a five unit DNA polymerase accessory protein needed for replication and repair

Spinocerebellar ataxia

- Autosomal Dominant Cerebellar Ataxia (ADAC)
- Progressive degeneration of cerebellum, brainstem, spinal cord
- Types 1,2,3,6 are the most common forms of spinocerebellar ataxia
- There are more than 30 types

Spinocerebellar ataxia

- ADAC I
- SCA Type 1
- CAG repeats in ataxin-1 gene at 6p22.3
- Represses Notch signaling
- Onset in fourth decade
- Ataxia, spasticity, hyperreflexia, cognitive impairment, ophthalmoplegia
- Involves pontine tegmentum

Spinocerebellar ataxia

- SCA Type 2 (olivopontocerebellarr atrophy)
- CAG repeats in ataxin-2 gene at 12.p24.12
- Negative regulator of endocytic EGFR internalization at the plasma membrane.
- Ataxia, saccadic eye movements, myoclonus or dystonia, polyneuropathy, cognitive decline
- Hot cross bun sign in pons on T2 weighted MRI

Spinocerebellar ataxia

- SCA Type 3 (Machado-Joseph)
- CAG repeats in ataxin-3 gene at 14q32.12
- Deubiquinating enzyme affected
- Three types; most common peresents between age 20-50
- Spasticity, dystonia late atazia, opthalmoplegia, polyneuropathy pontine tegmentum
- SCA Type 4
- Mutated gene not identified; located at 16q22.1
- Progressive peripheral neuropathy; impaired tactile, vibratory, proprioceptivon
- Adult onset

Spinocerebellar ataxia

- SCA Type 6
- CACNA1A gene at 19p13.13
- Voltage gated Calcium channel
- Onset in adolescence
- Unsteady gait, postural instability, cerebellar ataxia

Spinocerebellar ataxia

- ADAC II
- SCA Type 7
- CAG repeats in ataxin-7 gene at 3p14.1
- Adolescent- or adult-onset progressive cerebellar ataxia and cone-rod retinal dystrophy
- Or infantile or early-childhood onset with multi-organ failure, an accelerated course
- Associated with retinal degeneration
- Dysarthira, dysmetria, ataxia, hyper-reflexia

Spinocerebellar ataxia

- ADAC III
- SCA Type 5
- SPTBN2 gene at 11q13.2
- Defective β-III spectrin fails to stabilize glutamate transporter
- Pure cerebellar syndrome as affects Purkinje cells

Spinocerebellar ataxia

- Other SCA types not categorized as ADAC I-III
- SCA Type 31
- TGGAA pentanucleotide repeats in BEAN gene at 16q22.1
- Ubiquitin ligase impaired
- Onset in childhood
- Gait ataxia, dysarthria, cerebellar atrophy

Episodic ataxia

- Recurrent episodes of poor coordination and balance
- Autosomal dominant
- Types 1, 2, 5 most commonly seen
- Type 4 is late onset
- Type 8 has onset in infancy

Episodic ataxia

- Type 1
- Onset 2-15 years of age
- Vertigo, dysarthria, weakness, tremor, seizure
- Lasts seconds
- Myokymia (muscle cramping, stiffness, and continuous, fine muscle twitching that appears as rippling under the skin) manifest in inter-ictal period
- KCNA1 gene at 12p13.31
- Potassium gated voltage channel

Episodic ataxia

- Type 2 most common form
- Onset 2-20 years of age
- Vertigo, dysarthria, diplopia, weakness, tonic upper gaze, headache, seizure, dystonia, cognitive impairment
- Lasts hours
- Nystagmus, ataxia in inter-ictal period
- CACNA1A gene at 19p13.13
- Calcium P/Q gated voltage channel
- Acetazolamide-responsive
- Locus ceruleus norepinephrine release to stress as trigger

Episodic ataxia

- Type 3 very rare
- Onset 1-40 years of age
- Vertigo, diplopia, weakness, tinnitus, headache, visual blurring
- Episodes last 1 minute to 6 hours
- Myokymia in inter-ictal period
- Gene abnormality not known

Episodic ataxia

- Type 4
- Onset 20-60 years of age
- Recurrent attacks of vertigo and diplopia
- Brief episodes
- Nystagmus with abnormal smooth pursuit in inter-ictal period
- Gene abnormality not known
- Type 5
- Onset age 20
- Recurrent attacks of vertigo and diplopia
- Lasts hours
- Nystagmus, ataxia in inter-ictal period
- CACNB4 gene at 2q22.3
- Calcium P/Q gated voltage channel

Episodic ataxia

- Type 6
- Onset 5-14 years of age
- Vertigo, weakness, seizures
- Lasts for hours or days
- Nystagmus, ataxia in inter-ictal period
- SLC1A3 gene at p13.2
- Glutamate transporter
- Type 7
- Onset before age 20
- Vertigo, dysarthria, weakness
- Lasts for hours or days
- Gene abnormality not identified

Episodic ataxia

- Type 8
- Infancy onset
- Vertigo, weakness
- Lasts up to 24 hours
- Nystagmus, ataxia, myokymia in inter-ictal period
- UBPR gene at 1p36.13
- Ubiquitin protein ligase

Ataxia Telangiectasia

- Classic ataxia-telangiectasia
- Progressive cerebellar ataxia
- Onset 1-4 years of age
- Oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency
- Frequent infections
- Increased risk for malignancy, particularly leukemia and lymphoma.
- Individuals with A-T are unusually sensitive to ionizing radiation

Ataxia Telangiectasia

- Non-classic
- Include adult-onset as well as early-onset dystonia.
- Sardinian, Amish, Moroccan Sephardic populations at risk
- Autosomal recessive
- ATM gene at 11q22.3
- Defective serine/threonine kinase does not activate DNA repair phosphorylate p53
- Micrscopic examination demonstrates nucleomegaly
- AFP>10ng/ml