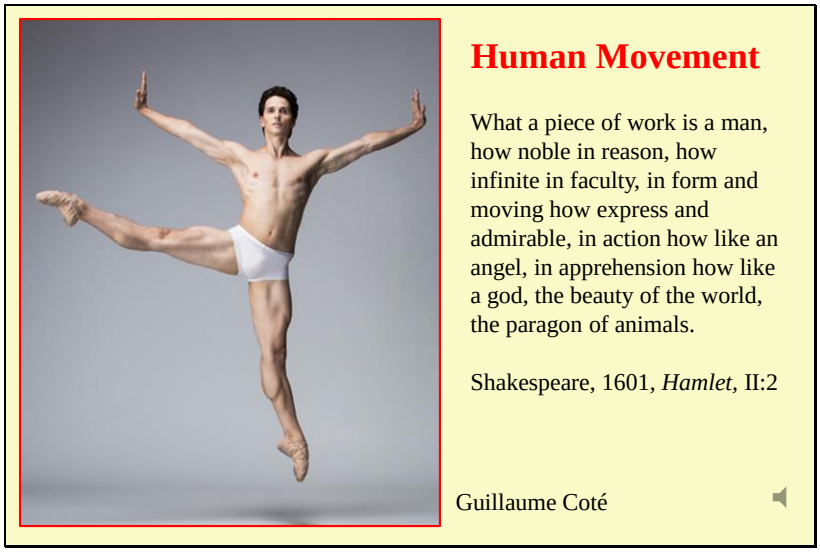
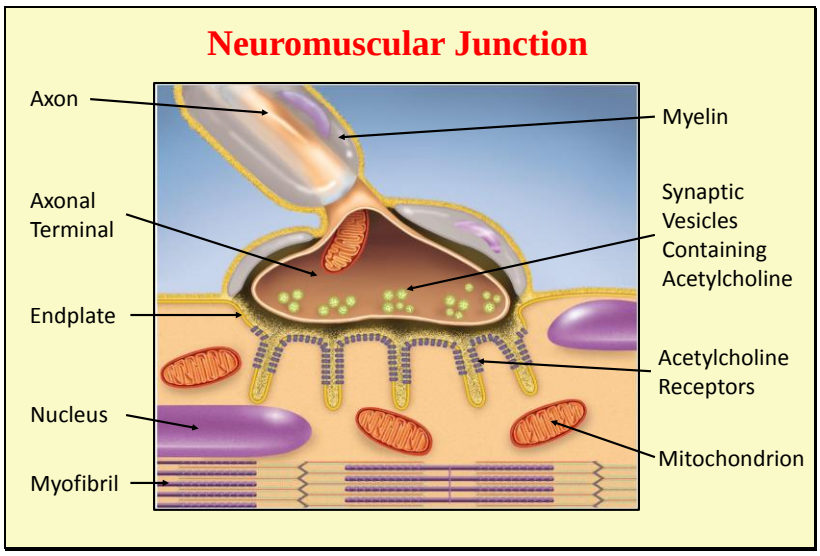


The dancer is Guillaume Coté from the National Ballet. The voice is John Gielgud. The pertinent part of the speech is the idea that human beings are "in form and moving how express and admirable."

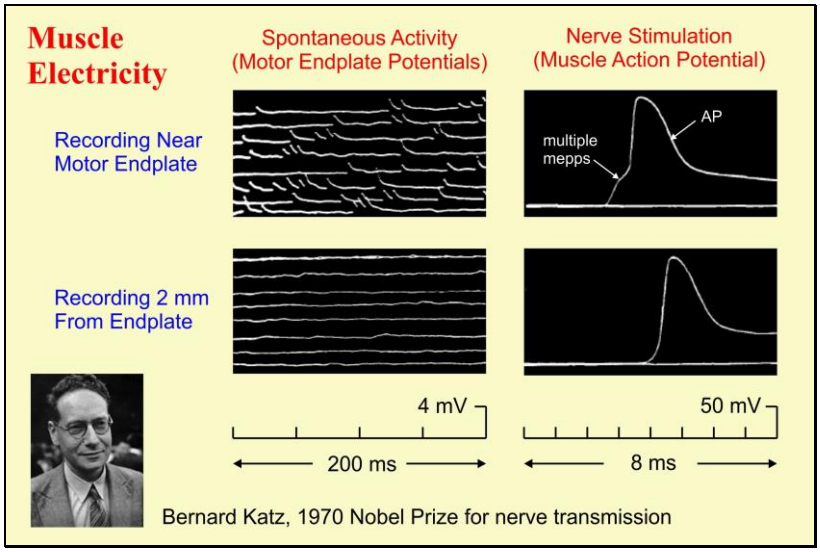
Movement can only be seen with vide. This is a clip from the YouTube video *Lost in Motion*, directed by Ben Shirinian, with music composed by James LaValle. In form and moving how express and admirable. If you pay close attention in class you will be able to dance like this ☺ . Let us try a cabriole en tournant.

https://www.youtube.com/watch?v=4OR-n3Rg6E8



Last week we learned about synapses between neurons and about reflexes mediated through the spinal cord. This week we shall consider the neuromuscular junction – a special synapse where the nerve terminals make contact with a muscle cell rather than with another neuron.

When the nerve terminal is activated, the synaptic vessels release the neurotransmitter acetylcholine. This activates receptors on the motor endplate region of the muscle membrane. The muscle cell contains multiple nuclei (purple). Actin and myosin are the contractile myofibrils.



Bernard Katz' studies of the neuromuscular junction contributed significantly to our understanding of all synapses.
The motor end-plate potentials can be recorded from only one region of the muscle cell – the region of the neuromuscular junction.

If multiple vesicles release transmitter simultaneously or in rapid succession, the end-plate depolarizes sufficiently that the threshold is reached for a conformational change in the sodium channels, and a muscle action potential (AP) is generated.
This is conducted along the length of the muscle fiber at a rate of about 5 m/s.
The muscle action potential is similar to the nerve action potential but it lasts longer 2-4 ms rather than 1-1.5 ms.

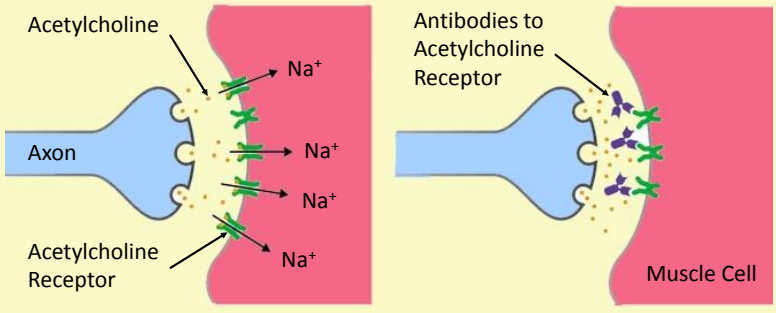
The Nobel Prize in 1970 was shared with Ulf von Euler and Julius Axelrod (both of whom studied the chemistry rather than the physiology of neurotransmission).

Curare

The natives of Guyana extracted a poison from a special vine and placed it on arrows or blowgun darts. The poison killed by causing muscle paralysis - the wounded animal stopped breathing. The poison was called *curare* which derives from the Indian words for "bird" and "kill." The paralysis is caused by the chemical blocking the acetylcholine receptor at the muscle endplate. Curare was first used to cause muscle relaxation during surgery by Harold Griffith, an anesthesiologist at the Montreal Homeopathic Hospital in 1942.

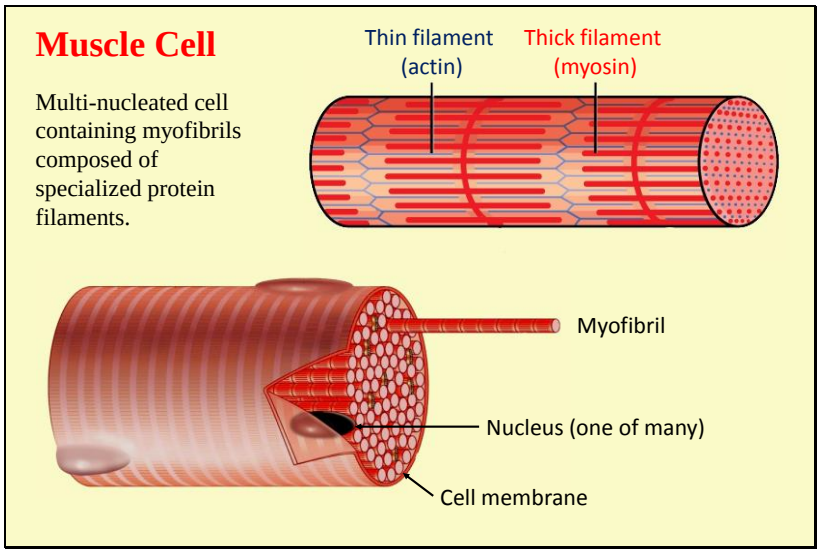
The neuromuscular junction can be blocked by curare.
The Montreal Homeopathic Hospital became the Queen Elizabeth Hospital, which itself closed in 1996.

Myasthenia Gravis

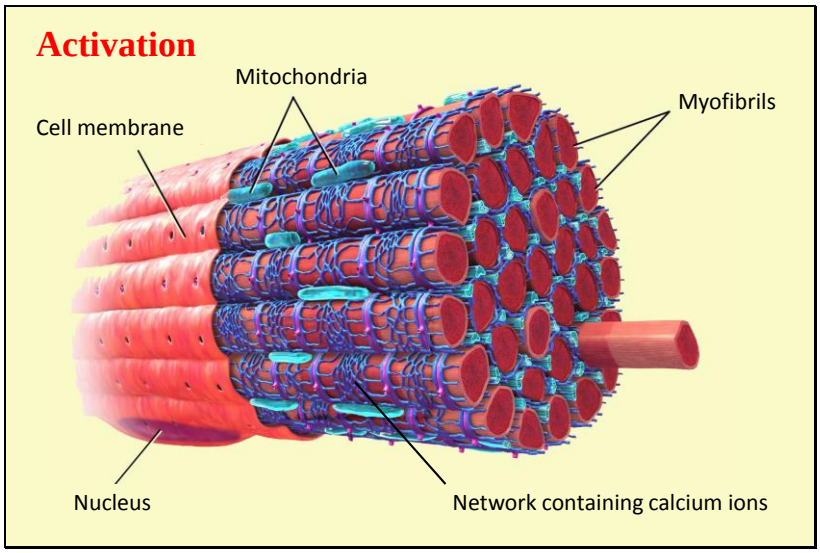


In myasthenia gravis, the acetylcholine receptors are blocked by antibodies. This decreases the amount of muscle activation. Antibodies also lead to breakdown of the receptors so that fewer receptors are available for activation.

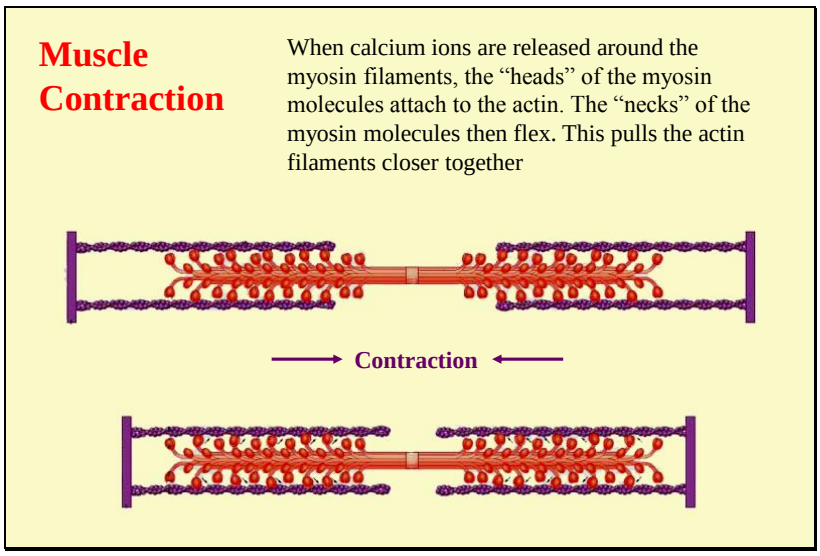
Myasthenia gravis is a disorder of the neuromuscular junction. It is like a mild form of curare poisoning – the receptors are blocked by antibodies rather than by curare.
Acetylcholine is normally broken down by the acetylcholinesterase enzyme located on the postsynaptic membrane.The treatment of myasthenia gravis uses drugs that block these enzymes – cholinesterase inhibitors. This makes more transmitter available for a longer time so that the transmitter can overcome the antibodies in competition for the receptors. The most common drug used to inhibit the cholinesterase enzyme is pyridostigmine (Mestinon).



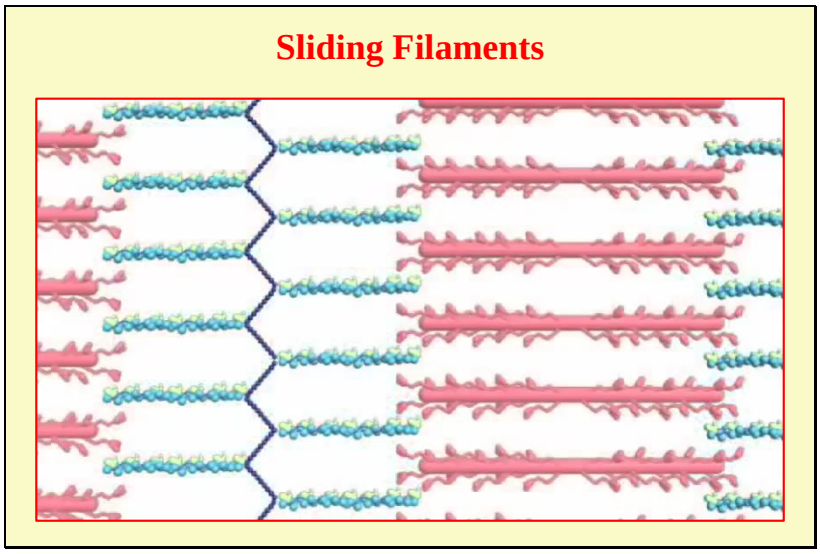
To return to the normal muscle. The upper illustration shows one of many myofibrils packed into the muscle cell (lower illustration).
After its initiation at the neuromuscular junction, the action potential moves along the membrane and activates the protein filaments in the myofibrils: actin and myosin.



The action potential causes the release of calcium ions from a special intracellular network that surrounds the myofibrils.

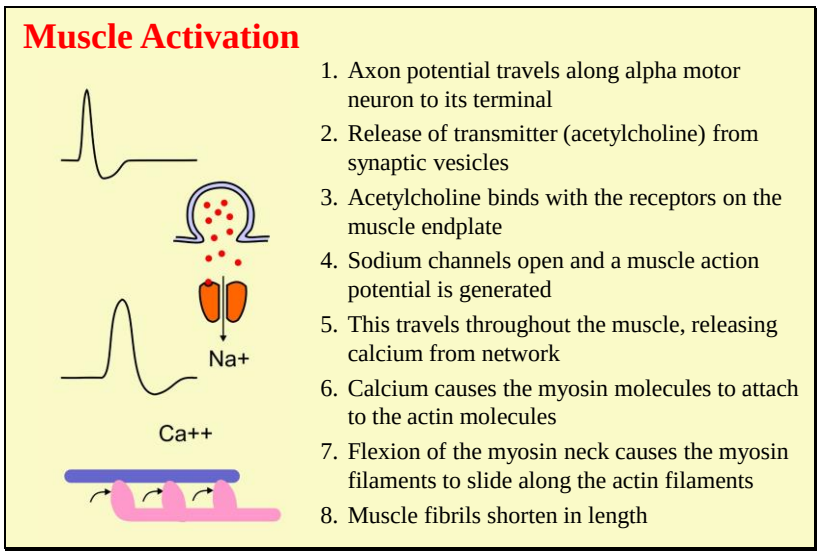


The action potential releases calcium ion from the network into the fluid around the myosin filaments.
Under the influence of the calcium, the necks of the myosin molecules (red) flex and move the myosin along the actin filaments (blue).

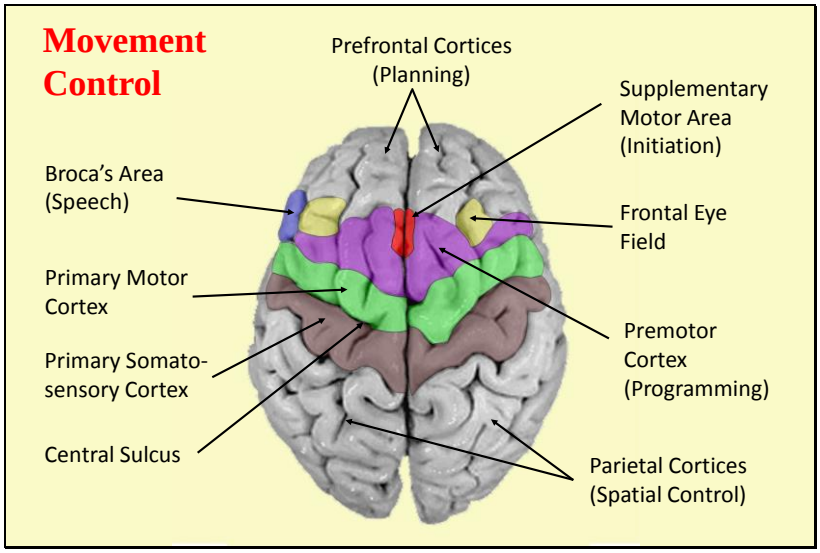


This is an animation of what happens during muscle contraction.
Row, row, row your boat
Gently down the stream.
Merrily, merrily, merrily, merrily,
Life is but a dream.

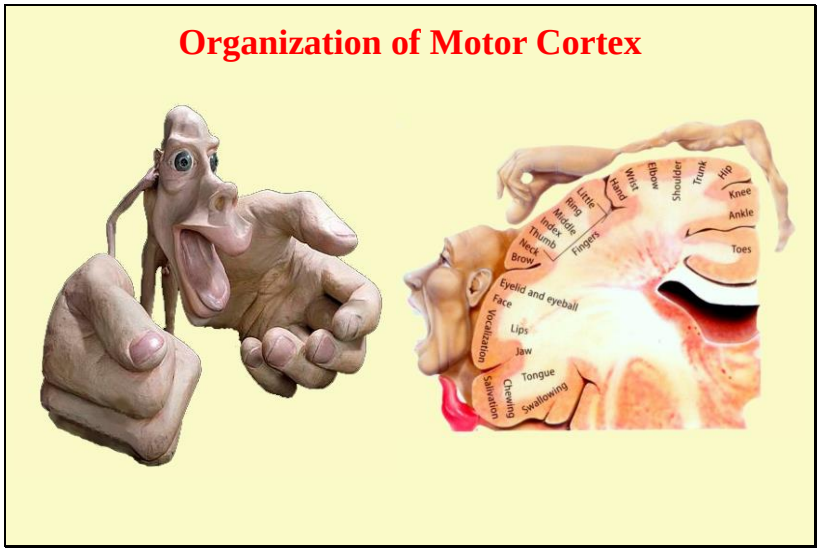
A longer version is
https://www.youtube.com/watch?v=0kFmbrRJq4w



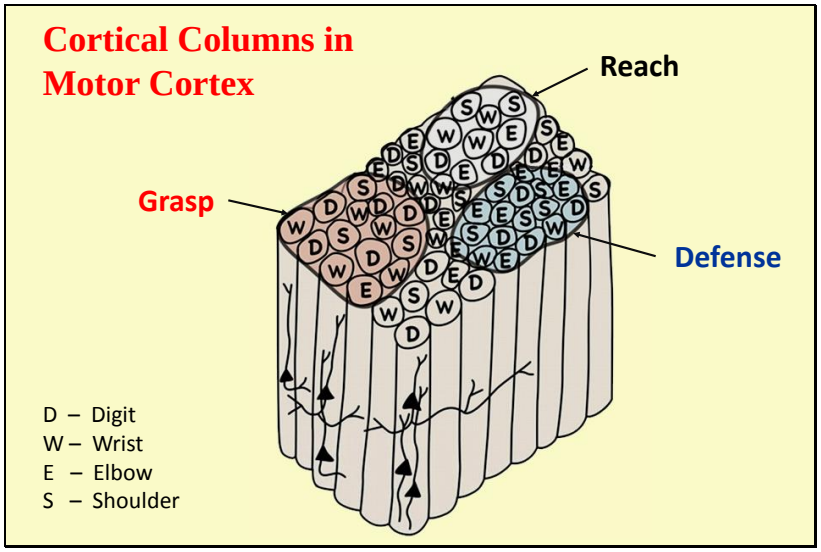
This slide summarizes the steps involved in initiating a muscle contraction.



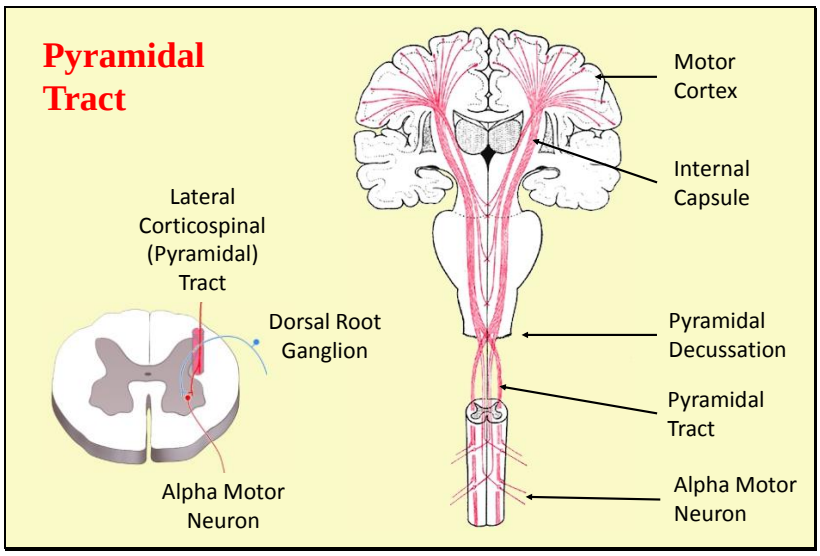
The muscles are at one end of the motor system. The opposite end is in the frontal lobes.
The frontal cortex has areas that act to plan (frontal poles), initiate (supplementary motor area), and program (premotor cortex) movements.
The frontal lobe also has special regions that control speech (left hemisphere) and eye movements (both hemispheres).
The final common pathway for muscle activation descends from the primary motor cortex in the precentral gyrus down to the spinal cord via the pyramidal tract. The pyramidal tract is named because it crosses over in the medulla in a structure called the pyramid. It is thus "pyramidal" in two senses. The cell bodies for the axons in the pyramidal tract are large pyramidal cells in the motor cortex.



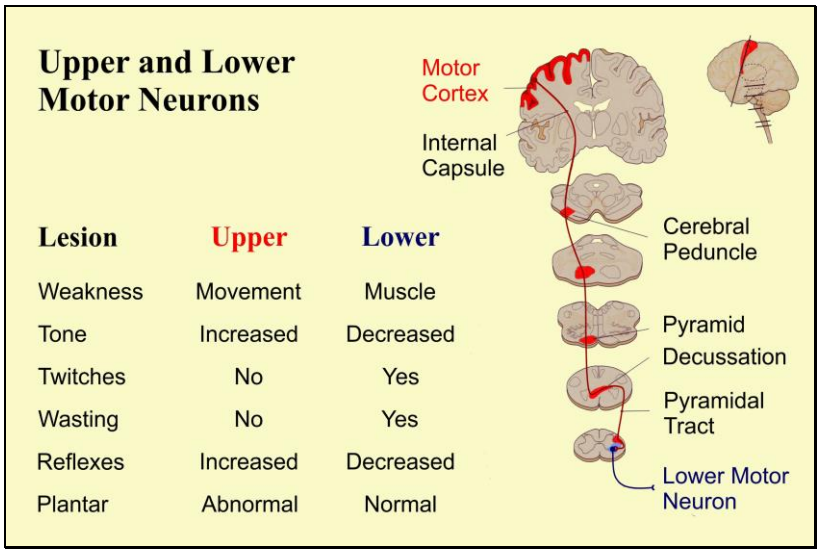
As in the sensory cortex, the area of cortex devoted to body movements varies with the precision of the movements. The hands and lips take up much more of the cortex than the legs and arms.



Like other areas of cortex, the primary motor cortex in the precentral gyrus is organized in columns.
Groups of columns are concerned with types of movements, with each column controlling the action of a localized set of muscles



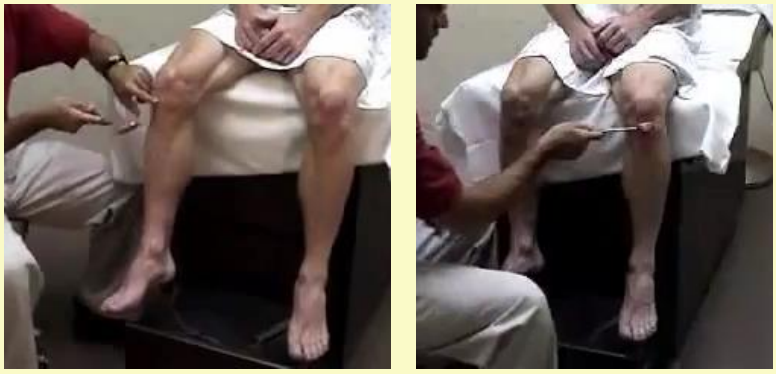
The motor cortex sends instructions down to the alpha motor neurons in the ventral horn of the spinal cord through the pyramidal tract.
This descends through the internal capsule, then down the midbrain and pons into the medulla where it decussates (forms the number X) and then travels down the spinal cord in the lateral columns.
The fibers in the pyramidal tract terminate on motor neurons in the ventral horn of the spinal cord



The main motor pathway to the muscles therefore involves two neurons – the upper motor neuron in the motor cortex and the lower motor neuron in the ventral horn of the spinal cord.
Lesions to the motor pathway cause weakness. The signs and symptoms depend on whether the upper or lower motor neuron is damaged. (Or both)
Tone and reflexes are generally increased in upper motor neuron weakness.
Twitches and wasting are characteristic of lower motor neuron weakness.

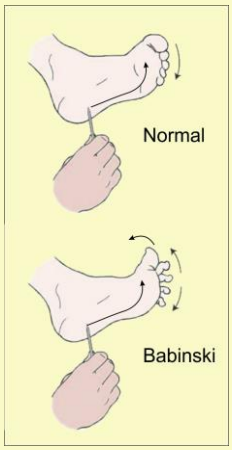
Patellar Reflex ("Knee Jerk")

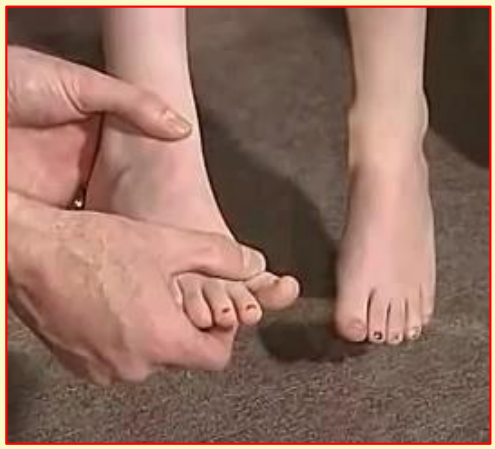
Patient suffered a stroke (cerebrovascular accident) involving the left cerebral hemisphere and now has weakness on the right side.



The increased reflexes on the left are characteristic of an upper motor neuron lesion.
https://www.youtube.com/watch?v=jK0JS2OsvKA

Plantar Responses



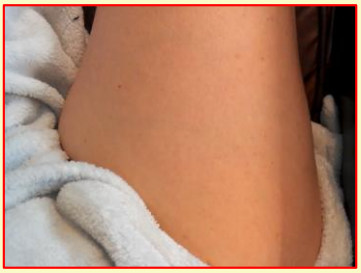


The plantar reflex is elicited by noxious stimulation to the lateral sole of the foot.
Normally the big toe goes down. With an upper motor neuron lesion the big toe goes up. This abnormal reflex also goes by the name Babinski. Josef Babinski was a student of Charcot at the Salpêtrière hospital in Paris.
https://www.youtube.com/watch?v=y4RFNz8tXl0

Elicitation of the reflex requires skill – the stimulus must not be too painful or there will be a withdrawal reflex, nor insufficiently noxious or there will be no reflex. In England it is said that one must use the key of a Bentley ☺ (A neurologist can only afford a Bentley if she is very good)

Amyotrophic Lateral Sclerosis

Also known as Lou Gehrig's Disease after the New York Yankees baseball player (1923-39). ALS is a degenerative disease that affects both upper and lower motor neurons. "Amyotrophy" means wasting of the muscles, and "lateral sclerosis" refers to the degeneration of the pyramidal tract in the lateral columns of the spinal cord. The disease is characterized by progressive weakness, increased reflexes, wasting and muscle twitching ("fasciculations").



Amyotrophic lateral sclerosis is a degenerative disease that affects both the upper and lower motor neurons.
Video is at
https://www.youtube.com/watch?v=X5YjSJsRH1g

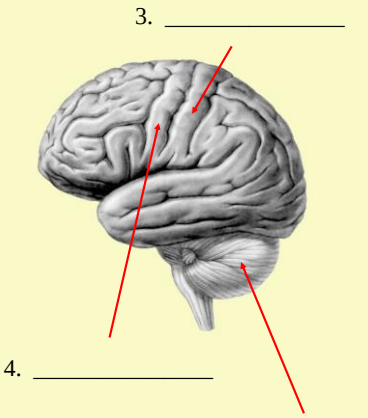
Quiz 4A

1. The chemical transmitter in the neuromuscular junction is

A) dopamine
B) acetylcholine
C) myosin
D) myelin

2. Most fibers in the pyramidal tract cross from one side to the other in the

A) internal capsule
B) midbrain
C) medulla
D) spinal cord



Motor Control

Movements are very difficult to control, especially when the mover must adapt to an unknown environment. Despite the movies, robots cannot yet perform much better than a human toddler. Robotic failures are similar to what happens in diseases of the motor system – falls, tremors, inattention, inability to do two things at once.

Movement requires:

- **feedback** routines to correct for errors.
- **feedforward** programs to anticipate what will happen.

Human movement involves complex interactions between

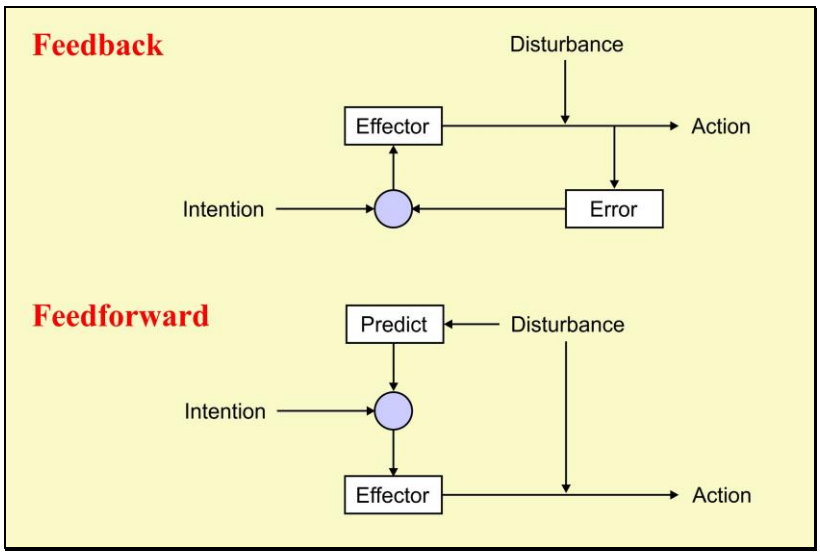
- **cerebral cortex** (plans, visual control)
- **basal ganglia** (movement in space, learned programs)
- **cerebellum** (error correction, sequencing, learned programs)
- **vestibular system** (body position)

We have looked at the activation of muscles in the peripheral nervous system. In the second half of this session we shall consider the control of the muscles by the central nervous system.

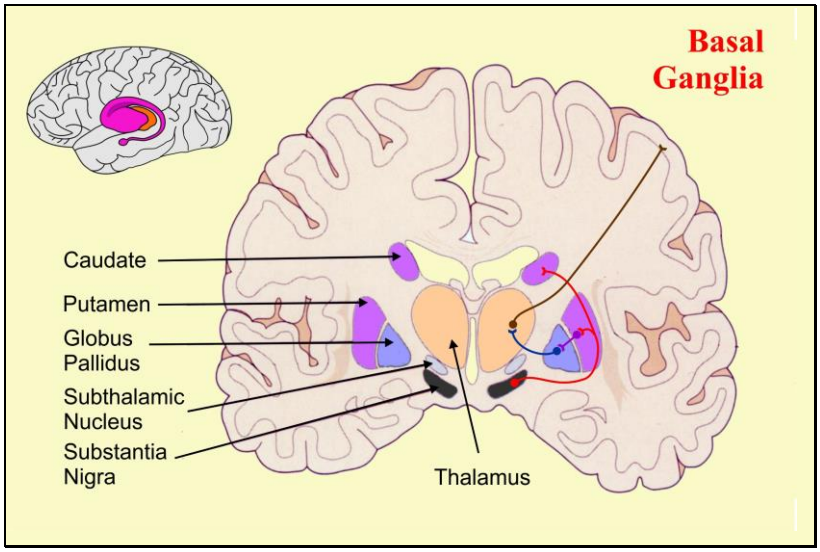
DARPA Challenge 2015

These videos are from the competition held by the US Defense Advanced Research Projects Agency. The competition is to determine which robot best performs the actions of a human being in a battlefield or emergency situation.
The robots are not self-contained. They are operated by human beings through a computer that transmits instructions through radio connections.

More “epic fails” are at
https://www.youtube.com/watch?v=l2Qlwl1NmRc



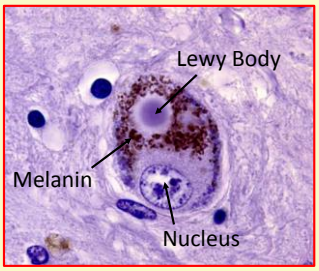
A good motor system uses feedback to perform an action that is being disrupted. The error is continually measured and the movement compensated.
A very good system also uses feedforward to predict and compensate for the effects of a disturbance.In the human brain these feedback and feedforward circuits are located in the basal ganglia and the cerebellum.

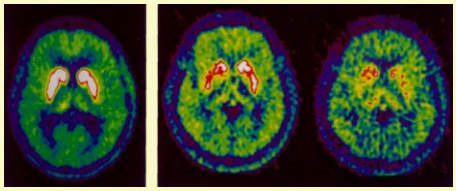


The basal ganglia are the regions of gray matter in the center of the cerebral hemispheres. The nuclei are shown on the left and the main connections on the right.
The main parts of the basal ganglia are the caudate and putamen (also known as the striatum because they are “grooved” by the internal capsule) and the globus pallidus.
The substantia nigra, a black nucleus in the midbrain, sends fibers (red) to the striatum.
The striatum acts on the globus pallidus (purple), which projects to the thalamus (blue), which sends feedback to the motor cortex (black).

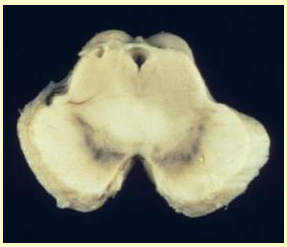
Substantia Nigra

Because its neurons contain melanin granules, this midbrain nucleus is normally black. The neurons connect to the caudate and putamen (striatum) through the nigrostriatal pathway. The transmitter is dopamine. As the neurons degenerate the dopamine concentration in the caudate decreases:





Normal Early PD Late PD



The substantia nigra is located in the midbrain, just inside the descending pyramidal tracts. It is normally black (see illustration of a cross section of the midbrain at the lower right).
In the nigrostriatal pathway the transmitter is dopamine.
Parkinson's Disease affects the substantia nigra and removes the normal effects of dopamine on the striatum.
The characteristic finding on neuropathology is the spherical Lewy body, although no one really knows how this mixture of synuclein and other proteins occurs.

Parkinson's Disease

Pathology: degeneration of dopamine cells in the substantia nigra, with abnormal accumulation of a protein called synuclein in the form of Lewy bodies.

Cause: in most patients cause is unknown; some cases are hereditary; some are caused by toxins; some follow encephalitis.

Presentation: resting tremor; rigidity; slowness of movement; instability; stooped posture; shuffling gait; lack of facial expression.

Associated Symptoms: depression; difficulty making decisions; in some cases dementia.

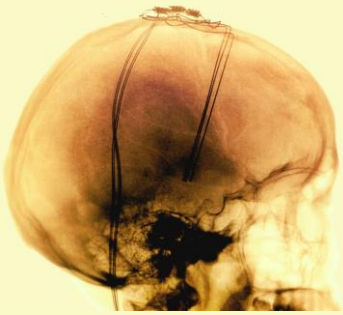
Progression: slow deterioration over many years

Parkinson's disease was described by James Parkinson in 1817 as the "shaking palsy"
The disease affects 1% of people over 60 years old and 4% of those over 80 years.

Treatment of Parkinson's Disease

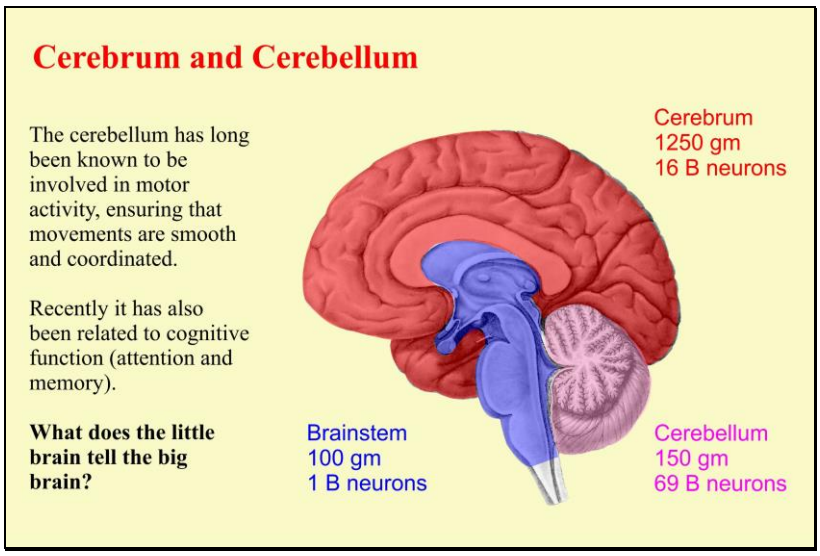
Drugs: L-DOPA (dihydroxyphenylalanine) is administered orally in high doses. This crosses into the brain and is converted to the neurotransmitter dopamine. Other drugs are sometimes used to counteract its unwanted side effects. L-DOPA works well against the rigidity and slowness of movement but is not as effective against the tremor.

Deep Brain Stimulation: Electrical stimulation via an electrode inserted in the basal ganglia (often near the subthalamic nucleus) can reduce tremor. This has replaced the older surgical approaches that made lesions in the basal ganglia.

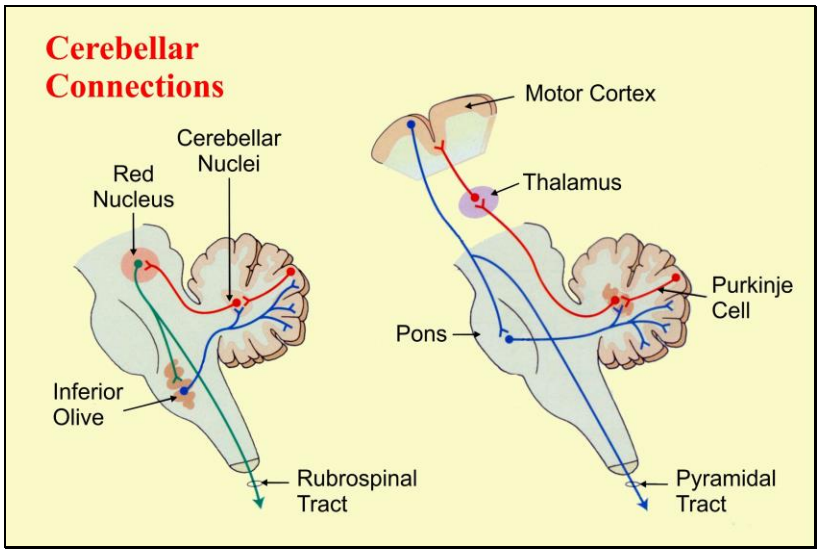


This video demonstrates the dramatic effects of deep brain stimulation on Parkinsonian tremor.

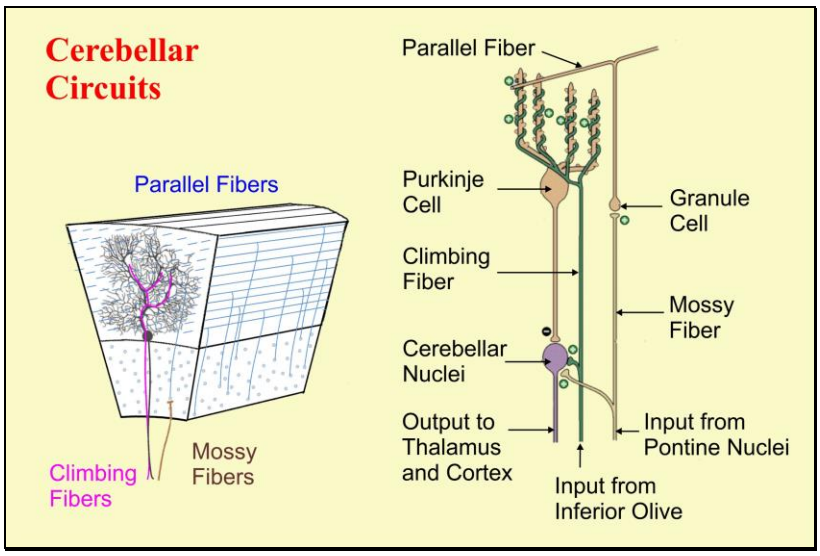
The video is available at
https://www.youtube.com/watch?v=mO3C6iTpSGo



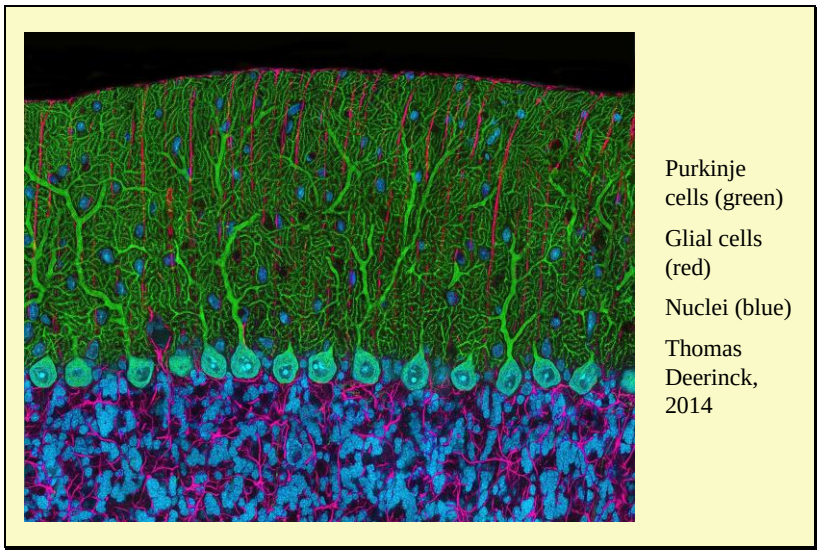
As well as the basal ganglia, the cerebellum is also involved in motor control.
This slide is from a previous presentation. As noted then, the cerebellum has many more neurons than the cerebrum (but fewer connecting fibers).
Unfortunately we still do not know what the little brain tells the big brain.



We should start on the right of this illustration.
The cerebellum receives input from the motor cortex through the pontine nuclei.
It then sends feedback to the cortex through the thalamus.
A feedforward connection is provided through the red nucleus which sends information down to the spinal cord through the rubrospinal tract.
Note that the midbrain is very colorful – it has both the red nucleus in the cerebellar pathway and the substantia nigra which projects to the striatum.



The main output of the cerebellum comes from the Purkinje cells and goes via the deep cerebellar nucleus to the thalamus and cortex and to the red nucleus.
The huge dendritic trees of the Purkinje cells integrate activity coming from the pontine nuclei through the mossy fibers and from the inferior olive through the climbing fibers. These inputs are arrayed orthogonally (at right angles) – much like a computer memory chip.
The cerebellar cortex may serve as a computer calculating the exact times and amounts of muscle activity needed for a particular skilled movement.



This is a specially stained section of the cerebellar cortex. The nuclei in the lower part of the section are mainly those of granule cells and glial cells.

Cerebellar Disease

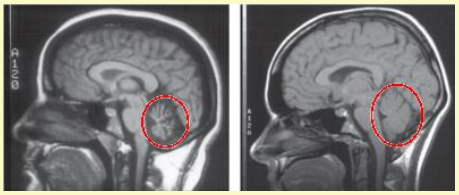
The cerebellum is especially important for the correction of movement errors and in the sequencing of movements. Cerebellar disorders are generally called **ataxia:**

(i) inability to move finger smoothly to nose, intention tremor

(ii) wide-based and staggering gait, difficulty walking heel-to-toe

(iii) slowness in rapid alternating movements, irregular speech

(iv) attention problems (especially multitasking)

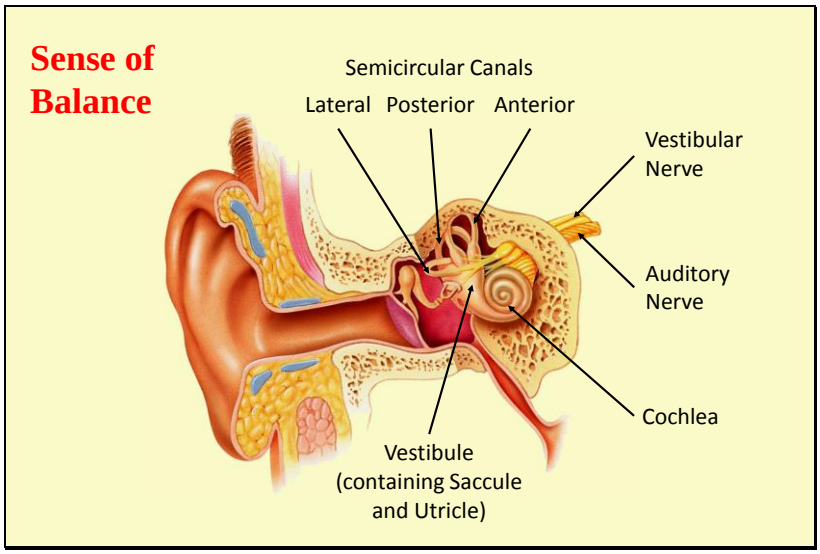


MRI showing atrophy of the cerebellum (left) compared with normal (right)

Cerebellar disease results in disordered movement – ataxia ("without order")

This illustrates mild ataxia on the finger to nose test.
The sweater states that "Ataxia is not a foreign cab."
https://www.youtube.com/watch?v=-dFMisBl1aM

This video shows the wide-based and clumsy gait of a patient with ataxia.
https://www.youtube.com/watch?v=yhgUOY2ohUE



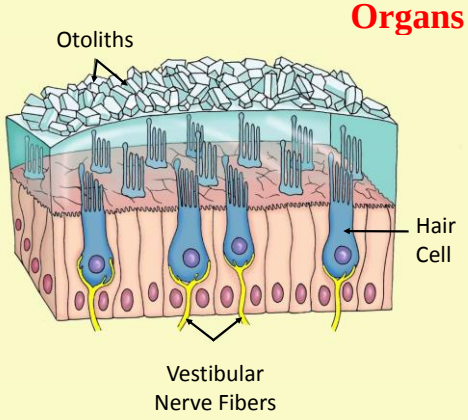
Important to our motor control is the sense of balance.
This is mediated through the vestibular end organ in the inner ear – the saccule, utricle and semicircular canals.
The eighth cranial nerve consists of the vestibular nerve and the auditory or cochlear nerve. We shall consider the cochlea next week.

Otolith Organs

Otoliths are grains of calcium carbonate fixed on top of hair cells in the saccule and utricle by a gelatinous material.

Movement of the otoliths relative to the hair cells will excite or inhibit the cells depending on the direction of movement.

As the head moves, the inertia of the otoliths bends the hairs. Otolith organs measure linear acceleration, and (because of gravity) head position relative to the ground.



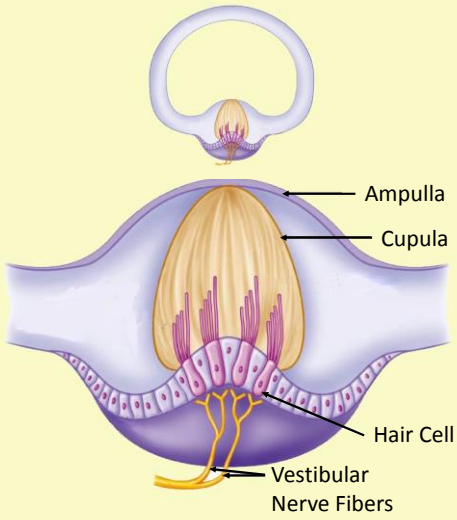
If the body moves to the right the otoliths do not move as fast and bend the hair cells to the left. This movement of the hairs is then sensed by the hair cells and transmitted to the vestibular nerve fibers.

Semicircular Canals

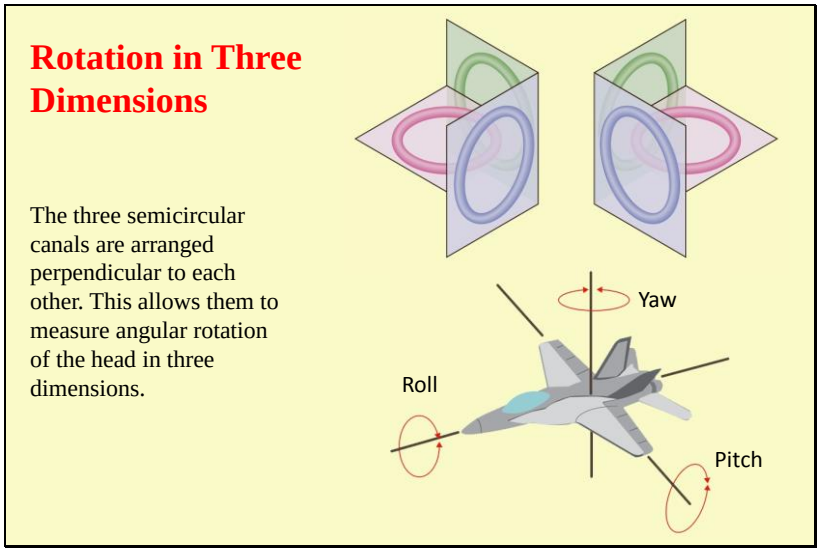
When the head rotates, the fluid in the semicircular canals does not rotate as quickly because of inertia. The fluid deflects the cupula which bends the hairs on the hair cells.

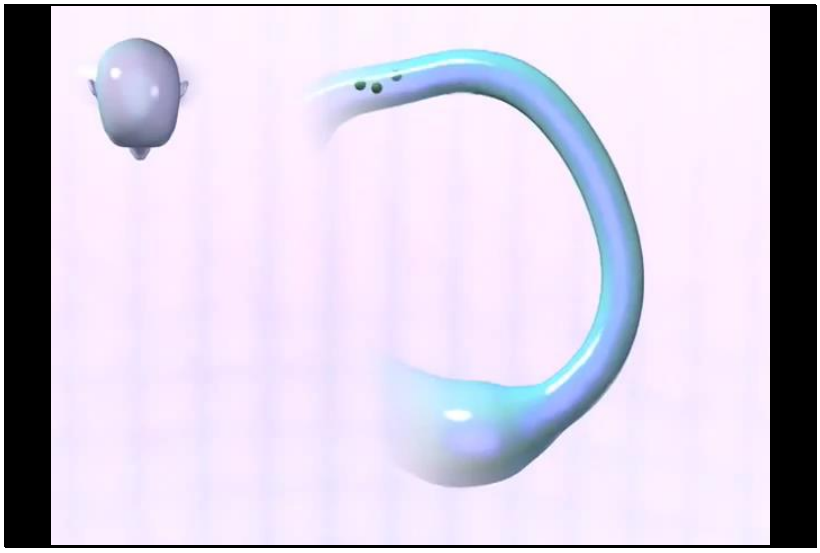
These will be excited or inhibited depending on the direction of rotation.

This measures angular acceleration (rotation) of the head.



The otoliths are sensitive to linear movements.
The semicircular canals are sensitive to rotation.

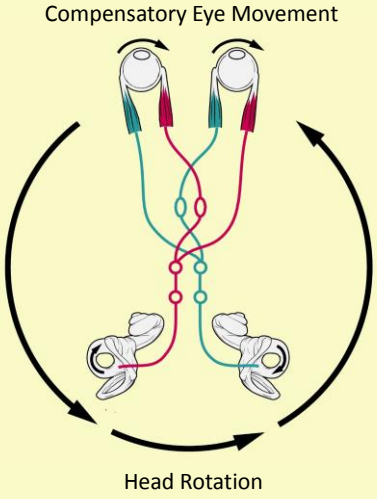




This animation shows the movements of the fluid in the semicircular canal as the head rotates. The three green spheres demonstrate the fluid motion. The fluids move after the actual head motion because of inertia.
You should look at the head movement (upper left) then watch how the fluid follow after the movement (green spheres) and see how this fluid movement deflects the cupula (at the bottom)
The full video is at
https://www.youtube.com/watch?v=dSHnGO9qGsE

Vestibulo-Ocular Reflex

As the head turns, the eyes turn in the opposite direction maintain the same visual input. If the rotation continues, the eyes keep flicking back ("nystagmus") to pick up another focus of gaze. This reflex involves the semi-circular canals, the vestibular nucleus, and the cranial nerves controlling the muscles that move the eyes. The reflex is calibrated under the control of the cerebellum.

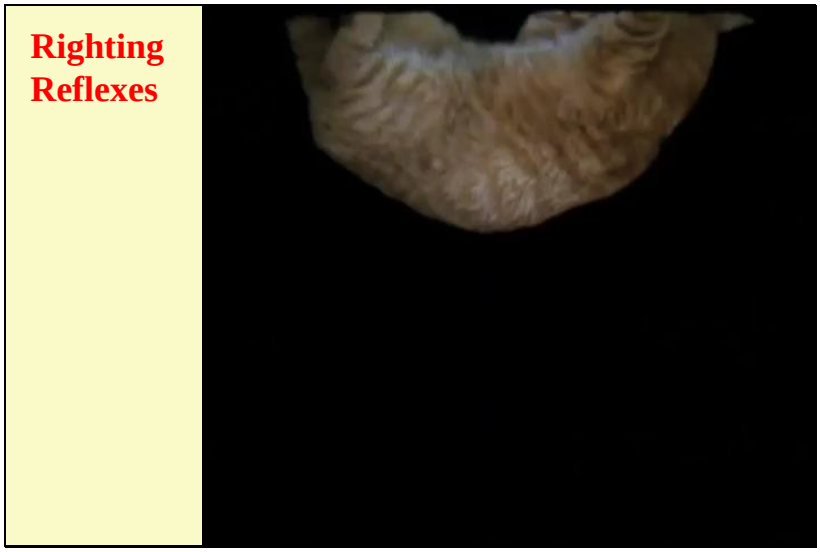


The purpose of the vestibulo-ocular reflex is to maintain a stationary visual input while the head is turning.

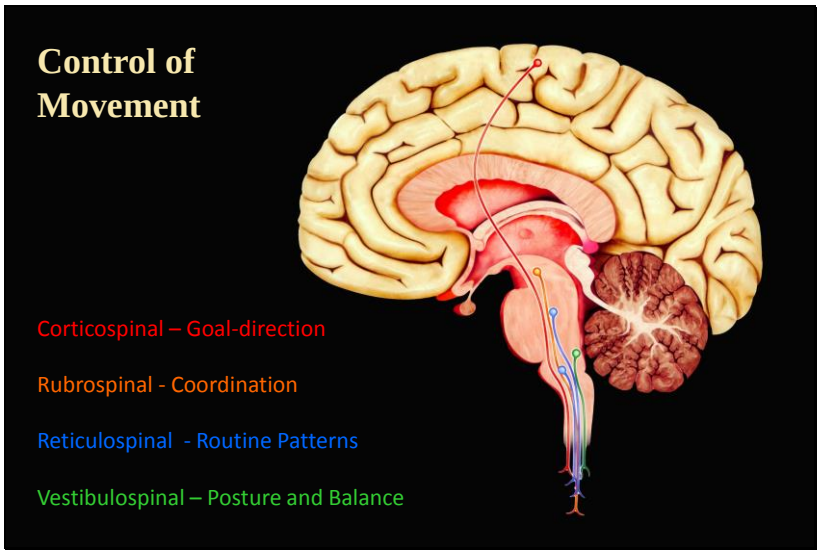
This video shows nystagmus that is caused by rotation.
The nystagmus persists after the rotation stops because the fluid in the semicircular canals keeps rotating (inertia).
The goggles serve two purposes:

- they magnify the eyes and make the nystagmus more visible
- they prevent the subject from seeing anything to fixate on. Fixation can over-ride nystagmus.

Video is available at
https://www.youtube.com/watch?v=RYTYTy_5Xn0ide



The vestibular system helps us to control our bodies in space. When an animal falls, its vestibular system initiates the righting reflex that makes it land on its feet.
The full video is at
http://video.nationalgeographic.com/video/cats_domestic_ninelives



Movement is controlled by many different brain systems.
The reticular system organizes basic rhythmic movements such as breathing and walking.
All of these systems project down to the neurons of the ventral horn of the spinal cord.

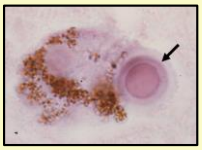
Quiz 4B

1. The chemical transmitter in the nigrostriatal pathway is

A) acetylcholine
B) dopamine
C) glutamate
D) serotonin

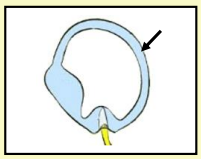
2. Which of the following is **not** associated with Parkinson's Disease

A) tremor
B) rigidity
C) slowness of movement
D) sensory loss



3. _____

4. _____



5. _____

Heather Ogden is the wife of Guillaume Coté. This is a clip from the YouTube video Lost in Motion II, directed by Ben Shirinian, with music by Leonard Cohen and choreography by Guillaume Coté.

https://www.youtube.com/watch?v=Lxl3AuL3_Qs

The lyrics to the song Avalanche are:

Avalanche (Leonard Cohen)

Well I stepped into an avalanche,
it covered up my soul;
when I am not this hunchback that you see,
I sleep beneath the golden hill.
You who wish to conquer pain,
you must learn, learn to serve me well.
You strike my side by accident
as you go down for your gold.
The cripple here that you clothe and feed
is neither starved nor cold;
he does not ask for your company,
not at the centre, the centre of the world.

When I am on a pedestal,
you did not raise me there.
Your laws do not compel me
to kneel grotesque and bare.
I myself am the pedestal
for this ugly hump at which you stare.

You who wish to conquer pain,
you must learn what makes me kind;
the crumbs of love that you offer me,
they're the crumbs I've left behind.
Your pain is no credential here,
it's just the shadow, shadow of my wound.

I have begun to long for you,
I who have no greed;
I have begun to ask for you,
I who have no need.
You say you've gone away from me,
but I can feel you when you breathe.

Do not dress in those rags for me,
I know you are not poor;
you don't love me quite so fiercely now
when you know that you are not sure,
it is your turn, beloved,
it is your flesh that I wear.

The meaning of the song is difficult to determine. It may present the Buddhist view of reality as an avalanche that covers the true soul. However, there are many different interpretations: http://www.leonardcohenforum.com/viewtopic.php?t=28468