Synapses and Neural Networks

…we are led to think that the tip of a twig of the [axon's] arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a connection of one nerve cell with another might be called a *synapsis*.

Charles Scott Sherrington in Michael Foster's *Textbook of Physiology* (1897)

Graham Johnson, 2005

The essence of the human brain is in its synapses.

The word "synapse" was first used by Charles Sherrington in a chapter in Foster's *Textbook of Physiology*. The synapse is the place where one neuron makes contact with another. The etymology combines "haptein, come in contact, touch" with "syn, together."

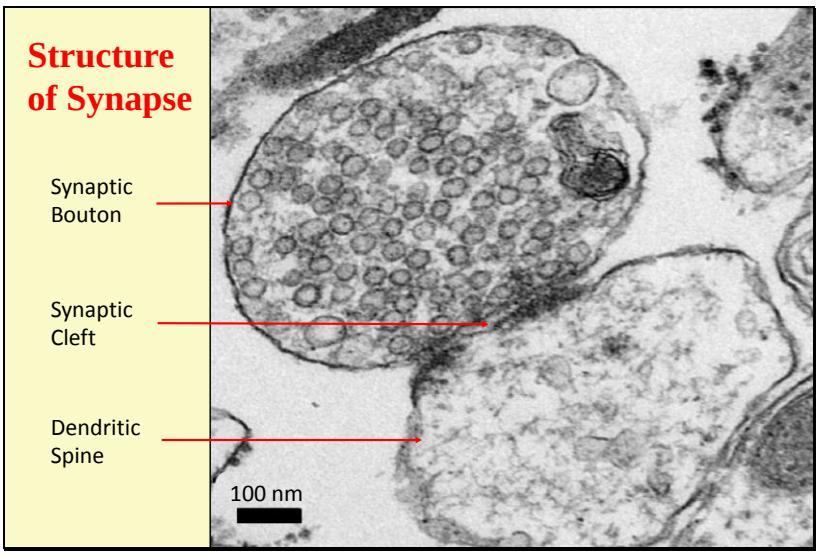
Sherrington and Foster had initially considered "syndesm" (bond), but they discussed possible names with a Greek scholar at Cambridge, A. W. Verall, a translator of Euripides. Verrall preferred "synapse" (contact). This fits with the neuron theory which requires that neurons be separate from each other though in contact.

Although proposed in 1897, the synapse was not clearly understood until the early 1950s when neurophysiology showed that the synapses functioned chemically and electron microscopy showed the anatomical structure of the synapse.

There are over 10 trillion synapses in the human brain.
The pattern of their activity encodes the soul.

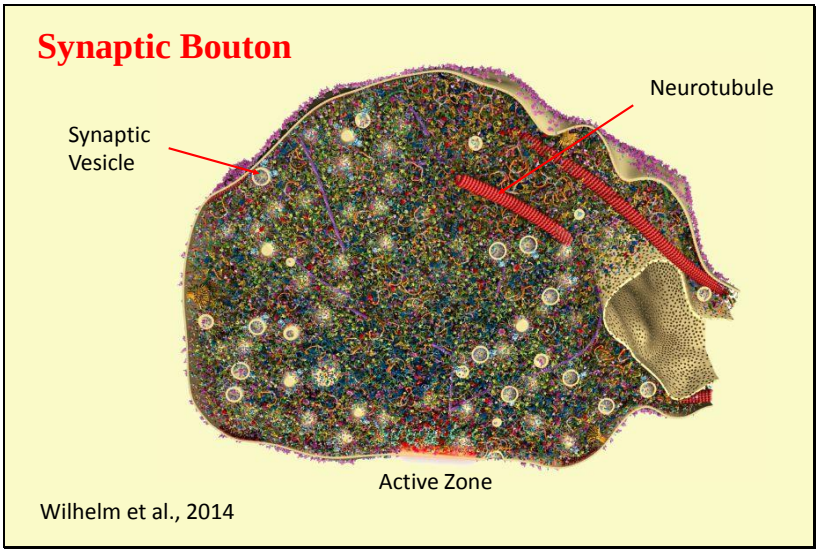
Last week we talked about the neuron, how it maintained a resting membrane potential (polarization), how an action potential could be triggered if this potential reached a threshold level (excitation) and how this action potential could travel along the axon (conduction).

Today we shall consider what happens when it reaches the axon terminals and transfers information to another neuron across a synapse (transmission).

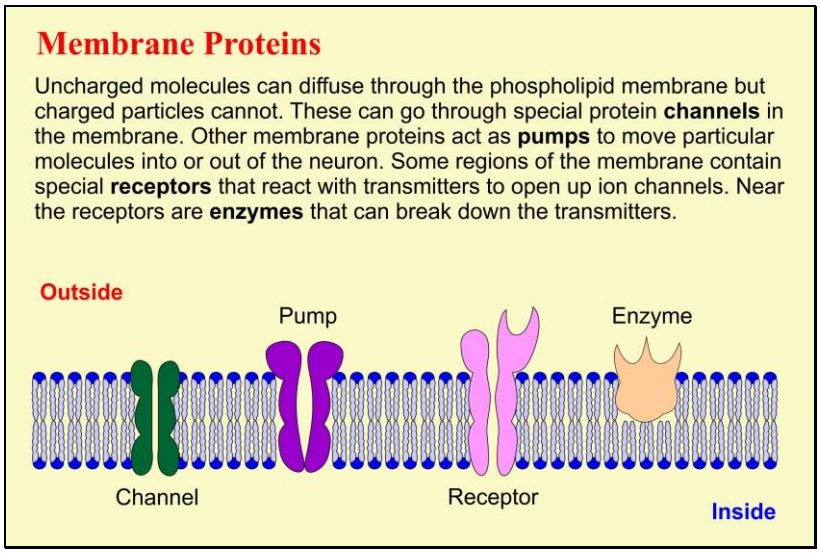


The synapse was not fully visualized until the electron microscope. Using light microscopy anatomists could see structures that suggested the locations where contact occurred – dendritic spines and synaptic boutons, for example. However, Golgi stains seldom showed both of the two neurons involved in a synapse and, when they did, it was difficult to see the synapse clearly.

This electron-microscope slide shows an axonal terminal (synaptic bouton) synapsing on a dendritic spine. Within the bouton are multiple synaptic vesicles containing neurotransmitter and some mitochondria to provide the energy for synaptic function.
Between the axonal terminal and the spine there is a small space – the synaptic cleft.
The postsynaptic membrane is fuzzy – it contains special receptors and enzymes to respond to the neurotransmitter released at the presynaptic membrane.



The preceding illustration is from a recent study analyzing all the different chemical constituents of the synaptic bouton. Each color represents a different protein.
Most striking are the neurotubules which transport material to the axonal terminal and the synaptic vesicles which contain the neurotransmitter.
Among the proteins in the cytoplasm are enzymes for the metabolism of the neurotransmitter.
Special proteins attached to the membrane adjacent to the post synaptic neuron – the active zone – open the vesicles to release the transmitter into the synaptic cleft.
Other proteins in the membrane form channels for calcium ions. Others act us transporters to bring the transmitter back into the presynaptic bouton for reabsorption into the vesicles.

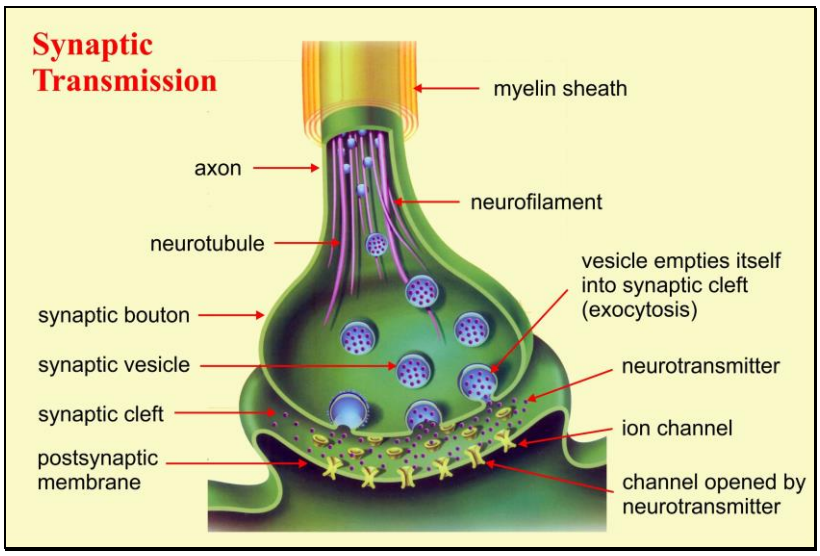


This slide is from last week's lecture. Then we were then concerned with the polarization, excitation and conduction of the neuron's membrane. Important to these processes were the sodium pump which was essential to maintaining the resting membrane potential, and the voltage-sensitive sodium channel which was transiently opened when the membrane was excited and the action-potential generated.

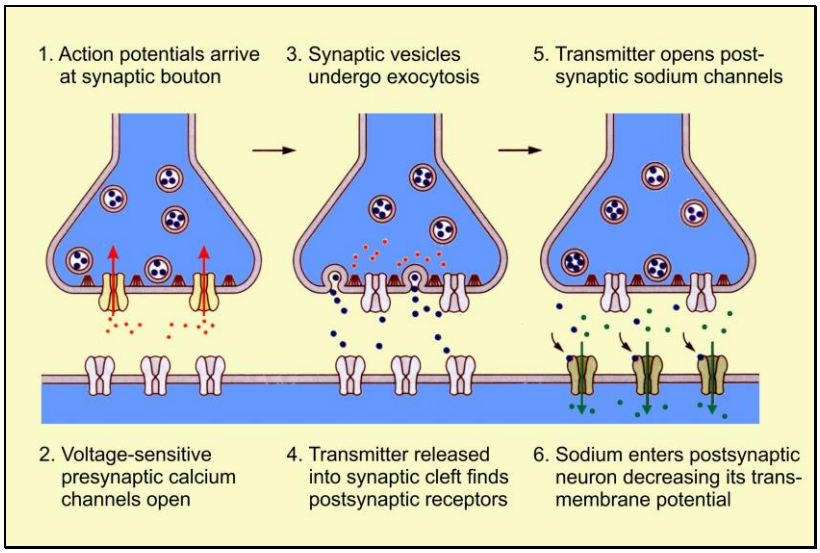
The function of the synapse is transmission. This requires some additional membrane proteins.

In the presynaptic membrane there are special calcium channels. These let calcium into the presynaptic bouton and the calcium initiates the release of the transmitter from the presynaptic vesicles.

In the postsynaptic membrane there are receptor protein (or ligand-gated ion channels). These receptors interact with the neurotransmitter released from the presynaptic membrane.
The neurotransmitter may be broken down by special enzymes in the membrane.
Or it may be taken back up into the synaptic bouton by a special pump or "transporter."



This illustration shows the release of neurotransmitter at the synapse.
When an action potential reaches the synaptic bouton, neurotransmitter is released from the vesicles into the synaptic cleft.
The transmitter attaches itself to a special protein in the postsynaptic membrane: the ligand-gated ion channel. This opens to allow ions to enter into the postsynaptic neuron, thereby changing its membrane potential.
Information has been transmitted from one neuron to another

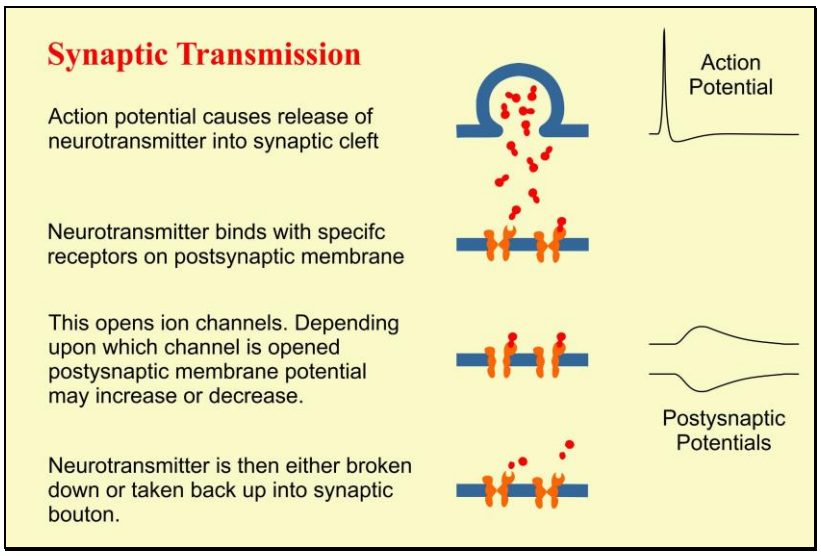


This slide shows the sequence of events during synaptic transmission. This particular example shows an excitatory synapse. If sufficient channels are opened the postsynaptic membrane may reach threshold and an action potential would then be generated. If a different type of ion channel were activated by the neurotransmitter, the post-synaptic membrane potential could be increased, making it more difficult to activate the postsynaptic neuron – an inhibitory synapse.

This animation shows what happens when an action potential reaches the synaptic bouton. At this synapse the transmitter is acetylcholine (a two-part molecule) and the ligand-gated ion-channel is for sodium.

The video is available at
https://www.youtube.com/watch?v=CltFCbbi0Vw

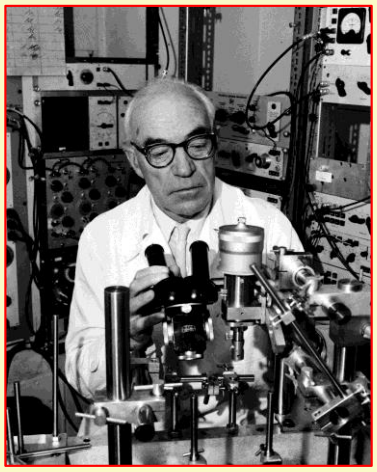
This movie showing the synapse is from Carter *The Human Brain Book*



This diagram summarizes the steps involved in synaptic transmission.

Note that the effect on the post-synaptic membrane may be either to increase or decrease the membrane potential
This depends upon which ion channels are opened by the transmitter.
The synapse may therefore be either excitatory or inhibitory.

The effect of the transmitter is brief – usually lasting between several milliseconds and several tens of milliseconds. The transmitter is either broken down by enzymes or re-absorbed into the presynaptic bouton by special “re-uptake” transporters.

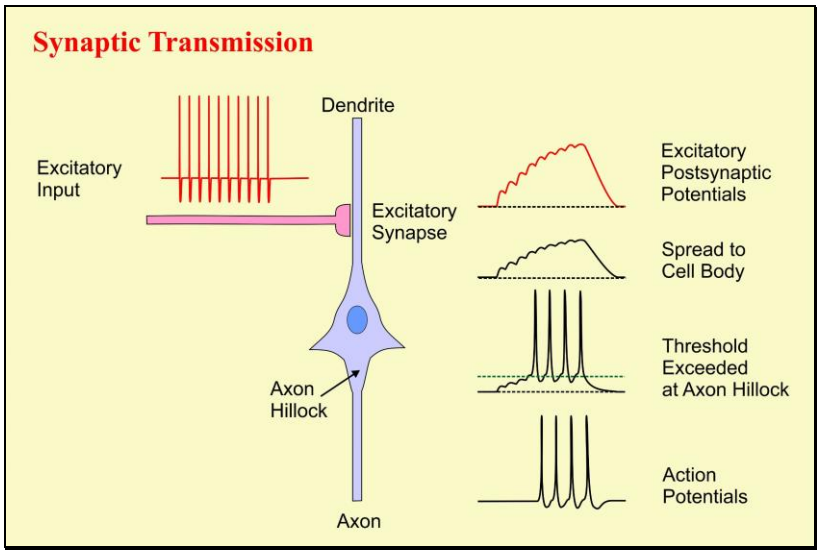


John Eccles (1903-1997)

John Eccles was born in Australia. Though trained in medicine he became more interested in basic neurophysiology. He was awarded a Rhodes scholarship to study with C. S. Sherrington at Oxford. Though he initially thought that the synapse was electrical, his experiments showed that is was chemical. He was the first to record excitatory and inhibitory post synaptic potentials. He shared the Nobel Prize with Hodgkin and Huxley in 1963. In his later life he wrote extensively about the relations between brain and mind.

John Eccles was the scientist who first clearly demonstrated the neurophysiology of synapses. He initially thought that synapses functioned by direct electrical transmission from one cell to another. However, his experiments showed otherwise.

He was active in the Pontifical Academy of Sciences, and organized for them a symposium on the *Brain and Conscious Experience* (1966). A later influential book was *The Self and Its Brain* (1977) with Karl Popper. Philosophy comes easily tothsoe who study the brain.



This shows what happens electrically at a simple excitatory synapse on the dendrite of a pyramidal neuron in the cerebral cortex.

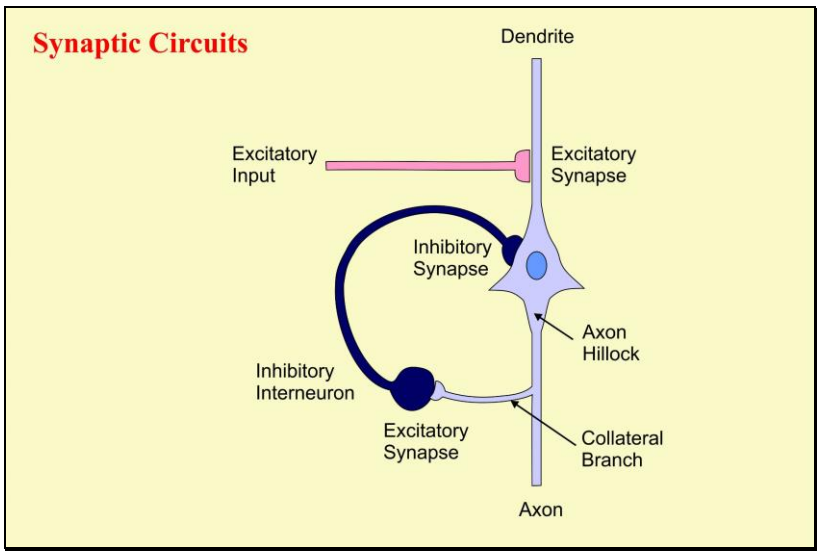
Each arriving action potential releases transmitter from the synaptic bouton.
Multiple transmitter-releases cause a summating excitatory postsynaptic potential.

This spreads to the cell body and then to the axon hillock. There is some decrease in the potentials with the spread.

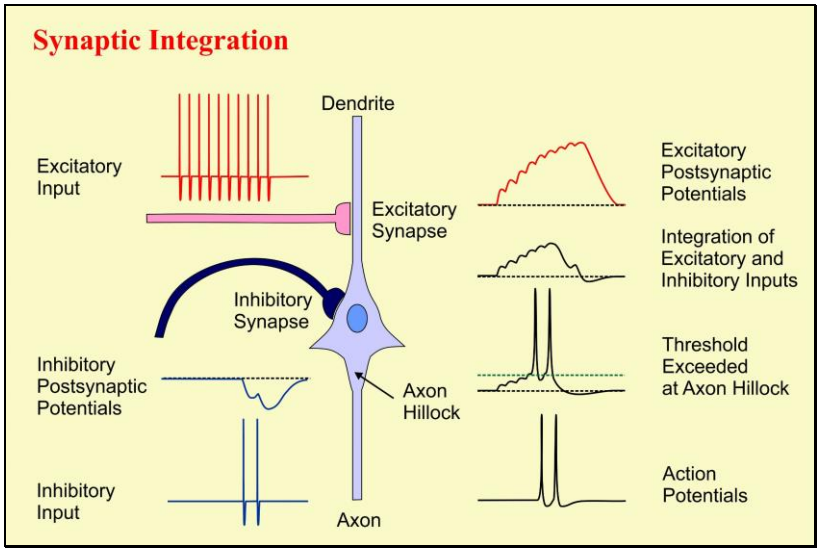
The axon hillock contains voltage-dependent sodium channels and if the membrane potential there reaches threshold it generates action potentials.

These action potentials are conducted down the axon.

Thus there is a simple transmission of excitation from input to output.

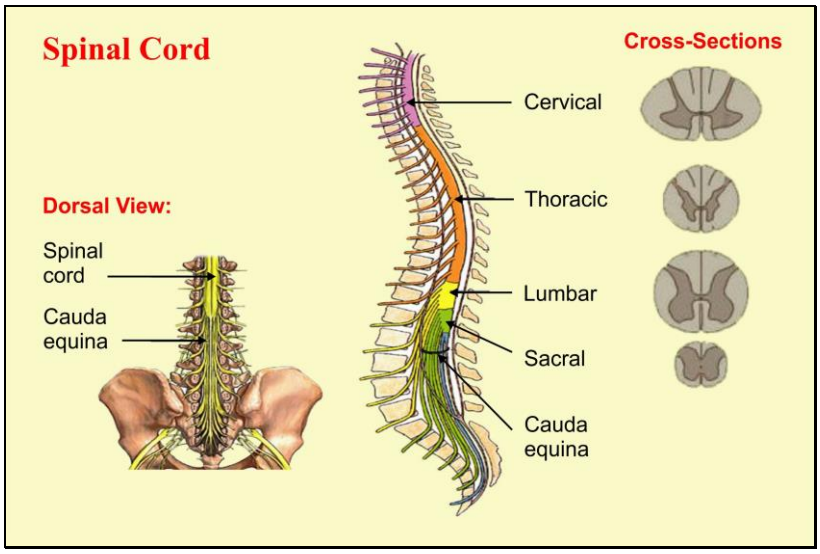


The cortex contains multiple synapses. Some are excitatory; some are inhibitory.
An inhibitory transmitter causes the postsynaptic membrane to become more negative. It does this by opening different ion channels from those opened by the excitatory synapse. For example it may open potassium or chloride channels rather than the sodium channels opened by excitatory transmitters. A more negative potential makes it harder for the neuron to be brought to threshold for excitation.
In this illustration, a collateral branch of the axon leading away from the pyramidal cell excites an inhibitory interneuron that feeds back onto the pyramidal neuron.



This illustration shows what can be recorded in such a synaptic circuit.
Excitation of the dendrite causes action potentials at the axon hillock.
Axon collaterals then activate inter-neurons that connect back to the pyramidal neuron.
The interneuron causes inhibition at the cell body. This is delayed by the time taken to activate the interneuron and for it to release its inhibitory transmitter.

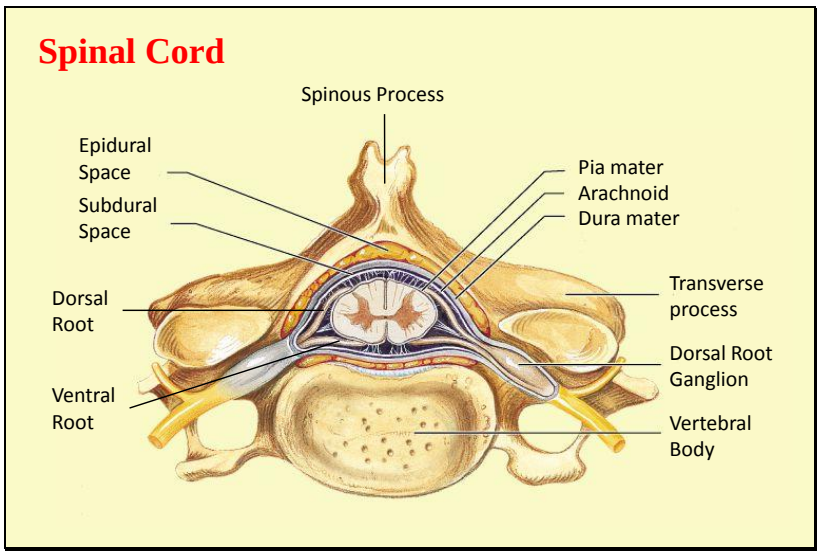
The result is a cortical cell that responds to the onset of a stimulus but not to its continuation. The neuron thus integrates all of its inputs – both excitatory and inhibitory in order to "decide" whether to respond of not.



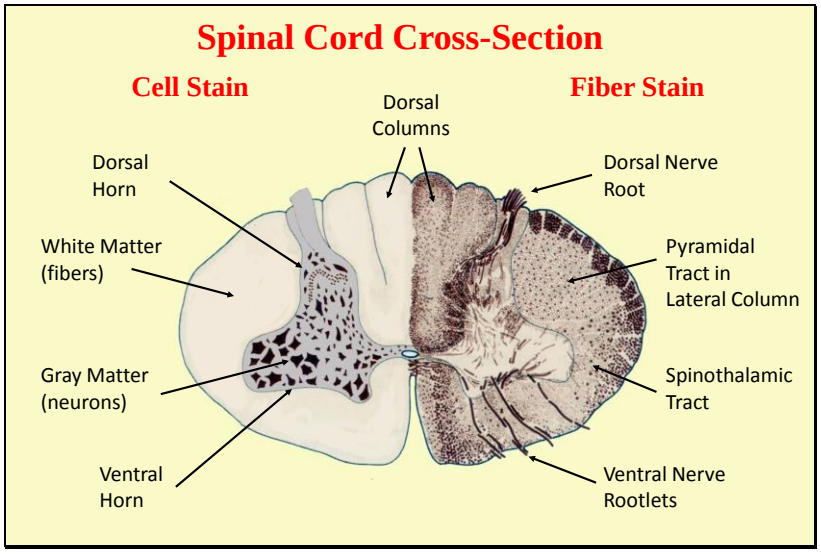
To understand how synapses function in the nervous system, we can start with the spinal cord. This descends within the vertebral canal from the foramen magnum at the base of the skull to the mid-lumbar region.

The spinal cord is enlarged in the neck and lumbar regions because of all the extra neurons required to innervate the arms and the legs.

From the lowest point of the spinal cord (at the midlumbar region) the nerve roots for the lumbar and sacral nerves extend down in a large bundle called the horse's tail – cauda equina.



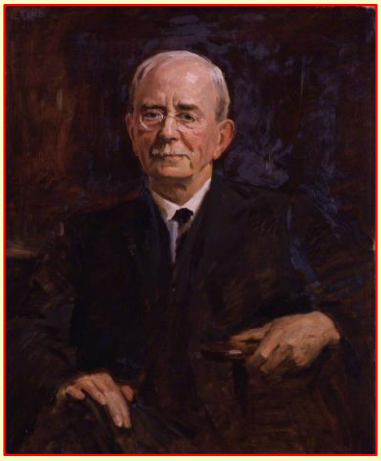
This cross section shows the spinal cord within the vertebral canal in the neck.
The spinal cord has the same coverings as the brain – pia mater, arachnoid and dura mater. The space between the bone and the dura is where anesthetists inject for epidural anesthesia.
On each side of the cord are two spinal nerve roots: the dorsal nerve root carries sensory information into the cord and the ventral nerve root carries motor instructions out to the muscles.
The cell bodies of the dorsal nerve root are in the dorsal root ganglion. This is located where the nerve root exits the spinal canal.
The cell bodies of the ventral nerve root are in the grey matter of the spinal cord.



This slide illustrates the contents of the spinal cord.
The cell bodies of the neurons are located in gray matter. The nerve fibers are in the white matter. The white matter is white because of the myelin sheaths around the fibers.

The gray matter is divided into the dorsal horn which has neurons receiving connections from the incoming sensory fibers, and the ventral horn which contains the motor neurons that innervate the muscles.
The fibers in the spinal cord go up and down the cord in "columns"
The main connections are the

dorsal columns which carry fine touch sensation up to the brain.
pyramidal tracts which carry motor instructions down to the motor neurons in the ventral horn
lateral spinothalamic tract which carries pain and temperature sensation up to the brain.

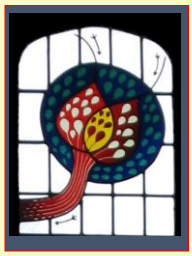


Charles Scott Sherrington (1857-1952)
Portrait by Reginald Eves, 1927

Charles Scott Sherrington

Sherrington studied the spinal reflexes of the decerebrate cat. He postulated an integration of sensory information at "synapses" in the spinal cord. He shared the Nobel Prize with Edgar Adrian in 1932.

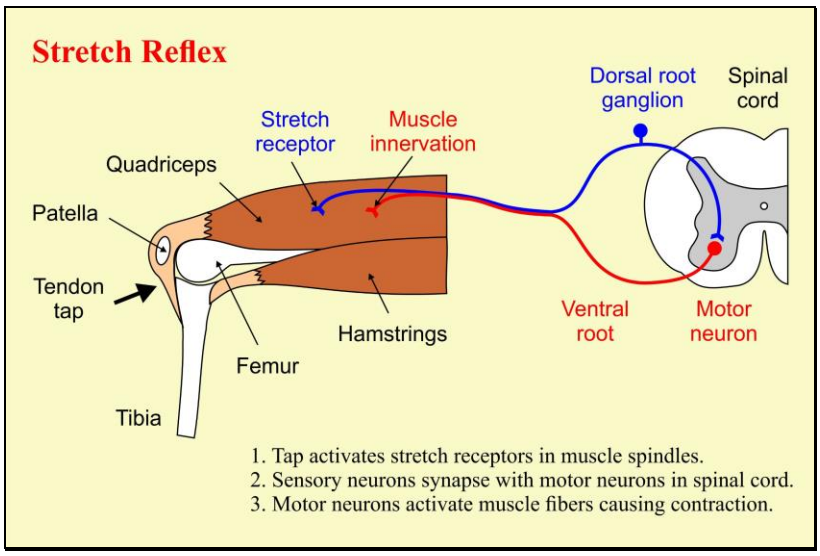
Stained-glass memorial window in Cambridge showing synaptic integration.



Sherrington was a neurophysiologist who studied synaptic function. Perhaps my only true claim to fame is that I attended the same school as he did, but only briefly.

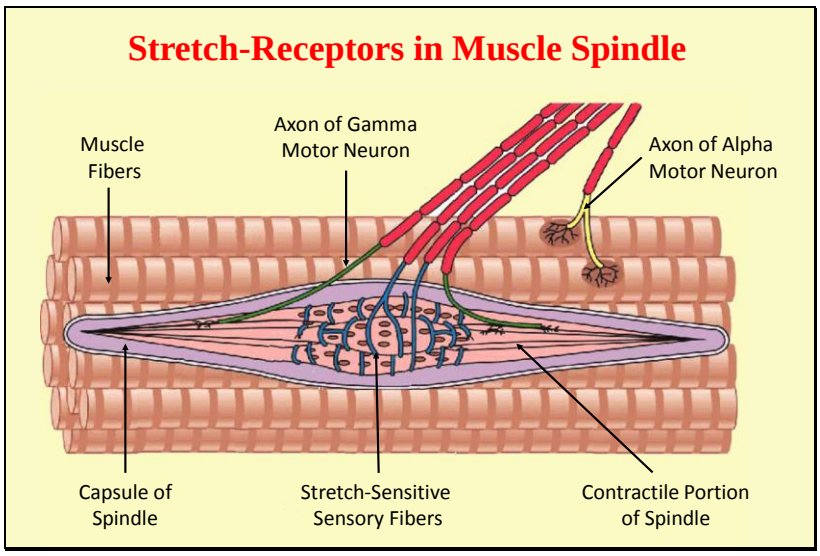
Edgar Adrian, with whom Sherrington shared the Nobel Prize in 1932, was the scientist who described the "all-or-none" law of neuronal responses that we discussed last week.

Sherrington proposed that synapses allowed information to be integrated from different sources. The stained glass window in Cambridge is based on one of his diagrams, showing two sources of input being integrated before leading to output in the neurons leaving inthe ventral root of the spinal canal. Each input excites motor neurons. Combining both inputs does not give the sum of the individual responses, because the inputs overlap on some neurons – "occlusion." Although immortalized in stained glass, occlusion is not much studied now.

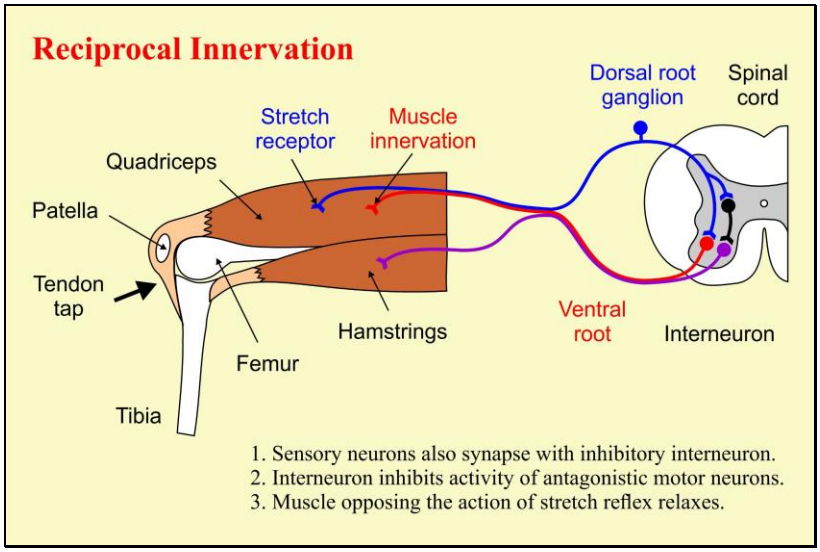


The patellar reflex (knee jerk) is a simple reflex involving only one synapse in the spinal cord.
Tapping the tendon briefly lengthens the muscle. This stretching is detected by special sensory fibers in the muscle (blue).
The stretch information is conducted to the spinal cord via the dorsal nerve roots.
The sensory fibers synapse with the motor neurons (red) which have their cell bodies in the ventral horn of the gray matter in the spinal cord.
The motor neurons send out impulses which activate the quadriceps muscle and cause it to contract – making the lower leg (tibia) swing forward.

The stretch reflex can become hyperactive following a lesion to the brain or spinal cord.
This patient has a hyperactive reflex on his right and a normal reflex on his left.



The stretch receptors in a muscle are located in specialized muscle fibers called spindles.
The sensitivity of the receptor can be adjusted by contracting or releasing the muscle portion of the spindle. This is done through gamma (or beta) motor neurons.
Alpha motor neurons activate the actual muscle fibers that are responsible for contracting the muscle and moving the limb.

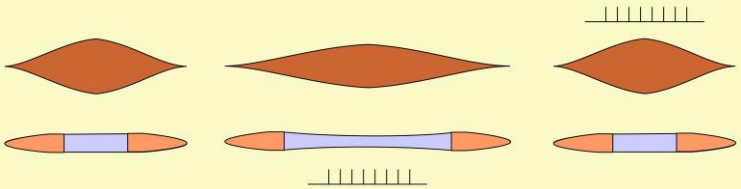


As well as evoking the monosynaptic reflex causing the quadriceps to contract, the stretch receptors also connect to inhibitory interneurons (black) which inhibit the motor neurons (purple) going to the hamstrings. This ensures that the hamstrings are relaxed while the quadriceps contract.

Function of Stretch Reflex

The stretch reflex maintains the length of a muscle:

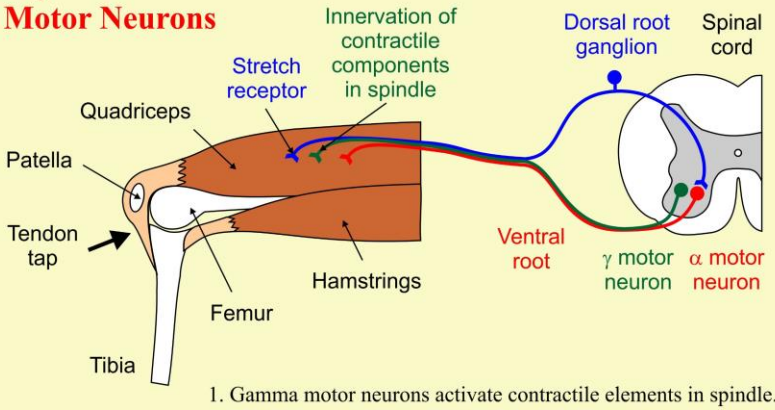
If the muscle lengthens, the stretch-receptor is activated. This reflexly activates the motor neurons and the muscle contracts, thus shortening the muscle back to what it was before.



Conversely, if the muscle shortens, the stretch receptor reduces its response and the reflex muscle-contraction decreases, thus allowing the muscle to lengthen.

The quadriceps stretch reflex can be used to maintain a standing posture. If the knee starts to bend the stretch reflex is activated and the quadriceps contracts, thus keeping the knee straight.

Alpha and Gamma Motor Neurons

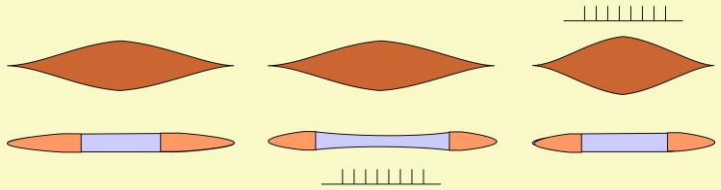


1. Gamma motor neurons activate contractile elements in spindle.
2. This increases the sensitivity of the spindle stretch-receptor.
3. Alpha motor neurons are reflexly activated by stretch reflex.

Alpha motor neurons activate the main muscle fibers.
Gamma motor neurons (green) activate the contractile parts of the spindle receptor.

Sensitivity of Stretch Reflex

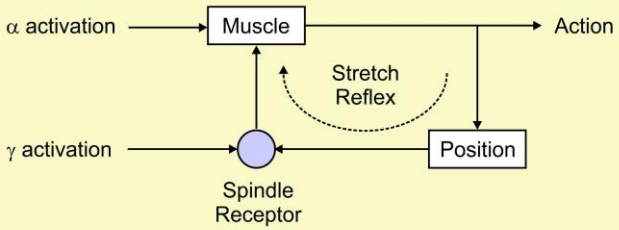
If the gamma motor neurons are activated, the contractile portions of the spindle receptor are shortened. This activates the stretch-receptor, reflexly activating the alpha motor neurons. The muscle contracts reducing its length.



Thus the gamma motor neurons can control the overall position of the joint that the muscle operates, and adjust the general background "tone" of the muscle. Specific movements are initiated by the alpha motor neurons.

The gamma motor system adjusts the sensitivity of the spindle. When the gamma neurons activate the contractile parts of the muscle spindle (orange) the sensory part of the spindle (gray) is stretched even though the muscle itself is not stretched. It is therefore a useful way to change the muscle tone or joint position.

Muscle Control



Most voluntary movements involve α and γ co-activation. The α activity controls the precise movements (particularly of the more distal muscles) whereas the γ activity sets the basic position of the limb.

In general the alpha motor neurons are used to perform precise and rapid motor acts, whereas the gamma system maintains the general position of a limb. Alpha is ballistic; gamma is tonic.

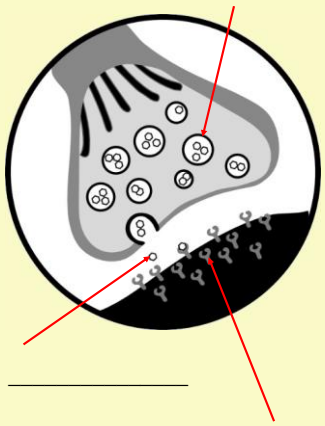
Quiz 3A

1. Neurotransmitters

A) are released from the postsynaptic neuron
B) are produced in the thyroid gland
C) generate action potentials
D) alter ion channels in the post-synaptic membrane

2. Postsynaptic potentials

A) can be excitatory or inhibitory
B) last for less than 1 millisecond
C) are larger than the resting membrane potential
D) occur in the brain's white matter

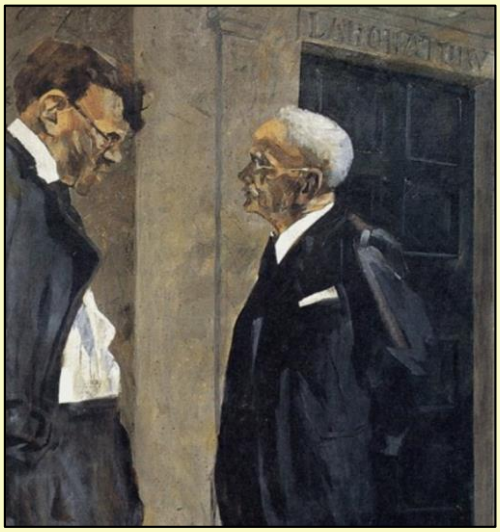


Teacher and Students

Charles Scott Sherrington (Nobel, 1932)

John Carew Eccles (Nobel, 1963)

Other students of Sherrington were Ragnar Granit (Nobel, 1967), Harvey Cushing, and Wilder Penfield

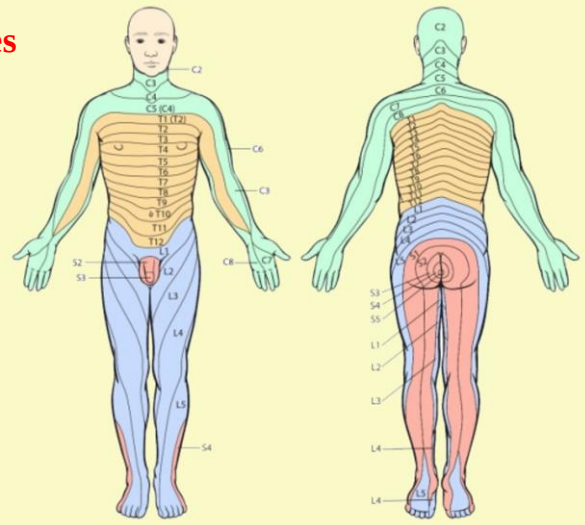


The genealogy of neurosciences has many "family trees." Eccles who demonstrated the function of synapses studied with Sherrington who first proposed the idea of the synapse.

If I were to trace my family tree, it goes back to Edgar Adrian – the man who gave us the "all or none" law. He trained Hallowell Davis who taught Robert Galambos who supervised my doctoral thesis.

Dermatomes

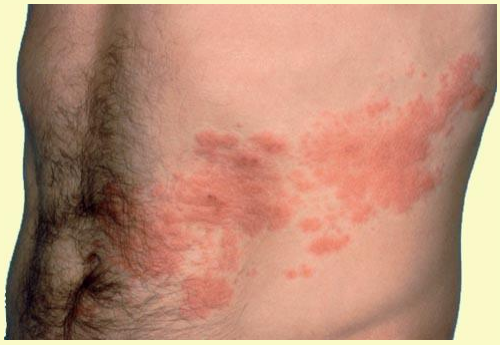
Each area of the skin below the head is innervated by a different spinal nerve root. Irritation of the nerve root causes pain that is perceived as coming from its dermatome.



As well as processing the muscle stretch reflexes, the dorsal nerve roots also provide sensation to the skin.
Cervical nerve roots (green) innervate the neck and arms.
The legs are innervated by the lumbar (blue) and sacral (pink) nerve roots.

Shingles (Herpes Zoster)

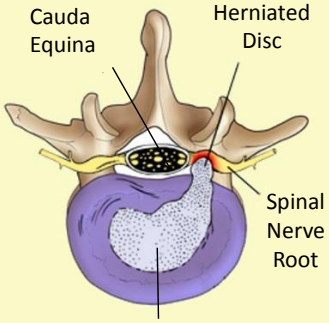
The virus of chicken pox can become dormant in the dorsal root ganglion. When reactivated it can move down the nerve root and cause a painful rash in the dermatome of that nerve root.



An attack of shingles can be treated with anti-viral medication. A vaccine can also be used to prevent the disease.

Herpes zoster is a painful rash in the distribution of one of the spinal nerve roots. Or in the distribution of the trigeminal nerve branches in the face.
It is a reactivation of the varicella (chicken pox) virus which has remained dormant since childhood.
Common antiviral agent is acyclovir. The vaccine is important for older people since it can either prevent the disorder or attenuate its manifestations.

Lumbar Disc Disease



Pain and numbness experienced in dermatome of the compressed nerve root. Weakness in muscles supplied by that nerve root.

An extrusion of the intervertebral disk can put pressure on a spinal nerve root causing pain and numbness in its sensory distribution and weakness in its motor distribution. This is "sciatica." The MRI shows a normal disk, one that is bulging and one that has herniated.

An L5 nerve root compression gives pain going down to the toes. An S1 nerve root compression gives pain going down to the heel.

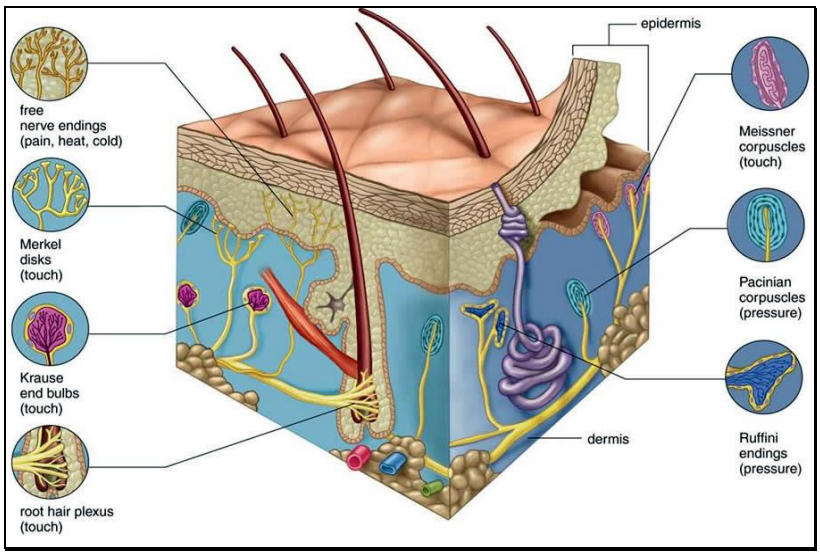
Sensations

Sherrington classified sensations as
- "exteroceptive" (concerned with the outside world)
- "proprioceptive" (concerned with the position of the body in space)
- "interoceptive" (concerned with internal organs)

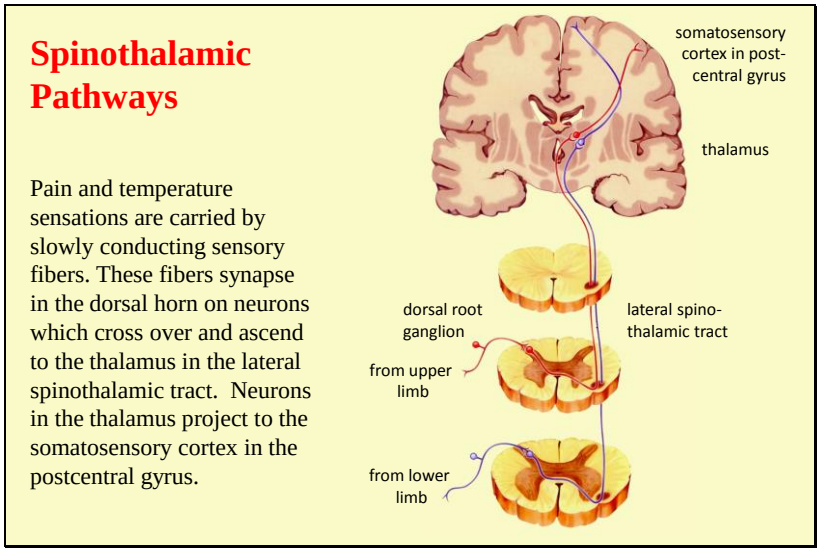
Though we are very accurate in the first two types of sensation, we are not generally conscious of our internal organs. They become perceptible when the neuronal activity is intense. The sensations are not well localized and are often painful.

Body sensations are mediated by two different pathways:
- spinothalamic (light touch, pain, temperature, internal organs)
- dorsal columns (fine spatial and temporal discriminations, position)

Exteroceptive sensations are visual, auditory and olfactory.
Somatosensory sensation is proprioceptive (joint-position sense), exteroceptive (actively touching or feeling objects) and interoceptive (e.g., gut sensations – these are not very precise and are often interpreted as painful)



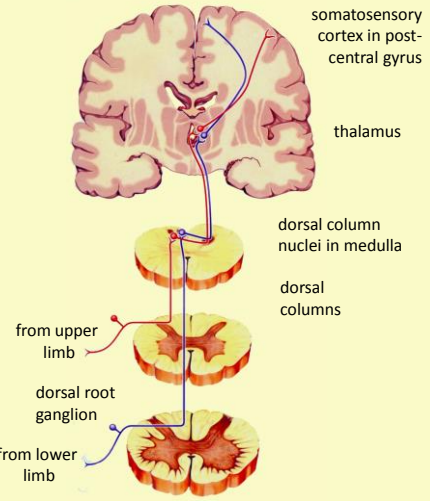
The skin is full of many different kinds of receptors, most named after the histologists who discovered them. The free nerve endings mediate pain and temperature. The other receptors mediate more discriminative touch sensations.



Two main pathways carry information about the body to the cortex.
The evolutionarily older pathway is the lateral spinothalamic tract.
It is responsible for pain and temperature.
Pain and temperature fibers synapse in the dorsal horn and activate neurons that cross over to the other side of the spinal cord. The spinothalamic tract carries information about the contralateral body.

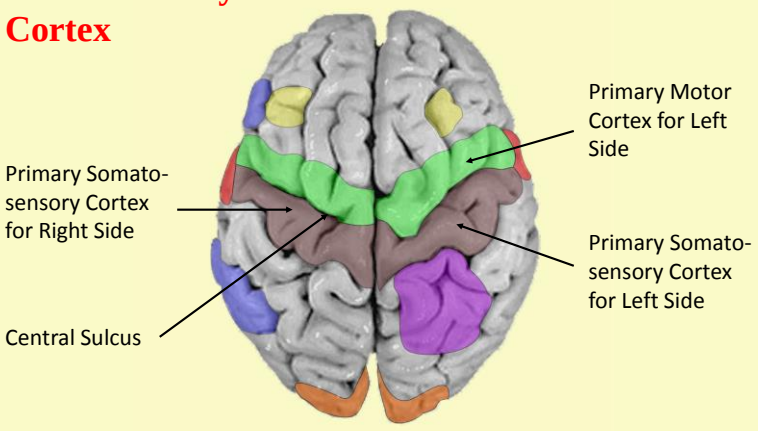
Dorsal Columns

Fine skin sensations and proprioception are carried by rapidly conducting sensory fibers. These fibers go directly into the dorsal columns and do not synapse until the medulla. Neurons in the dorsal column nuclei then cross over and ascend to the thalamus. Neurons in the thalamus project to the somatosensory cortex in the postcentral gyrus.

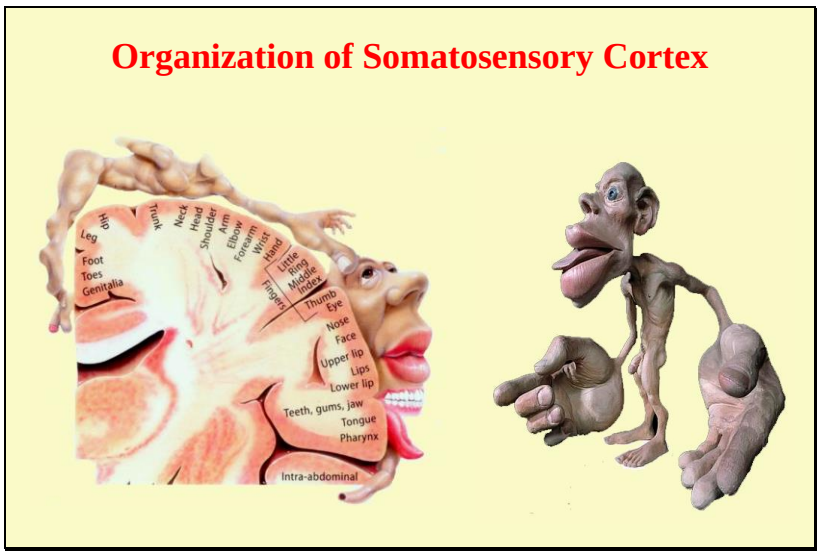


The dorsal columns carry fine touch and joint position. They evolved when fish came to land and developed limbs. The columns travel ipsilateral to the sensation. The fibers synapse and cross over when they reach the medulla.

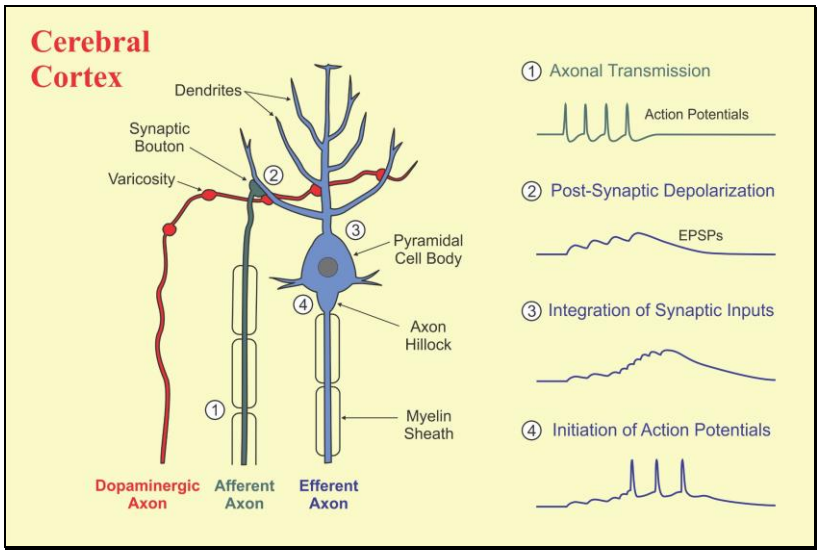
Somatosensory Cortex



The primary somatosensory cortex is in the postcentral gyrus (brown).
The right side of the body goes to the left hemisphere and *vice versa*.



The area of the cortex devoted to a particular part of the body varies with the sensitivity of the region. Hands and lips occupy far more space on the postcentral gyrus than arms and legs

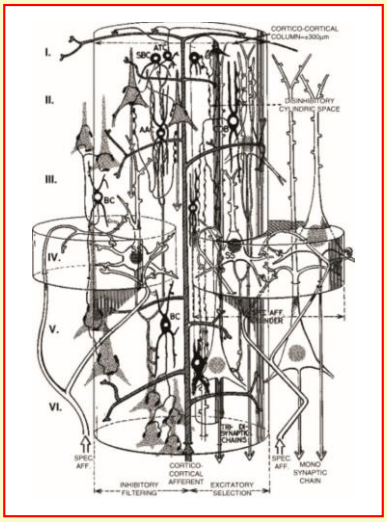


Sensory information arrives at the cortex from the thalamus and synapses on the pyramidal cells. These then respond and send the information on to other parts of the brain. Neuromodulator systems can alter the response depending on the context. We shall consider these systems in a later session.

Cortical Columns

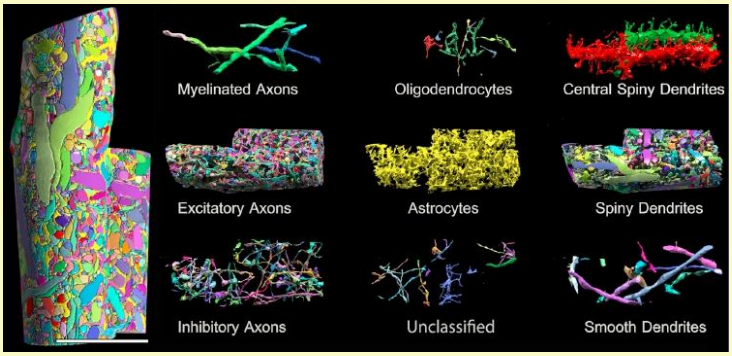
The cerebral cortex is organized into multiple overlapping columns. In the somatosensory cortex, each column receives input from a specific region of the body.

János Szentágothai (1912-1994)



The somatosensory cortex is organized as a set of columns each dealing with a specific part of the body.
Each column receives input from the thalamus. There are multiple excitatory and inhibitory connections within the column
The diagram is from Szentagothai, a famous Hungarian anatomist.

Reconstruction of Somatosensory Cortex



All the cells in a tiny volume (0.13 mm^3) of mouse cortex were mapped. The region contained dendrites from 2 pyramidal cells, several axons synapsing on those dendrites, and multiple glial cells. 7 µm. (Kasthuri et al., 2015)

This shows a recent analysis of all the cells present in a tiny volume of somatosensory cortex of the mouse – the upper part of a cortical column.
The region is shown vertically on the far left and horizontally in the rest of the figure.
There are two main dendrites from pyramidal cells (spiny dendrites – upper right). These have multiple branches.
A few myelinated fibers enter the region (upper left). These have multiple unmyelinated terminal branches – mainly excitatory.

Synapses and Neural Networks

The great topmost sheet of the mass, that where hardly a light had twinkled or moved, becomes now a sparkling field of rhythmic flashing points with trains of traveling sparks hurrying hither and thither. The brain is waking and with it the mind is returning. It is as if the Milky Way entered upon some cosmic dance. Swiftly the head mass becomes an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of subpatterns.

Charles Scott Sherrington (1942)

This video shows a computer reconstruction of a cortical column. As the neurons are activated they become brighter.
The movie comes from the Cajal Blue Brain Project, which uses super-computers to model cortical activity.

https://www.youtube.com/watch?v=HN1iX_3CXLY

The quote is from Sherrington. He is describing the activation of the cortex when an animal awakens.
His main metaphor is the “enchanted loom”
The loom weaves its pattern in the synapses.

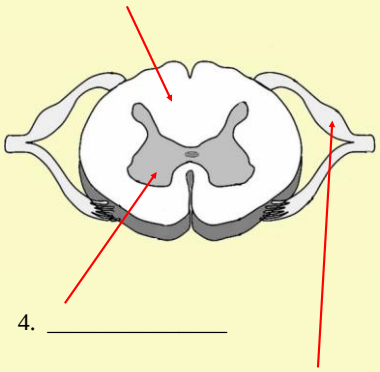
Quiz 3B

1. The basic pathway for the stretch reflex does not involve

A) sensory receptors in the skin
B) stretch receptors in muscle spindles
C) alpha motor neurons
D) dorsal root ganglion neurons

2. The left spinothalamic tract carries information about

A) pain and temperature
B) joint position sense
C) the left side of the body
D) the right side of the face



Synapses and Neural Networks

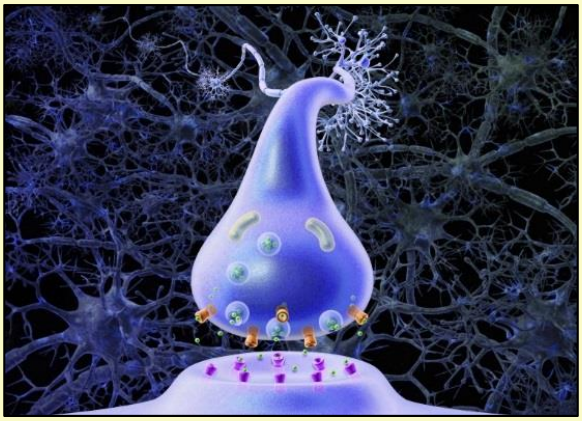


Illustration from Wellcome Images

Music of Cortical Neurons from Alain Dextexhe

This illustration shows the vesicles releasing neurotransmitter (green), which then attaches to the postsynaptic receptor (purple) and is taken back up into the presynaptic bouton by re-uptake transporter molecules (orange).

The music played with this slide comes from the cortex. Multiple different neurons were recorded and each neuron was assigned a particular tone.
This and other neuronal music can be downloaded from
http://cns.iaf.cnrs-gif.fr/alain_music.html