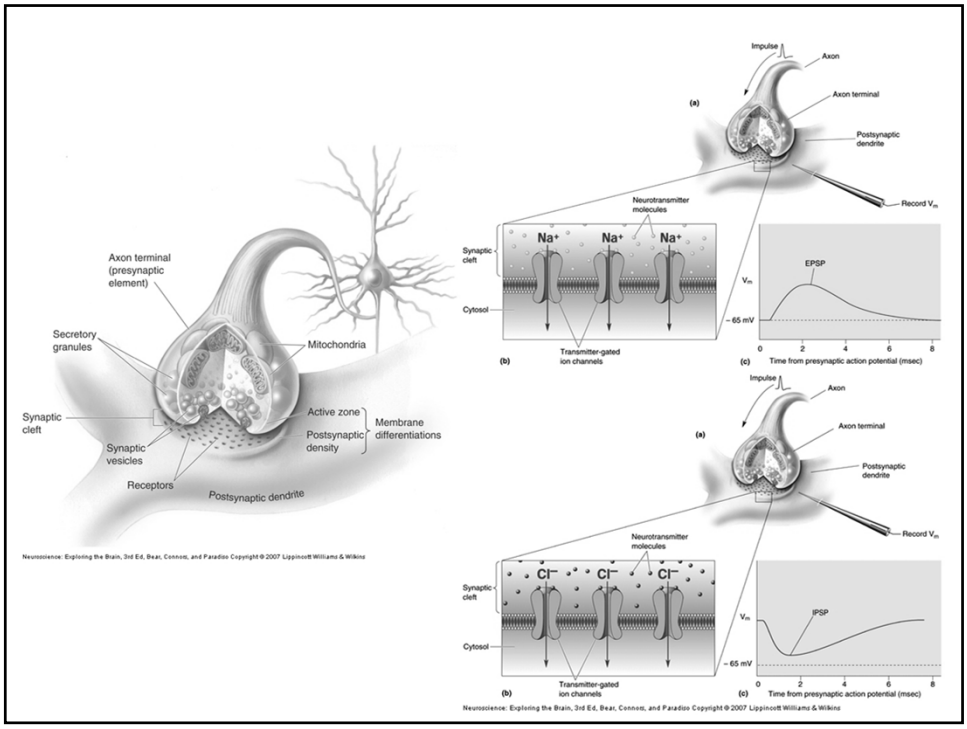
Axon terminal (presynaptic element)
Secretory granules
Mitochondria
Synaptic cleft
Active zone
Postsynaptic density
Membrane differentiations
Synaptic vesicles
Receptors
Postsynaptic dendrite
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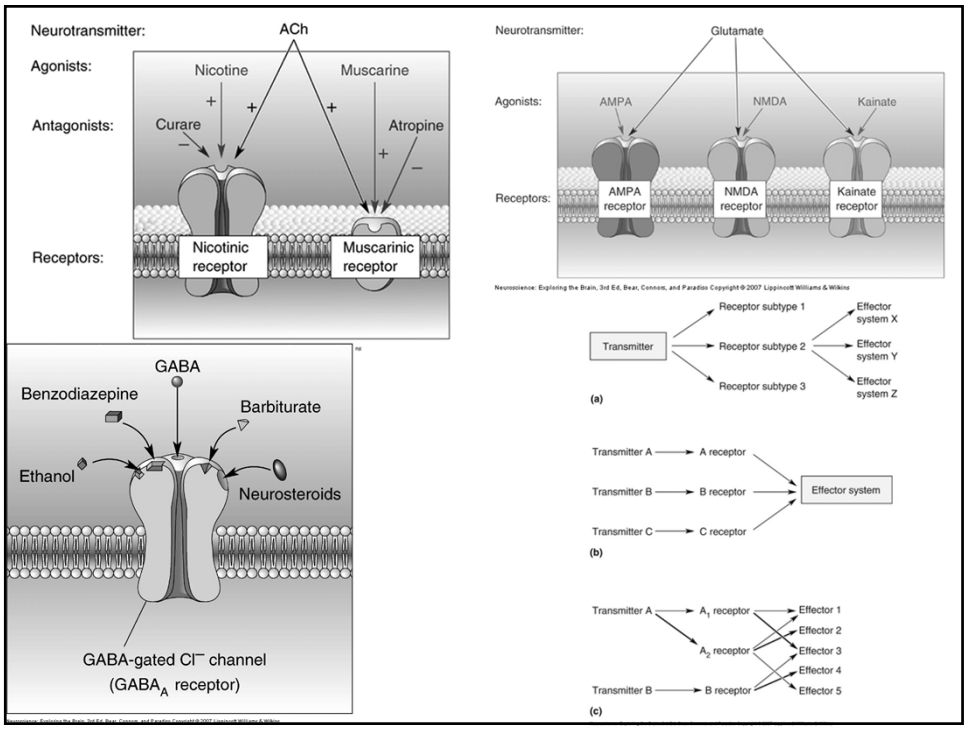
Impulse
Axon
Axon terminal
Postsynaptic dendrite
Record V_m
Neurotransmitter molecules
Synaptic cleft
Cytosol
Na^+
Transmitter-gated ion channels
EPSP
V_m
−65 mV
Time from presynaptic action potential (msec)
Cl^-
IPSP


Neurotransmitter:
ACh
Agonists:
Nicotine
Muscarine
Antagonists:
Curare
Atropine
Receptors:
Nicotinic receptor
Muscarinic receptor
GABA
Benzodiazepine
Barbiturate
Ethanol
Neurosteroids
GABA-gated Cl^- channel
($GABA_A$ receptor)
Glutamate
AMPA
NMDA
Kainate
AMPA receptor
NMDA receptor
Kainate receptor
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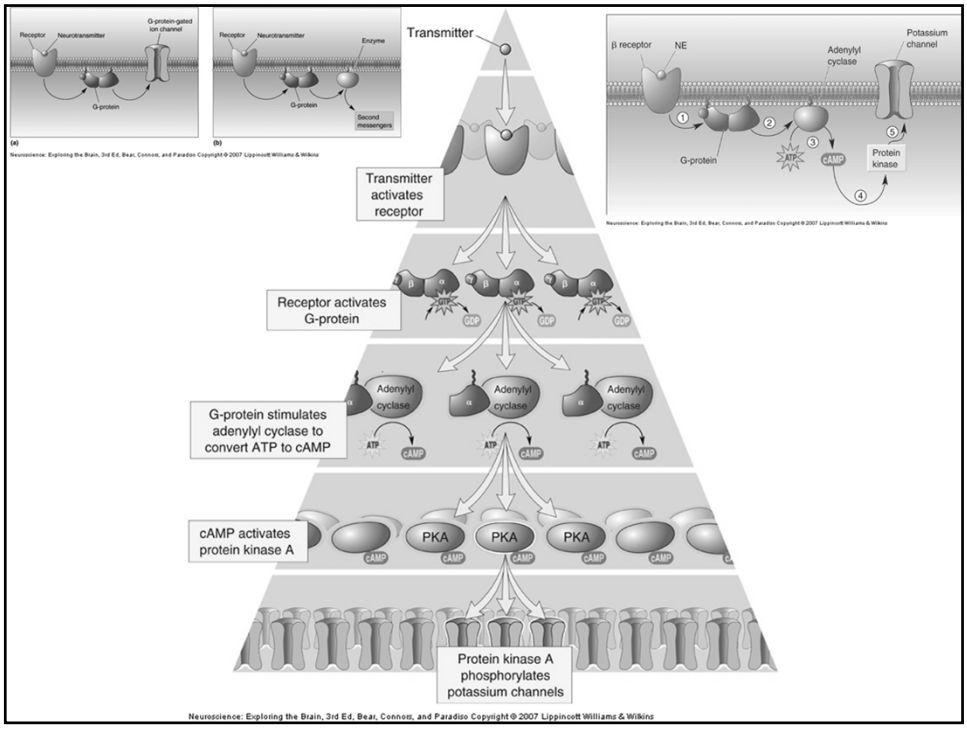
Transmitter
Receptor subtype 1
Receptor subtype 2
Receptor subtype 3
Effector system X
Effector system Y
Effector system Z
(a)
Transmitter A
Transmitter B
Transmitter C
A receptor
B receptor
C receptor
Effector system
(b)
A_1 receptor
A_2 receptor
Effector 1
Effector 2
Effector 3
Effector 4
Effector 5
(c)


Receptor
Neurotransmitter
G-protein-gated ion channel
G-protein
(a)
Receptor
Neurotransmitter
Enzyme
G-protein
Second messengers
(b)
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Transmitter
Transmitter activates receptor
β receptor
NE
Adenylyl cyclase
Potassium channel
G-protein
ATP
cAMP
Protein kinase
Receptor activates G-protein
GDP
G-protein stimulates adenylyl cyclase to convert ATP to cAMP
Adenylyl cyclase
ATP
cAMP
cAMP activates protein kinase A
PKA
Protein kinase A phosphorylates potassium channels
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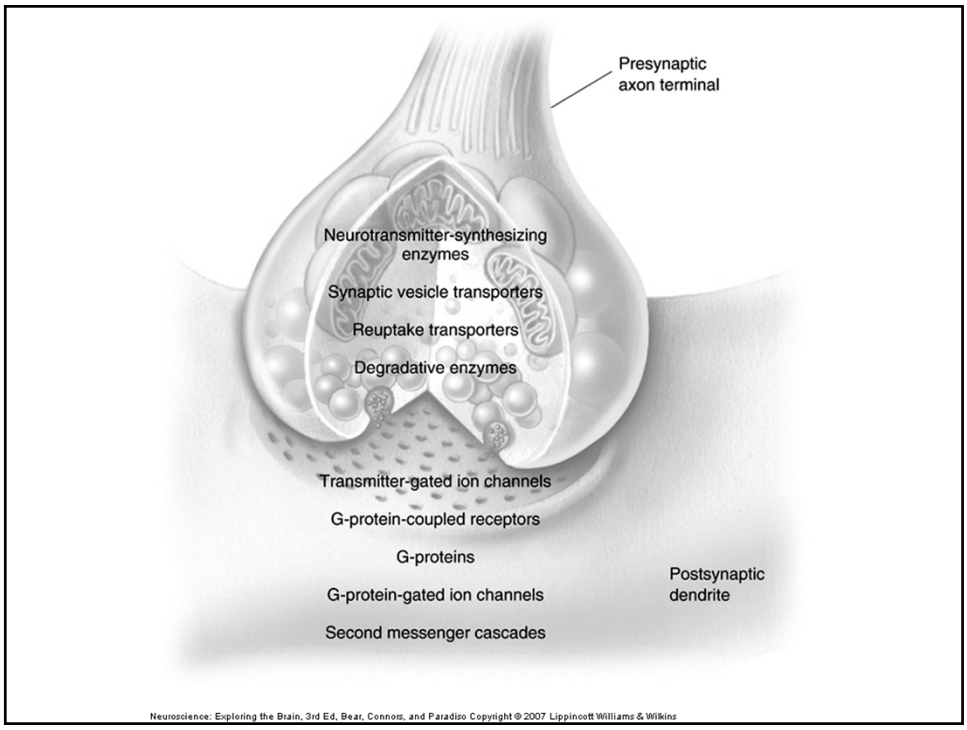
Presynaptic axon terminal
Neurotransmitter-synthesizing enzymes
Synaptic vesicle transporters
Reuptake transporters
Degradative enzymes
Transmitter-gated ion channels
G-protein-coupled receptors
G-proteins
G-protein-gated ion channels
Second messenger cascades
Postsynaptic dendrite
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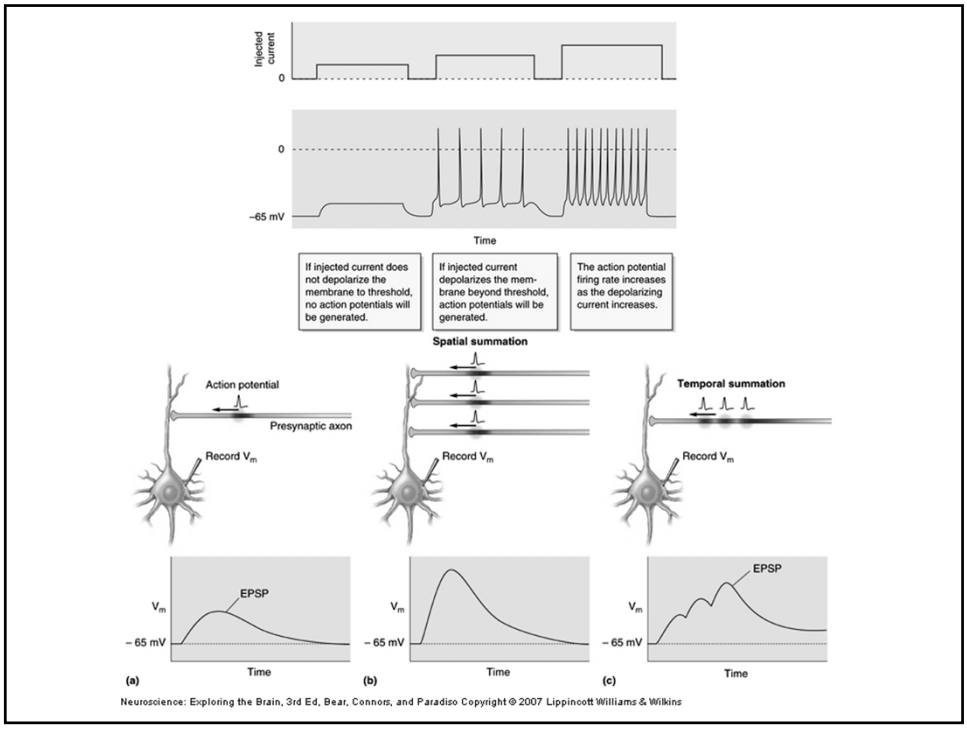
Injected current
0
0
–65 mV
Time
If injected current does not depolarize the membrane to threshold, no action potentials will be generated.
If injected current depolarizes the membrane beyond threshold, action potentials will be generated.
The action potential firing rate increases as the depolarizing current increases.
Spatial summation
Action potential
Presynaptic axon
Record V_m
Temporal summation
EPSP
V_m
– 65 mV
Time
(a)
(b)
(c)
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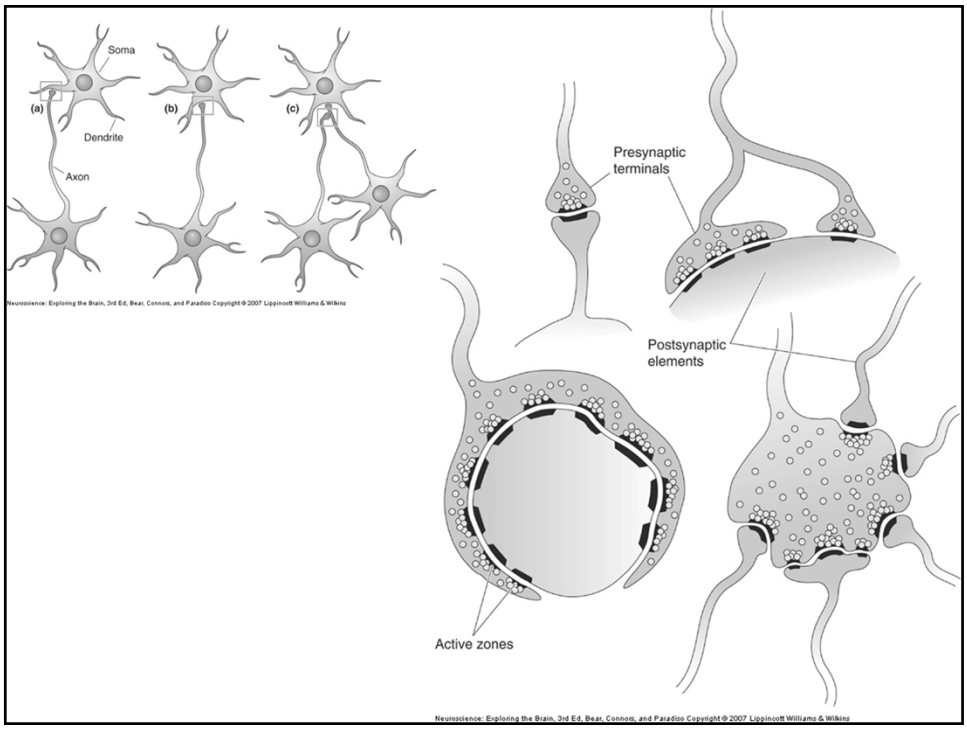
Soma
(a)
(b)
(c)
Dendrite
Axon
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Presynaptic terminals
Postsynaptic elements
Active zones
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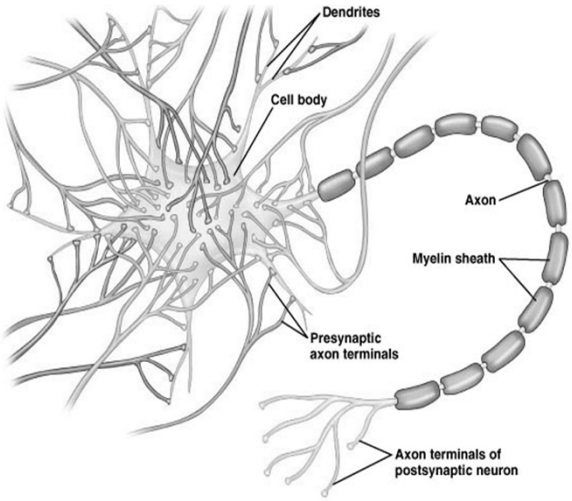
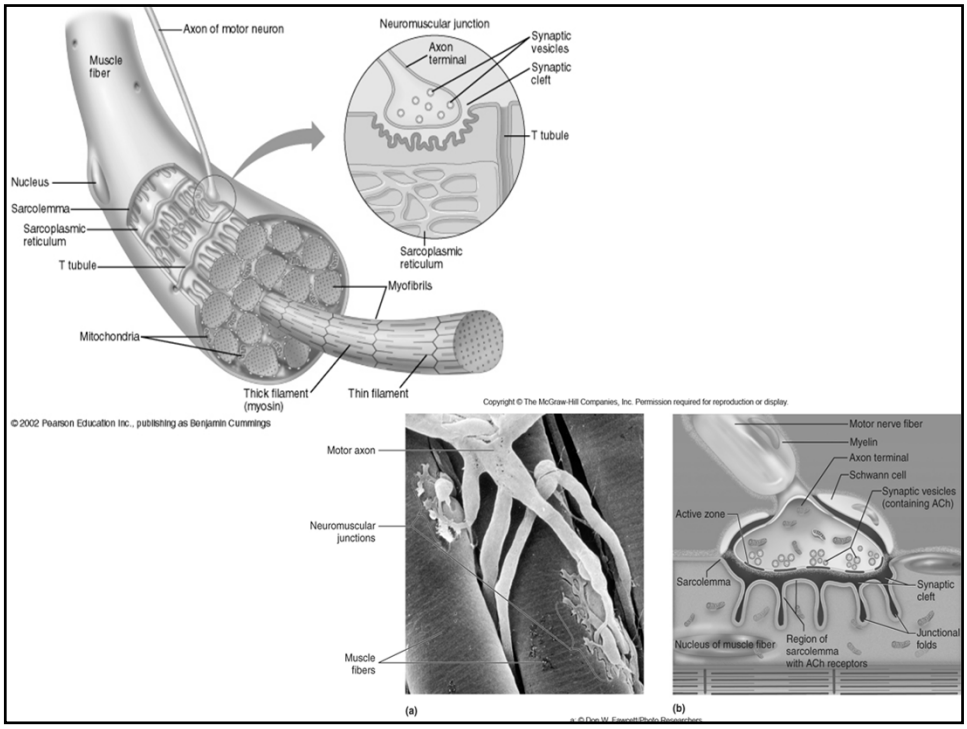
Neural Activation of Muscle

- Neuromuscular Junction (NMJ)
- Twitches, Tetani and Fatigue
- Motor Units




Axon of motor neuron
Muscle fiber
Neuromuscular junction
Axon terminal
Synaptic vesicles
Synaptic cleft
T tubule
Nucleus
Sarcolemma
Sarcoplasmic reticulum
T tubule
Sarcoplasmic reticulum
Myofibrils
Mitochondria
Thick filament (myosin)
Thin filament
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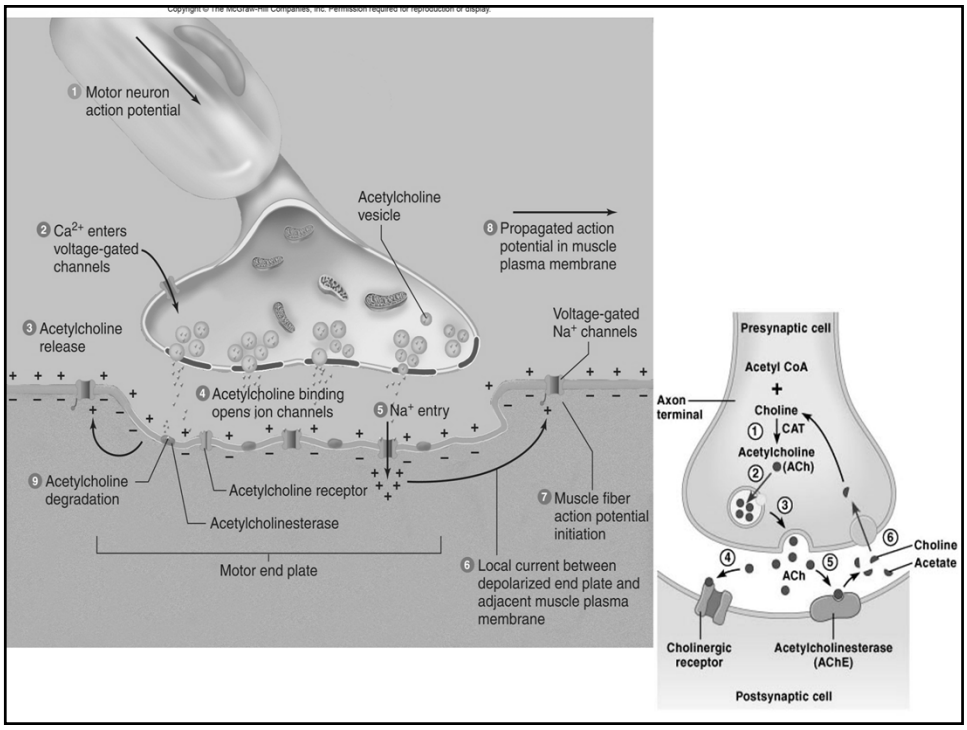
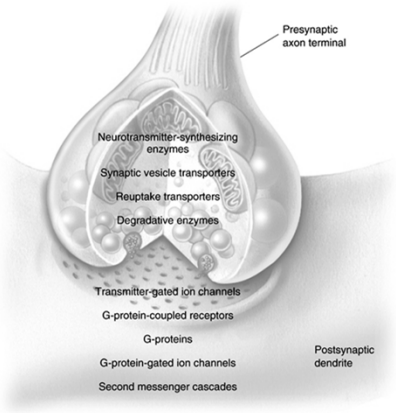
Motor axon
Neuromuscular junctions
Muscle fibers
(a)
Motor nerve fiber
Myelin
Axon terminal
Schwann cell
Synaptic vesicles (containing ACh)
Active zone
Sarcolemma
Synaptic cleft
Nucleus of muscle fiber
Region of sarcolemma with ACh receptors
Junctional folds
(b)


1 Motor neuron action potential
2 Ca2+ enters voltage-gated channels
3 Acetylcholine release
Acetylcholine vesicle
8 Propagated action potential in muscle plasma membrane
Voltage-gated Na+ channels
4 Acetylcholine binding opens ion channels
5 Na+ entry
9 Acetylcholine degradation
Acetylcholine receptor
Acetylcholinesterase
7 Muscle fiber action potential initiation
Motor end plate
6 Local current between depolarized end plate and adjacent muscle plasma membrane
Presynaptic cell
Acetyl CoA
Axon terminal
Choline
CAT
Acetylcholine (ACh)
Choline
Acetate
ACh
Cholinergic receptor
Acetylcholinesterase (AChE)
Postsynaptic cell



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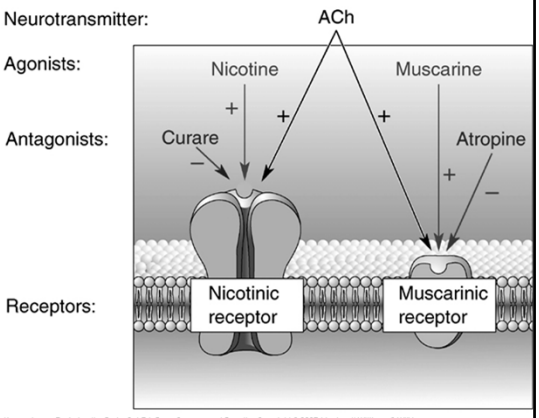

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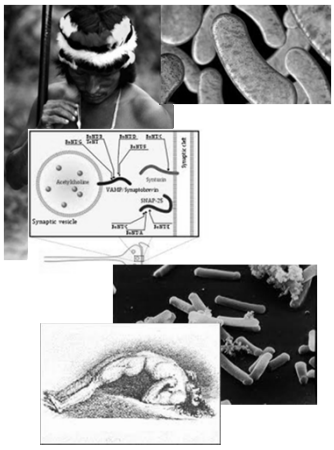
Drugs/Molecules Affecting the NMJ

- Curare
  - ***Inhibitor of AChR-binding site***
- Botulinum Toxin
  - ***Blocks release of ACh from NMJ***
  - ***Causes flaccid paralysis***
- Tetanus Toxin
  - ***Blocks inhibition of motorneurons***
  - ***Causes rigid paralysis***
- Acetylcholine Agonists
  - ***Nicotine, Methacholine, Carbachol***
- Desensitizing Agents
  - ***Succinyl choline***



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Drugs/Molecules Affecting the NMJ

- Acetylcholine-Esterase Inhibitors
  - ***Physostigmine and Neostigmine are derived from plants***
  - ***Diisopropyl fluorophosphate is a human-made "nerve gas"***
  - ***Used clinically for myasthenia gravis and early stages of Alzheimer's Disease***
- Black widow spider venom
  - ***complete depletion** of **acetylcholine***
  - ***initial spasms and then paralysis.***
- Cobra toxin
  - ***specifically blocks the acetylcholine receptor***
  - ***slow breakdown of toxin***

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Drugs/Molecules Affecting the NMJ

- Myasthenia gravis
  - ***Symptoms include poor muscle tone***
  - ***Autoimmune disease in which AChRs are attacked***
  - ***AChE inhibitors are effective treatments***
- Eaton-Lambert syndrome:
  - ***Antibodies to the calcium channel in the nerve terminal***
  - ***decreased release of quanta of acetylcholine***
  - ***Syrntoms are proximal weakness, often with autonomic features (blurred vision and dry mouth); reflexes are absent.***

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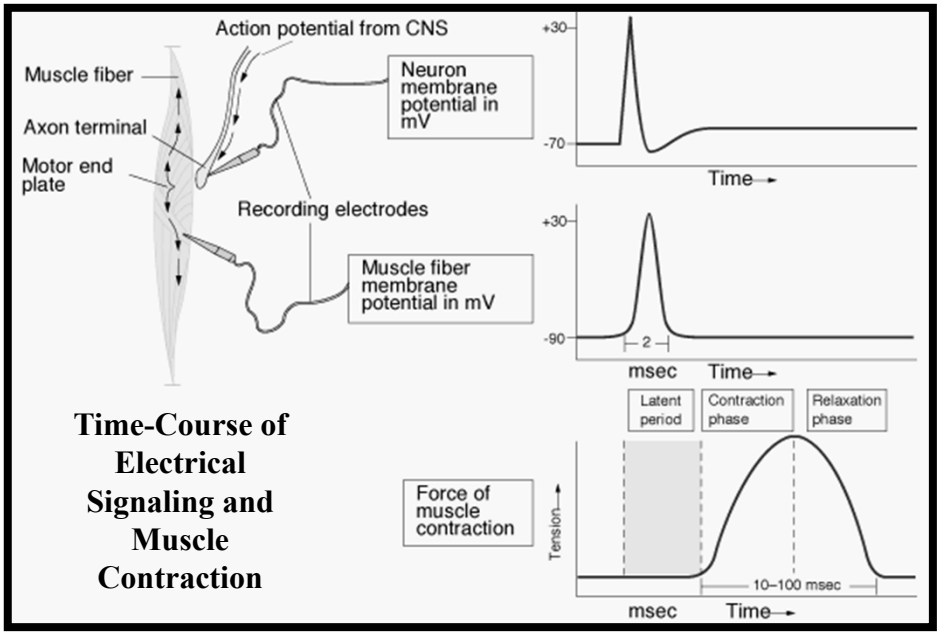
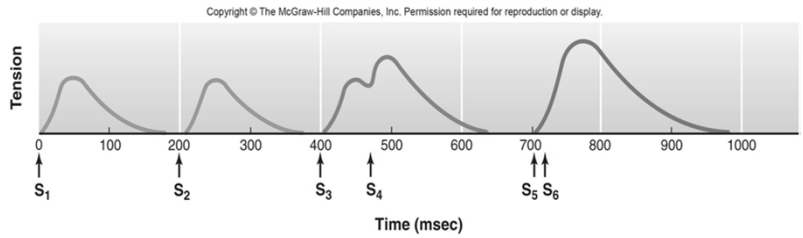
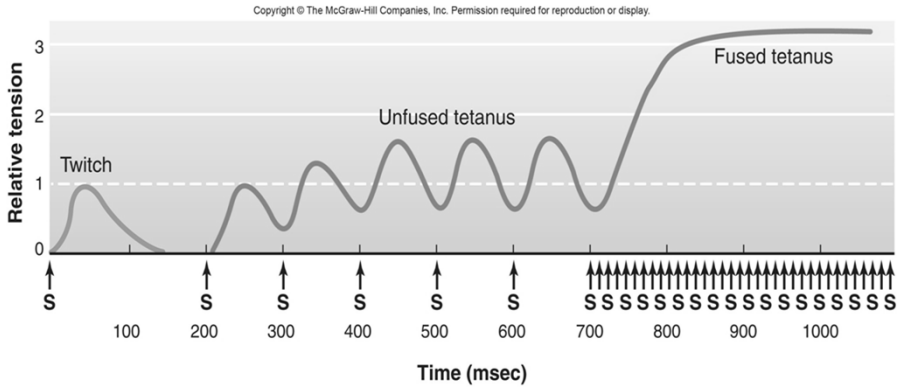
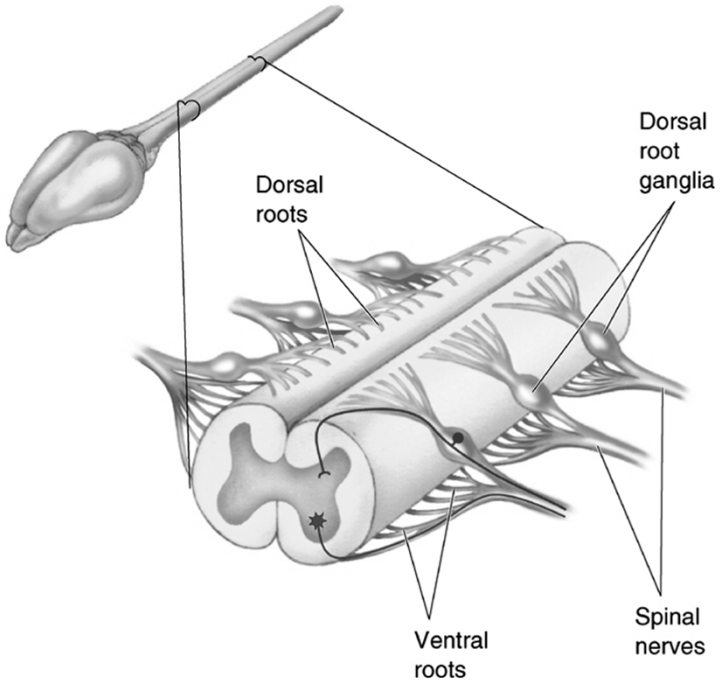


Time-Course of Electrical Signaling and Muscle Contraction





Motor Systems and Motor Control



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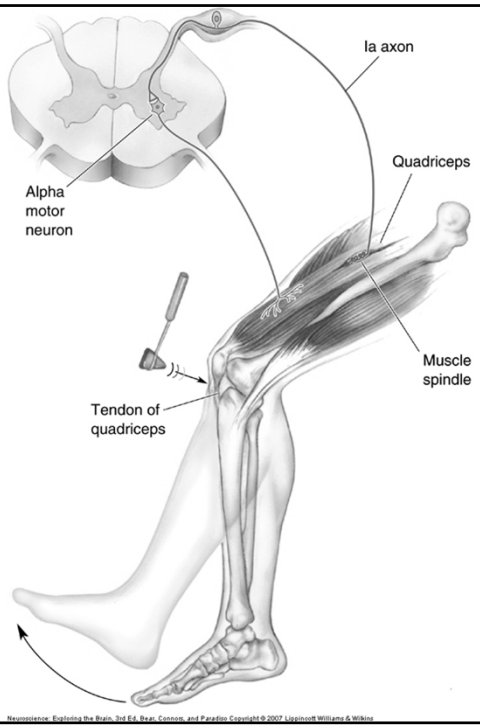


Motor Movements

Reflex Responses

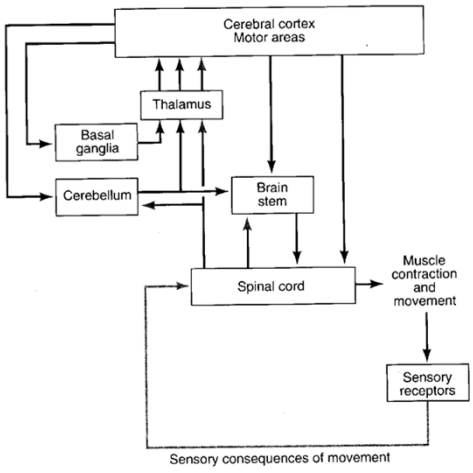
(Spinal Cord)

Rhythmic Motor Patterns

(Brainstem)

Voluntary Movements

(Cerebral Mechanisms)



Reflex Responses

Muscle Control

Must convey accurately timed commands not only to one muscle group but to many groups.

Agonist and Antagonist muscle groups.

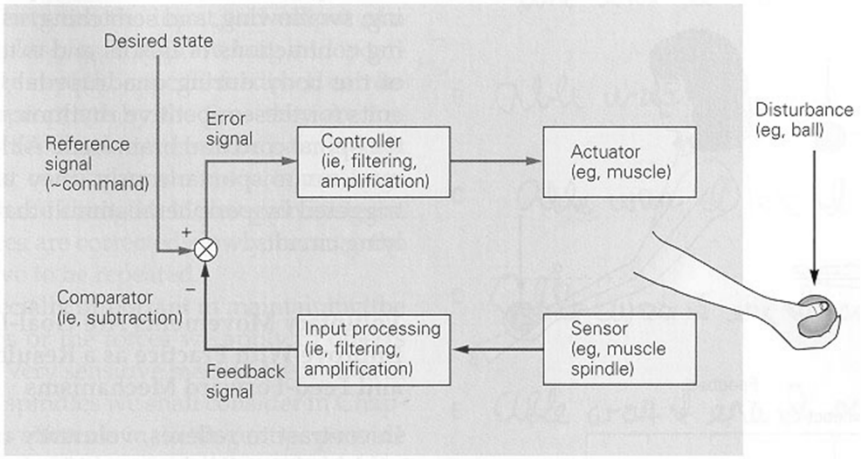
Motor Plant

Sensory Systems

Are vital to the correct functioning of motor systems

Feedback Mechanism

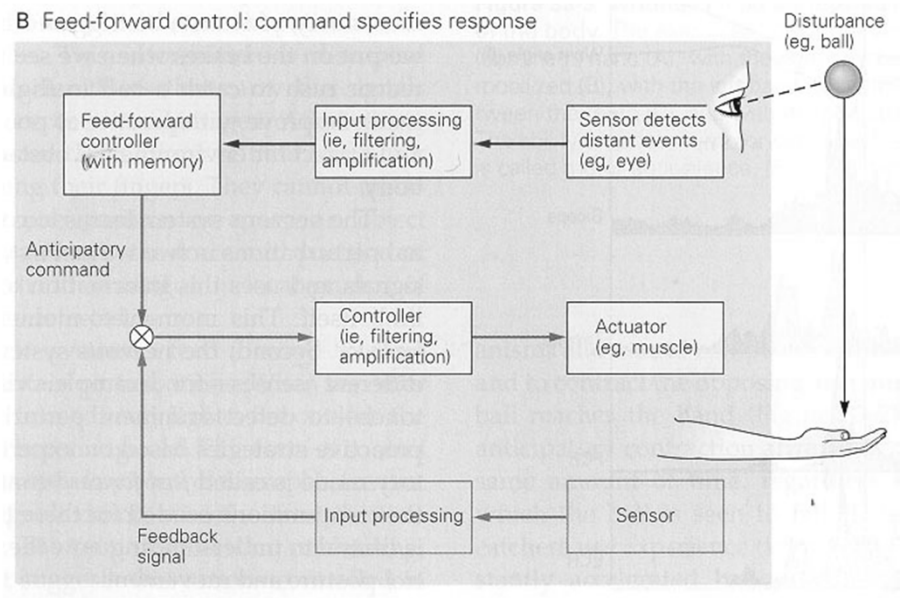
A Feedback control: command specifies desired state

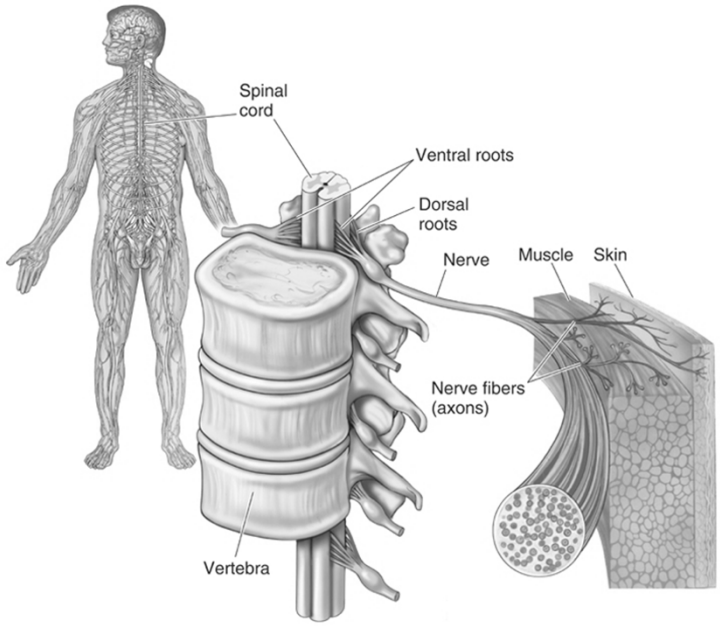


- **Slow Processing**
- **Mainly limited to slow movements & sequential acts.**

Feed Forward Mechanism

- **Predicting movements**
- **Quick dynamic movements**





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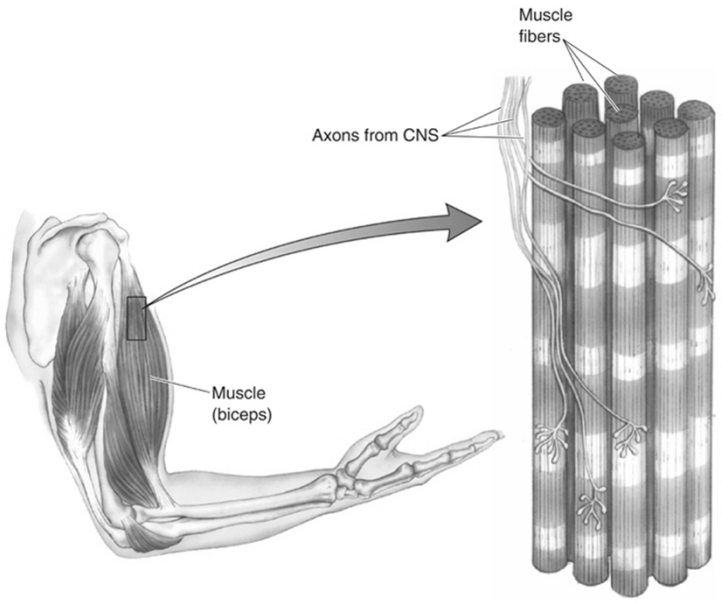
Muscle Receptors, Spinal Reflexes, and Local Control of Motor Movements



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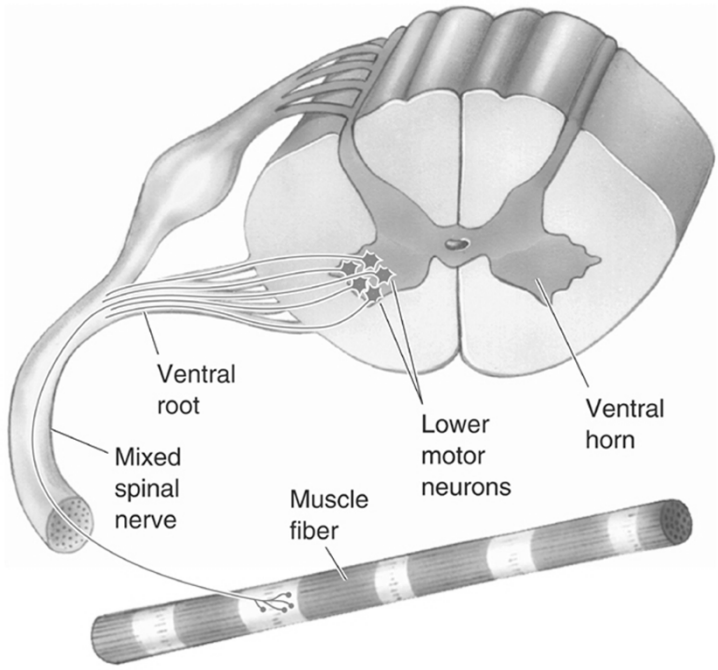

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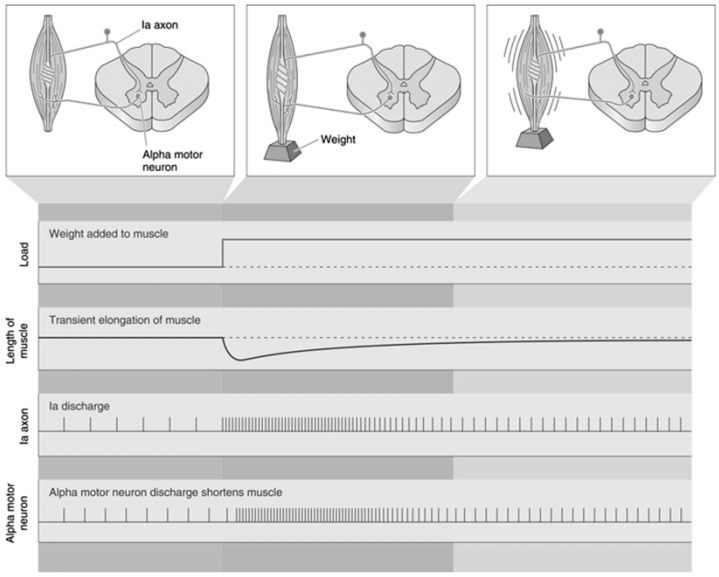

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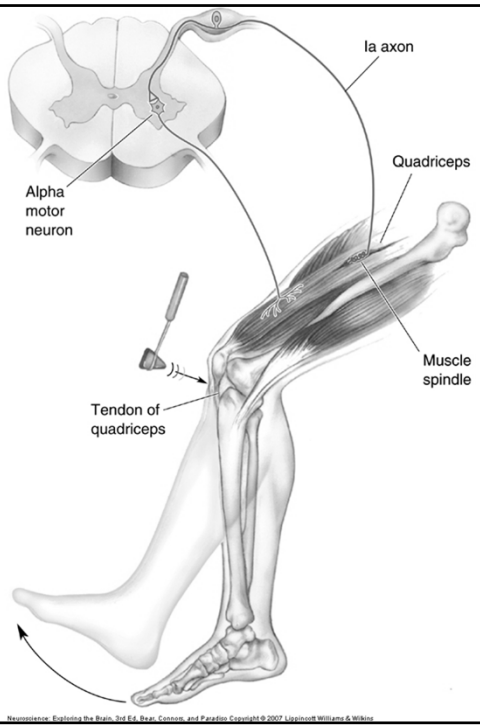


Muscle Stretch Receptors:

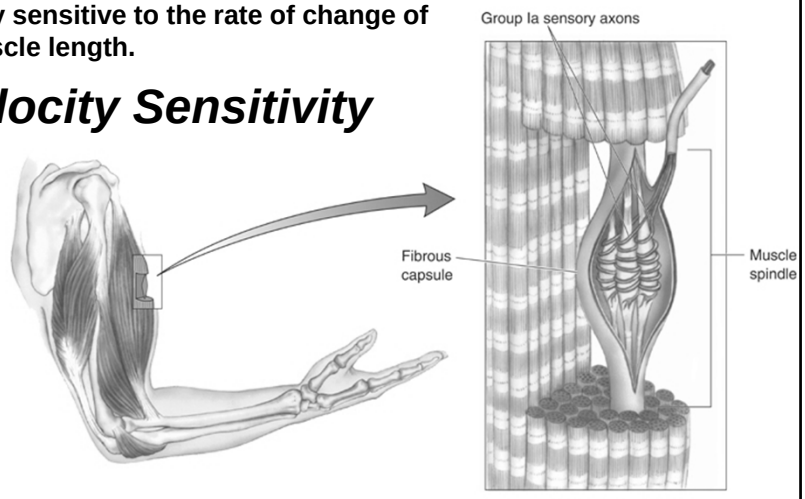
- **Muscle Spindles**
- **Golgi Tendon Organs**

Muscle Spindle Receptors:

Specialized muscle fibers
- **Nuclear chain fibers**
- **Nuclear bag fibers**

Very sensitive to the rate of change of muscle length.

Velocity Sensitivity



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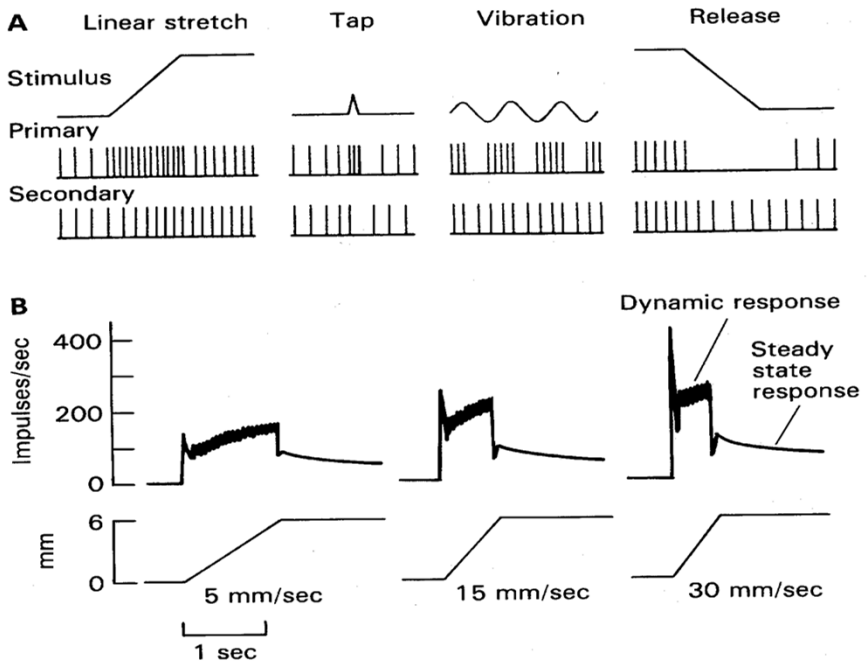
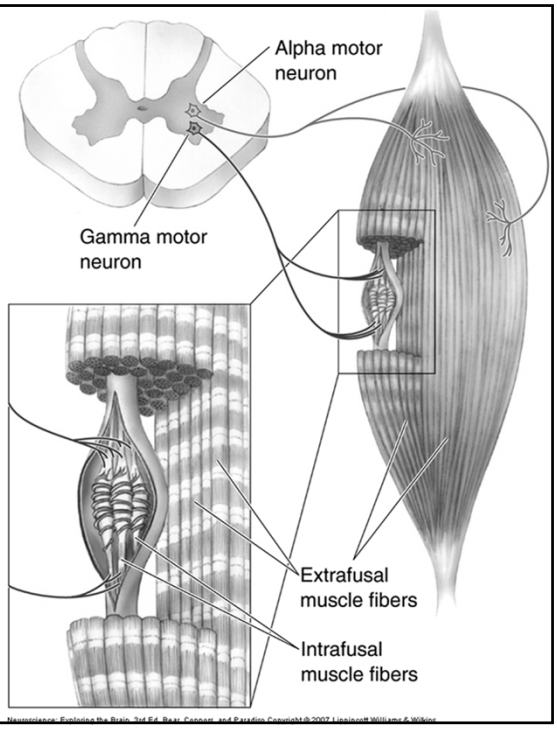


Muscle Spindle Receptors:

- **Motor neuron innervation is located on ends of intrafusal fibers.**
- **Regulate muscle length.**
- **Regulate muscle sensitivity**

Gamma Motor Neurons



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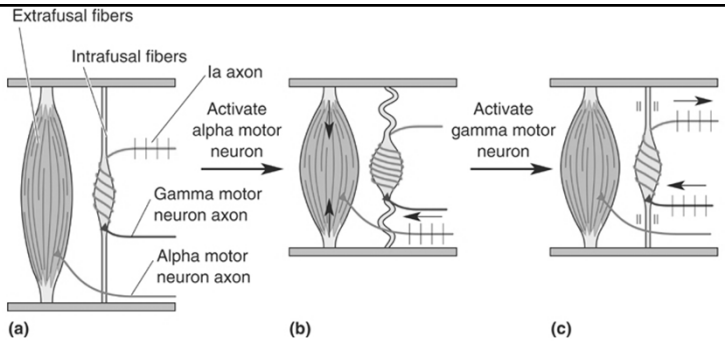

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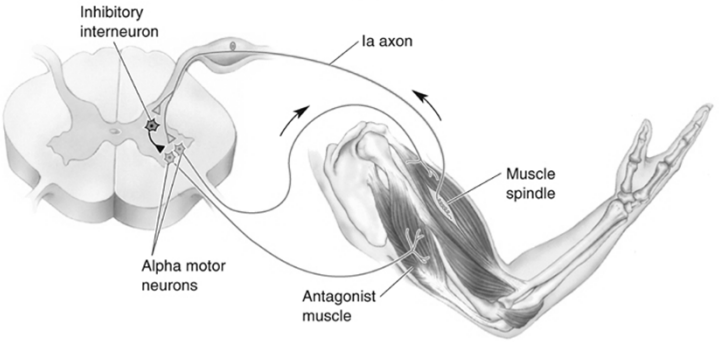

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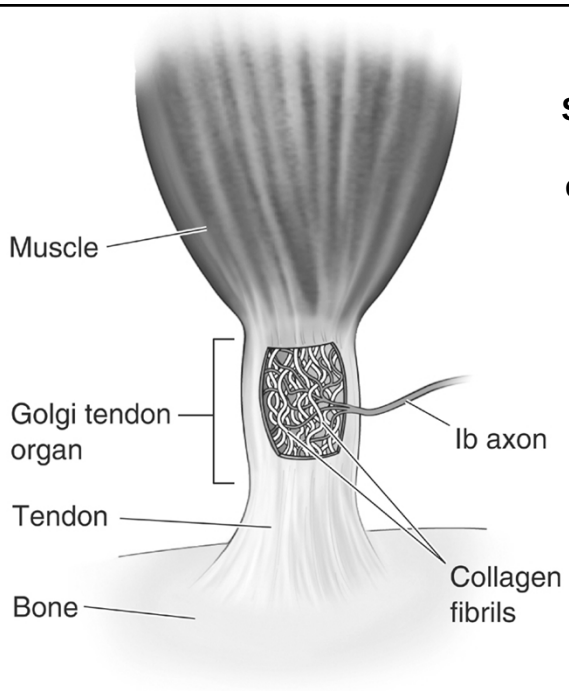
Golgi Tendon Organ:

- **Located at the junction of muscle and tendon.**
- **Loss myelination & braids itself within the collagen fibers of the tendon.**



Stretching of capsule compresses nerve endings, causing the neuron to fire.

Very sensitive to changes in tension of muscle.

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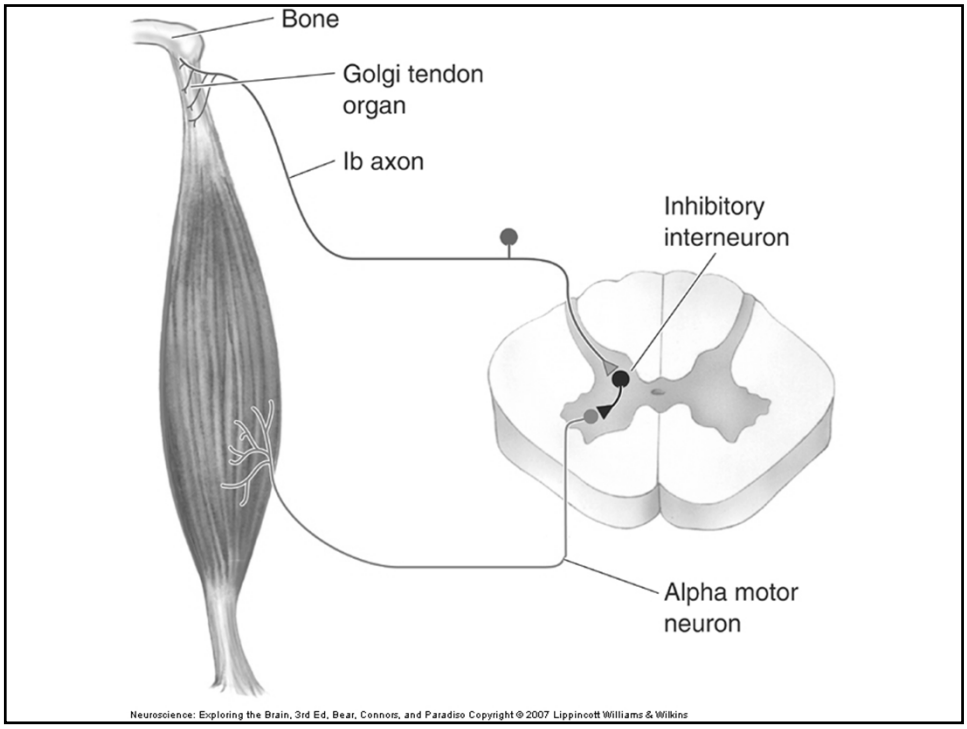
Bone
Golgi tendon organ
Ib axon
Inhibitory interneuron
Alpha motor neuron
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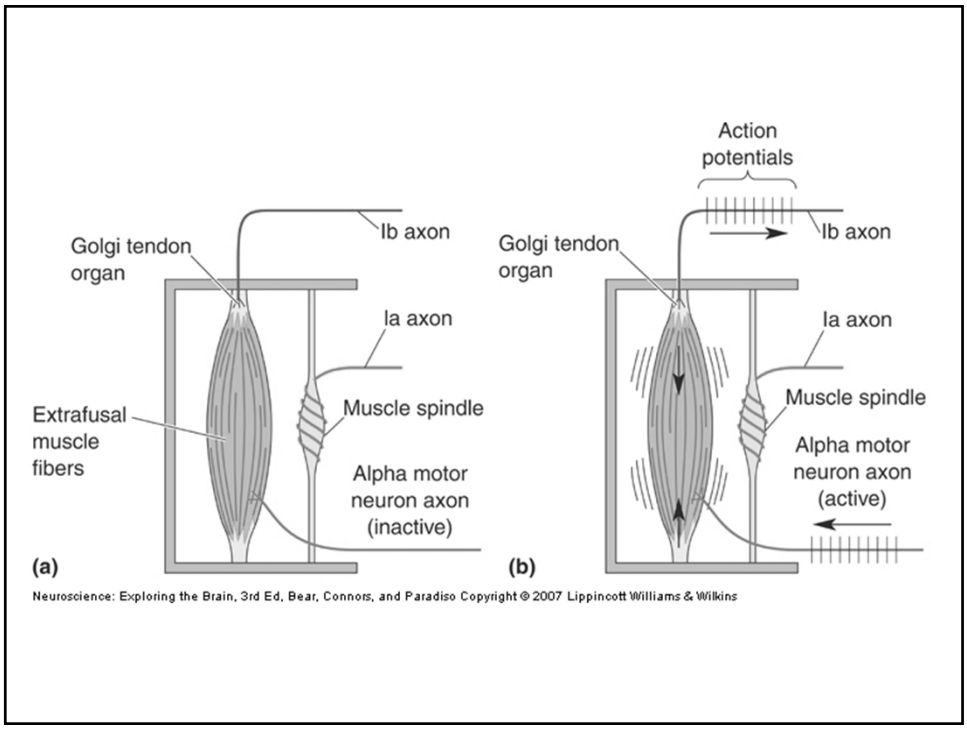
Golgi tendon organ
Ib axon
Ia axon
Extrafusal muscle fibers
Muscle spindle
Alpha motor neuron axon (inactive)
(a)
Action potentials
Golgi tendon organ
Ib axon
Ia axon
Muscle spindle
Alpha motor neuron axon (active)
(b)
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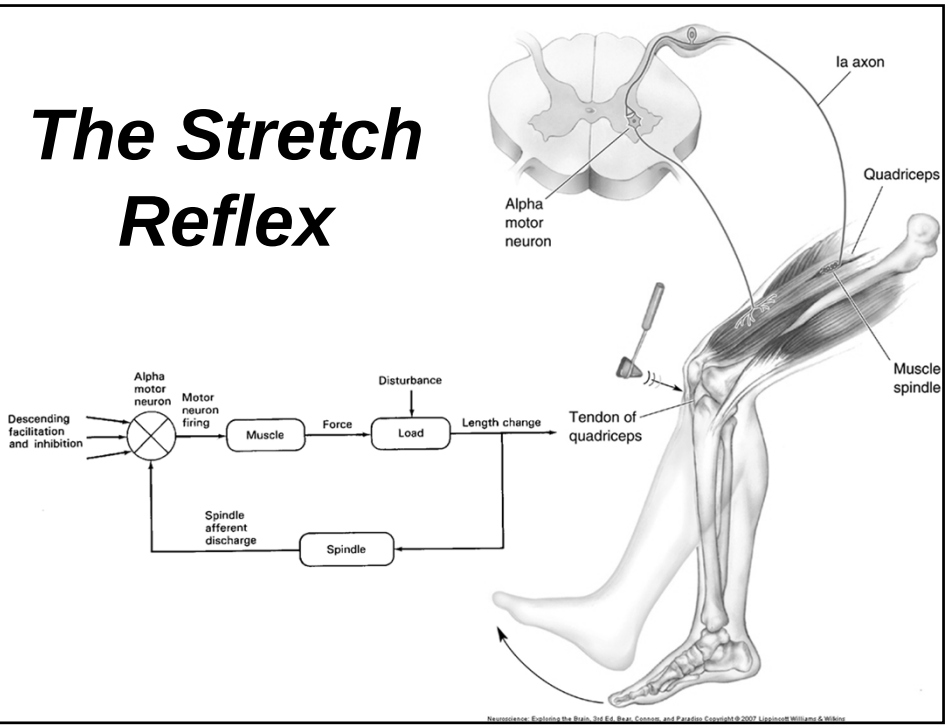
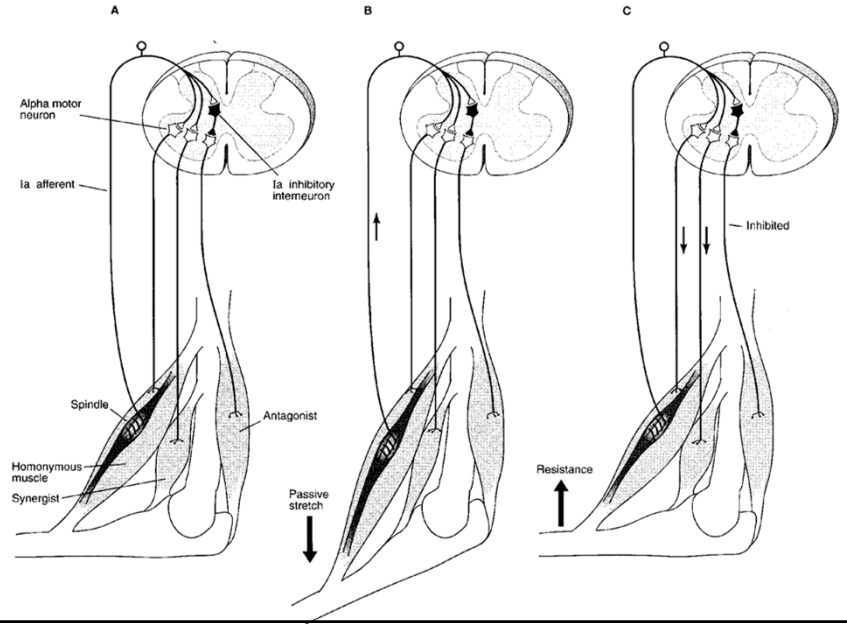
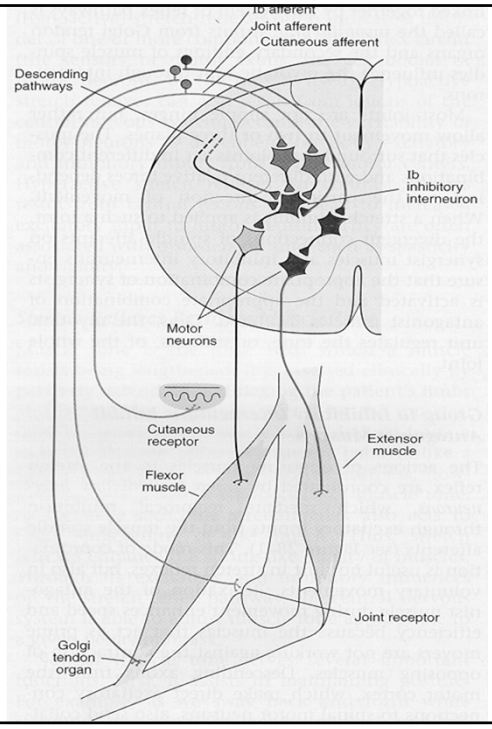
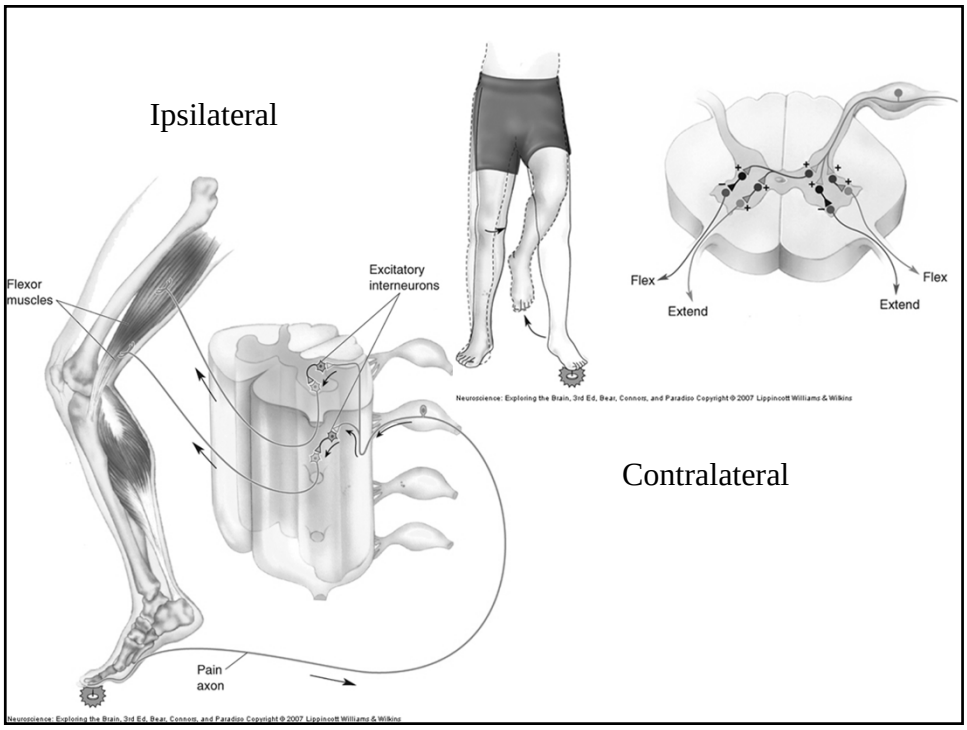
The Stretch Reflex



Myotatic Reflex




Ib afferent
Joint afferent
Cutaneous afferent
Descending pathways
Ib inhibitory interneuron
Motor neurons
Cutaneous receptor
Extensor muscle
Flexor muscle
Joint receptor
Golgi tendon organ


Ipsilateral
Flexor muscles
Excitatory interneurons
Flex
Extend
Flex
Extend
Contralateral
Pain axon
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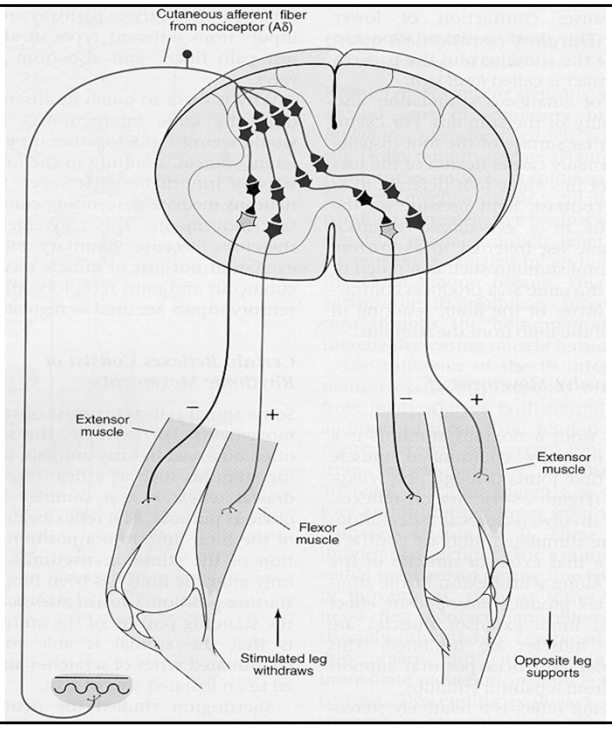
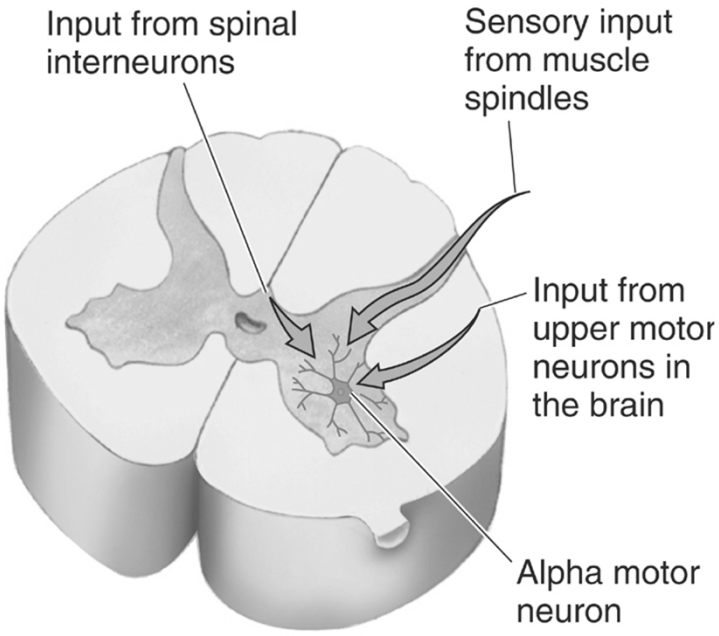
Flexion - Withdrawal Reflex





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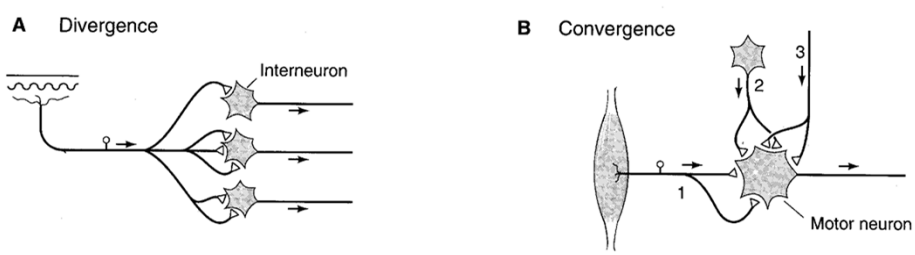
Neural circuits (microcircuits) within the spinal cord play an essential role in motor coordination.

Interneurons are a vital player in these microcircuits.

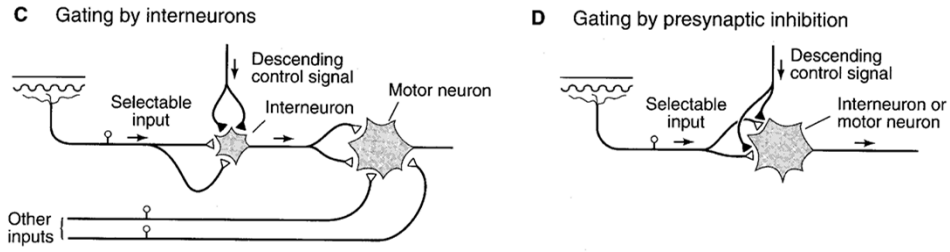
Interneurons can be either inhibitory or stimulatory within the circuits they are residing.

Divergence - the distribution of the output of a single neuron (or a group of neurons) to a number of target neurons by branching of the axon.

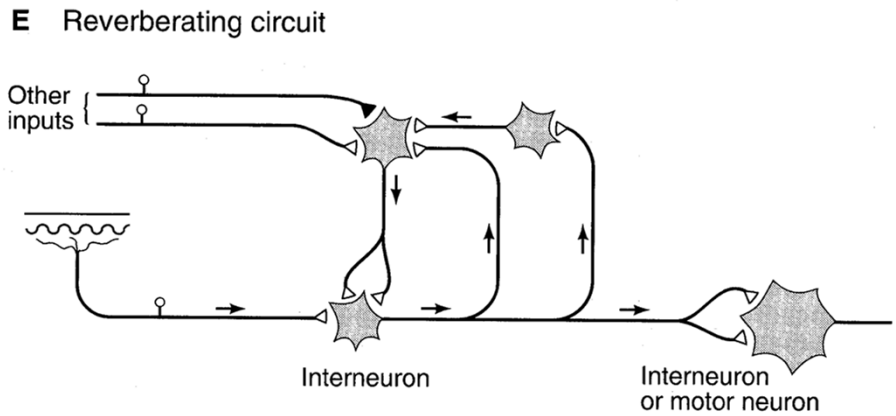


Convergence - the processing of input from several neurons (or groups of neurons) onto one neuron (or neuronal group).

***Gating* - intermediate neurons (interneurons) or intermediate connections utilized by higher centers to preselect which of several possible responses will follow a stimulus.**



Spatial Organization

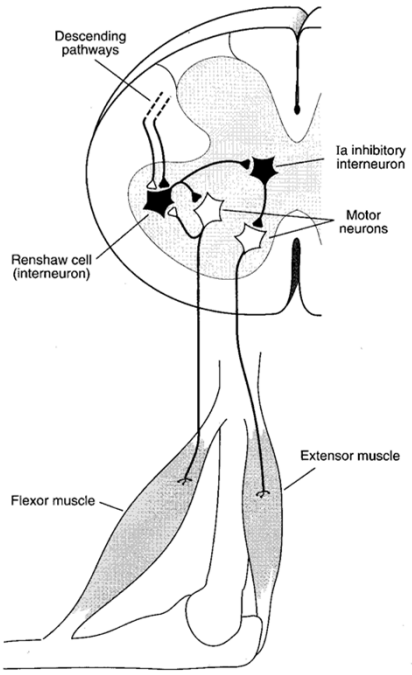


Temporal Organization

Renshaw Cell (neuron) - Inhibitory interneuron

The connections of Renshaw cells to presynaptic motor neurons form a negative feedback system, which regulates the firing rate of the motor neurons.

They not only inhibit certain motor neurons, they also disinhibit antagonist motor neurons.

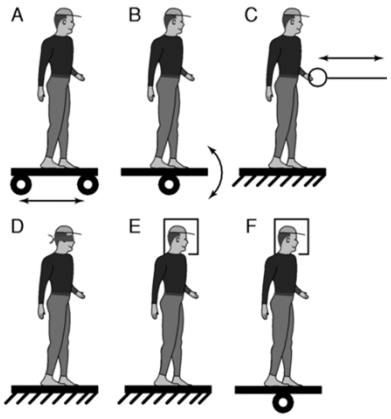


Spinal and Postural Mechanisms

Posture

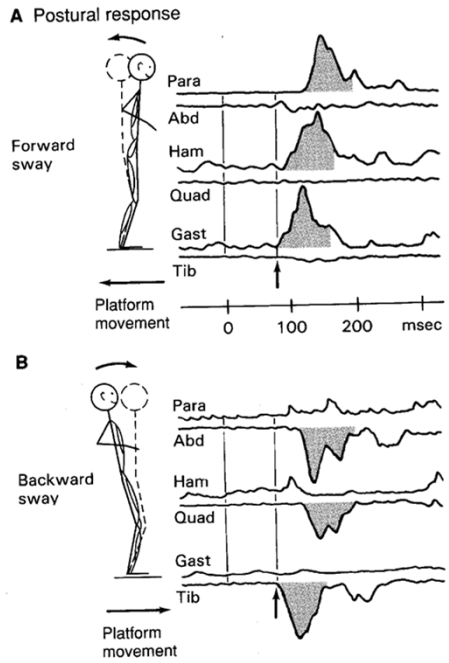
Reasons for Postural Motor Mechanisms:

- Support the head and body against gravity and other external forces.
- Maintain the center of the body's mass: aligned and balance.
- Stabilize supporting parts of the body while other muscles are being moved.



Mechanisms:

- Anticipatory or Feedforward
- Compensatory or Feedback

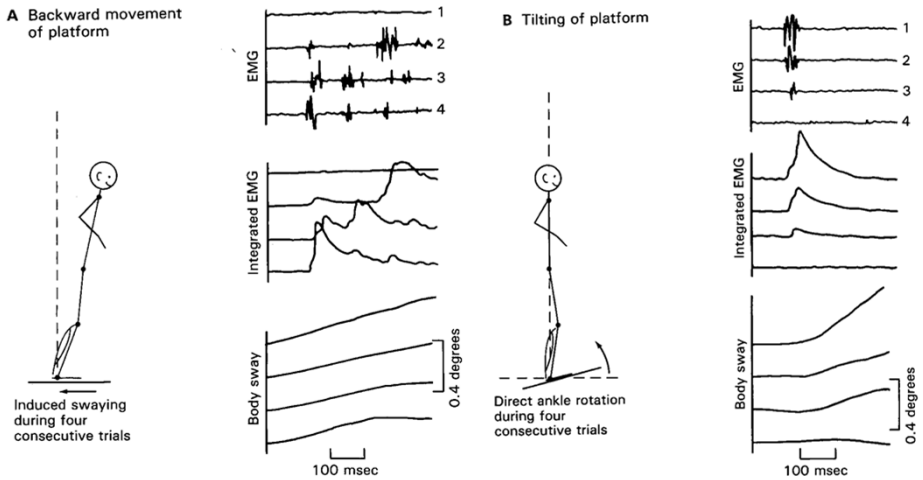


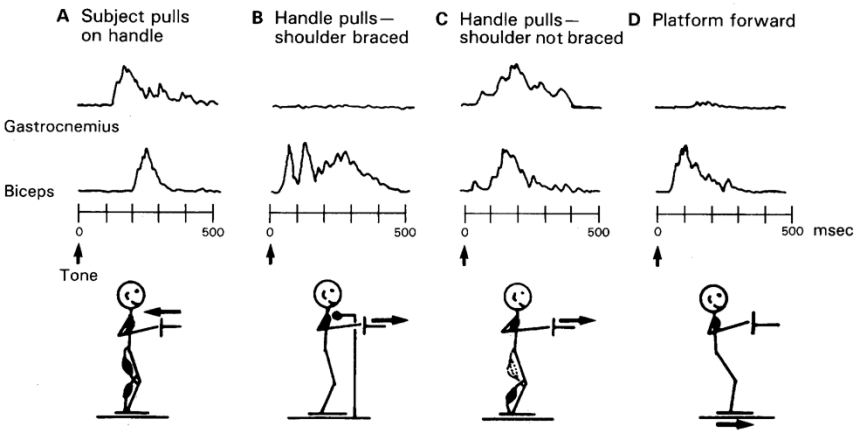
The first muscles to contract are those that are closest to the base of support." (ks&j, pg 597)

Triggering mechanism:

- **Muscle proprioception**
- **Vestibular sensation**
- **Visual sensation**

"An individual's postural response to a stimulus is shaped by experience, and the form of the response is adjusted so that balance is maintained." ks&j pg. 598





"Postural muscles contract to maintain equilibrium before destabilizing movements are executed.

Postural adjustments anticipate the occurrence of changes that would cause the loss of balance.

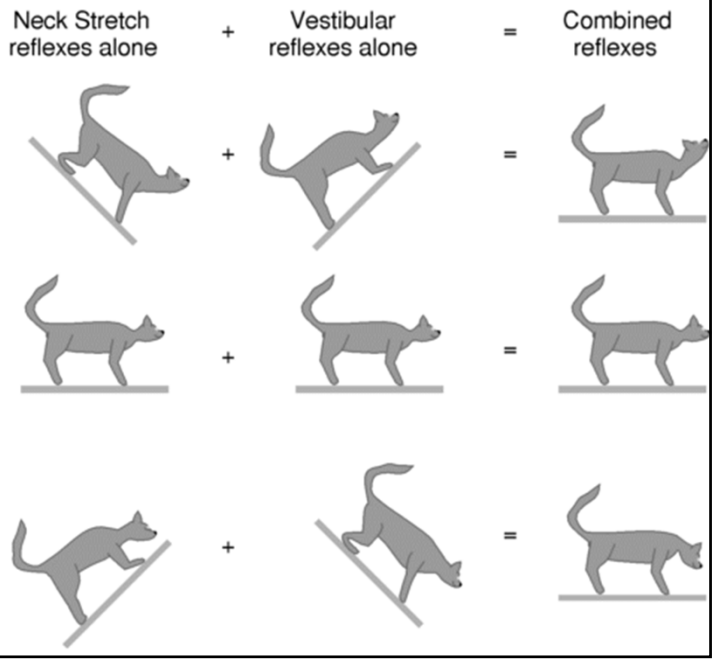
This feedforward control is essential for coordinating posture with voluntary movement.

When changes actually occur, feedback mechanisms produce rapid corrective responses. When we can predict the nature of the change, but not its exact timing, higher motor centers enhance or reduce the strength of short-latency pathways that operate automatically.

Vestibular and Neck Reflexes

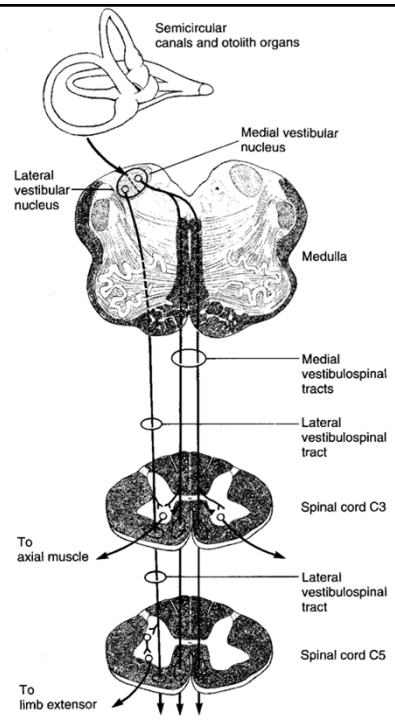
Vestibular reflexes are evoked by changes in the position of the head.

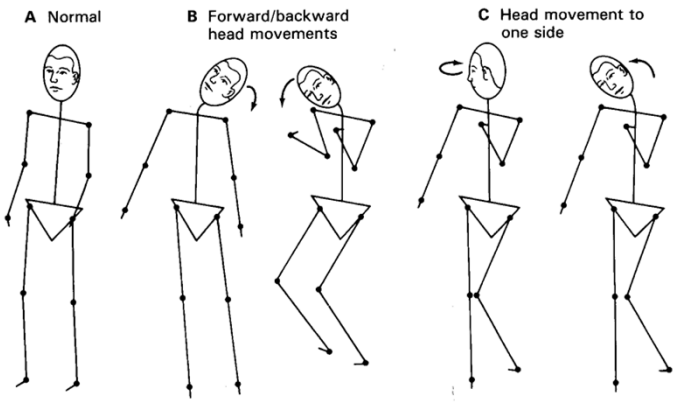
Neck reflexes are evoked by tilting/bending of the neck.



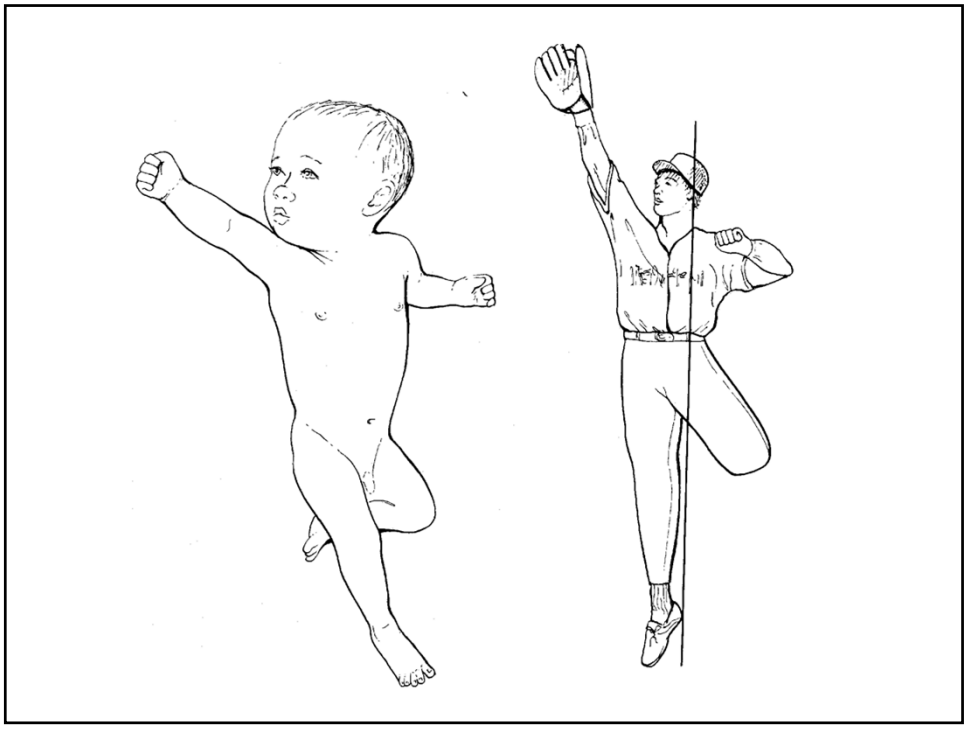
***Vestibulocollic reflexes* - counteract head movements keeping the head stable.**

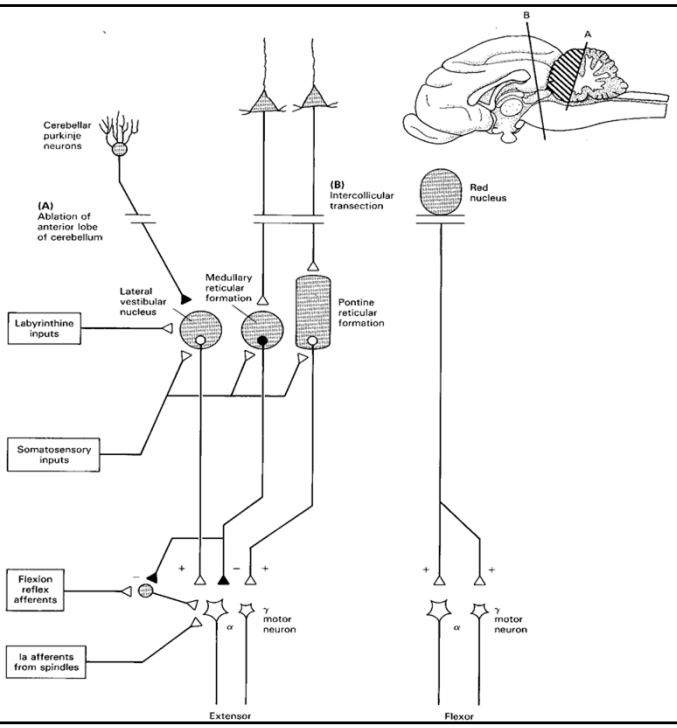
***Vestibulospinal reflexes* - contract the limb muscles and prepare the subject for landing during falls.**



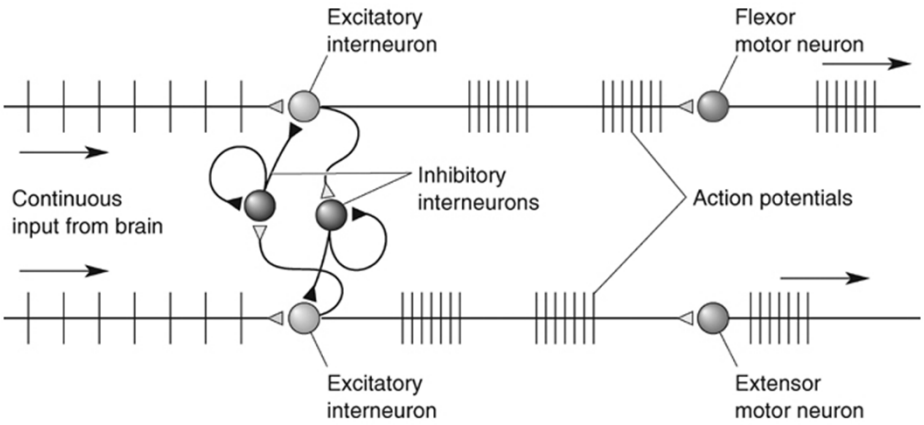


Cervicocollic reflexes contract neck muscles that are stretched. (vestibulocollic reflexes)





Rhythmic Movements



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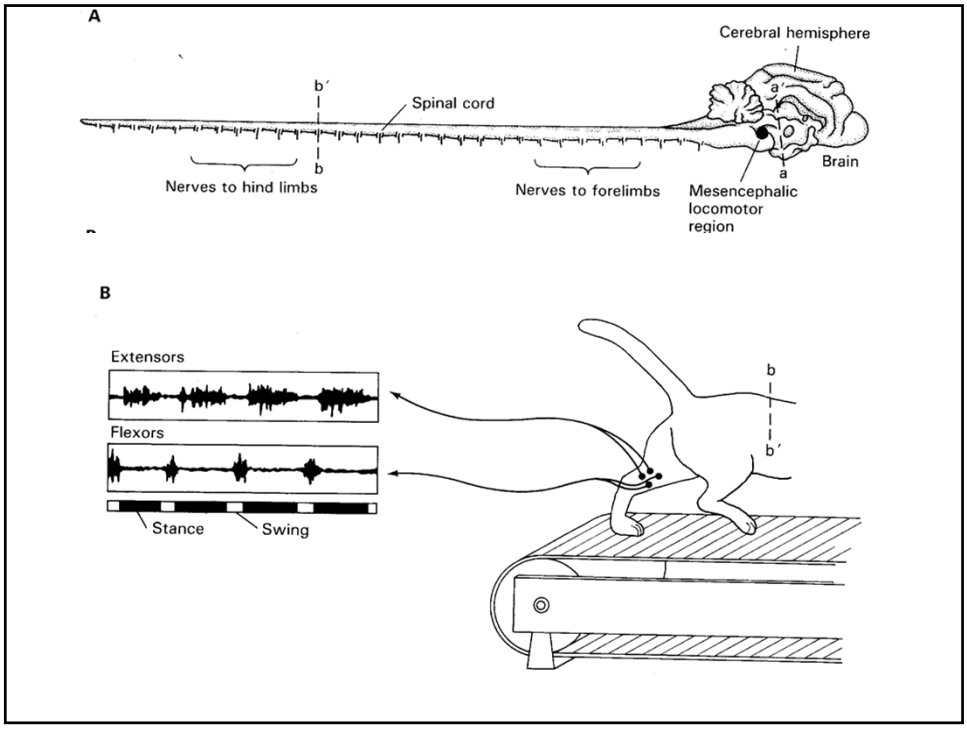
Spinal Circuits for Rhythmic Locomotor Patterns

- ***Normal locomotion is attributed to spinal circuits.***
- ***Decerebrate and sensory lesioned preparations both demonstrated rhythmic activity for locomotion.***
- ***Central pattern generators for locomotion are innate and specialized for each limb individually.***
- ***Mesencephalic locomotor region controls locomotor activity (Dopamine, Norepinephrine, Glutamate (NMDA))***



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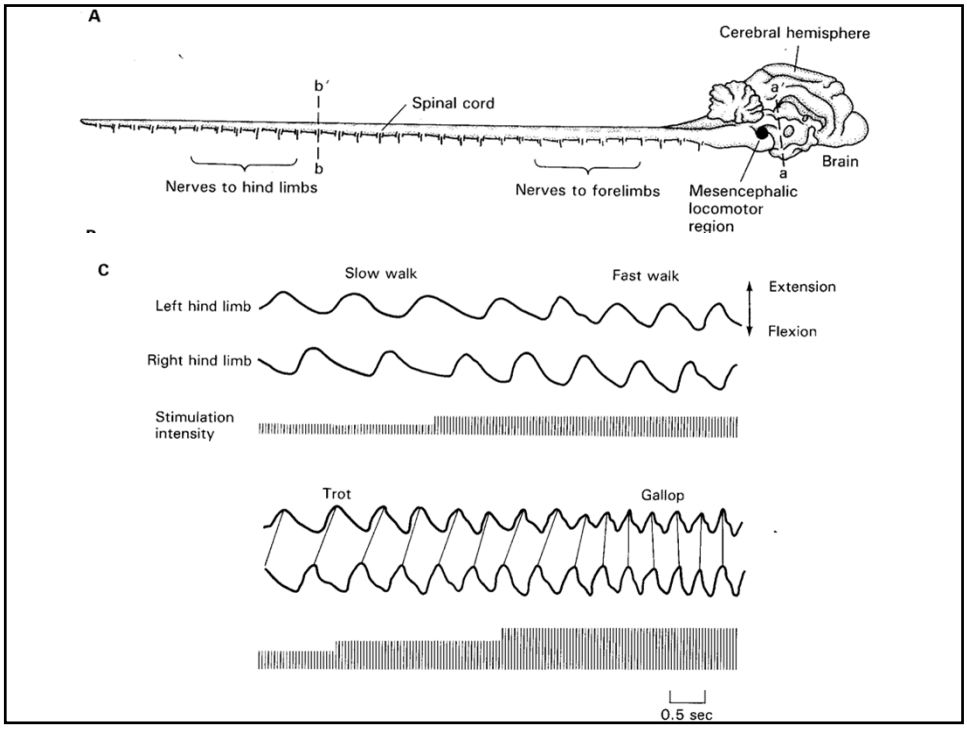


Control of Voluntary Motor Movement by the Brainstem Nuclei

3 Main Brainstem Motor Pathways

Ventral Pathway -

- Terminate in the ventromedial part of the spinal grey matter.
- Influence motor neurons that innervate axial and proximal muscles.

Lateral Pathway -

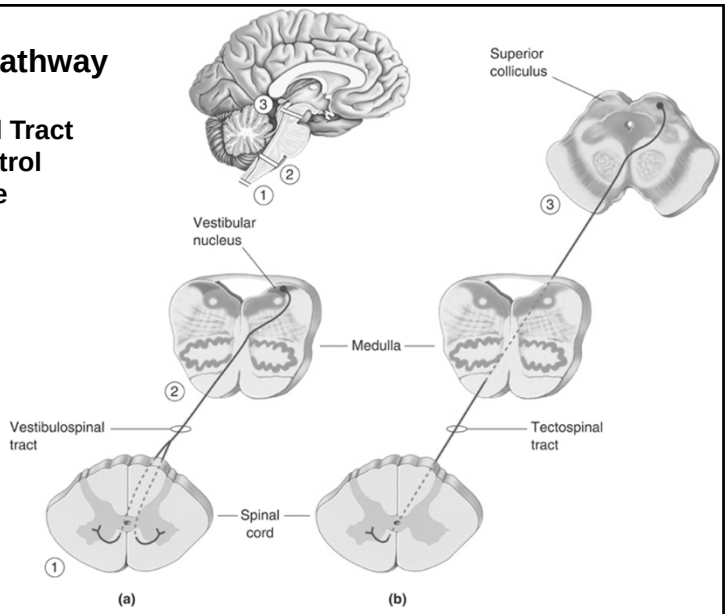
- Terminate in the dorsolateral part of the spinal grey matter.
- Influence motor neurons that control distal muscles of the extremities.

Aminergic Pathway -

- Terminate at all levels of the spinal cord.
- Modulate excitability of neurons at all levels of the cord.

Ventral Pathway

Vestibulospinal Tract
- **Reflex control and posture**



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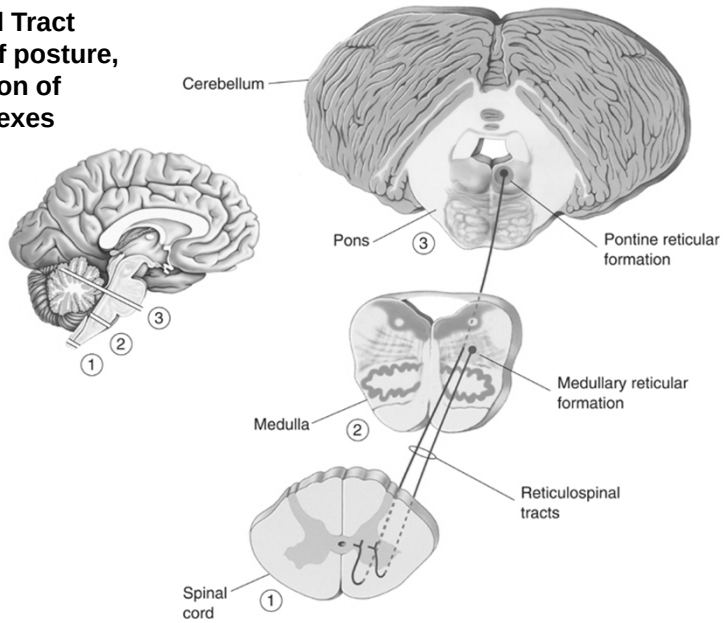
Tectospinal Tract
- **Coordination of head and eye movements**

Reticulospinal Tract

- **Control of posture, suppression of spinal reflexes**



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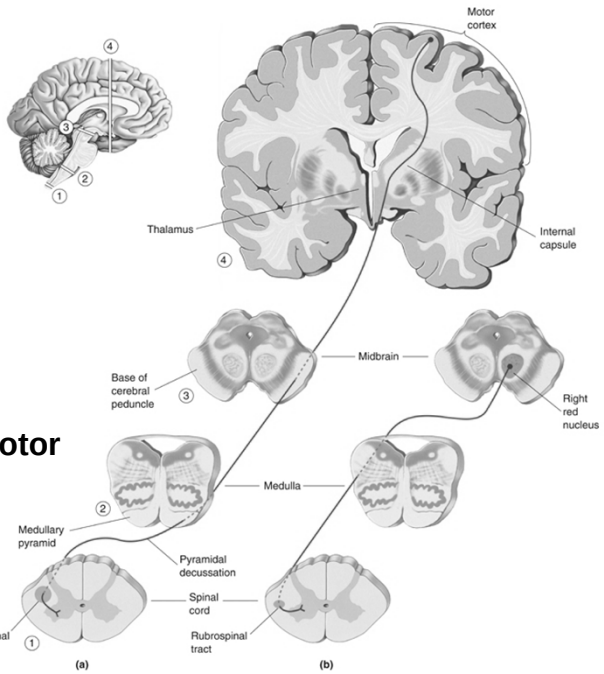
Lateral Pathway



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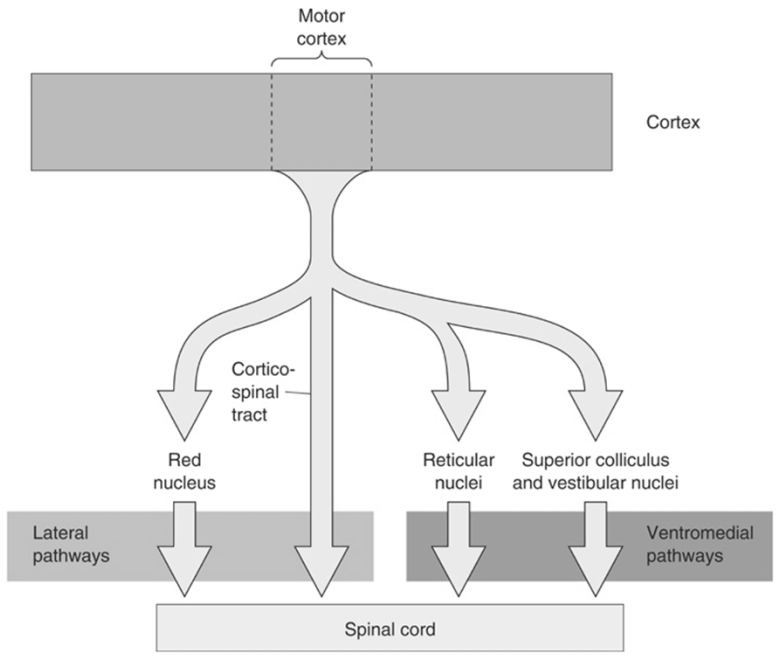
Rubrospinal Tract

- **Medial & Lateral**
- **Red nucleus**
- **Control of fine motor movements**



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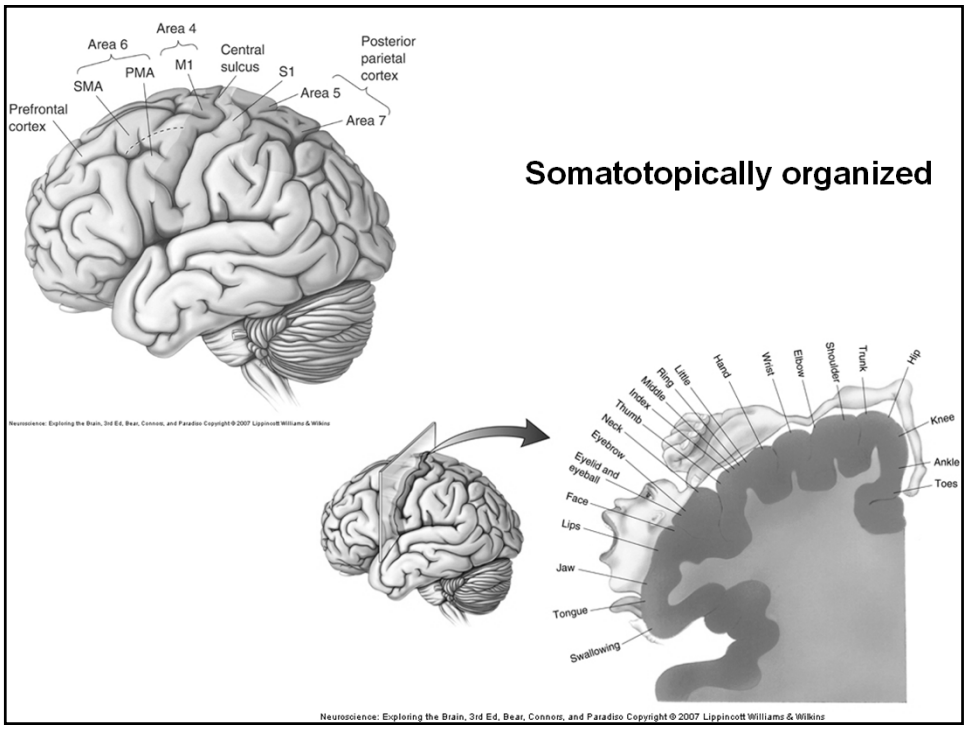
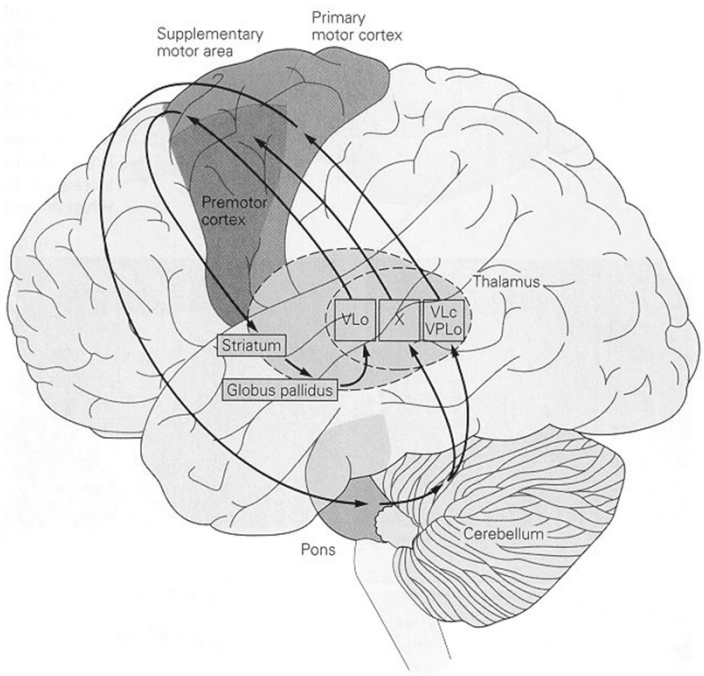
Voluntary Movement & Cortical Control of Motor Movement

- **Differs from the postural and spinal reflexes.**
- **Different strategies to achieve same goal.**
- **Improves with experience.**
- **Doesn't need to use stimuli to elicit activity.**





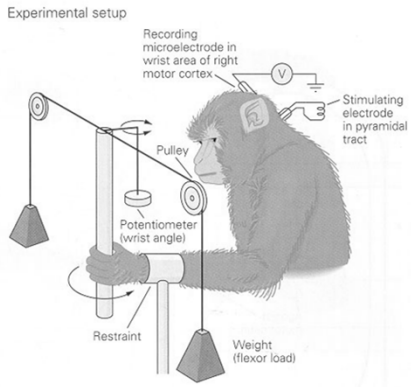
Primary Motor Cortex

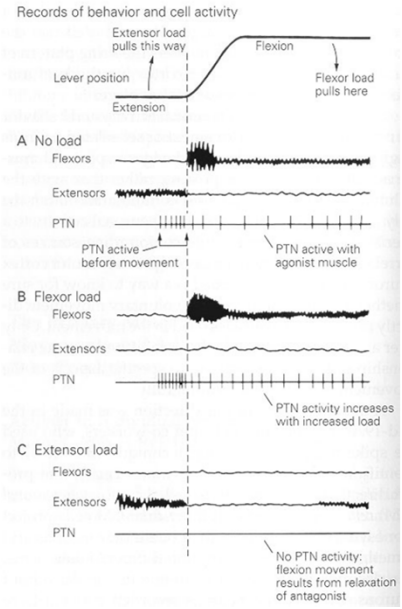
Neurons encode for the force of contraction.

Individual neurons will control small groups of muscles.

- **usually distal muscles.**
- **more than one muscle (or group of muscles) may be activated by a single cortical neuron.**
- **divergence of cortical neurons at the brainstem and spinal cord level.**
- **Make direct and powerful excitatory connections with alpha motor neurons**
- **Although the corticospinal tract projects to motor nuclei controlling proximal and distal muscles, the corticospinal tract is the only pathway that controls the distal muscles of the fingers.**

Primary Motor Cortex (Precentral Gyrus, Area 4)

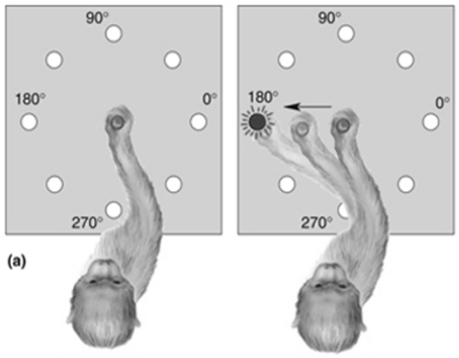


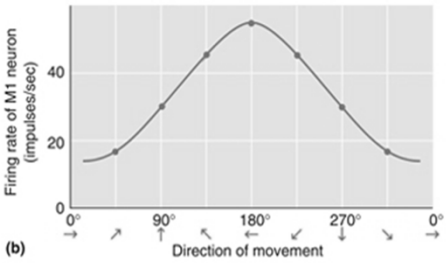


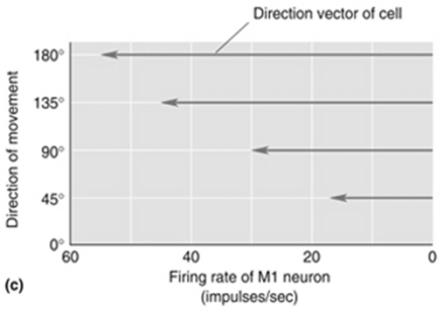
Individual neurons will encode for the amount of force to be exerted and not the position of the limb.

This activity typically occurs before the contraction of the muscle.

Individual neurons vary there activity with the direction of movement.







Voluntary behavior (movement) is determined by the activity of a rather large population of neurons and cannot be predicted from the discharge patterns of any one neuron.

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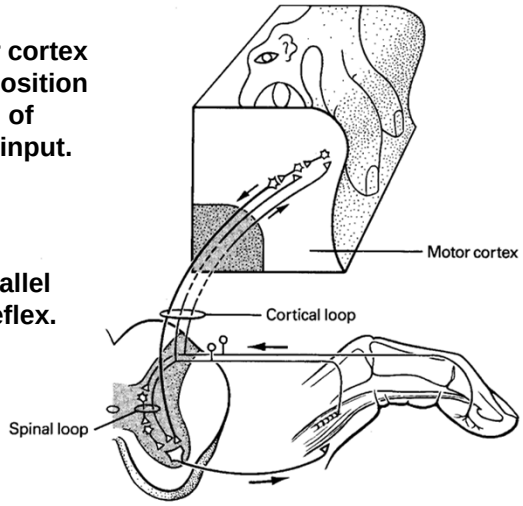
Neurons in the primary motor cortex are kept informed about the position of the limb and the speed of movement through sensory input.

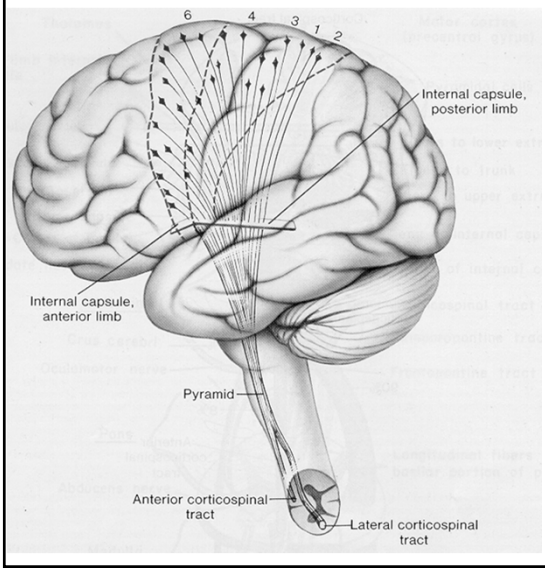
Motor cortex functions in parallel with the spinal cord stretch reflex.

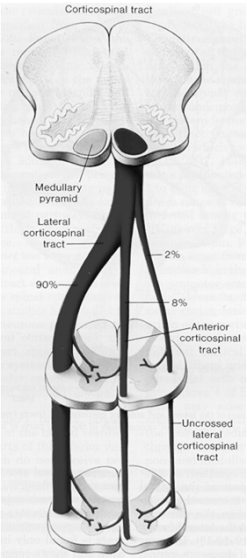


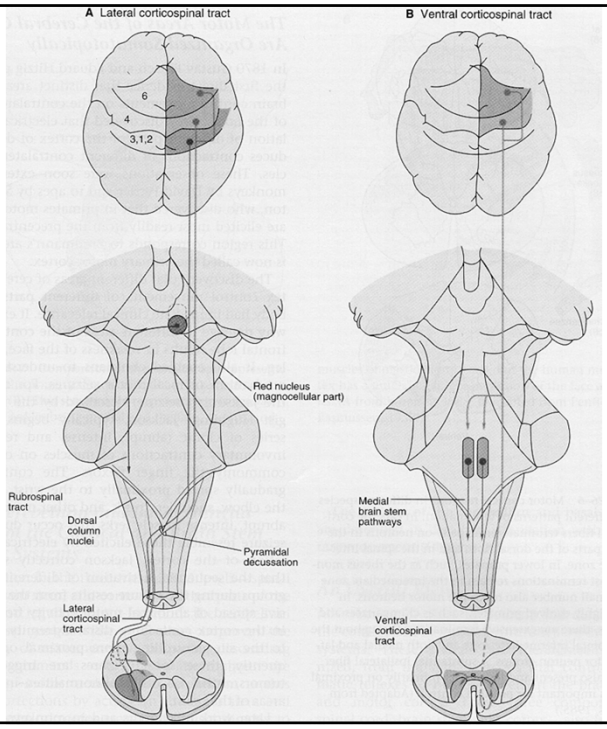
Provide assistance, supplementing the stretch reflex, when the moving limb encountered an unexpected obstacle.

Primary Motor Cortex Projections

Corticospinal or Pyramidal Tract



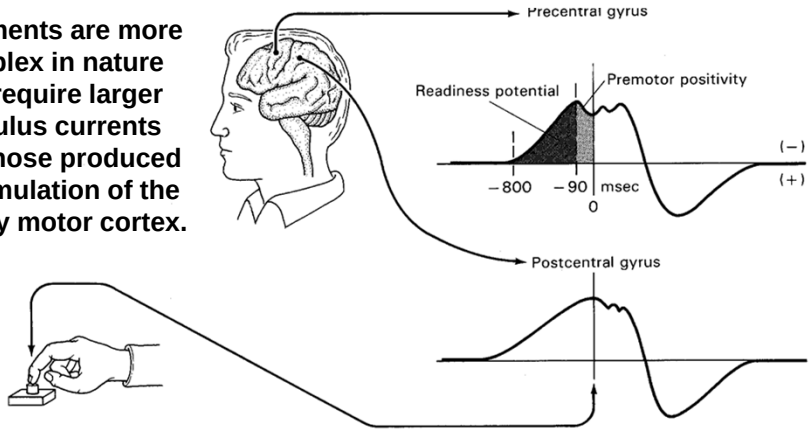




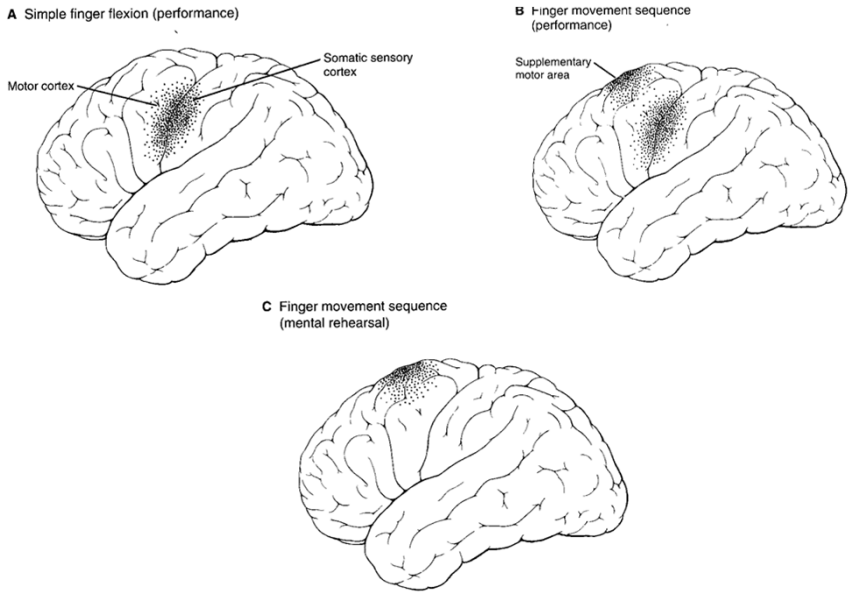
Premotor Areas of Cortex (Supplementary motor area and Premotor cortex, Area 6)

Programming and preprogramming complex sequences of movement.

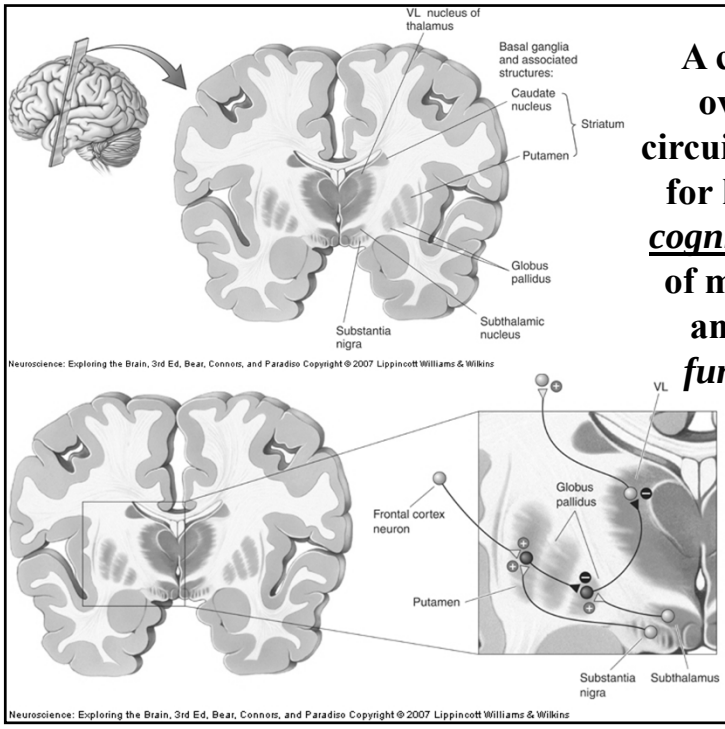
Movements are more complex in nature and require larger stimulus currents than those produced by stimulation of the primary motor cortex.



Supplementary Motor Cortex is only important in programming and planning of complex movements, not executing them.



Basal Ganglia Involvement in Motor Control

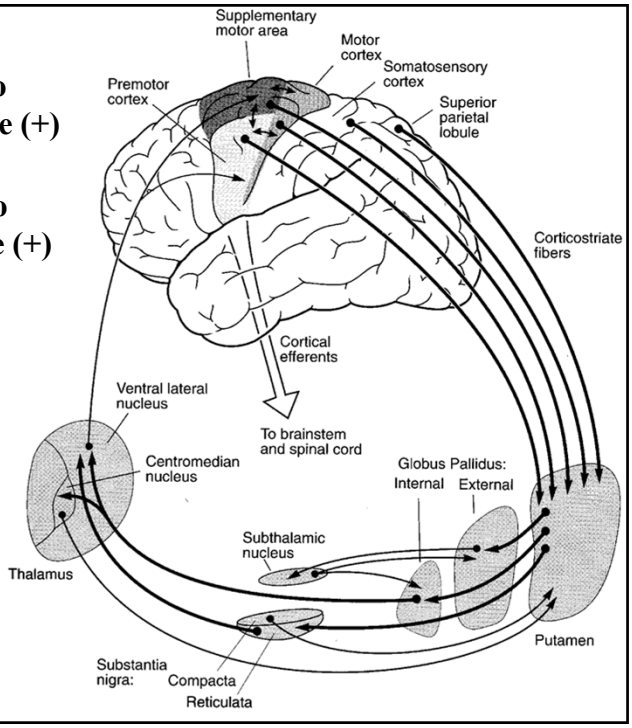


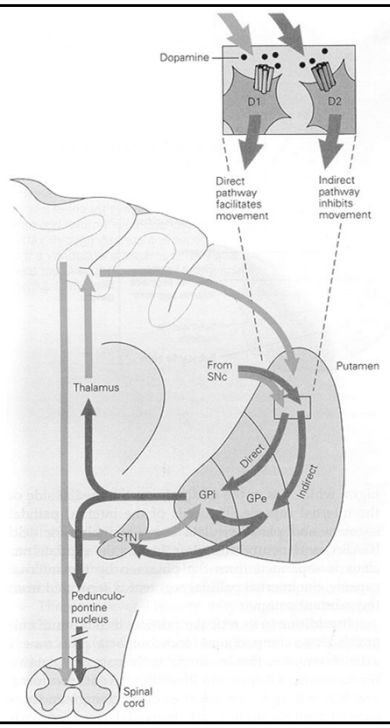
A collection of overlapping circuits responsible for higher order *cognitive* planning of motor control and *cognitive functioning in general*.

Cortical Inputs to Striatum = Glutamate (+)

Thalamic Inputs to Striatum = Glutamate (+) and Opioid ?

Most output connections utilize GABA (-) as their neurotransmitter.





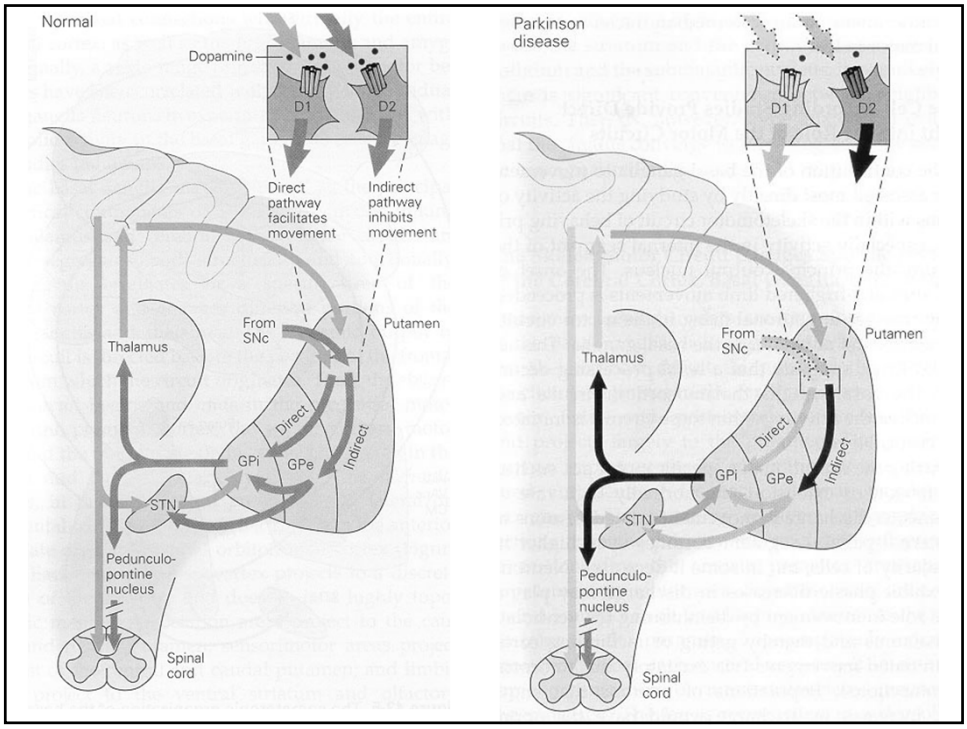
What do the Basal Ganglia do?

- **Selectively facilitate some movements and suppress others.**
- **Compare commands for movement from the precentral motor fields with proprioceptive feedback from the evolving movement.**
- **Involved in the initiation of internally generated movements.**

Movement Disorders of the Basal Ganglia

Parkinson's Disease: clinical make-up

- Alternating tremor (resting tremor): "pill-rolling", oscillating
- Plastic rigidity, increase tone in all muscles
- Flexed posture
- Difficulty in moving (akinesia, hypokinesia)
- Mask like facial expression, absense of arm movements when walking
- Massive degeneration of Substantia Nigra, Striatum, and frontal cortex

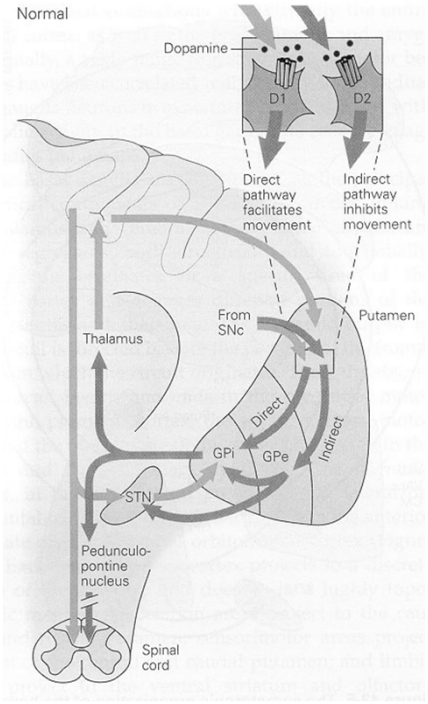


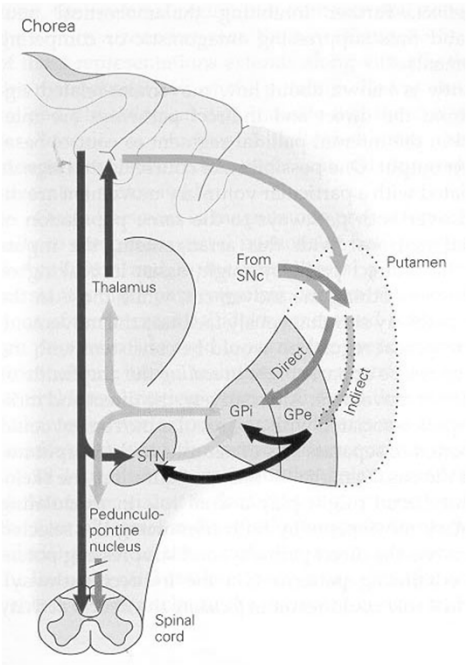
Huntington's Disease: clinical make-up

- Severe Choreiform motor disability, random and continuous
- Decrease in muscle tone
- Reflexes and sensations are normal
- Athetosis
- Progressive, inherited, onset usually 35 - 40 yrs of age.
- Atrophy of striatum

Huntington's disease results from a gene mutation causing abnormal repetition of the DNA sequence CAG that codes for the amino acid glutamine. The resulting gene product, a large protein called huntingtin, has an expanded stretch of polyglutamine residues, which leads to disease via unknown mechanisms.

Huntington's disease affects both sexes equally. The caudate nucleus atrophies, the inhibitory medium spiny neurons in the corpus striatum degenerate, and levels of the neurotransmitters γ-aminobutyric acid (GABA) and substance P decrease.

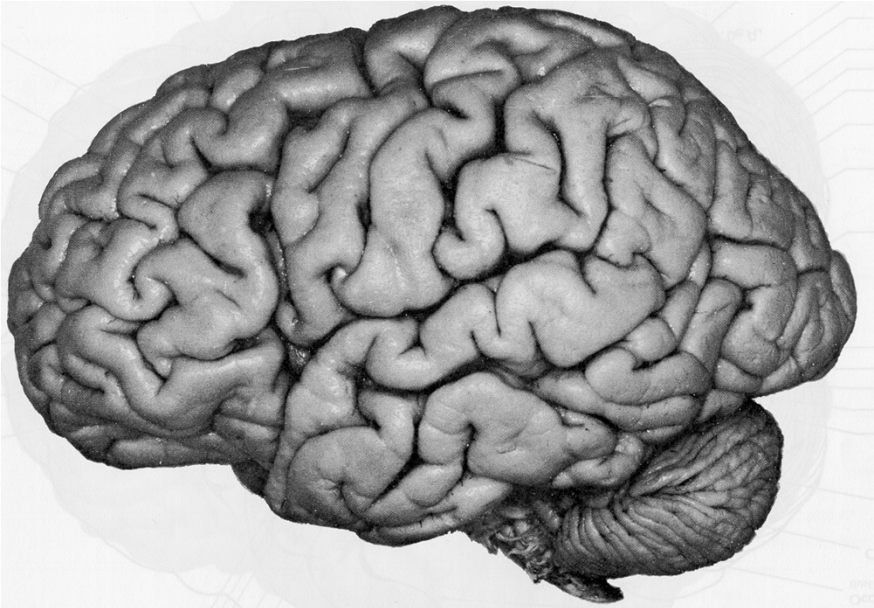


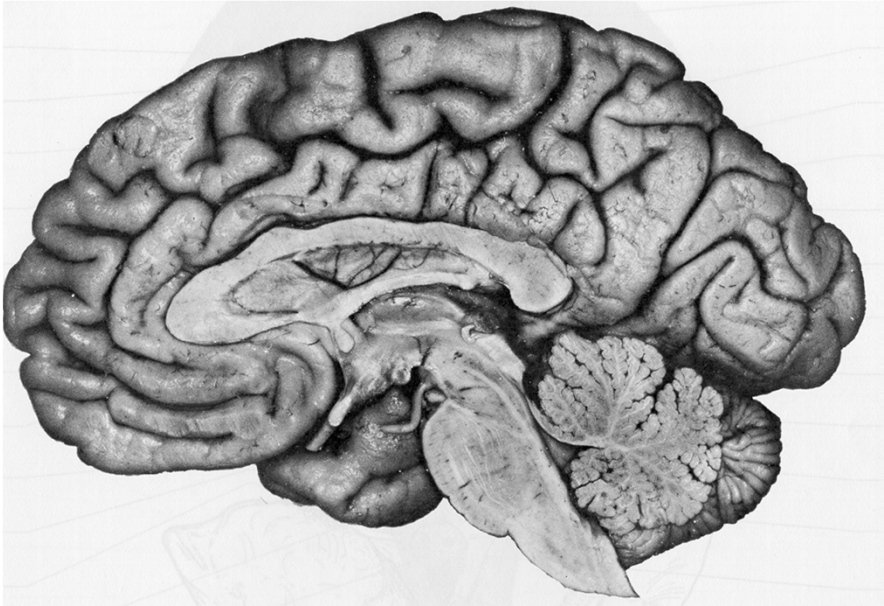


Athetosis:

Hemiballism:

The Cerebellum and the Control of Motor Movement





Cerebellar Function:

Regulates movement and posture indirectly by adjusting the output of the major descending motor systems of the brain.

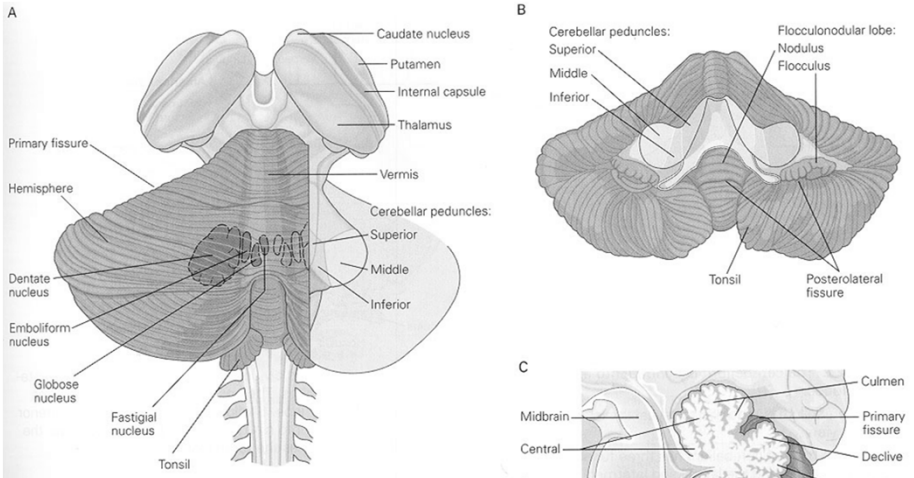
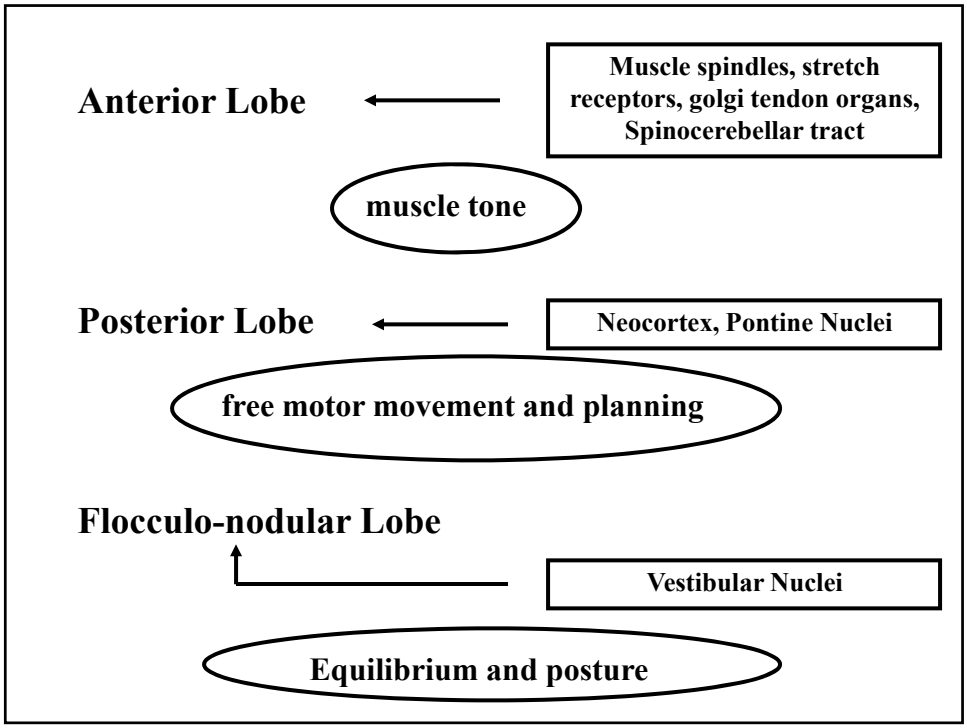


Figure 42-1 Gross features of the cerebellum, including the nuclei, cerebellar peduncles, lobes, folia, and fissures. (Adapted from Nieuwenhuys et al. 1988.)

A. Dorsal view. Part of the right hemisphere has been cut out to show the underlying cerebellar peduncles.

B. Ventral view of the cerebellum detached from the brain stem.

C. Midsagittal section through the brain stem and cerebellum, showing the branching structures of the cerebellum.



Cellular Circuitry of the Cerebellum

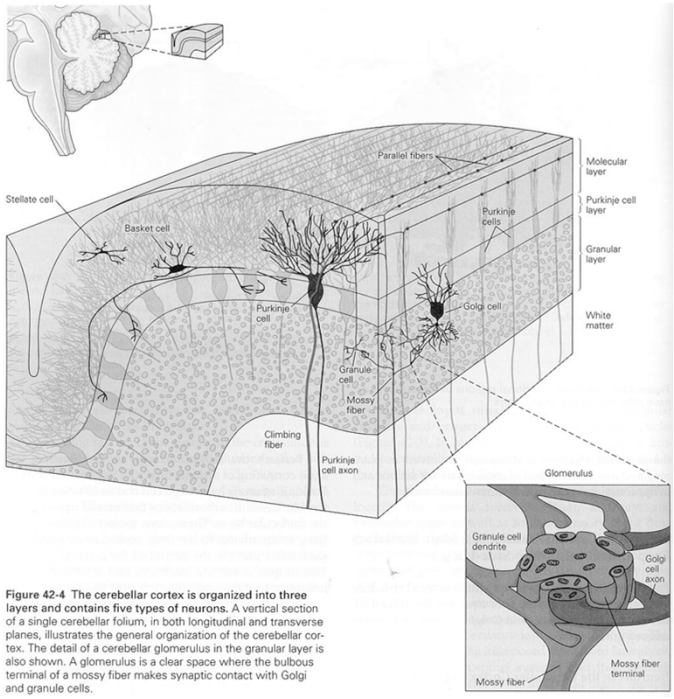


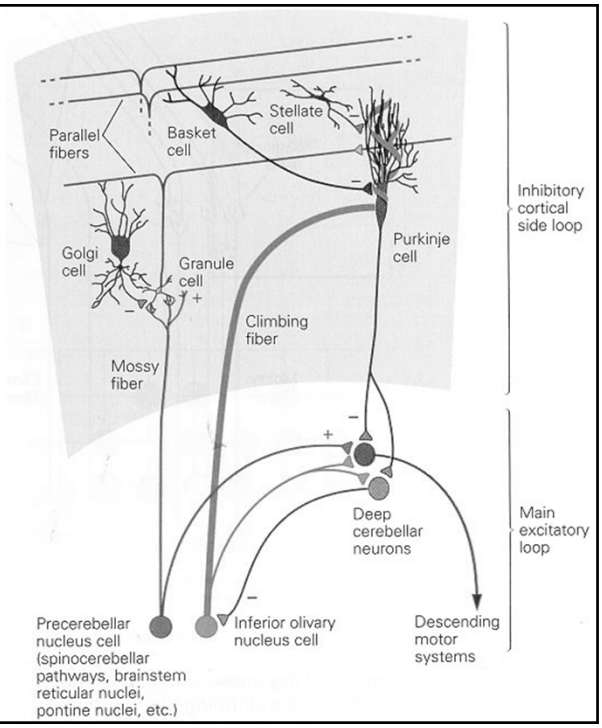
Figure 42-4 The cerebellar cortex is organized into three layers and contains five types of neurons. A vertical section of a single cerebellar folium, in both longitudinal and transverse planes, illustrates the general organization of the cerebellar cortex. The detail of a cerebellar glomerulus in the granular layer is also shown. A glomerulus is a clear space where the bulbous terminal of a mossy fiber makes synaptic contact with Golgi and granule cells.

Cells of the Molecular Layer

- **Stellate**
  - receive stimulatory input from parallel fibers
  - deliver inh. Input from Purkinje Cells
- **Basket Cells**
  - receive stim. input from parallel fibers
  - deliver inh. Input to Purkinje Cells

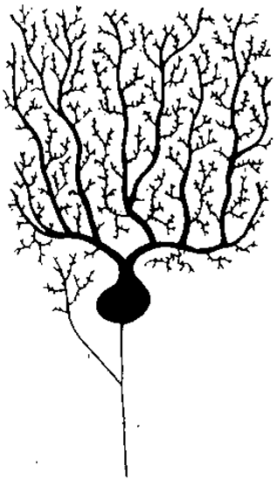
Cells of Granule Layer

- **Granule Cells**
  - receive stim. input from mossy fiber pathway
  - deliver powerful stim. Input to Purkinje Cells by parallel fibers
- **Golgi Cells**
  - receive stim. input from parallel fibers and adjacent granule cells
  - deliver inh. Input to granule cells



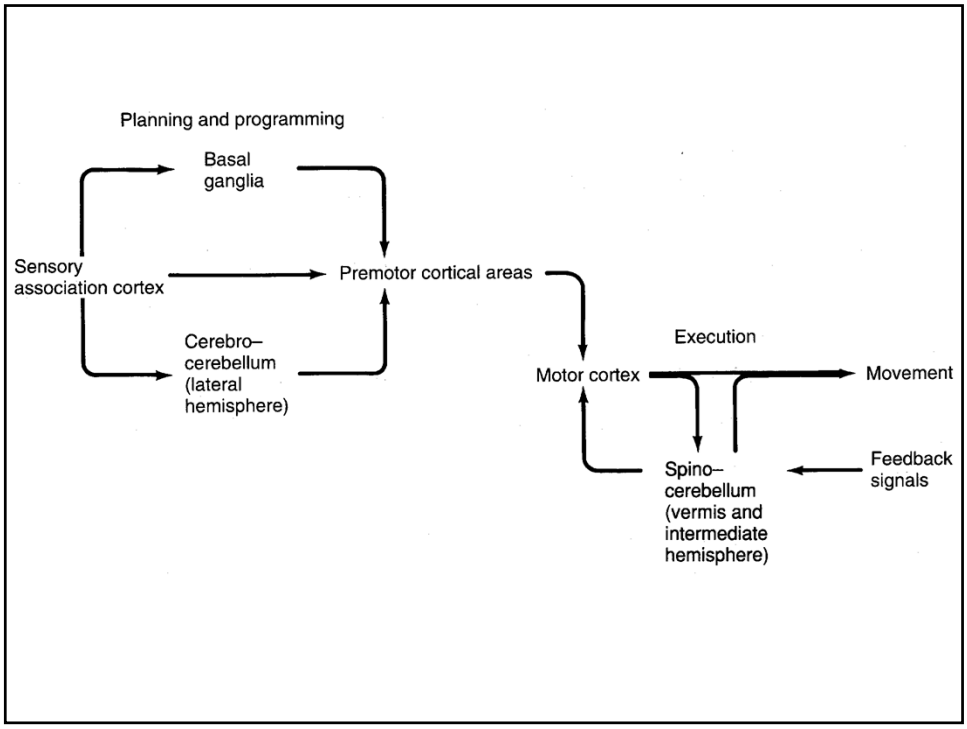
Purkinje Cells - The most important cell in the cerebellum.

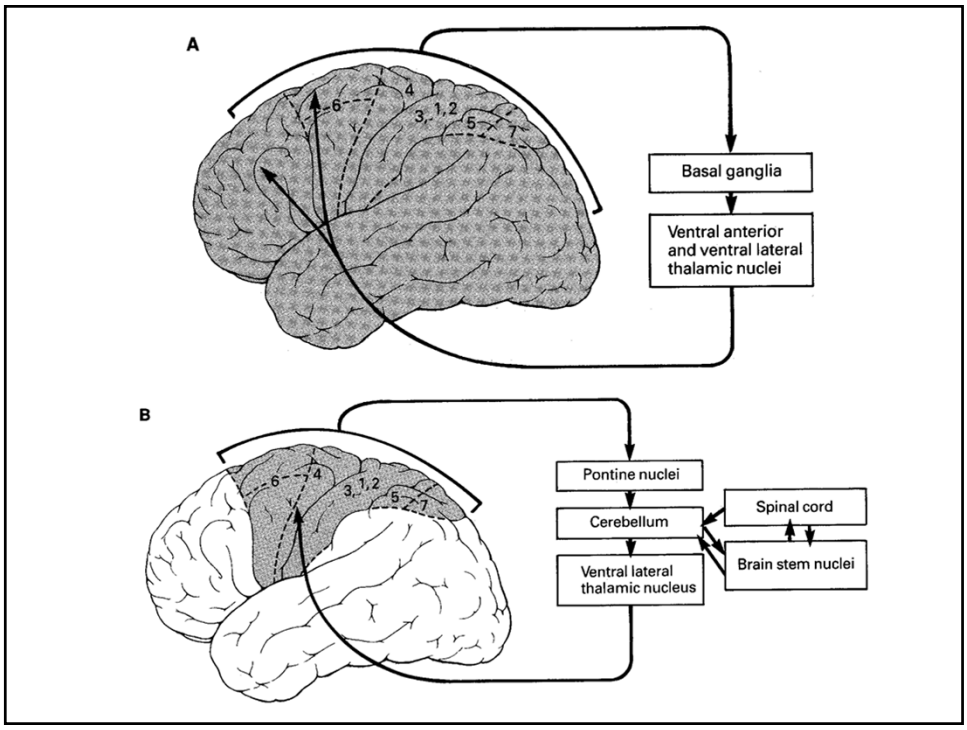
- **Inhibitory**
- **Only output neuron of the cerebellum**
- **Large dendritic tree receiving both stimulatory and inhibitory information**

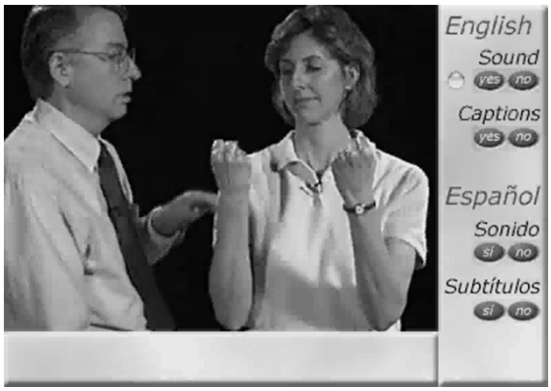


Cerebellum acts as a comparator that compensates for errors in movement by comparing intention with performance.

- **Receiving information about plans for movement from structures concerned with programming and execution (*Corollary Discharge*).**
- **Receiving information about motor performance from sensory systems during movement (*Reafferance Feedback*).**
- **Sends information to descending motor systems.**


Planning and programming
Basal ganglia
Sensory association cortex
Premotor cortical areas
Cerebro–cerebellum (lateral hemisphere)
Execution
Motor cortex
Movement
Spino–cerebellum (vermis and intermediate hemisphere)
Feedback signals


A
6
4
3, 1, 2
5
7
Basal ganglia
Ventral anterior and ventral lateral thalamic nuclei
B
6
4
3, 1, 2
5
7
Pontine nuclei
Cerebellum
Spinal cord
Brain stem nuclei
Ventral lateral thalamic nucleus

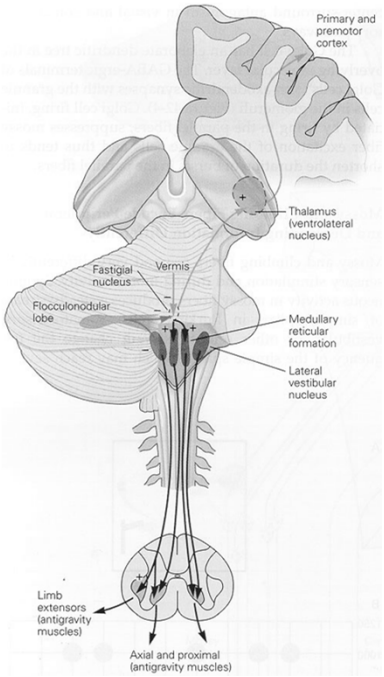


Control of Motor Circuitry

Vestibulocerebellum

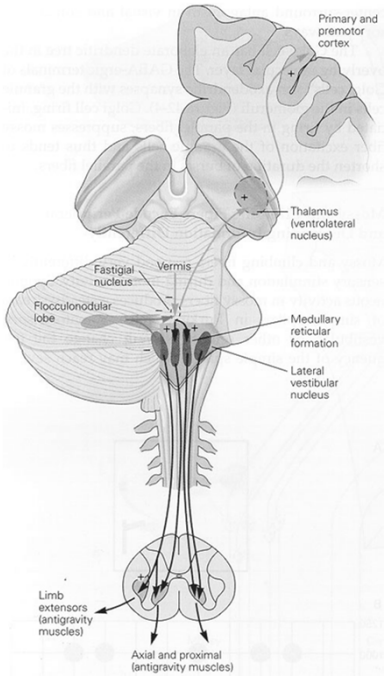
Governs eye movements and body equilibrium

Control of axial and proximal limb muscles that are used to maintain balance.



Spinocerebellum (2 parts)

- **Originates from Vermal region of cerebellum**
- **Inputs from special senses, vestibular apparatus, and spinocerebellar tracts.**
- **Axial and proximal motor control of ongoing execution of movement.**

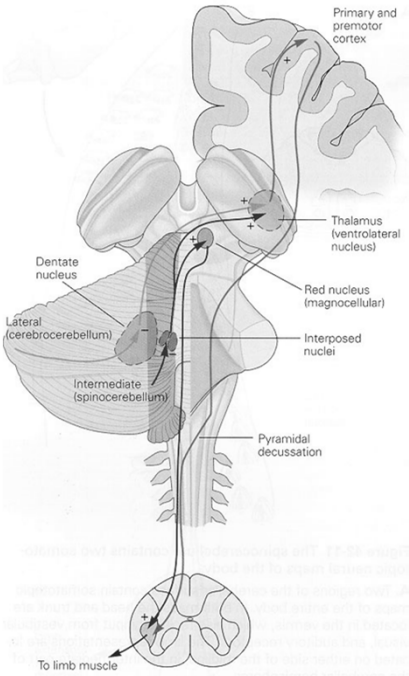


Spinocerebellum

Two (2) sections

Originates from Intermediate region of cerebellum
Inputs from spinocerebellar tracts (distal body parts).
Distal motor control of ongoing execution

.



Sensory Input

↓

Intermediate region

↓

Interpositus Nuclei

Red Nucleus
(Bilaterally)

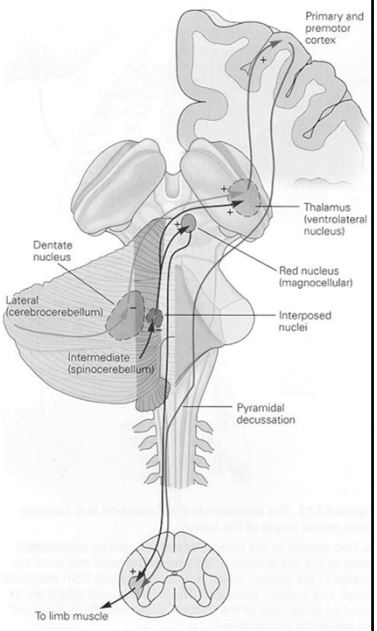
↓

Rubrospinal pathway

Thalamic Nuclei
(Bilaterally)

↓

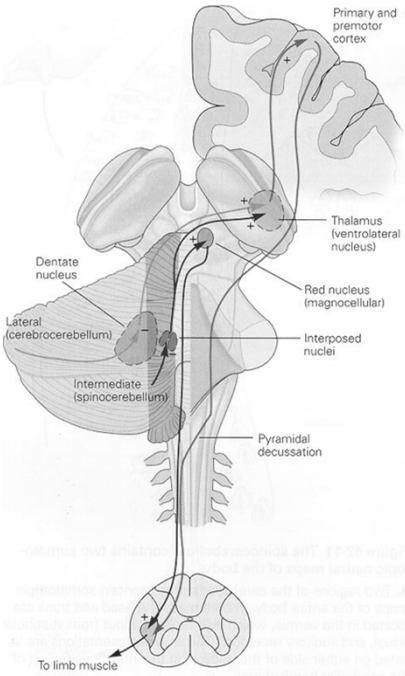
Motor Cortex



Cerebrocerebellum

Two (2) sections

Originates from Lateral posterior lobe of cerebellum

Inputs from Sensory/motor cortex, premotor, and parietal cortex by way of the pontine nuclei.

Achieving precision in control of rapid limb movements and in tasks requiring fine dexterity.