
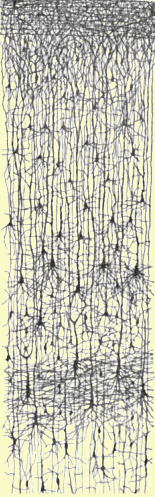


**Neurons:  
Structure  
and  
Function**



My attention hunted, in the flower garden of the gray matter, cells with delicate and elegant forms, the mysterious butterflies of the soul, the beating of whose wings may some day – who knows? – clarify the secret of mental life ... Even from the aesthetic point of view, the nervous tissue contains the most charming attractions. Is there in our parks any tree more elegant and luxuriant than the Purkinje cells of the cerebellum or the *psychic cell*, that is the famous cerebral pyramid?



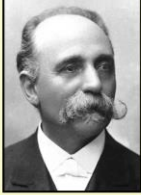
Santiago Ramón y Cajal (1852-1934)  
*Recuerdos de mi Vida*, 1917

In the preceding session we considered the brain in its normal (macro) size. Today we shall begin by looking at its fine structure through the microscope.

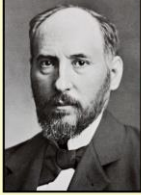
The brain contains neurons and glia. The functions of the brain in terms of information-processing depend mainly on the neurons. The glia provide structural and metabolic support.

The quotation on the slide is from the great Spanish neuro-anatomist Cajal. He made thousands of beautiful drawings of the microscopic anatomy of the brain's neurons – that he lovingly called the “butterflies of the soul.” The illustrations are two of his most famous drawings – one of a Purkinje cell in the cerebellum, and the other of the pyramidal cells in the cerebral cortex.

**1906 Nobel Prize in Physiology and Medicine**



Camillo Golgi  
(1843-1926)



Santiago Ramón y  
Cajal (1852-1934)

The prize was awarded jointly to Golgi and Cajal “in recognition of their work on the structure of the nervous system.” Golgi discovered his silver stain in 1873. This showed some but not all neurons and defined their processes. Golgi proposed that neurons were connected by a network of fibers. Cajal improved on Golgi’s technique but concluded that neurons were separate from each other with processes that were “in contiguity but not in continuity.” Their Nobel lectures stated their contradictory theories. The “neuron doctrine” of Cajal ultimately prevailed.

In order to see the neurons, Cajal used a silver stain invented by the Italian anatomist Golgi. The stain is intriguing since it stains only a small proportion of neurons in a section, but stains them completely so that all their connections become visible. A few individual neurons are shown in exquisite detail whereas, the others are invisible.

Golgi and Cajal shared the Noble Prize in Physiology and Medicine in 1906.

In their acceptance speeches, they presented completely different views of the nervous system.

They certainly did not win the peace prize ☺

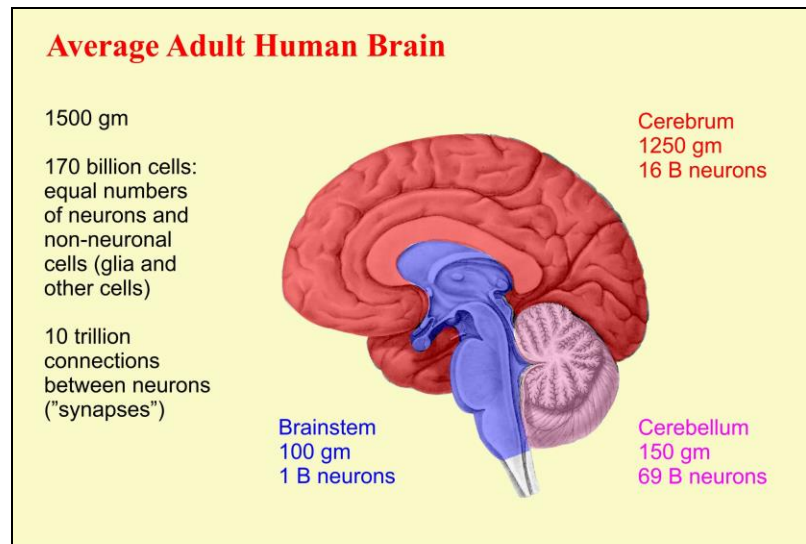
Golgi proposed that the brain was a vast network of connected fibers and that the neurons existed mainly to support and maintain this network. This was the “reticular theory.”

Cajal proposed that the network of fibers was composed of multiple thin extensions of the neurons. Each neuron and its fibrillary extensions was separate from those of other neurons. The neuron was just like any other cell in the sense that it was self-contained. This was the “neuron doctrine.”

Cajal was quite acerbic in his Nobel Lecture:

“True, it would be very convenient and very economical from the point of view of analytical effort if all the nerve centres were made up of a continuous intermediary network between the motor nerves and the sensitive and sensory nerves. Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity.”

Over the ensuing years it became clear that Cajal was right. Neurons are self-contained, but make multiple contacts with each other through “synapses.” These junctions were postulated by Sherrington, could not be directly observed until electron microscopy. We shall deal with synapses in next week’s presentation.



The brain contains about 170 billion cells, with equal numbers of neurons and glia. The neurons are the cells responsible for the main functions of the brain. They respond to stimuli and activate responses.

Originally, the glial cells were thought to glue the neurons in place.

However, they also provide essential metabolic support for the neurons and may play a role in learning and memory.

This slide provides the number of cells in the brain.

Of note is the fact that most of the neurons in the brain are in the cerebellum. The cerebellum is largely cortex and the cortex is packed with tiny cells. The cerebrum contains a lot more connecting fibers – these form the white matter within and between the hemispheres. These links between neurons may be the most important thing about the cerebrum. These interconnections allow multiple neurons in different areas of the cerebral cortex to function as networks – assemblies of cells that activate each other.

We shall look at the microscopic anatomy of the neurons first and then the glia.

## Neurons Compared to Other Cells

### Similarities

All cells are bounded by a **cell membrane**. Within the cytoplasm are the **nucleus** containing the DNA, and a set of organelles to carry out the cell's metabolism: **ribosomes** to manufacture material and **mitochondria** to provide the energy.

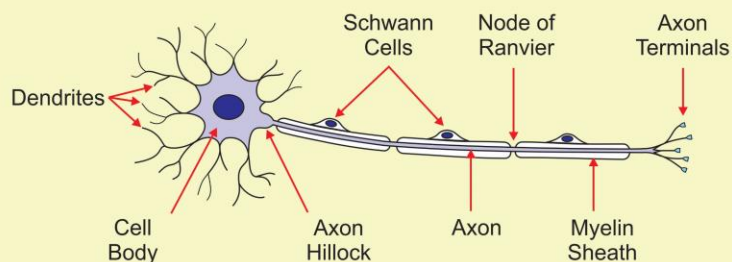
### Differences

1. Neurons have **elongated processes**: multiple dendrites and a single axon.
2. Neuronal membranes are **excitable**: this allows them to conduct information from one place to another.
3. Neurons have **synapses** that allow information to be transferred between neurons
4. Neurons **do not replicate**: the number of neurons in the brain remains stable from cradle to grave.

Probably the most important thing about neurons is that they can communicate with each other. Neurons do not replicate. Our neurons, for the most part, stay the same from cradle to grave – womb to tomb ☺

Although they do not replicate, neurons can regenerate their processes, provided the cell body is intact. Recovery and rehabilitation can then occur if new connections are made to take over from those that were lost. Another way to recover function would be to design new programs to take over for those that were lost when some neurons died.

### Typical Neuron



The dendrites receive information from other neurons. This input is integrated. If a threshold is reached, excitation occurs at the axon hillock and an electrical impulse travels along the axon. The myelin sheath increases the speed of the impulse. At the axon terminals information is transferred to another neuron or to a muscle.

This shows the main parts of a neuron. The neuron used in this example is an alpha motor neuron that sends its axon out of the spinal cord to terminate in a muscle. This neuron makes the muscle contract.

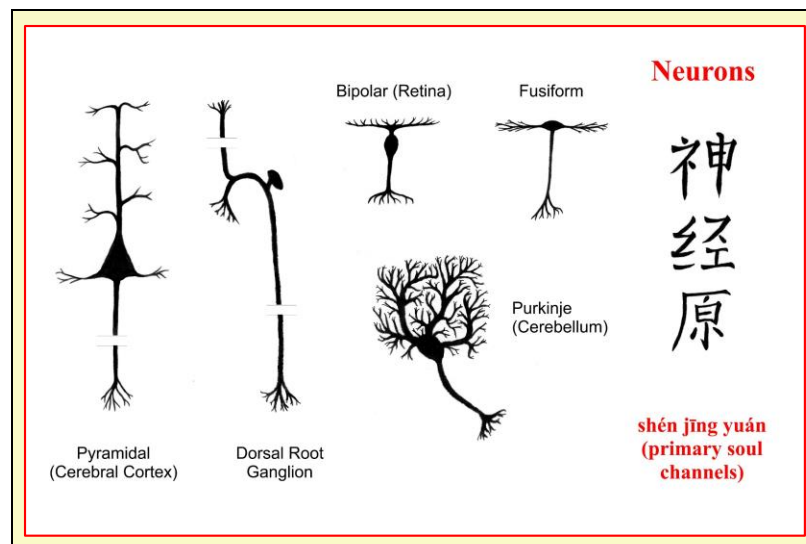
The flow of information in a neuron is from dendrite to axon. Dendrites receive and axons transmit information: D R A T

The axon hillock is the location where an electrical impulse is generated.

The axon is wrapped in a myelin sheath that is formed by Schwann cells. (If the neuron were in the central nervous system the myelin sheath would be made by oligodendroglia.) Myelin is white – thus the regions of the brain where there are mainly fibers are white whereas the regions where there are mainly cell-bodies are grey. You can remember this from Hercule Poirot who exercised the “little gray cells” of his cerebral cortex.

The nodes of Ranvier are spaces between the areas covered by myelin – these are locations where the electrical impulse travelling down the axon can be regenerated.

The axon of this peripheral nerve fiber terminates in a muscle (at a neuromuscular junction). If the axon were in the central nervous system, it would terminate on another neuron at a synapse.



This slide gives you a sense of the many different kinds of neurons in the nervous system.

The drawings were made with a calligraphy brush. The Chinese name of a neuron is shén jīng yuán – this may derive from a combination characters originally meaning “primary soul channel.” However, both translation and etymology are complicated.

We have already seen the Purkinje cell and the pyramidal cell. The pyramidal cell in the motor cortex can have a very long axon – from the cerebral cortex to the spinal cord where it synapses with other neurons that send axons out of the spinal cord to the muscles.

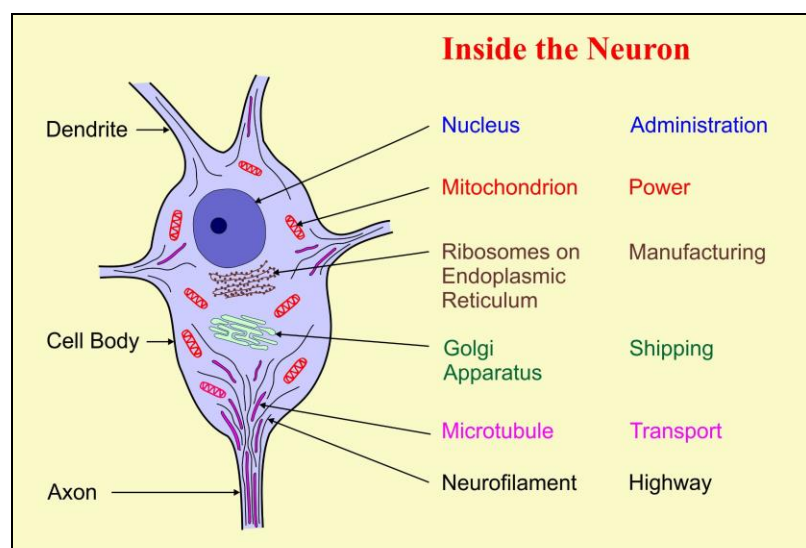
However, the longest neuron in the body is the sensory neuron that comes from the big toe. It has its cell body in the dorsal root ganglion within the lower lumbar spine. The central axon continues up the spinal cord to synapse in the medulla. The cell can therefore be more than five feet long in a normal adult male. And much, much longer in the giraffe ☺

This neuron in the dorsal root ganglion is intriguing since the relationship of dendrite to axon is not the same as in the typical neuron. The “dendrites” in this neuron are the peripheral branches

– these receive the stimulation from touch, pressure, etc. The axon begins right after these peripheral branches. In place of the axon hillock there is an excitable region of the axon that responds to the stimulation of the peripheral branches.

The bipolar cell in the retina transfers information from the retinal receptors to the ganglion cells. It is so small that it does not develop any action potentials.

The fusiform cell in the superior olivary nuclei in the brainstem compares information coming from the two ears in order to determine where a sound is coming from. Sounds from the left are louder (and earlier) in the left ear than in the right.



We can conceive of the neuron as a very efficient business. (Dr. Chang who provide much of the initial support for the LIFE institute would like this)

Administrative decisions are made in the nucleus.

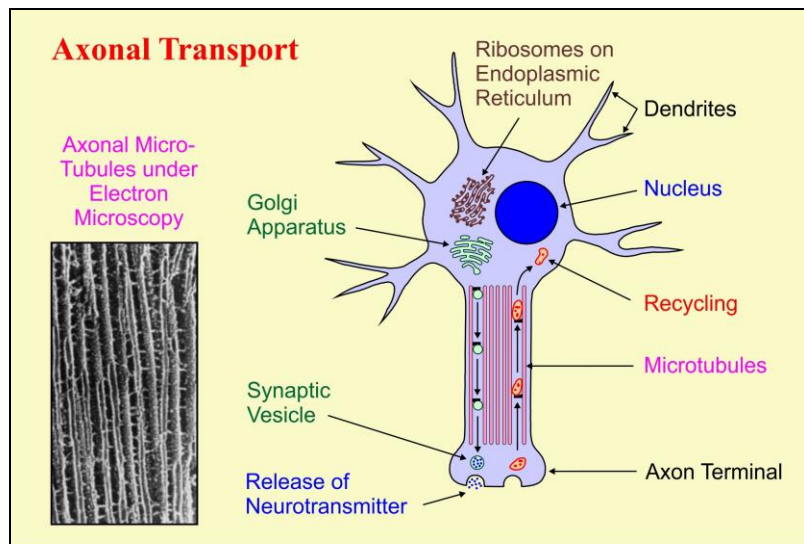
These decisions are communicated to the ribosomes by means of messenger RNA . The ribosomes manufacture the proteins and other products needed for the business.

Energy for the manufacturing comes from the mitochondria – the cell's power plants.

The manufactured products are packed and shipped through the Golgi apparatus.

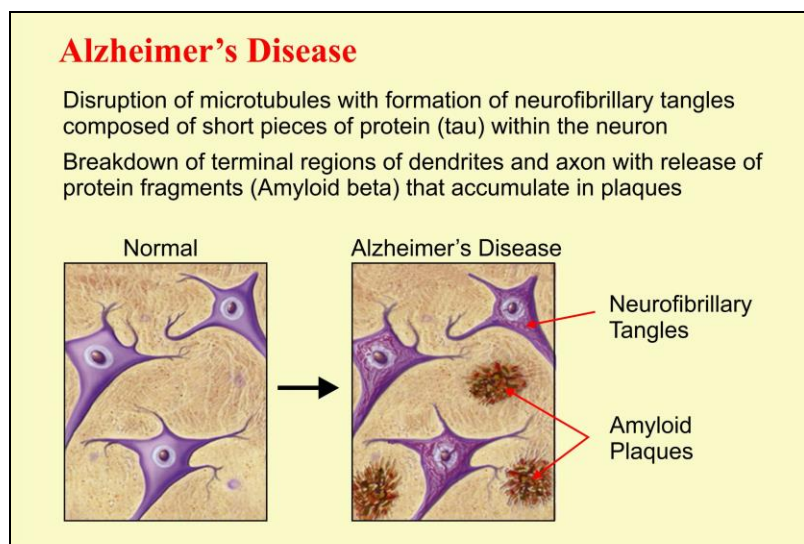
The delivery of the products to the nerve terminals is carried out by microtubules that move the products along neurofilaments down to where they will be used.





In many neurons it is a long way to the synaptic terminals. The axon contains microtubules that carry the manufactured products (proteins, synaptic vesicles, mitochondria, etc.) to the terminals. Material that has served its purpose, and messages about the state of the synapse are transported back to the cell body.

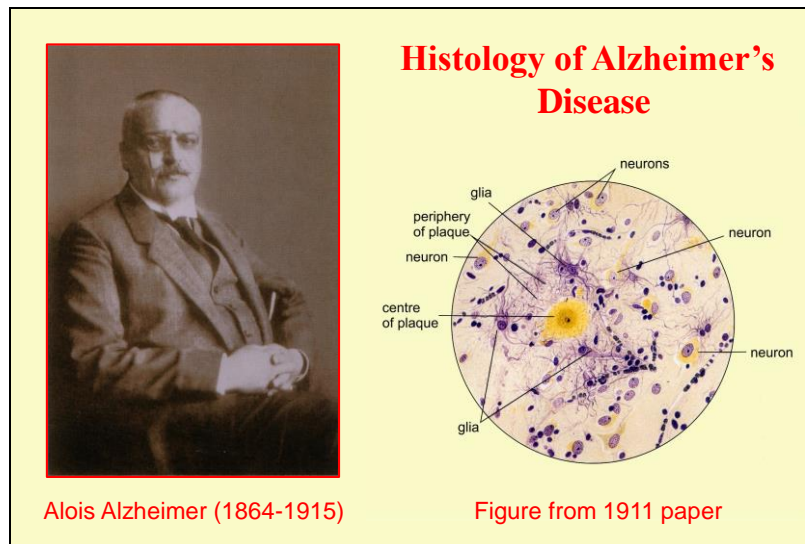
There are microtubules and neurofilaments going into the dendrites as well – these carry messages to and from the synapses on the dendrites.



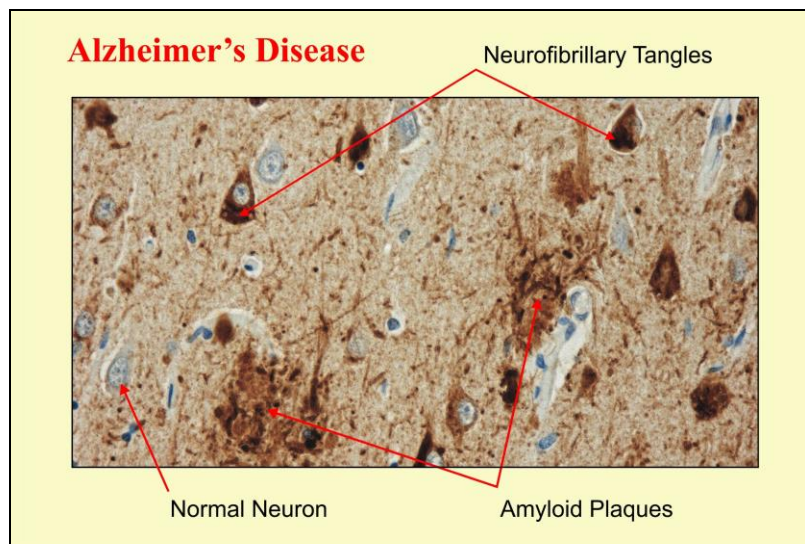
We do not know for certain the cause of Alzheimer's Disease. Some current hypotheses suggest that it may be a disorder of axonal transport. The microtubules break down and the broken pieces form neurofibrillary tangles within the neurons.

Perhaps because the distal regions of the axon are no longer properly supplied, the terminals break down and release material into the extracellular space that forms amyloid plaques.

Both of these abnormal processes disrupt the normal communication between neurons.

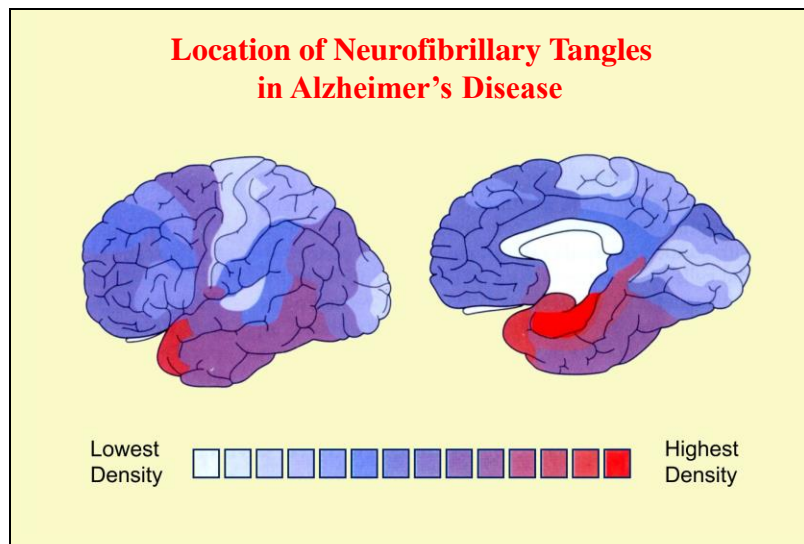


This slide shows one of Alzheimer's original illustrations of the histology of presenile dementia. The amyloid plaque is surrounded by reactive glial cells. The particular stain in this section does not show the neurofibrillary tangles.

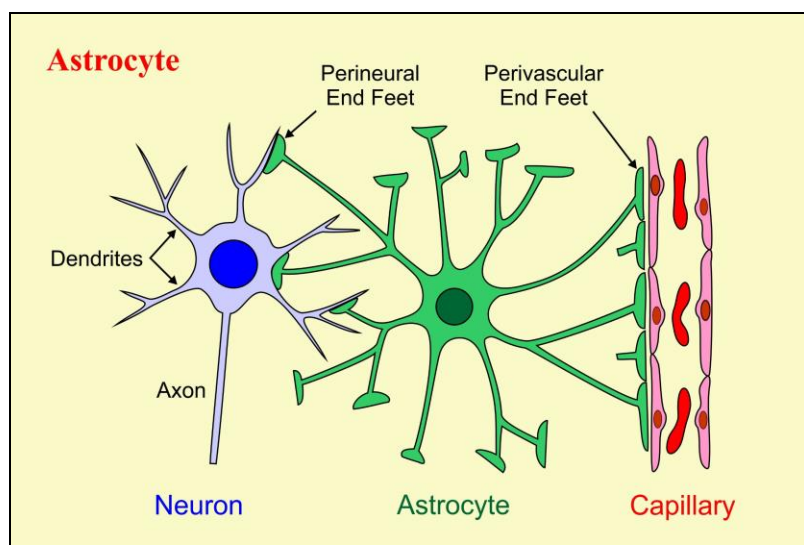


This is a recent microscopic section showing dark brown tangles within some of the neurons, as well as the plaques. The normal neurons are bluish whereas the diseased neurons are full of brown-stained tangles. The very elongated bluish regions are capillaries.





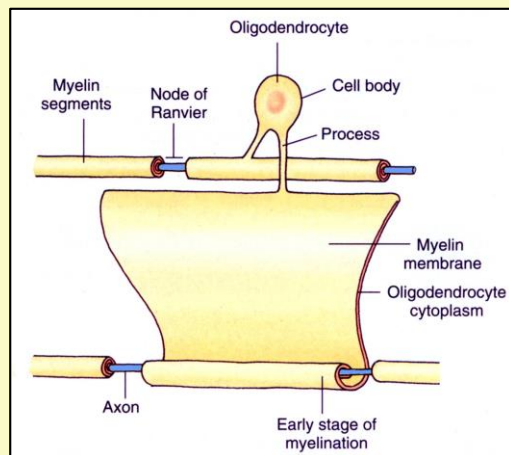
This diagrams show the lateral view of the left hemisphere (left) and the medial view of the right hemisphere (right). Neurofibrillary tangles occur most frequently in the anterior and medial parts of the temporal lobes. Since these regions (hippocampus and parahippocampal gyrus) are concerned with memory, amnesia is the initial presenting symptom of Alzheimer's Disease. Note that the sensory and motor cortices are relatively spared. Demented patients usually have normal sensation and move normally.



The brain contains as many glial cells as neurons. There are two main types of glia. The astrocyte – star cell – carries oxygen and nutrients from the blood vessels to the neurons. It also maintains the concentrations of ions around the neurons.

### Oligodendrocytes

To speed up neuronal conduction, axons are insulated with myelin. In the central nervous system this is formed by oligodendrocytes wrapping around the axon. In the peripheral nervous system, the myelin is formed by Schwann cells.

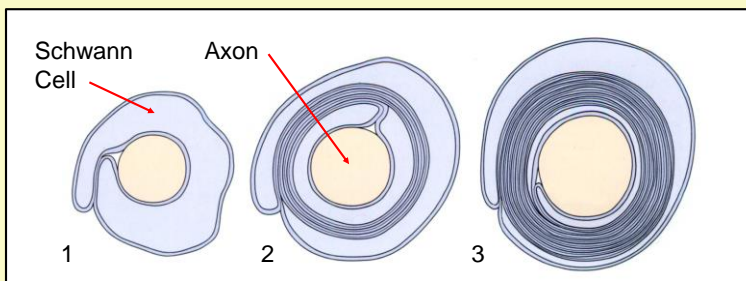


Oligodendroglia – glia cells with only a few processes – wrap around the axons to form the myelin sheath.

The myelin insulates the axons from each other and speeds up the transmission of impulses. We shall consider how this works in the second part of this session.

### Myelin Sheath

Schwann cells circle around the axons of peripheral nerves and envelop them in a myelin sheath.



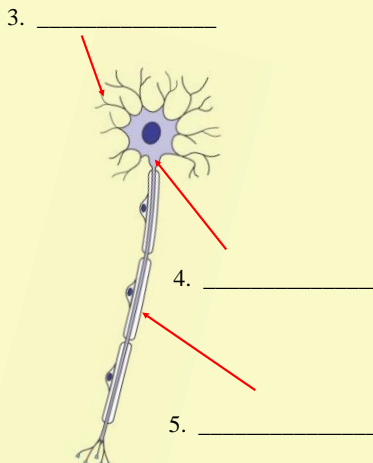
In the axons of the peripheral nervous system, the myelin sheath is formed by Schwann cells. The bottom diagram shows the process of myelination as the cell wraps itself around the axon. At the top right is an actual electron-microscopic view of a myelinated axon.

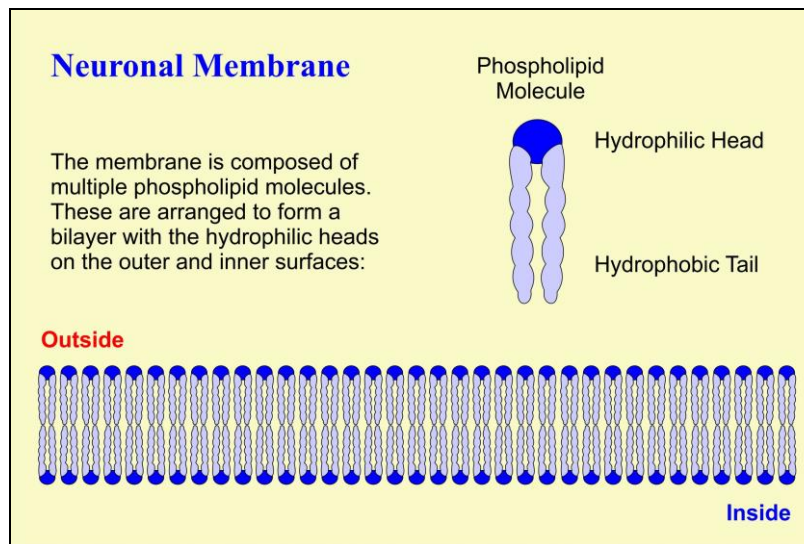


This shows an artist's impression of the cells of the brain (from Carter book). Blue-green astrocytes suck out the nutrients from the capillaries and deliver these to the neurons. Oligodendrocytes form the yellow myelin sheaths around the axons. In the orange-brown neurons you can see the nucleus, the axon hillock, the dendrites and the myelinated axon.

### Quiz 2A

1. The neurons of the brain
  - A) are separated from one another
  - B) are far more numerous than glial cells
  - C) replace themselves by replication
  - D) have no nuclei
2. The hippocampus
  - A) looks like a hippopotamus
  - B) shows neurofibrillary tangles in Alzheimer's Disease
  - C) receives its blood supply from the anterior cerebral artery
  - D) is located in the occipital lobe



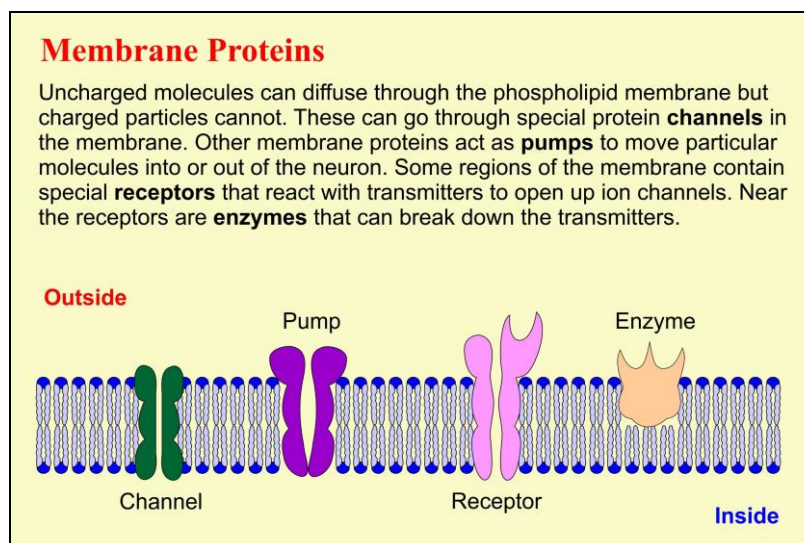


In the first part of this session we concentrated on the microscopic anatomy of the neurons. Now we shall consider their physiology – how they work. Neurons have a cell membrane just like any other cell. This keeps the inside in and the outside out.

The special characteristics of the membranes of neurons (and of muscle cells) are that

- (i) They are polarized – the inside is negative relative to the outside by 40-90 mV.
- (ii) They are “excitable.” When you poke them they respond.
- (iii) They conduct impulses from one place to another.

Polarization, excitation, conduction.



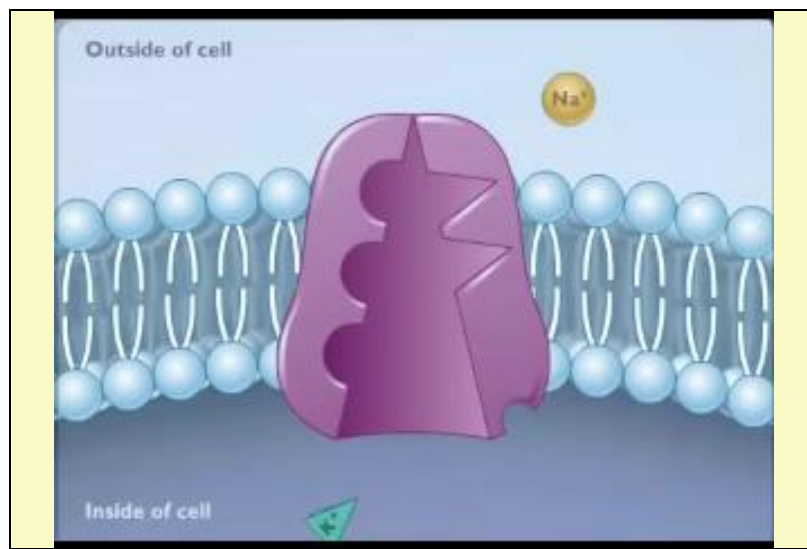
To understand how the neuron works we must know more about its membrane.

Inserted in the phospholipid bilayer are various proteins. Some of these act as channels to allow charged ions to enter or exit the cell. Charged ions cannot otherwise go through the phospholipid membrane.

Some of the proteins act as pumps to move ions in or out of the cell. The most important of these is the sodium pump. This moves sodium out of the cell and potassium into the cell. This creates a separation of charge across the membrane – making the cell electrically negative on the inside relative to the outside.

At the synapse there are special receptors that interact with neurotransmitters and enzymes to break down these transmitters – we shall consider these next week.

Today we are concerned with pumps and channels – the neuronal plumbing.



This animation shows how the sodium pump works to transfer sodium ions out of the neuron and potassium ions in.

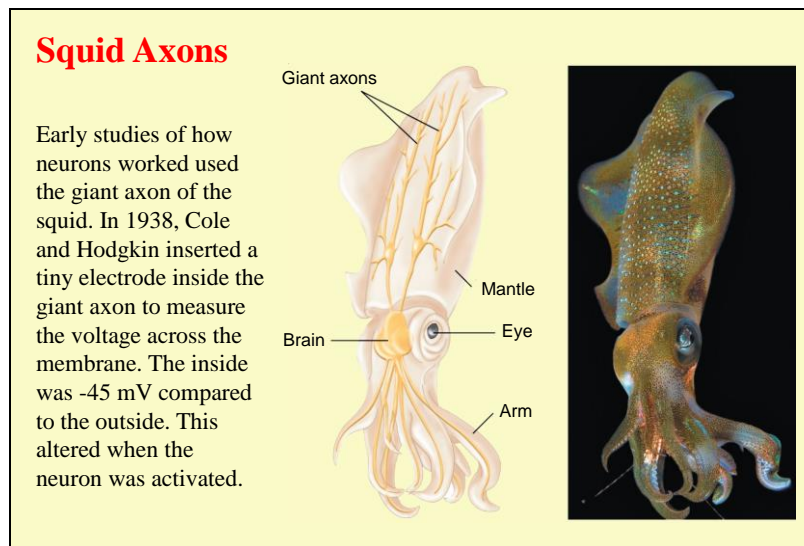
<https://www.youtube.com/watch?v=P-imDC1txWw>

This pumping process makes the intracellular ionic concentrations different from the extracellular concentrations.

Inside the cell potassium ions have high concentrations and sodium ions low; the extracellular concentrations are the opposite.

This difference in ionic concentrations causes the membrane to be “polarized” – the inside negative relative to the outside.





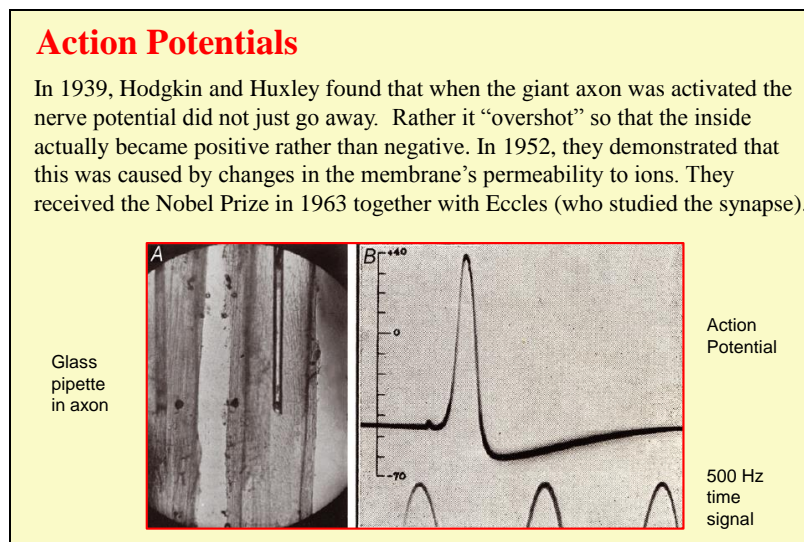
Polarization, excitation, conduction.

The excitability of neurons was first understood in experiments with the squid.

In order to activate the mantle for jet propulsion, the squid has a giant axon. The typical diameter of this axon is about  $0.5\text{ mm}$ . Axons with large diameters conduct more rapidly than thin axons.

The two giant axons in the squid activate all the muscle fibers in the squid mantle – their almost synchronous contraction causes rapid jet propulsion as water is squeezed out of the mantle.

(Note that even small squids have giant axons – the physiologists did not have to capture a giant squid. 😊)

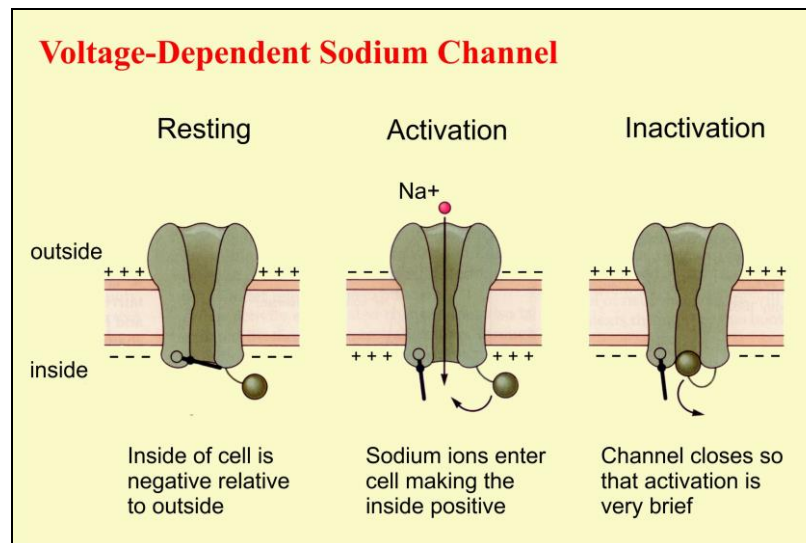


Hodgkin and Huxley were able to place a thin glass pipette within the squid giant axon. The left side of the illustration shows the pipette in the axon – a fancy mirror arrangement allows both top and side views.

The first thing determined about the giant axon was that it was electrically negative on the inside.

Further studies showed that when the axon was activated it reversed the potential across the membrane. This was therefore not just a loss of the resting potential but rather an active process of ion-exchange.

Alan Hodgkin had worked on radar during WWII. Andrew Huxley came from a very famous family – he was the grandson of Thomas Huxley, the tenacious supporter of Darwin (Darwin's bulldog), and the half-brother of Aldous Huxley who wrote *Brave New World*.



Now we turn to the special ion channels in the neuron's membrane – these are responsible for the ion exchange when the membrane is excited.

In the resting state the membrane is negative on the inside.

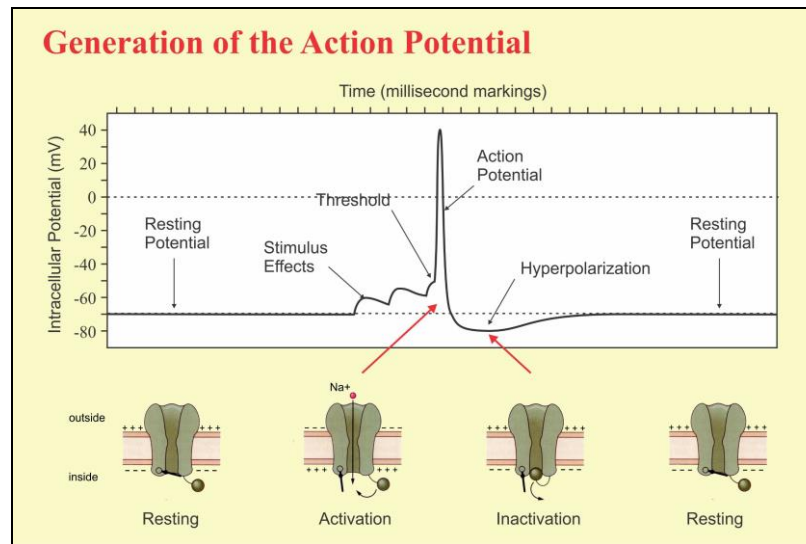
When the neuron is excited the sodium channel opens. Excitation can occur mechanically or by imposing an electric current on the membrane to bring it to a "threshold" level. The electrical current probably causes various charged area of the channel to move.

As the channel opens positive sodium ions pour into the cell – like flushing a toilet.

This changes the polarization of the membrane – now it is positive on the inside.

Just like when you flush the toilet, a ball and chain mechanism stops the flow of ions.

While the channel is closed, the adjacent pumps slowly transfer out the excess sodium ions and the membrane returns to normal.



If we make electrical measurements during the excitation process this is what we record. We are recording from inside the cell. At rest this is negative relative to the outside.

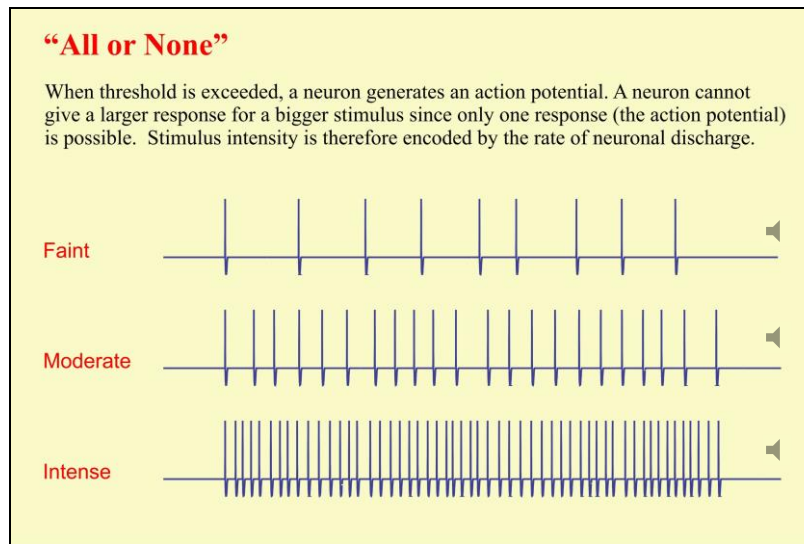
As the neuron is stimulated, it reaches a threshold level. The channel then reconfigures itself to let sodium ions pour into the cell. The membrane potential goes away – depolarization. It even briefly becomes positive on the inside.

Inactivation occurs and the neuron is no longer permeable to sodium ions. The pumps remove all the excess sodium that entered the cell and then some – causing the membrane to become briefly even more negative on the inside – hyperpolarized.

The hyperpolarization lasts for several milliseconds. Because it requires a greater stimulus to overcome the hyperpolarization, it is difficult for the neuron to fire more rapidly than several hundred times a second,

I have just shown the changes that occur in the voltage-dependent sodium channel when an action potential is generated. The actual changes in the membrane during the action potential are more complex. Other ion channels are also affected. Each changes according to slightly different time course.

Life is always more complicated than teacher lets on 😊



The action potential either occurs or it does not – it is “all or none.” This characteristic of the neuronal response was discovered by Edgar Adrian just before the first World War. Adrian shared the Nobel Prize with Sherrington in 1932.

The neuron therefore cannot give a bigger action potential for a bigger stimulus.

The only way to indicate that a stimulus is more intense is for the neuron to fire more rapidly:

10/s 25/s 65/s

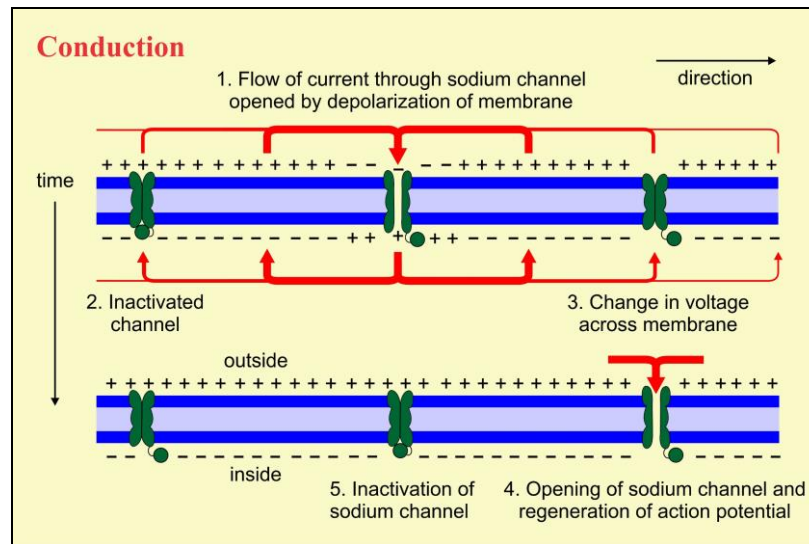
What happens is that an intense stimulus causes sufficient ongoing depolarization to overcome the hyperpolarization that follows an action potential.

Neurophysiologists often listen to their recordings – that way they can quickly hear how rapidly the neuron is responding.

Note that all neurons behave this way. A neuron coming from the eye will generate a series of action potentials when stimulated by light. The brighter the light the faster the rate of discharge. A neuron coming from the ear will have the same kinds of discharges. The louder the sound the faster the discharges.

The central nervous system knows what type of stimulus it is from where it is coming from – the “labelled line.” This was related to the “doctrine of specific nerve energies” originally formulated by Johannes Müller. He had thought that each perceptual system used a specific type of energy. The new understanding was that the nature of perception is defined by the pathway over which the sensory information is carried. The information was always carried in the same electrical way. )

The brain knows how intense the stimulus is by the frequency of discharge – “rate coding.”



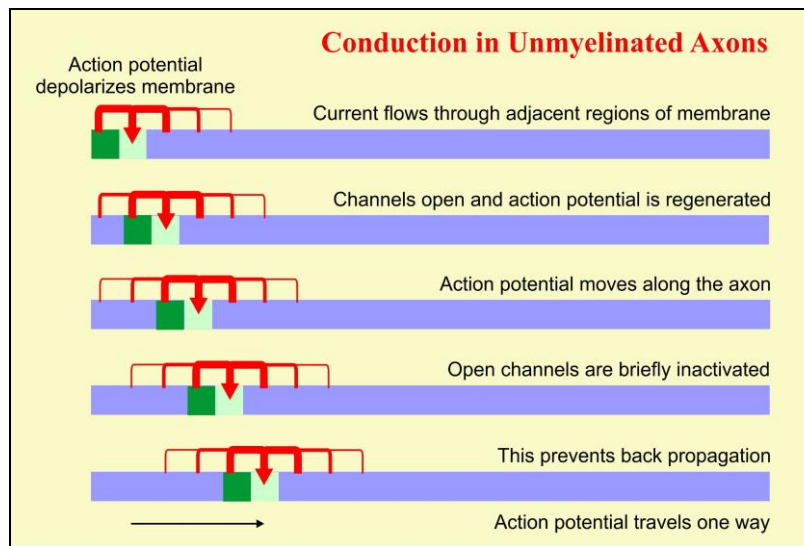
Polarization, excitation, conduction.

This slide demonstrates the conduction of the action potential from one region of the axon to the next. In this diagram the AP is being conducted from left to right.

Each of the two diagrams shows only one wall of the axon. The outside of the cell is above the lipid bilayer and the inside below. The upper diagram occurs earlier in time.

1. When the sodium channels are opened, sodium ions flow into the cell. This sets up currents within and outside the neuron.
2. These currents have no effect on the channels where the action potential is coming from (left side) since they are inactivated.
3. Further ahead on the axon, however, the flow of current causes a sufficient change in membrane potential to reach threshold.
4. The next channel opens and the action potential regenerates.
5. The originally open sodium channel is now inactivated, preventing any backward conduction. Normally the action potential goes only one way.





This slide shows the conduction of the action potential along an unmyelinated axon. For simplicity, only the extracellular currents are indicated.

The flow of current depolarizes (light green) a region further along the axon.

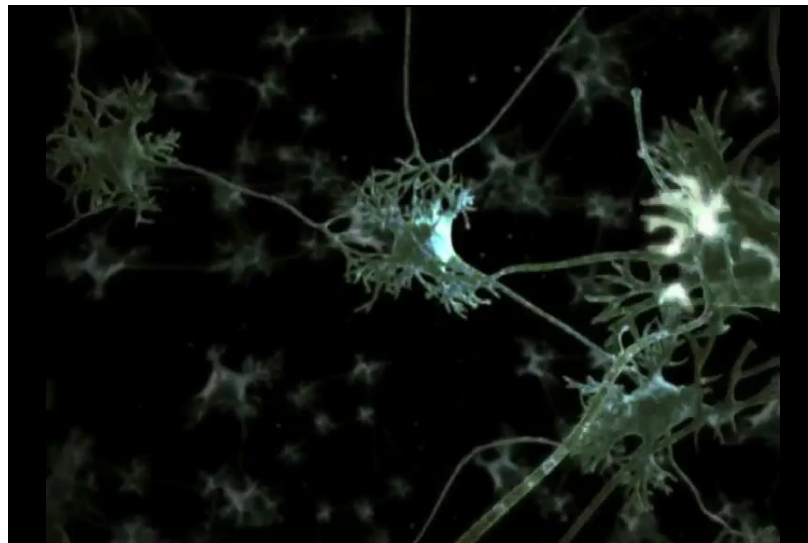
The channels behind the action potential cannot react because they are inactivated (dark green).

However, the channels ahead of (to the right of) the action potential are opened by the currents.

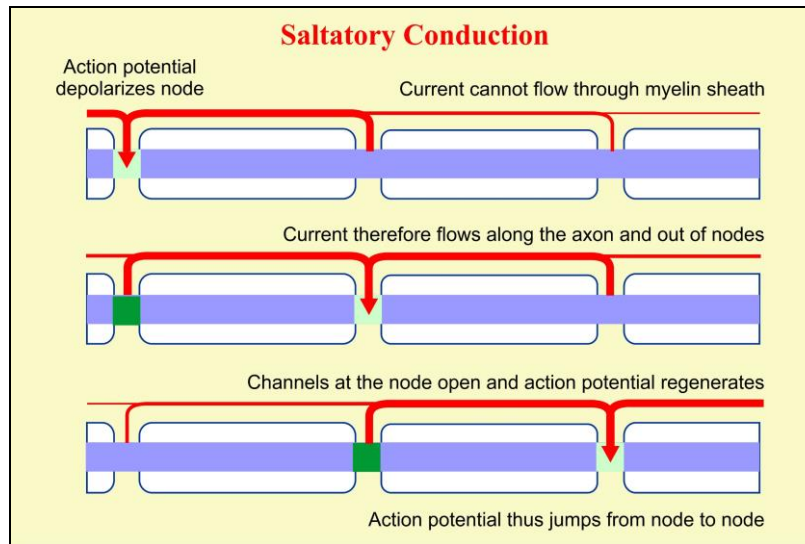
This regenerates the action potential. The action potential thus moves along the axon (toward the right). Back propagation is prevented by the inactivation of previously active channels.

Conduction velocity in thin unmyelinated fibers is very slow – typically 1 or 2 m/s (~5 km/hr)

The conduction velocity can be increased if the diameter of the axon is increased. This allows the intracellular currents to travel much further down the axon before crossing the membrane and returning. The squid giant axon is about 0.5 mm in diameter and can conduct at 25 m/s.



This animation showing the conduction of the nerve impulse is from *The Human Brain Book* by Carter. It is also provided on the Human Brain webpage



It is important to have rapid conduction velocities but it is not feasible to have many axons all as large as the squid giant axon. There are hundreds of axons coming from the hands – if they were all 0.5 mm wide we would have peripheral nerves that were larger in diameter than the arm!

A myelin sheath serves the same purpose as making the axon larger. Since the intracellular current is prevented by the sheath from exiting across the membrane, the intracellular current extends down to the next node of Ranvier.

This makes the action potential jump from one node to the next – “saltatory” conduction. The conduction velocities of myelinated fibers can reach 120 m/s. (450 kph – faster than a falcon in flight.)

## Multiple Sclerosis

### Presentation:

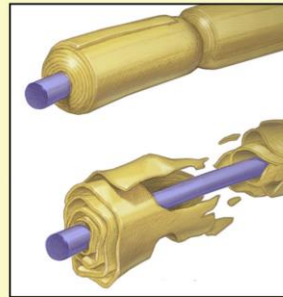
weakness or numbness on one side or in legs and not the arms  
 painful loss of vision in one eye  
 rapid movements of the eye (nystagmus)  
 double vision (diplopia)  
 electric-shock sensations with neck movement  
 tremor  
 fatigue

### Course:

remissions and relapses are common

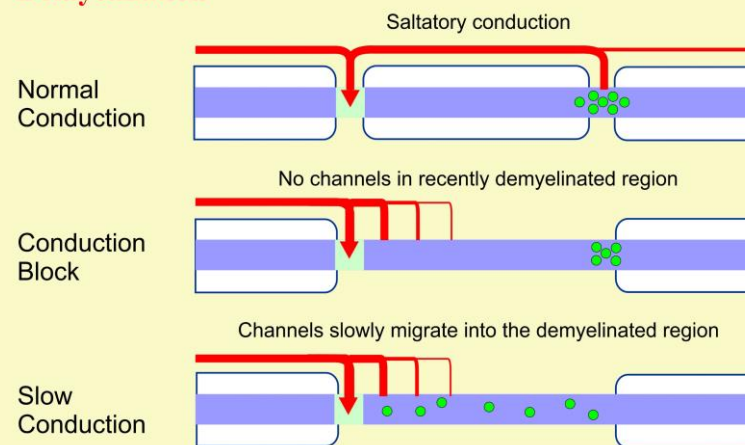
### Cause:

breakdown of the myelin sheath around nerve fibers, probably mediated by an auto-immune process



Multiple sclerosis is a disease that affects the myelin sheath. What causes the disease is not yet known, but the effect is a breakdown of the myelin within the central nervous system. The symptoms and signs of multiple sclerosis vary with the regions of the brain that are affected. The disease often goes through periods of remission and relapse.

## Demyelination



This shows the effects of demyelination on nerve conduction.

In the normal myelinated fiber the sodium channels are concentrated at the nodes of Ranvier.

When the nerve is demyelinated, initially the axon cannot conduct because there are no channels in the demyelinated region of the axon.

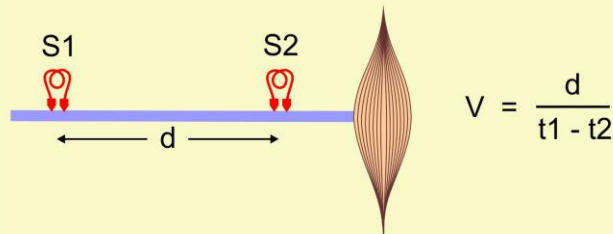
Slowly the channels migrate into the demyelinated region and then the nerve fiber can conduct, but only slowly.

Function returns, but there are still some problems because of the slowness of conduction.

For example when multiple sclerosis affects the optic nerve – optic neuritis – vision is initially lost, but after a couple of weeks the vision returns, but color vision remains disordered.

### Nerve Conduction Velocity

Prior to 1850, scientists had assumed that nerves acted instantaneously. Hermann von Helmholtz showed that nerves impulses had a finite velocity. He stimulated a frog nerve at two different locations and measured the times of the muscle response. He found a velocity of about 35 m/s (126 km/hr). Later studies showed velocities of 5-120 m/s for myelinated nerves and 0.5-2 m/s for unmyelinated nerves.



How can we measure the speed of the nerve fibers?

This slide gives the only mathematical formula in the course. Those of you who hate mathematics can doze off for a minute or two ☺

You stimulate the nerve at one location (S1) and record the time of the response (t1).

You then stimulate the nerve at a location closer to the muscle (S2) and record the time of its response (t2).

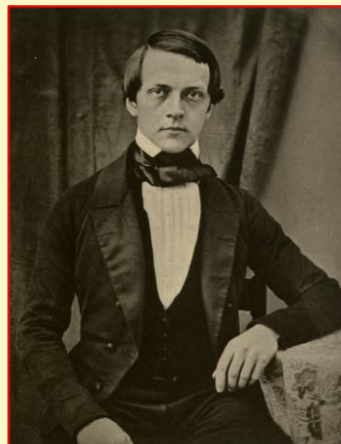
The velocity is then the distance between the two locations (d) divided by the difference in the times.

The fastest human nerve fibers conduct at speeds of over 400 km/hr. Faster than the fastest Ferrari.

### Human Reaction Times

Using a similar technique to that for studying the velocity of the nerve impulse in frogs, Helmholtz measured the reaction times to touching the skin at the foot and at the thigh, or at the fingers and at the shoulder. He calculated the human sensory nerve conduction velocity at 60 m/s.

Helmholtz also estimated how long it took for the brain to perceive the stimulus and enact a response. If the subject was highly attentive, this took about 100 ms.



Hermann von Helmholtz, 1848

We can use a similar approach to measure the speed of thought.

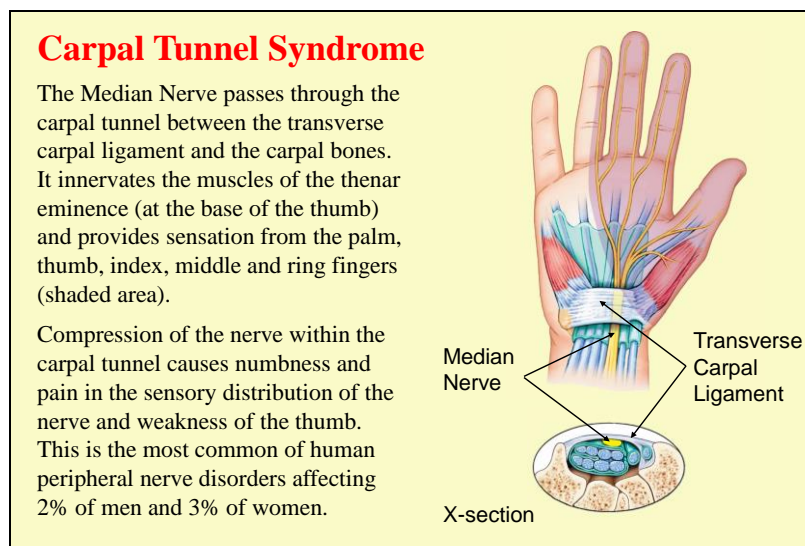
The fastest time to press a button following a stimulus is about 160 ms (if you are young and very fast ☺):

30 ms to reach the brain,  
100 ms for perceiving the stimulus and initiating the response,  
30 ms to go out to the muscles.

The normal average for an adolescent is about 210 ms  
By the age of 70 years we have slowed to about 250 ms. We lose just under a millisecond a year.

You can try yourself:

<http://www.humanbenchmark.com/tests/reactiontime>

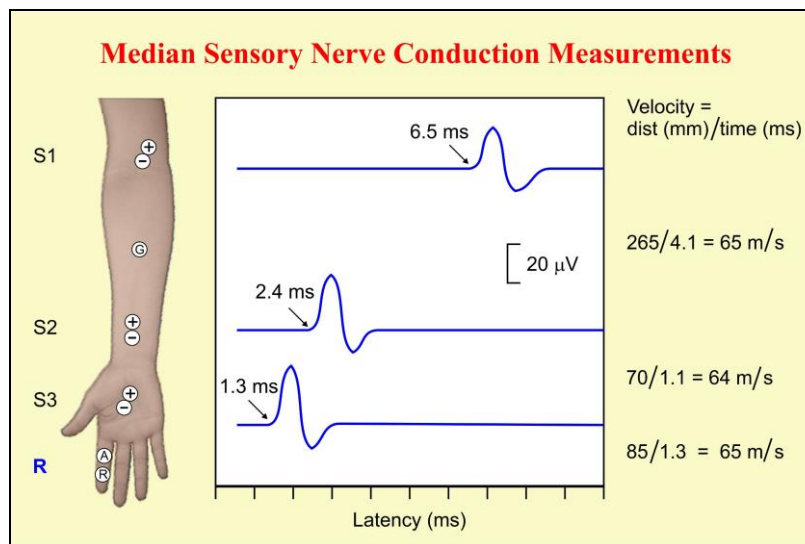


Carpal tunnel syndrome is the most common disorder of the peripheral nerves.

One way to test for carpal tunnel syndrome is to measure nerve conduction velocities. The motor nerve conduction is calculated by stimulating the nerve and measuring the time to activate the thenar muscles in the same way as Helmholtz. The main measurement is then the latency from the wrist to the muscle which should normally be less than 4 ms. In carpal tunnel syndrome the velocity in the arm is normal and the distal latency prolonged.



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Sensory nerve conduction velocities can be measured at the same time. We record the response from the nerves on the index finger.

Note that in this way of testing the sensory nerve fibers are conducting impulses in the opposite direction to normal - antidromic rather than orthodromic.

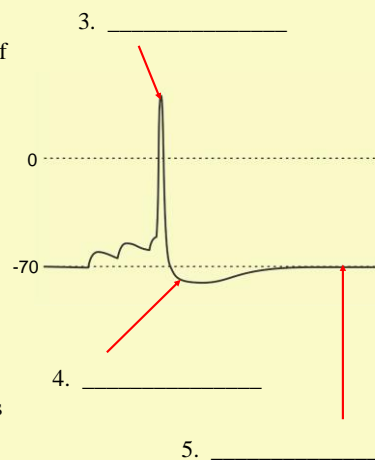
### Quiz 2B

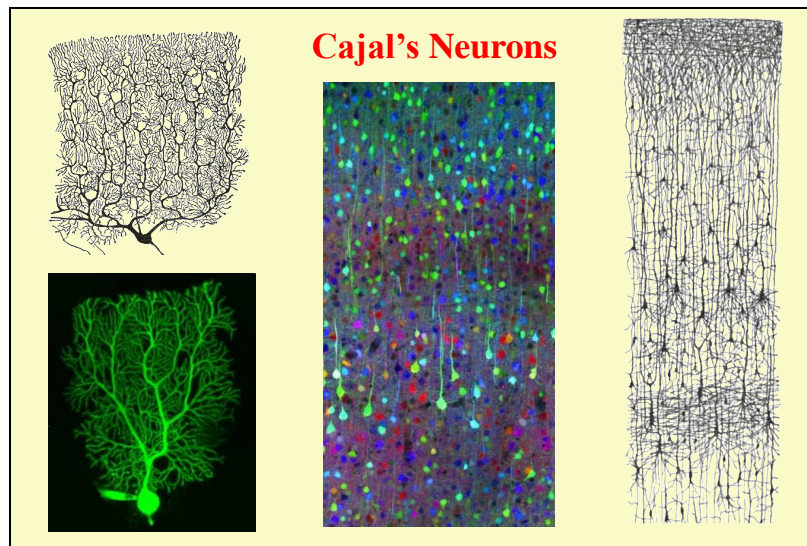
1. Compared to the outside, the inside of a resting neuron

- A) is positive
- B) has a higher concentration of potassium ions
- C) has a higher concentration of sodium ions
- D) contains fewer enzymes

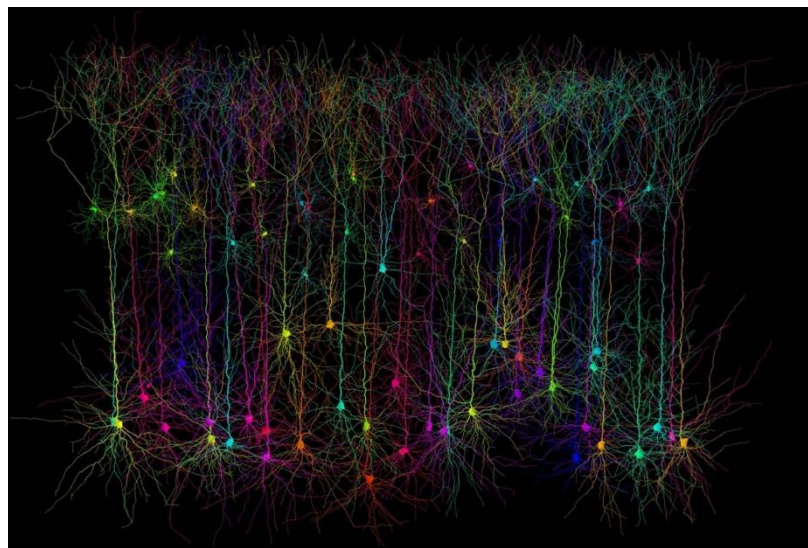
2. Unmyelinated nerve fibers

- A) conduct impulses more slowly than myelinated fibers.
- B) are only present in peripheral nerves
- C) cannot regenerate their axons
- D) are primarily affected in multiple sclerosis





This slide shows some modern pictures of the neurons described by Cajal. The Purkinje neuron has been injected with a fluorescent dye. The pyramidal cells have been stained with a special technique called “Brainbow,” which makes different neurons have different colors.



This is an artist's impression of a Brainbow-stained set of pyramidal neurons. Cajal in color!