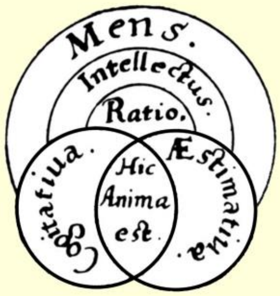
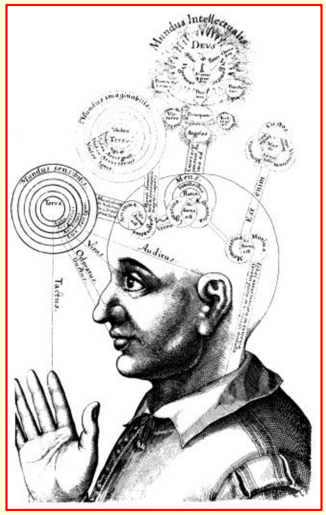
Brain



Hic Anima Est, Robert Fludd,, 1619)



Robert Fludd, *Utriusque cosmi, maioris scilicet et minori, metaphysica, physica, atque technica Historia* (*The metaphysical, physical, and technical history of the two worlds, namely the greater and the lesser.)* Johan-Theodori de Bry, Frankfort, 1619.

Robert Fludd summarized the medieval ideas of how the brain and mind worked, the brain being the minor cosmos and the universe the major. Within the brain are three ventricles. Within each resides the soul – *hic anima est*.

This presentation will not be able to cover all the history of the brain. It concentrates on:

- The medieval theory of the ventricles and the soul
- The origins of neuroanatomy
- Animal electricity – the early recordings
- Localization of function through lesions and through stimulation
- Neuronal cells and synapses, and their activation
- The quest for an image of the brain

Hippocrates of Kos (460-370 BCE)

On the brain: Men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, grieves, despondency, and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear, and know what are foul and what are fair, what are bad and what are good, what are sweet, and what unsavory

On Epilepsy: This disease is in my opinion no more divine than any other; it has the same nature as other diseases … The fact is that the cause of this affection is the brain

The preceding quotations are from writings attributed to Hippocrates. The second concatenates parts of two separate works. Hippocrates was the first clearly to attribute mind to brain. Before most thinking had considered the heart to be the locus of the soul. Hippocrates also disputed that epilepsy was a sacred disease.

Galen of Pergamon (129-210 CE)

bronze medal by Armindo Viseu

Galen was a careful observer of disease and an astute prognosticator. He wrote extensively and soon became one of the most sought after physicians in Rome. He had gained a good knowledge of anatomy by dissecting animals and observing the effects of wounds in soldiers and gladiators.

Nevertheless he bequeathed to posterity two major mistakes:

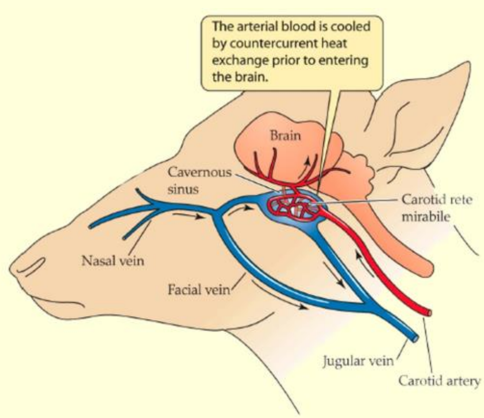
1. the idea of the humors black bile, yellow bile, blood, phlegm
2. the concept of the brain's vital spirits distilled from the blood through the *rete mirabile*

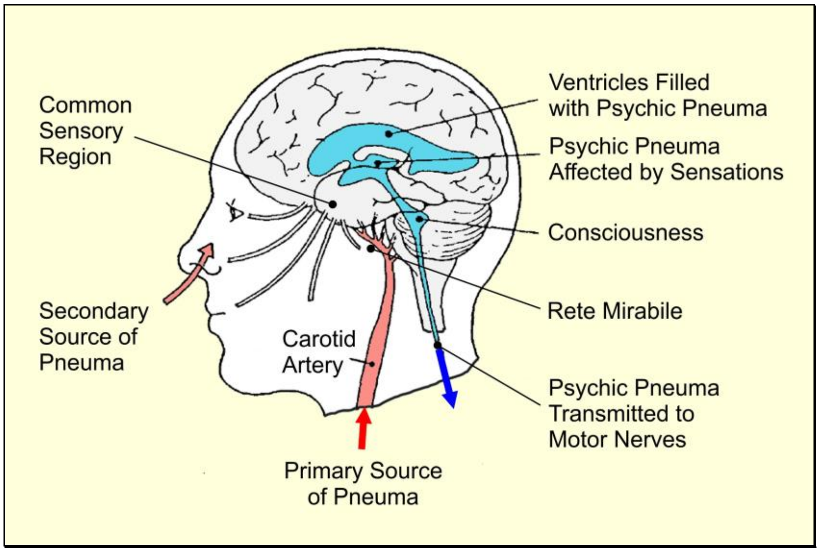
The medal shows Galen withdrawing an arrow from a wounded soldier.

One should not fault Galen his mistakes. He theorized as best he could. His version of the humors was based on ideas going back to ancient Greece and to India. He did not know that the brain vasculature of man differed from that of sheep. Roman law prohibited the dissection of cadavers. The problem was that until the Scientific Revolution everyone accepted his word as indisputable. And no one bothered to check.

Rete Mirabile

Many mammals have a vascular *rete mirabile* (wonderful network) at the base of the brain. The arterial blood passes through venous blood that has been cooled in the nasal cavity. Human beings have no noticeable *rete mirabile*. Perhaps our carotid sinus is the evolutionary residual of the *rete mirabile*.

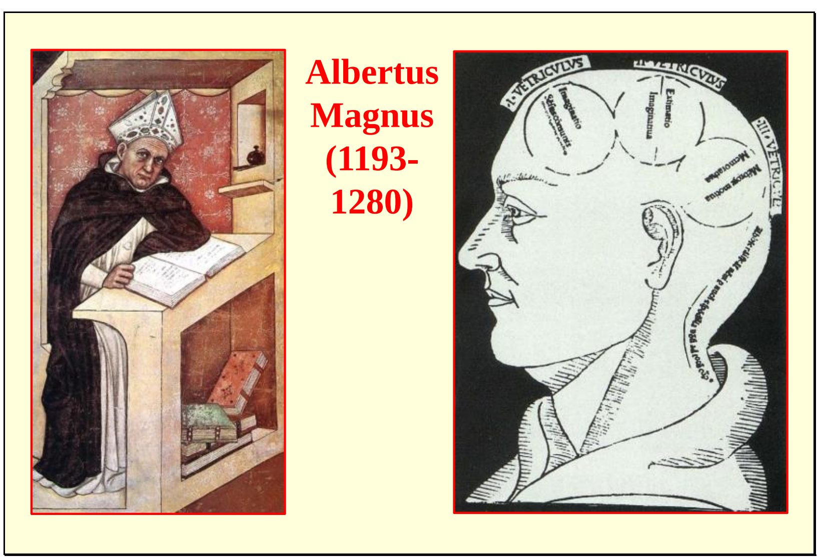




This diagram illustrating Galen's thinking about the brain is adapted from Freemon, F. R. (1994). Galen's ideas on neurological function. *Journal of the History of Neurosciences*, 3, 263-271.

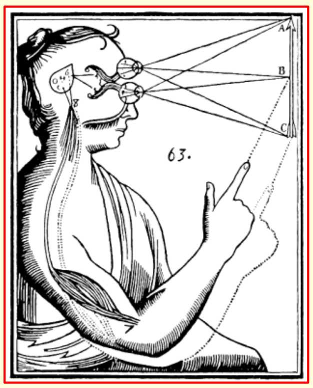
Pneuma (breath, soul) is brought from the heart to the brain's *rete mirabi*le where it is converted to psychic pneuma (vital spirits) which fill the ventricles of the brain. These receive impressions from the world through the senses and send out instructions to the muscles through the spinal cord.

The ideas of Galen were the basis of the *Doctrine of Ventricle Localisation of Mental Functioning* written by the Syrian Bishop Nemesius (4th Century CE). Essential to the doctrine were a *sensus communis* (common sensory region) in the anterior brain. The lateral ventricles gathered the sensory information and the third ventricle housed the intellect that decided what to do with it. The fourth ventricle stored memory. These ideas are evident in the diagram of Robert Fludd in the opening slide of this presentation.



The posthumous portrait on the left is from a 1352 fresco in Treviso, Italy, by Tommaso da Modena. Albertus Magnus is generally considered one of the greatest philosophers of the Middle Ages. He wrote extensively on Aristotle, alchemy, astrology, morality and theology. He commented on many of the Arabic texts that had preserved the theories of Galen. The woodcut at the right is from a 1490 edition of his *Philosophia pauperum.* This is in the tradition of the "pauper's bible" – a bible with pictures for those that could not read.

Three ventricles are numbered. The first houses the imagination and the sensus communis, the second thought/opinion (about sensations, the third memory and the activation of the limbs. The descending Latin sentence states "The nerves radiate through the neck and the vertebrae to the whole body." Modern neuroanatomy names the ventricles the left and right lateral, the third ventricle and the fourth.



from *Treatise on Man*, written in 1632, withdrawn in 1633 because of Galileo's trial, finally published in 1662

Consciousness

If we reject all of which we can entertain the smallest doubt, and even imagine that it is false, we can easily suppose that there is neither God, nor sky, nor bodies, and even that we ourselves have neither hands nor feet, nor body. Yet we cannot in the same way suppose, while we doubt of the truth of these things, that we ourselves are nothing, for there is a repugnance to conceiving that what thinks does not exist at the very time when it thinks. So "I think, therefore I am" [*cogito ergo sum*] is the first and most certain idea that occurs to anyone who philosophizes in an orderly way.

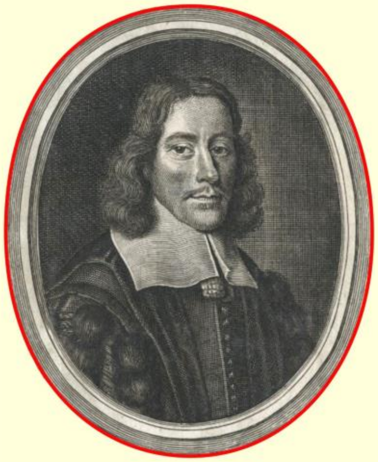
René Descartes, 1644

Galen's concepts of the brain pervaded European thought for centuries. Even Descartes, the man who doubted everything, accepted his ideas without question.

Descartes began to write about how the human brain worked in his *Treatise on Man*. The illustration shows the eyes being activated by visual input. This sends fluid to the pineal gland which directs the fluid to the muscles causing the arm to point to the perceived object. This was Descartes' main addition to Galen's idea of how the brain functioned.

Fearing that the Church would not agree with his science, he decided first to provide a philosophical basis for his work – *The Discourse on the Method* (1637). Here he proposed a method of doubting everything until we are left with something that we cannot doubt – that we are conscious of our doubt. This led him to his famous *je pense donc je suis* or *cogito ergo sum*. The idea was first expressed in French and then in Latin in the *Principia Philosphiae* of 1644. Descartes used this irrefutable fact as a firm foundation on which to base an understanding of ourselves, the universe and God. The conscious thinking self is thus the basis of all we know. In

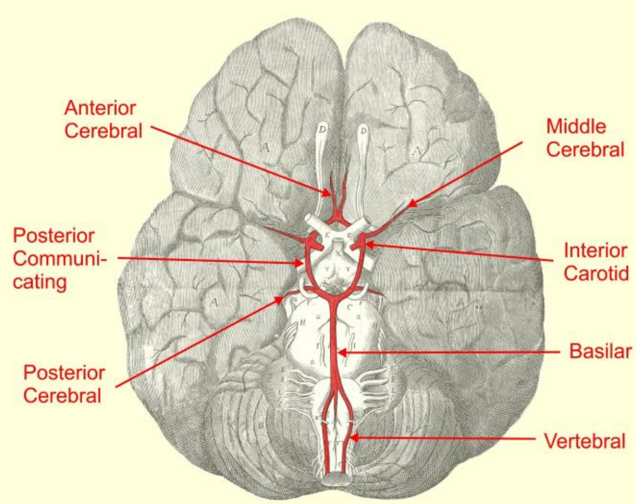
Les passions de l'âme (1649), Descartes proposed that the pineal gland was *le principal siège de l' âme* (the seat of the soul).



Thomas Willis (1621-1675)

Graduating with an M. B. from the university of Oxford in 1846, Willis became a practicing physician and anatomist. He was a member of the Oxford Experimental Philosophy Club, which included Robert Boyle, Christopher Wren, Robert Hooke, Thomas Sydenham, and Thomas Millington. In 1664 he published his *Cerebri Anatome*. Willis was assisted in his dissections by Richard Lower and the plates were drawn by Christopher Wren.

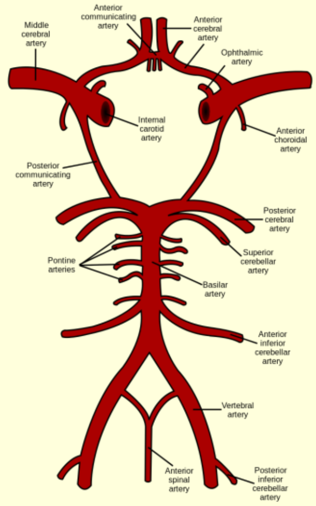
Vesalius (1514-1564) had provided good images of the human brain, and had shown that there was no *rete mirabile*. However, it was not until Willis that neuroanatomy became established. Willis was the first to number the cranial nerves in their current sequence, and the first to describe the cerebral arteries accurately.



This is one of Wren's illustrations for *Cerebri Anatome*. Wren became the architect of St Paul's Cathedral that was built after the Great Fire of London in 1666.

Circle of Willis

Thomas Willis is remembered in the name of the circulatory anastomosis among the arteries supplying the brain. The main connecting arteries are the anterior and posterior communicating arteries. These connections allow blood to supply the different regions of the brain even if one of the main supplying arteries (carotid or vertebral) is blocked.



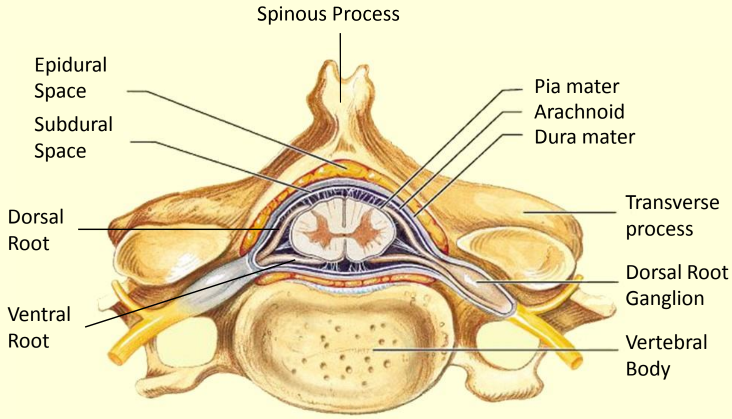
In the years that followed Willis, anatomists began to dissect the brain and follow its pathways. One of these anatomists was Charles Bell

Charles Bell (1774-1832)

Bell was a Scottish surgeon and anatomist. In 1811 he privately published *An Idea of a New Anatomy of the Brain* describing his experiments with dissecting and stimulating different parts of the spinal cord in animals. His results indicated a separation of motor and sensory functions. with the dorsal roots (and columns) being sensory and the ventral roots motor. François Magendie (1783-1855), a French physiologist, confirmed these findings in 1822.

Bell is also known for his 1829 clinical description of the paralysis of the face following damage to the VII cranial nerve – Bell's palsy.
There was much controversy about priority in the description of the distinction between the function of the dorsal and ventral roots. Bell had published privately and had not actually demonstrated the sensory function. Magendie showed this by the painful responses elicited by stimulation in puppies. Ultimately the law distinguishing dorsal and ventral roots became known as the Bell-Magendie law.

Spinal Cord



This cross section shows the spinal cord within the vertebral canal in the neck. The epidural 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.

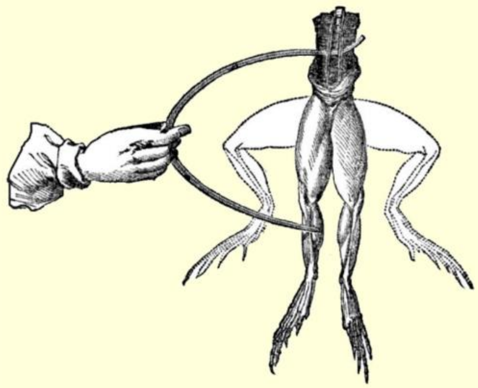
Luigi Galvani (1737-1798)

Many early experiments had shown that nerves and muscles were sensitive to electrical stimulation. Galvani reported in 1791 that he could cause frogs' legs to twitch in much the same way by connecting the spinal cord to the muscle through a metal wire. He suggested that this was due to "animal electricity." Much controversy ensued: Volta (1745-1827) attributed his results to the generation of electricity at the junction between dissimilar metals. This may have been true in some cases, but in others Galvani had indeed shown that the nervous system operated electrically.

The statue of Galvani, showing him observing the responses of a frog, is located in the Piazza Galvani just outside the University of Bologna.

Galvani's Frogs

The illustration shows Galvani's key experiment. The controversy was whether the connection between the spinal cord and the muscle was composed of two metals and thus capable of generating currents. In later experiments muscles could be caused to twitch by direct contact between spinal nerve and muscle.



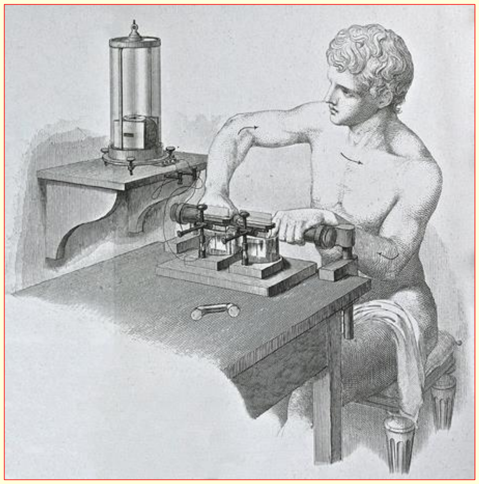
The electrical stimulus from the nerve to the muscle was most likely the negative injury potential or cut-end potential. Nerves and muscles were later shown by du Bois Reymond to be negative at their cut end relative to their uncut region. This is actually evidence that the cell membrane is polarized such that it is negative on the inside and positive on the outside. This was not clearly known until the experiments of Cole, Hodgkin and Huxley in the mid 20^{th} Century.

In order to show that the nerves and muscles generated electricity, scientists needed to obtain very sensitive instruments for measuring tiny currents. These were called galvanometers in honor of Galvani.

Emil Heinrich du Bois-Reymond (1818-1896)

Du Bois Reymond studied with Johannes Müller in Berlin and later succeeded him as Professor of Anatomy and Physiology. He published a series of volumes on *Investigations of Animal Electricity* (1848-1884). Perhaps most importantly he showed that when a muscle was activated the potential measured at its surface became negative. He called this the action potential.

Du Bois Reymond used non-polarizable electrodes – the electrodes were connected to the tissue using a blotting paper soaked in saline. (Current non-polarizable electrodes use a mixture of silver and silver chloride.) These prevented the build-up of electrical potentials at the interface between electrode and tissue. For demonstration purposes du Bois Reymond used a human subject:



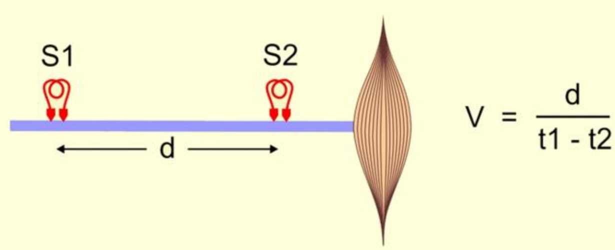
"Du Bois-Reymond's most famous experiment proceeded as follows. He attached the leads of his galvanometer to platinum plates resting in "conducting vessels" filled with saline. After immersing his fingers in the electrolyte, he waited for the galvanometer needle to come to rest. All of a sudden, he tensed one of his arms. The needle jumped." (Finkelstein, 2015)

The quotation is from Finkelstein, G. (2015). Mechanical neuroscience: Emil du Bois-Reymond's innovations in theory and practice. *Frontiers in Systems Neuroscience*, 9, 135.

Du Bois Reymond's student Julius Bernstein later (1875) made more precise measurements of the action potential and found that this negative change lasted about 1 millisecond. He also investigated the change in ions during the action potentials.

Nerve Conduction Velocity

Prior to 1850, scientists had assumed that nerves acted instantaneously. Hermann von Helmholtz (1821-1894) showed that nerve 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?
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 contact at speeds of over 400 km/hr. Faster than the fastest Ferrari.

Helmholtz was able to measure the brief times between stimulus and response using a slowly reacting galvanometer. If a constant current is passed for a brief period of time the deflection of the needle is proportional to the duration of the current. The circuit carrying the current from a battery to the galvanometer was closed by the stimulus and opened by the muscle movement.

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.

We can use a similar approach to measuring 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

Helmholtz made numerous contributions to science. He was the first to state the law of conservation of energy (1847) which became the first law of thermodynamics. As well as measuring the speed of nerve conduction, he also produced important studies of hearing and vision. He invented the ophthalmoscope – an instrument to observe the back of the eye. This required sending a light into the eye and focusing the returning beam so that the retina could be visualized. The 1881 portrait by Ludwig Knaus shows him holding the light source for the ophthalmoscope. The actual ophthalmoscope is on the table. Also in the painting are a tuning fork and resonator used in this studies of hearing.

Richard Caton (1842-1926)

A young lecturer in physiology at the Liverpool Royal Infirmary School of Medicine, Caton made the first recordings of the electrical activity of the brain in rabbits and monkeys. Using a sensitive moving-magnet reflecting galvanometer designed by Lord Kelvin, he found a negative variation at the cortical surface during activity. Caton was the Lord Mayor of Liverpool from 1907-8.

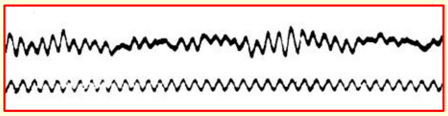
This is the text of Caton's report *The Electric Currents of the Brain* to the British Medical Association in 1875:

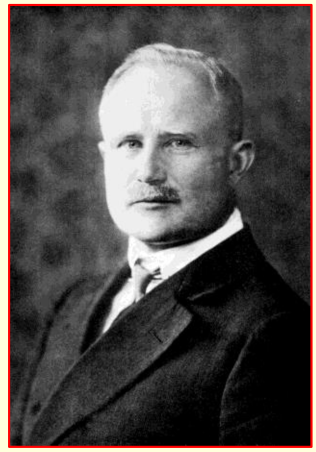
In every brain hitherto examined, the galvanometer has indicated the existence of electric currents. The external surface of the grey matter is usually positive in relation to the surface of a section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function. When any part of the grey matter is in a state of functional activity, its electric current usually exhibits negative variation. For example, on the areas shown by Dr. Ferrier to be related to rotation of the head and to mastication, negative variation of the current was observed to occur whenever those two acts respectively were performed. Impressions through the senses were found to influence the currents of certain areas; e. g. the currents of that part of the rabbit's brain which Dr. Ferrier has shown to be related to movements of the eyelids, were found to be markedly influenced by stimulation of the opposite retina by light.

After Caton many other physiologists, most of them unaware of Caton's work, reported on the electrical activity of the brain. It was not until the 1920s, however, that Hans Berger was able to record the human electroencephalogram (EEG) from the scalp.

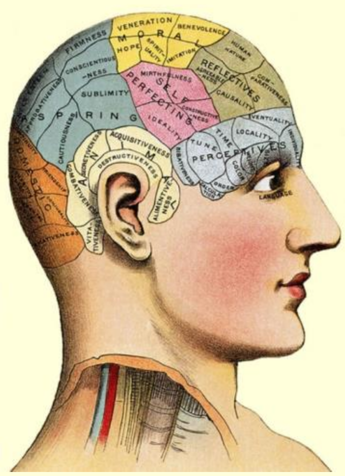
Electroencephalography

The first recordings of the electrical activity of the human brain were made by the psychiatrist Hans Berger (1873-1941) in Jena in the 1920s and 1930s. The top tracing in the recording below is from the scalp of his son Klaus. The bottom tracing is a 10/s timing signal. Berger named the rhythmic activity near 10/s “alpha”, and the faster activity “beta.” In 1938, Berger was summarily dismissed from his university position by the Nazis. Depressed by the war, he committed suicide in 1941.





The electroencepahalogram (EEG) became important in monitoring the state of consciousness and in diagnosing the different types of epilepsy.



Localization of Function

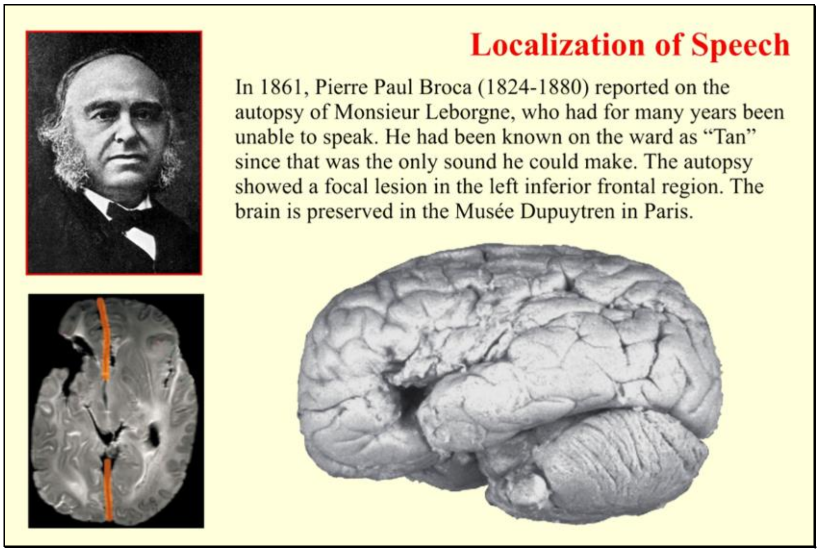
In the 19th Century, the phrenologists led by Franz Josef Gall (1758-1828) proposed that human abilities were localized to different regions of the brain.

Jean Pierre Flourens (1794-1867) showed that the cerebral hemispheres were necessary for intelligent behavior but he was unable to distinguish any focal areas within the hemispheres.

The controversy whether cognitive functions are localized or distributed in the brain continues to this day.

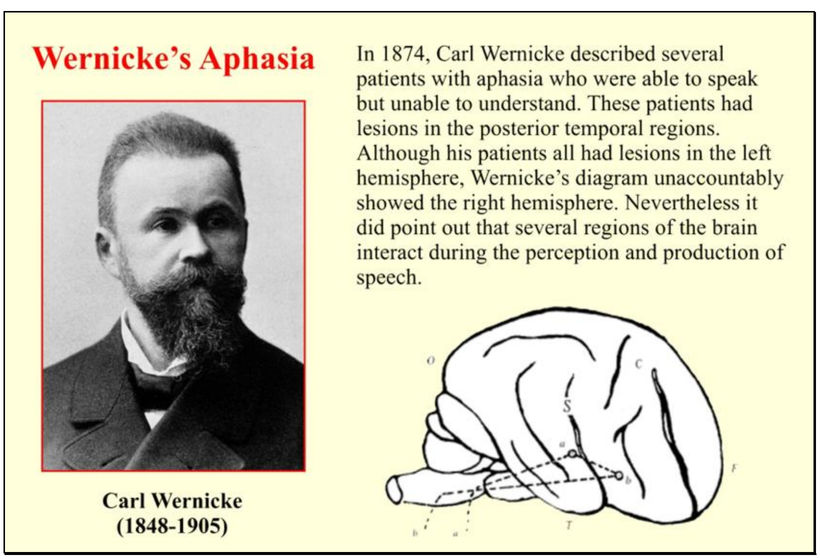
Now we turn to localization of function. Phrenology was the study of the mind. It assumed that particular abilities would be localized in specific regions of the brain. If a particular ability were enhanced in a person, the regions of cerebral cortex related to that ability would be increased. Furthermore, the regions of the skull overlying the part of the cerebral cortex devoted to that ability would become recognizably prominent.
Though the ideas of phrenology were totally illogical, some principles continue – that abilities might show some localization and that increased use of those functions increased the size of that region of the cortex.

The controversy between whether cognition is localized or distributed continues to this day. Some regions of the brain are essential to some functions, and without them these functions are not possible. However, the functions normally involve many other areas of the brain as well.

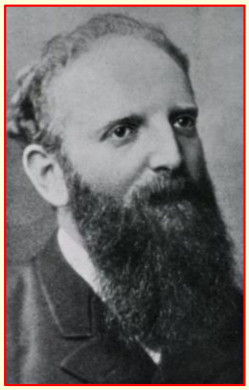


Those believing in the localization of function received some clear support when physicians began to look at the brains of patients with aphasia.

Interestingly the brains of other patients with similar findings that Broca had studied had lesions to other areas of the left hemisphere. The lesions were all left frontal but some were higher than M. Leborgne's. The MRI at the lower left was taken from Leborgne's preserved brain.



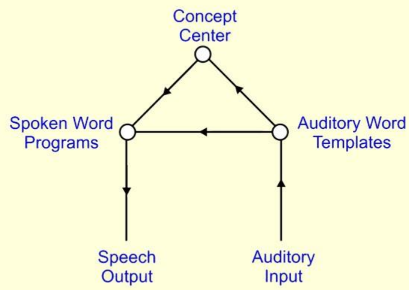
Wernicke suggested that the posterior temporal lobe was necessary for understanding speech and the inferior frontal lobe for producing speech. He did not pay attention to the fact that language defects involved the left hemisphere, and not the right.



Ludwig Lichtheim
(1845- 1928)

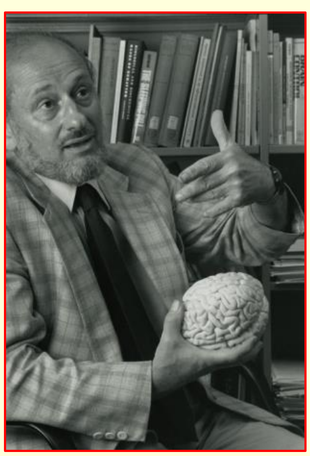
The House of Lichtheim

In 1885 Lichtheim published his ideas about the speech system with an influential diagram. Aphasia could be caused by lesions to any of the centers or by lesions disconnecting one center from another.



The third main father of aphasiology was Ludwig Lichtheim.
His speech diagram looks like a house.

Disrupting the connection between auditory center and the speech center would prevent the simple rapid repetition of auditory input, even though the patient could understand and peak normally.

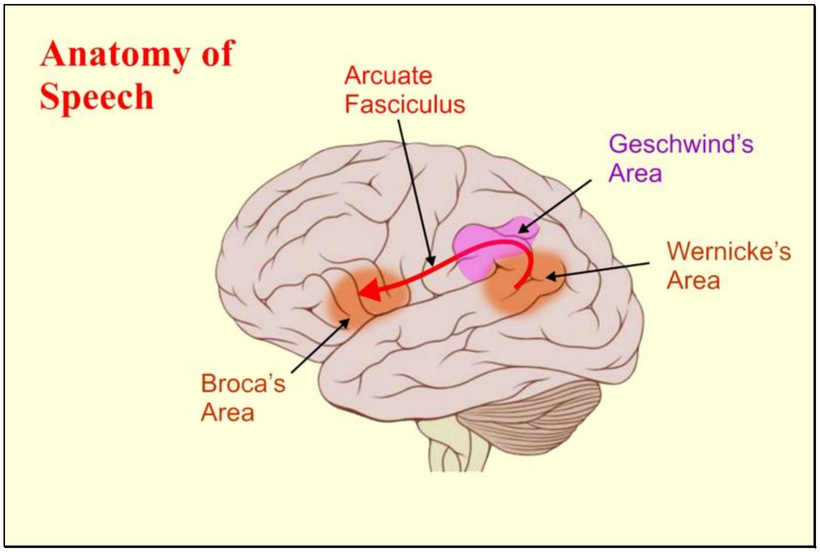


Norman Geschwind
(1926-1984)

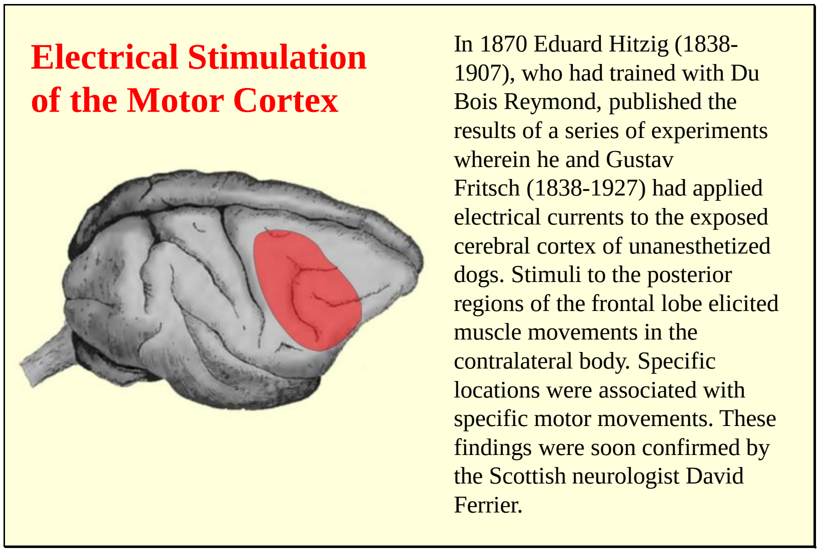
Disconnection Syndromes

Geschwind proposed that Lichtheim's concept center was located in the inferior parietal lobe, an area that was only fully developed in human beings. Lesions to the arcuate fasciculus could cause a "conduction aphasia" – patients had difficulty repeating phrases that were close to meaningless (such as "No ifs, ands, or buts"), although they could speak normally and could understand.

Norman Geschwind suggested an anatomical basis for the concept center, and proposed the idea of disconnection syndromes. The prototype disconnection syndrome is conduction aphasia. A lesion to the arcuate fasciculus disconnect Wernicke's area from Broca's area.



These are the main regions of the brain involved in speech and language in the classical (locationist) view.



Photograph at the publication of the 1954 book *Epilepsy and the Functional Anatomy of the Human Brain*

Wilder Penfield (1891-1976) and Herbert Jasper (1906-1999)

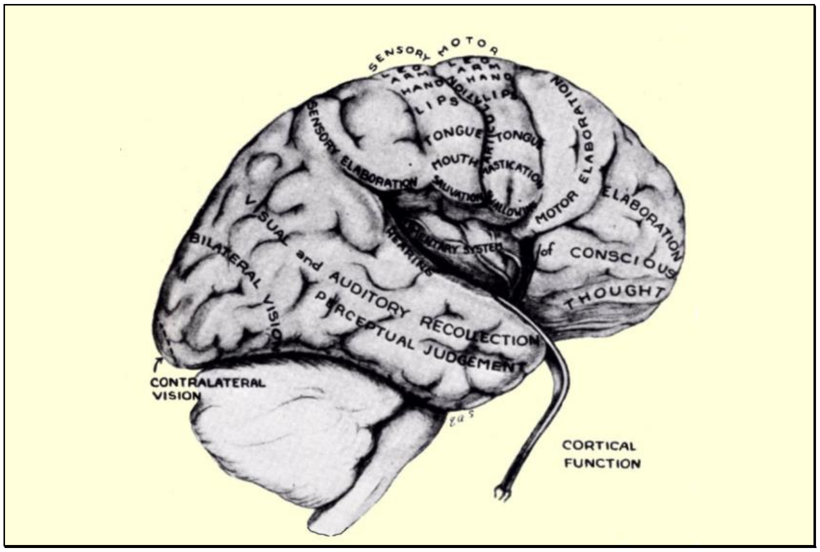
Working at the Montreal Neurological Institute Penfield and Jasper confirmed the mapping of the motor cortex in human subjects undergoing surgery for epilepsy. They also mapped the sensory cortex since their subjects were awake during the surgery.

Their main findings were that

- the motor and sensory cortices were arrayed so that the feet were medial and the face lateral
- the area of the cortex devoted to a particular body part varied with the amount that part was used – thus the hand was much more extensively distributed than the foot.

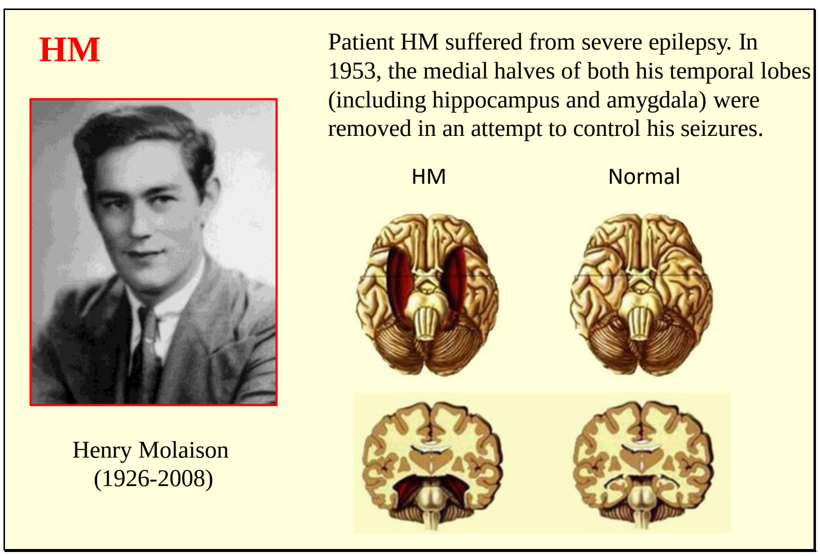
Organization of Motor Cortex

The experiments of Hitzig, Fritsch and Ferrier were later confirmed in human patients undergoing neurosurgery 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. A similar homunculus was mapped in the postcentral gyrus for sensation. You can tell that the homunculus illustrated here represents the motor cortex by the tiny size of the genitalia. These have a large sensory input but very little motor control.



As well as mapping the sensory and motor cortices, Penfield and his colleagues also recorded the effects of stimulation of other regions. They elicited complex experiences from regions of association cortex. In particular their patients produced remembered experiences following stimulation of the temporal lobe.

This relationship of the temporal lobe to memory was confirmed by the results of the surgical removal of the medial temporal lobes in an epileptic patient by a surgeon in Hartford Connecticut. The Montreal group did not perform bilateral operations.



Now we shall look as some of the disorders of memory – amnesia.
The most famous patient in neuropsychology is Henry Molaison – HM.
Dr. William Scoville, a neurosurgeon in Hartford Connecticut removed both his medial temporal lobes in order to control his epileptic seizures.

Brenda Milner (1918 -)

Pure Amnesia

After the operation, the Canadian neuropsychologist Brenda Milner found that HM was unable to form any new memories (anterograde amnesia) and had difficulty remembering past memories (retrograde amnesia) particularly for the three years preceding the operation.

However, unlike other patients with amnesia, his other mental abilities were unaffected. His general IQ was 112. His language was normal. His forward digit span was 6.

After the surgery he was unable to make new memories – anterograde amnesia – and he remembered only some of his past – partial retrograde amnesia.

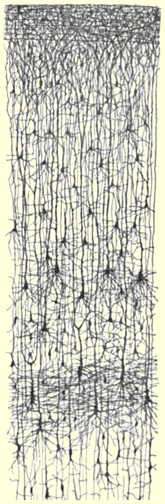
Brenda Milner – 100 years old – is still active at the Montreal Neurological Institute.

Luke Dittrich, the grandson of William Scoville, has published a recent book *Patient HM: A Story of Memory, Madness and Family Secrets.*

Neuronal Cells

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?

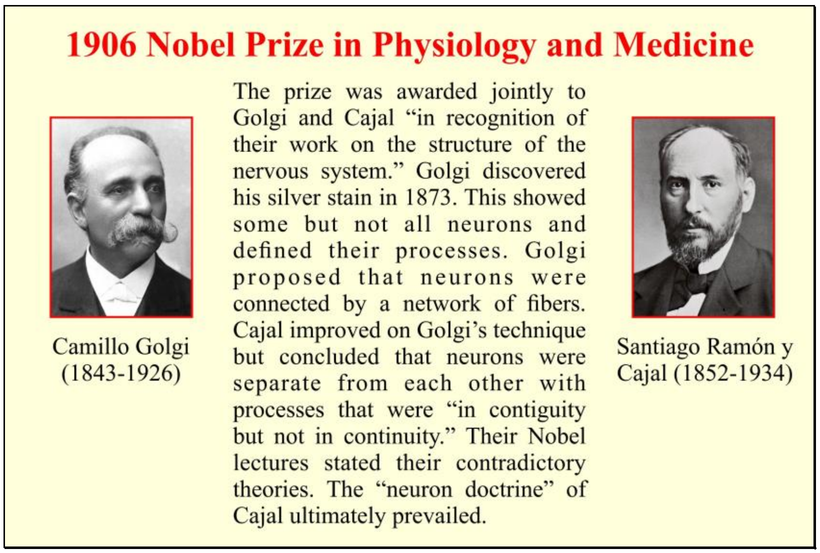
Santiago Ramón y Cajal (1852-1934)
Recuerdos de mi Vida, 1917



In the 1839 Theodor Schwann and Matthias Schleiden had proposed the cell theory. This was extended by Rudolf Virchow in 1855. This proposed that the basic unit of living organisms is the cell and that all cells derive from pre-existing cells *Omnis cellula e cellula*.

Toward the end of the 19th Century scientists began to study the cells of the brain. 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.



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.

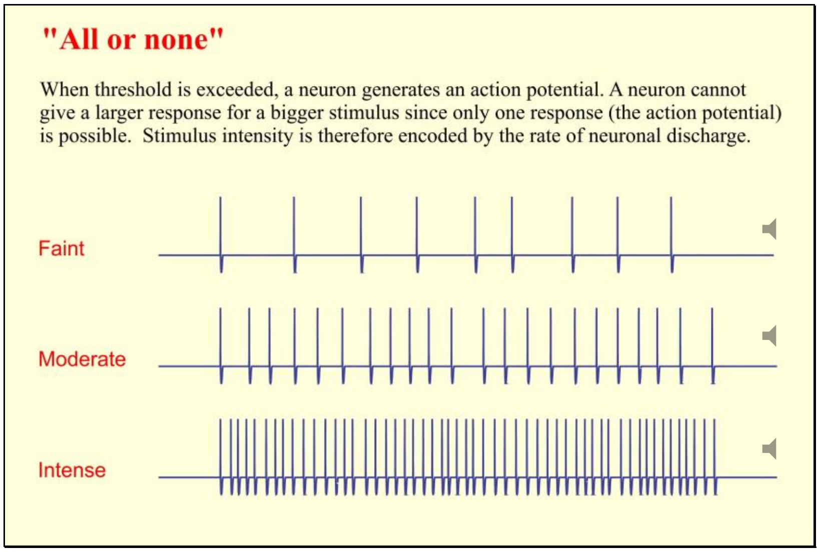
Golgi and Cajal shared the Noble Prize in Physiology and Medicine in 1906. In their acceptance speeches, they presented completely different views of the nervous system. They certainly did not win the peace prize ☺
Golgi proposed that the brain was a vast network of connected fibers and that the neurons 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.

Nevertheless neurons do work together as functional networks. These networks are composed of separate neurons that interact with each other.



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 almost 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.

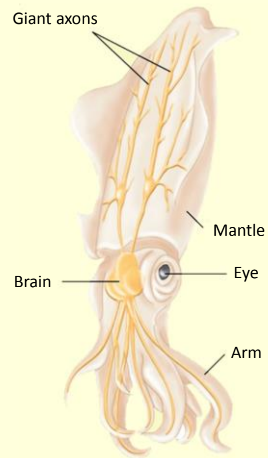
The central nervous system knows what type of stimulus it is from where it is coming from – the "labelled line." This idea was different from the old "doctrine of specific nerve energies" which proposed that each perceptual system used a specific type of energy. The new understanding was

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

(i) what the stimulus is by which neurons are active – “labelled line”
(ii) how intense the stimulus is by the frequency of discharge – “rate coding.”

Squid Axons

Early studies of how neurons worked used the giant axon of the squid. In 1938, Cole and Hodgkin inserted a tiny electrode inside the giant axon to measure the voltage across the membrane. The inside was -45 mV compared to the outside. This altered when the neuron was activated.

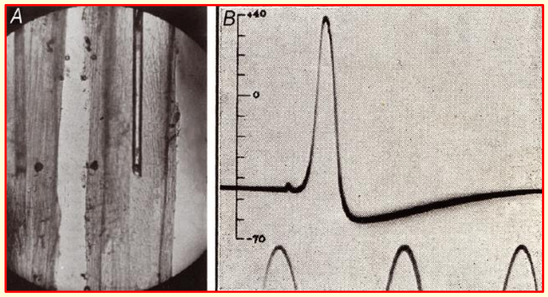


Polarization, excitation, conduction, transmission.
The inside of a neuron is negative – polarization.
The excitability of neurons was first understood in experiments with the squid.
In order to activate the mantle for jet propulsion, the squid has a giant axon. The typical diameter of this axon is about 0.5 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. ☺)

Action Potentials

In 1939, Hodgkin and Huxley found that when the giant axon was activated the nerve potential did not just go away. Rather it "overshot" so that the inside actually became positive rather than negative. In 1952, they demonstrated that this was caused by changes in the membrane's permeability to ions. They received the Nobel Prize in 1963 together with Eccles (who studied the synapse).

Glass pipette in axon



Action Potential

500 Hz time signal

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*.

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 synapse is the place where one neuron makes contact with another.

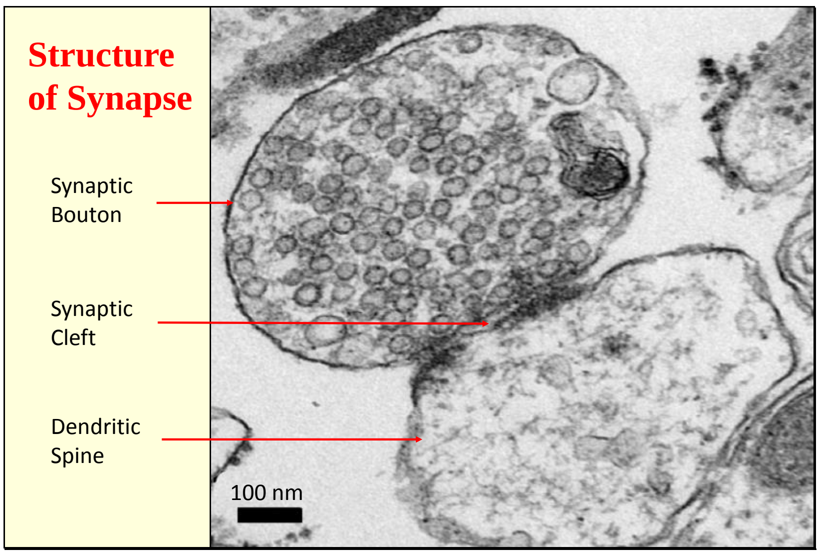
The word ”synapse” was first used by Charles Sherrington. The etymology combines “haptein, come in contact, touch” with “syn, together.” The poetic neurophysiologist might translate it as “kiss.”

A Greek scholar at Cambridge, A. W. Verall, a translator of Euripides, suggested the Greek word for “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 adult human brain – the brain of an infant has even more.

The pattern of their activity encodes the soul.



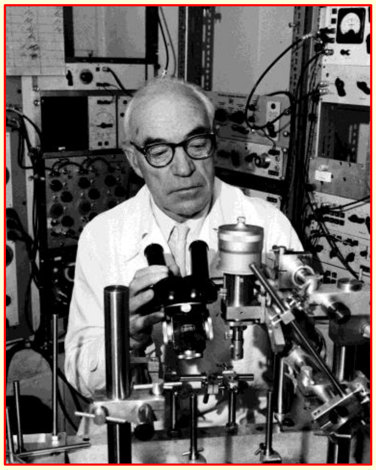
The synapse was not fully visualized until the electron microscope, which was invented in the 1930s. The first EM studies of the nervous system were not done until the 1950s.

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.



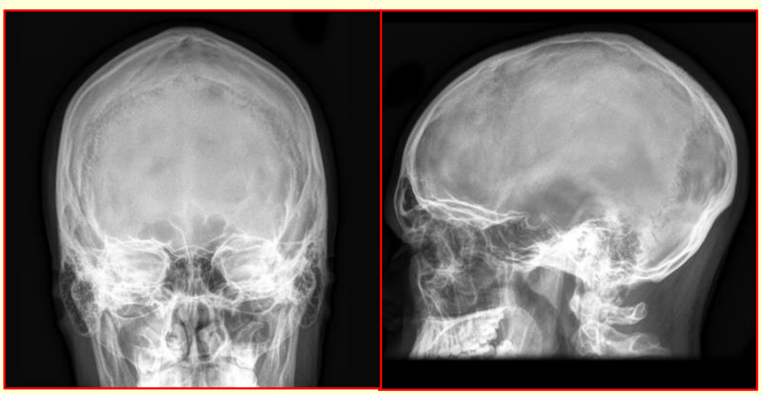
John Eccles (1903-1997)

John Eccles was born in Australia. Though trained in clinical 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.

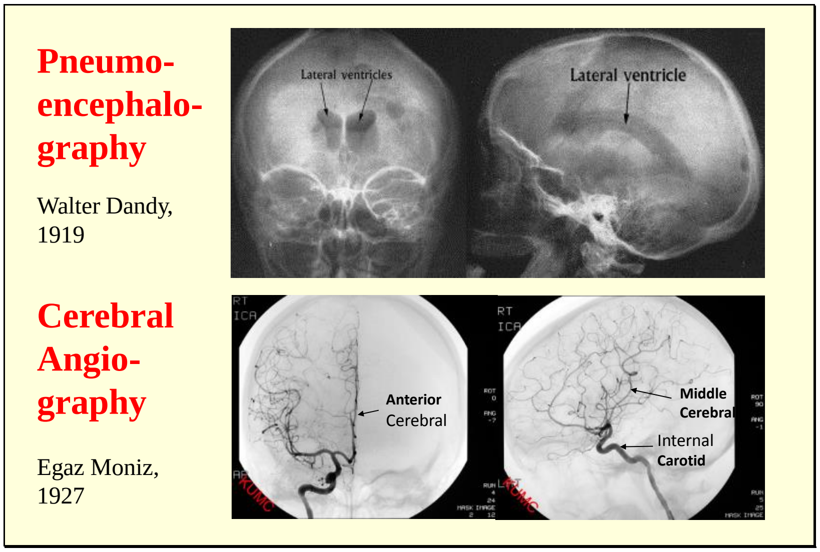
John Eccles was the scientist who first clearly demonstrated the neurophysiology of synapses. He initially thought that synapses caused direct electrical transmission from one cell to another. However, his experiments showed otherwise.

He was active in the Pontifical Academy of Sciences, and organized for them a famous 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 to those who study the brain.

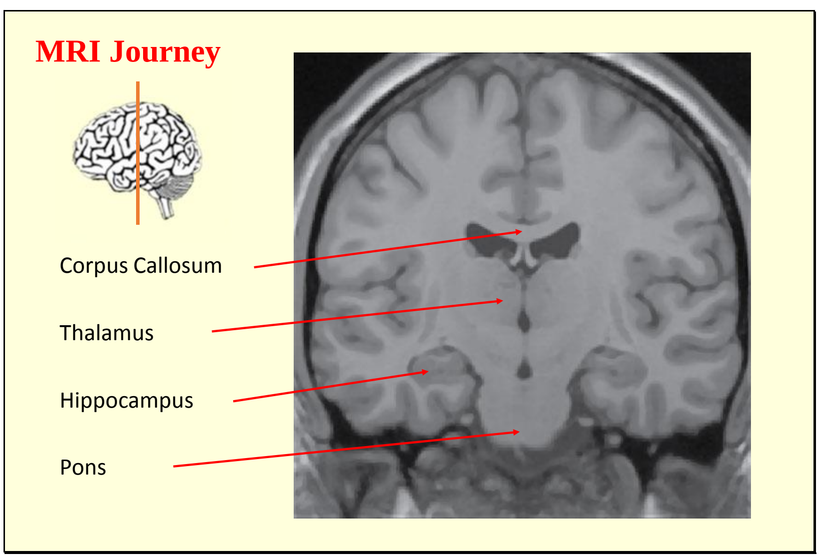
The Quest for an Image of the Brain



The first radiographs of the skull appeared in 1896. However, the skull x-ray did not show the brain.



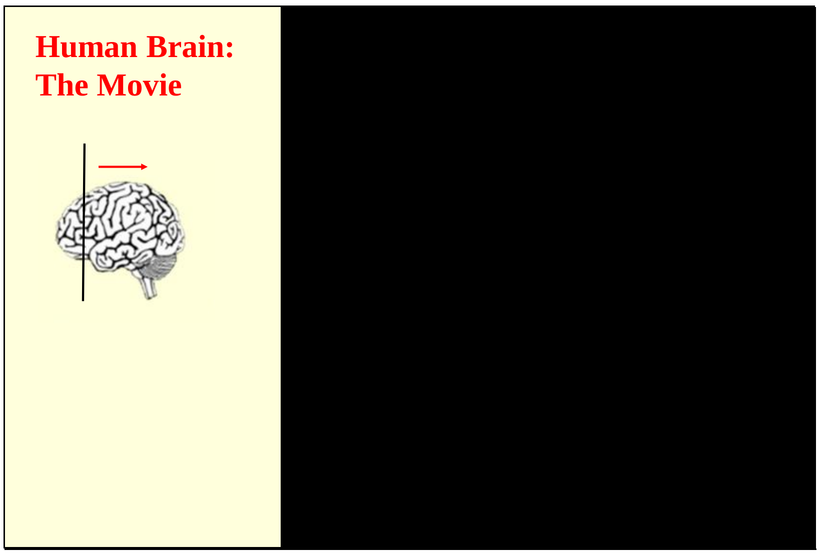
Egaz Moniz received the 1949 Nobel Prize for using prefrontal leucotomy to treat psychotic patients. The first operation was performed in 1935. This procedure became widely used and ultimately discredited.



Computerized axial tomography was first brought into clinical practice by Godfrey Hounsfield in 1971. This used a computer to calculate the relative x-ray density of tissue in a slice of the body from multiple x-rays sent at all through the plane of that slice. he received the Nobel Prize in 1979.

CAT scans were largely superseded with the invention of magnetic resonance imaging the 1970s by Paul Lauterbur and Peter Mansfield who shared the Nobel Prize in 2003.

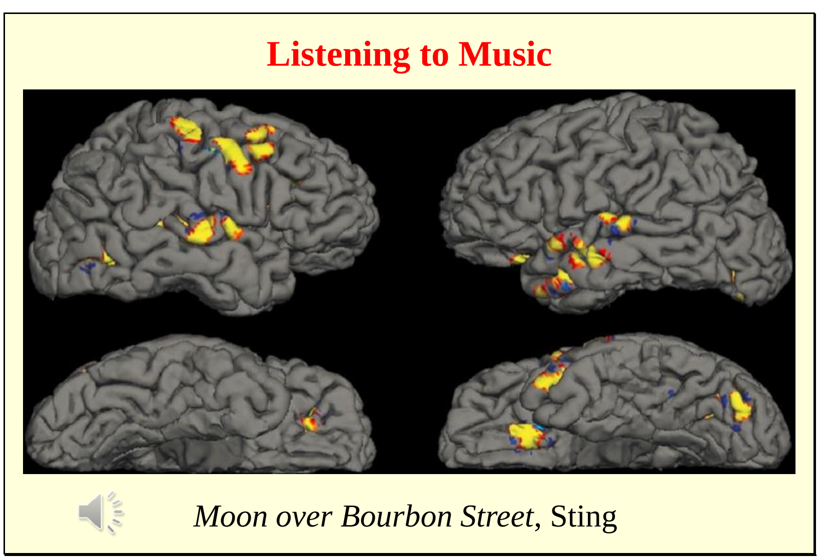
The illustration shows an MRI slice through the brain at the level of the thalamus. The hippocampus lies in the inferior horn of the lateral ventricle
The body of the lateral ventricle with the corpus callosum above and the fornix and choroid plexus below.



We can go through the sections like a movie.
Human Brain: The Movie.

If you wish to see more of this type of mri information
http://www.pbs.org/wgbh/nova/assets/swf/1/mapping-the-brain/mapping-the-brain.html

These movies are available at
http://creatureandcreator.ca/?page_id=1029



By measuring the changes in the MRI signal caused by changes in the blood oxygen level, scientists could measure the amount of blood flow in different regions of the brain. This technique is call BOLD – blood oxygen level dependence. Since the blood flow is determined by the amount of neuronal activity, they could also infer which regions of the brain were active during different states. This can therefore measure brain function as well as anatomy – functional MRI . Seiji Ogawa at AT&T Bell Labs first described the technique in 1990 and it was first used in human recordings by John Belliveau at Harvard University in 1991. He generally went by the name of Jack to distinguish himself from the famous hockey player.

This is Sting's brain as he listens to music. The recording is by Daniel Levitin from McGill University. Multiple areas of the brain are activated. Many are in the temporal lobe – these might have to do with auditory perception. Orbital regions of the frontal lobes are active – perhaps because of emotional effects of music. Some visual areas as well – the imagery that goes with music. There are some active areas in the somatosensory and motor areas of cortex – music is not music unless it makes you move.

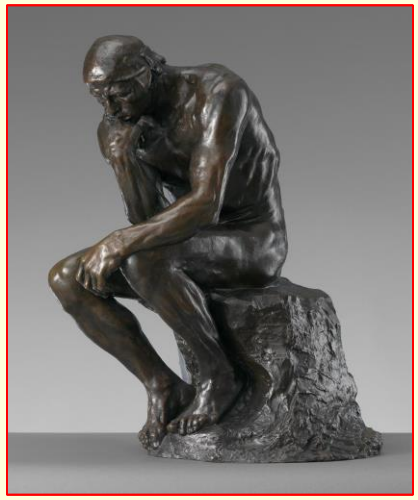
Lyrics of Moon over Bourbon Street:

There's a moon over Bourbon Street tonight
I see faces as they pass beneath the pale lamplight
I've no choice but to follow that call
The bright lights, the people, and the moon and all
I pray everyday to be strong
For I know what I do must be wrong
Oh you'll never see my shade or hear the sound of my feet
While there's a moon over Bourbon Street

It was many years ago that I became what I am
I was trapped in this life like an innocent lamb
Now I can never show my face at noon
And you'll only see me walking by the light of the moon
The brim of my hat hides the eye of a beast
I've the face of a sinner but the hands of a priest
Oh you'll never see my shade or hear the sound of my feet
While there's a moon over Bourbon Street

She walks everyday through the streets of New Orleans
She's innocent and young, from a family of means
I have stood many times outside her window at night
To struggle with my instinct in the pale moonlight
How could I be this way when I pray to God above?
I must love what I destroy and destroy the thing I love
Oh you'll never see my shade or hear the sound of my feet
While there's a moon over Bourbon Street

Brain



The Thinker
Auguste Rodin, 1884

This is the first casting of the sculpture. It is presently at the National Gallery of Victoria, Melbourne, Australia. It differs from later castings in the Florentine style cap.
The sculpture was initially conceived as sitting over the Gates of Hell.
https://www.ngv.vic.gov.au/essay/two-insights-into-auguste-rodins-the-thinker/