

ELECTROPHYSIOLOGICAL METHODS OF THE STUDY OF THE NERVOUS- AND MUSCULAR SYSTEMS

(Az ideg- és izom-rendszer elektrofiziológiai vizsgálómódszerei)

LECTURE 2

HISTORY OF ELECTROPHYSIOLOGY

(Az elektrofiziológia története)

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AIMS:

In this lecture the student will be familiar with the history of the electrophysiology through the work of many great scientists from the ancient times to the XXth century.

Physiology:

The science of the function of the living systems.

Electrophysiology:

The branch of physiology, where the electrical activity of organisms is studied.

The word "physiology" was used first in written text by Jean Fernel French doctor (1497-1558) in his book "Medicina Universa" (1552). He used the term to describe the study of the body's function.

Theodor Zwinger (1533-1588): "Physiologia medica" (1610) is the first book, which contains this word in the title as well.

ANCIENT TIMES

The first written document on bioelectric phenomenon is an Egyptian Hieroglyph (B.C. 4000). It describes the electric sheatfish or catfish as a fish that „releases troops". The Egyptians were familiar with the electric phenomena and its effect. The sheatfish could generate electric shocks with several hundred volts in amplitude, so if a catch included such a fish, the fishermen were forced to release all the captured fish because of the electric shock they received.



Egyptian relief illustrating a fishing scene

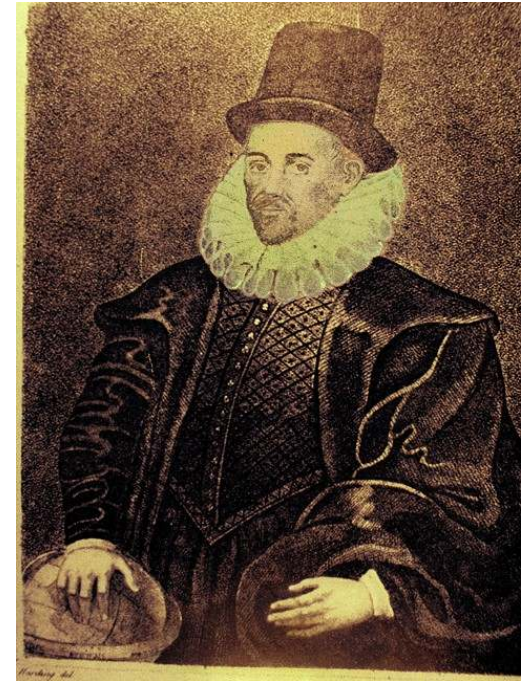
ANCIENT TIMES

The ancient Greeks used the torpedo fish (electric ray) to numb the pain of operations and child-birth. The first known therapeutic application of electricity written in *Compositiones Medicae* (A.D. 46): Scribonius Largus (Roman physician) used the torpedo fish to cure headache and gout arthritis with success.

Galen (130-200) was one of the greatest experimenters of the ancient times. Studied the relationship between the nervous system and respiration, carried out lesion experiments on the spinal cord of animals and described several cranial nerves. Elaborated the "ventricular-pneumatic doctrine": they thought that „animal spirits”, that arise from brain ventricles, are responsible for all of the functions of the body: the pneuma flowing through the hollow nerves induces muscular contractions or transfers sensations back to the brain. This viewpoint lasted for more than a thousand year because of the influence of the catholic church and the „three-cell theory”: a lot of knowledge was forgotten and practical experimenting (like dissection) was forbidden at that time.

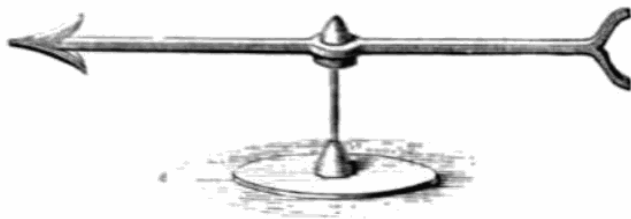
WILLIAM GILBERT (1544-1603)

English physician, physicist and natural philosopher. He studied magnetism, and concluded from his experiments that the Earth is magnetic and assumed that the centre of the Earth is iron. Studied the static electricity using amber and invented the first electric measuring instrument, the electroscope. Gilbert summarized his scientific work in his book *De Magnete* (About the Magnet) which was published in 1600. He can be considered as one of the fathers of electricity and magnetism.



THE ELECTROSCOPE

The electroscope is an instrument for measuring the electric charge. The first electroscope was invented by Gilbert around 1600 and it was called versorium. It was a thin pivoted metal needle fixed in a horizontal position on a wooden scaffold. The needle deflected when an object charged with static electricity was placed near the electroscope. The basis of electric charge detection is the Coulomb electrostatic force. The electroscope could only be used with static electricity and electrostatic machines, where enough charge was accumulated to deflect the needle. It gave only a qualitative measure from the magnitude of the charge, through the amplitude of the deflection. John Canton invented the pith-ball electroscope in 1754 and the gold-leaf electroscope was developed by Abraham Bennet in 1787.



Gilbert's versorium

(Sylvanus Phillips Thompson: *Elementary Lessons in Electricity and Magnetism*, 1902, MacMillan & Co., London, p.16, fig.11)

ELECTROSTATIC GENERATORS

An electrostatic generator is a device that produces static electricity, which is the buildup of charges on the surface of objects. Static electricity means high voltage with low current. Electrostatic machines transform mechanical energy into electric energy either by triboelectric effect (friction machines) or electrostatic induction (influence machines). The first friction machine was constructed by Otto von Guericke around 1663: it was a sulphur globe that could be rotated and rubbed by hand. Isaac Newton changed the sulphur to glass and J. H. Winkler changed the rubbing hand to leather. Later on, collecting conductors were connected to the friction machines to store the charges. The electric spark was a well known phenomenon in the laboratories at that time.

More about electrostatic machines: [link](#)

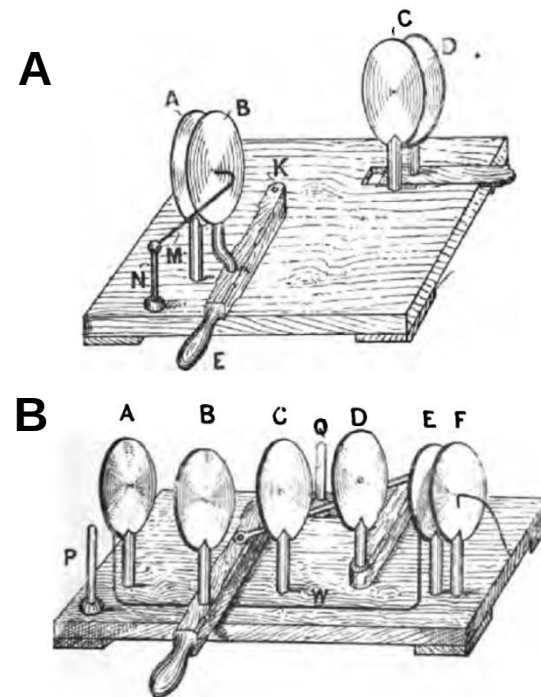


Friction machine
using a glass globe
(Hubert-François
Gravelot: *Die
Elektrisierte*, 1750)

TIBERIUS CAVALLO (1749-1809)

Cavallo was an Italian physicist and natural philosopher. He invented the multiplier in 1770 an instrument for amplification of electric charges at a level where it could be detected with electroscopes. Four metal plates, from which three were insulated and one conducting, were placed on a wooden board. Three of the plates were fixed on the board, and one could be freely moved. Charge multiplication was done by moving this free plate repeatedly back and forth from one fixed plate to the other.

Wilson's machine was a perfected version of Cavallo's multiplier, developed by William Wilson in 1804.



Cavallo's multiplier (A) and Wilson's machine (B)
(John Gray: *Electrical influence machines*, 1890, Whittaker & Co., London)

PIETER VAN MUSSCHENBROEK

(1692-1761)

Dutch scientist. He was a Professor of Mathematics, Philosophy, Medicine and Astrology. Static electricity could be generated by friction machines those times, but the method for the storage of electricity was unsolved. In 1746 he invented the first capacitor: the Leyden jar. He dipped a wire in a glass jar filled with water and tried to charge the water with a friction machine. His assistant held the glass jar in one of his hands and by accidentally touching the wire with his other hand, he got an electric shock. His hand acted namely as one of the plates of the capacitor while the electrically charged water was to other plate. The German cleric Ewald Georg von Kleist also invented the Leyden jar independently from Musschenbroek in 1744.



THE LEYDEN JAR

The Leyden jar was used in many experiments in the fields of electricity and also in electrophysiology and in electrotherapy. Like mentioned before, in Musschenbroek's experiment the outer plate of the capacitor was the human hand, the dielectric was the glass jar and the charged water served as the inner plate. Early versions of the Leyden jar followed this structure. Charging the water was possible with the help of friction machines through a metal nail that made contact with the water inside the jar.

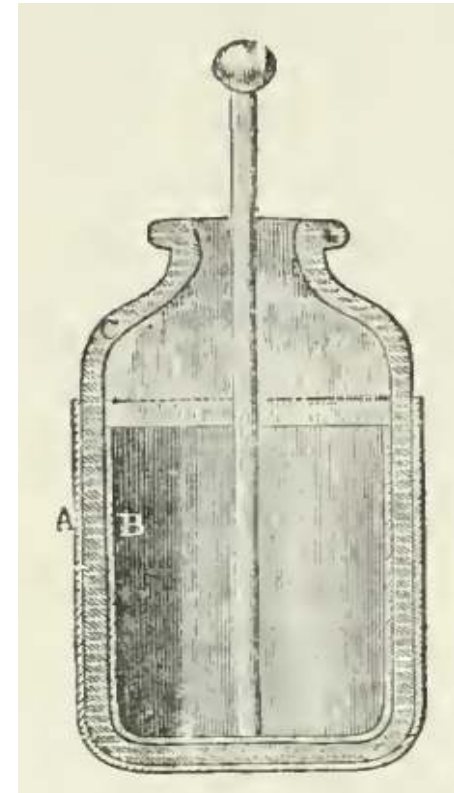


Leyden jar

W. Jerome Harrison and Charles A. White (1898)
Magnetism and Electricity, 5th Ed., Blackie and Son, UK, p. 107, fig. 64

THE LEYDEN JAR

The typical design of the Leyden jar consisted of conducting metal foils coating the outer and inner surfaces of a glass jar. The foils were separated from each other at the mouth of the jar. A rod electrode was placed in the jar and was connected to the inner foil. The jar was charged by an electrostatic generator via the electrode. The outer foil was grounded. Several jars could be combined to form a battery.



Leyden jar

Walter Larden (1903) *Electricity for Public Schools and Colleges*, Longmans Green & Co., New York, p.86

USE OF STATIC ELECTRICITY

Static electricity, sparks and the triboelectric effect originating from laboratories soon became a daily entertainment. But accidents with Leyden jars and electrostatic machines have proven that the human body is very sensitive to electricity, especially the muscles and the nerves. Shortly after these observations the electricity was used up to treating patients. This was a primitive form of electrotherapy based on the theory, that the fluids flowing in the nerves are electric in nature: neural disorders, paralysis and muscle cramps caused by hydrophobia were „cured” with the help of electricity. In some cases it worked very well: for example a paralytic hand of a patient almost fully recovered after the electrotherapy.

Also many animal experiments were conducted in those days to observe the relationship between the nerves and electricity: for example the stimulation of the spinal cord caused muscle twitches spreading all over the body, but had no effect on the heart.

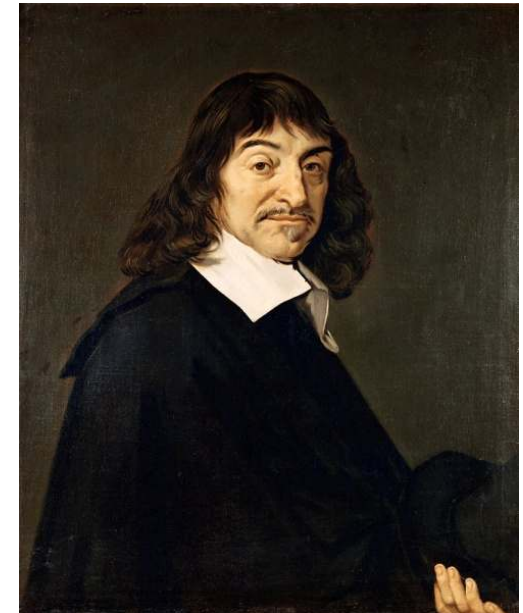
HENRY CAVENDISH (1731-1810) and the TORPEDO FISH

The torpedo fishes (or electric rays) are capable of producing an electric discharge of up to several hundred volts for self-defense and for stunning their preys. They have two electric organs on each side of the head and a specialized brain lobe, the electric lobe, for generating electric shocks. These animals turn up many times in the history, for examples see the „Ancient times” section.

Cavendish compared the electricity retrieved from electric rays with physical electricity: he got to the conclusion, that the two types of electricity are identical. He constructed a model of the torpedo fish (torpedo marmorata) from wood, leather and Leyden jars and could produce real electric shocks with this „artificial torpedo”. According to Cavendish, the properties of torpedoes suggest, that every animal contains „electrical fluid” (electrical current), and got to the conclusion that physical electric phenomena work on the same basis as the electric processes in the body of living organisms.

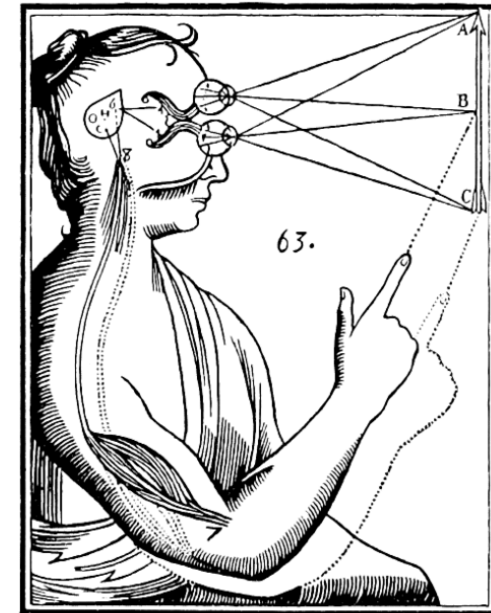
RENÉ DESCARTES (1596-1650)

French philosopher, mathematician and physicist. His two writings *Les passions de l'âme* (1649, Passions of the Soul) and *La description du corps humain* (1647, The Description of the Human Body) are of biological interest. For about 1500 years the popular view was that nerves function through the action of the „animal spirits” or „pneuma psychikon”. Movement was produced by these „moving spirits”, which travelled down the hollow nerves into the muscles. Descartes thought that these „spirits” were liquids or gases. In this era every phenomena was explained through a mechanical viewpoint, so the human body was considered as a complicated machine where the nervous mechanisms function like hydraulic automata. Ergo the body follows the laws of physics.



RENÉ DESCARTES (1596-1650)

Descartes had a modern view, but was in many aspects wrong. For example he suggested the pineal gland as „the seat of the soul”. The reason of his choice was because it was known that the soul is unitary, and unlike many areas of the brain the pineal gland appeared to be a unitary structure. Another reason for his choice, that the pineal gland was located near the ventricles, which were considered for many centuries the locations for imagination, cognition, and memory. So Descartes thought that the cerebrospinal fluid of the ventricles, influenced by the pineal gland, flowed through the nerves to muscles and controlled the body. With his theory Descartes isolated the mind (a non-material entity) from the body (a machine) and created the dualism.



RENÉ DESCARTES (1596-1650)

Because of the many analogies between humans and animals, Descartes suggested that human behavior could be studied through the investigation of animal behavior. For example he observed that both humans and animals have pineal glands. But because he believed that animals do not have a soul, he assumed that animals do not feel pain. This resulted in the spread of vivisection (the dissection of live animals) in experiments throughout Europe.

RENÉ DESCARTES (1596-1650)

The first clear discussion of a reflex also originates from Descartes: „if the fire A is close to the foot B, the small parts of this fire, which, as you know, move very quickly, have the force to move the part of the skin of the foot that they touch, and by this means pull the small thread C,C, which you can see is attached, simultaneously opening the entrance of the pore d,e, where this small thread ends ... The entrance of the pore or small passage d,e, being thus opened, the animal spirits in the concavity F enter the thread and are carried by it to the muscles that are used to withdraw the foot from the fire”

(R. Descartes, *De Homine*)



JAN SWAMMERDAM (1637-1680)

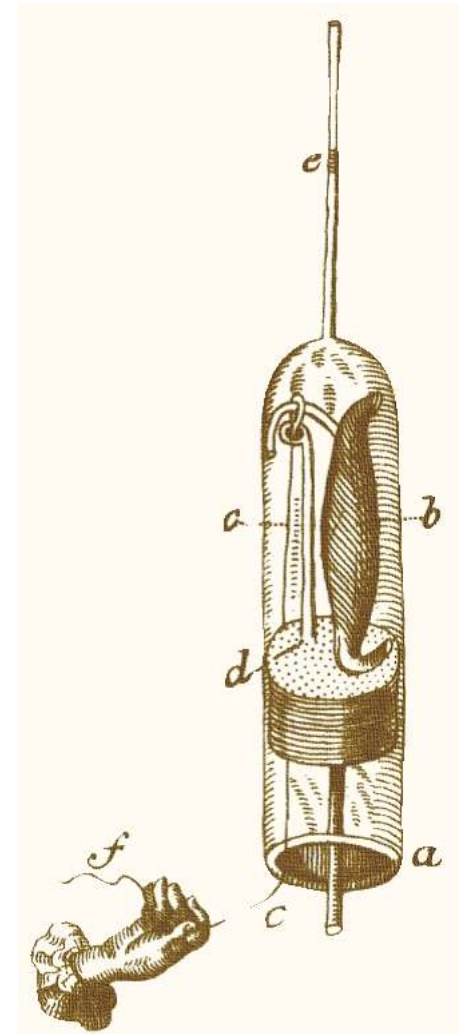
Dutch biologist, studied insects and carried out experiments on muscle contraction. Swammerdam was the first who observed and described the red blood cells.

Frogs were the best suited animals for experiment at this time because *”the nerves are very conspicuous in these animals, and may be easily discovered and laid bare.”* Swammerdam made the first isolated frog nerve-muscle preparation, which became widely used all over the world in neurobiological studies and high schools.

If the theory - that muscle contraction is caused by the „animal spirits” flowing in the nerves – is true, than the volume of the muscle has to increase on contraction. During the demonstration of this hypothesis, Swammerdam experienced that the contact of a silver wire and a brass wire used for moving the frogs nervus ischiadicus, irritates the nerve-muscle preparation and generates muscle contraction.

JAN SWAMMERDAM (1637-1680)

Swammerdam carried out the first electrophysiological experiment on a frog nerve-muscle preparation. The gastrocnemius muscle of the frog was placed in a closed, air-tight glass tube. A drop of water was on the top of the glass tube in the glass capillary. During the mechanical stimulation of the nervus ischiadicus the volume of the contracted muscle should increase according to the „animal spirit” hypothesis, with the drop moving upwards. He experienced the contrary: the volume of the muscle decreased during contraction or no movement of the water drop was observed. Swammerdam did not believe his own results, suggesting that they were the result of an artifact.

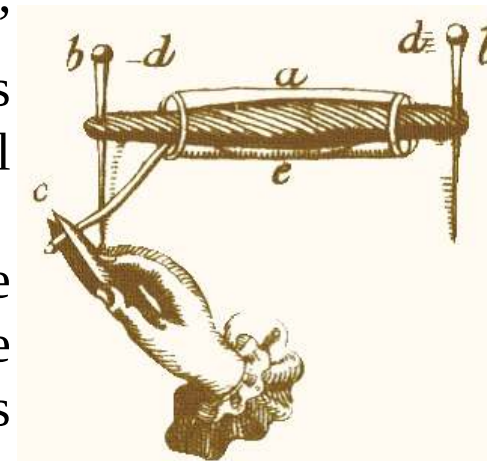
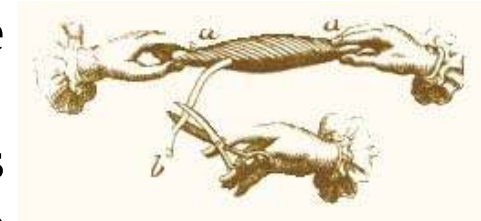


JAN SWAMMERDAM (1637-1680)

Swammerdam showed that cutting out the heart of a living frog has no effect on its ability to move, but if the brain is removed there is no more movement.

He showed in another experiment that no connection is needed between the muscle and the brain to evoke movements: touching the nerve ends on a dead frog with a scalpel caused muscle contraction (He called this „irritation” and this was one form of external stimulation). This was again contrary to Descartes’ theory where the „animal spirits” moved from the brain to the muscles.

The initial demonstration simply involved holding the muscle then stimulating the nerve (Upper figure on the right), but in his next experiment he put the muscle in a glass tube and fixed it with two needles through its tendons (Down figure on the right).

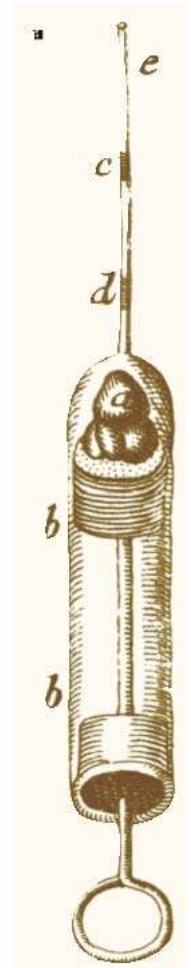


JAN SWAMMERDAM (1637-1680)

His experiment with a frog heart had the result that during contraction „*the drop of water adhering near the extremity of the tube (c), descends in a very remarkable and surprising manner...the drop thus fallen down (d), will, on the heart's dilating itself again, rise to its former situation(c).*” This completely contradicted Descartes's hypothesis again.

Swammerdam was the first who noticed the difference between sensory and motor nerves.

With his experimental design, the movement of a water drop in an airtight glass capillary, he invented the plethysmograph, which is a device for measuring changes in the volume of organs or the whole body.



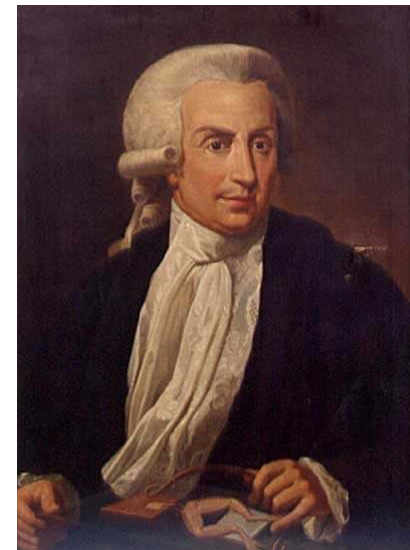
ALBRECHT VON HALLER (1708-1777)

Swiss anatomist, physiologist, naturalist and poet. He became a Professor of Anatomy, Surgery and Botany at the University of Göttingen in 1736. Studied physiology in Göttingen and carried out experiments to show that „sensibility” and „irritability” is a property of the organ or tissue. „Sensibility” means the ability to produce sensation, and after his findings only organs supplied with nerves are „sensitive”. „Irritability” is the reaction to a stimuli like muscle contraction generated by electric stimulation. His scientific work and results about this subject were published in 1753 in *De partibus corporis humani sensibilibus et irritabilibus* (On the sensible and irritable parts of the human body), which later helped to understand muscle physiology. With his findings Haller stated that nerves do not play a role in muscular motion, in contrast to the popular theory of „animal spirits” where the flow of „nervous fluid” from the brain through the nerves produced the movements.



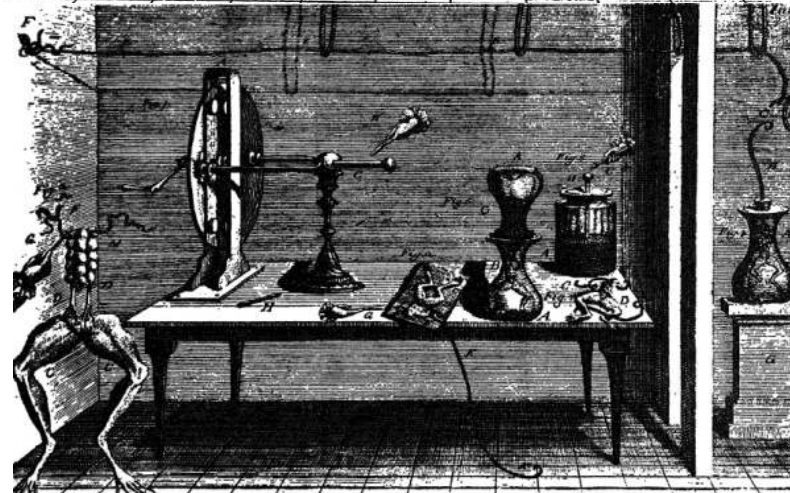
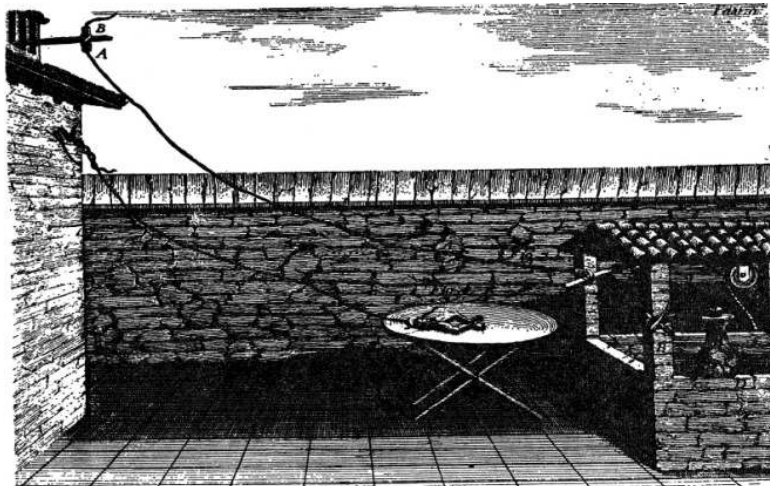
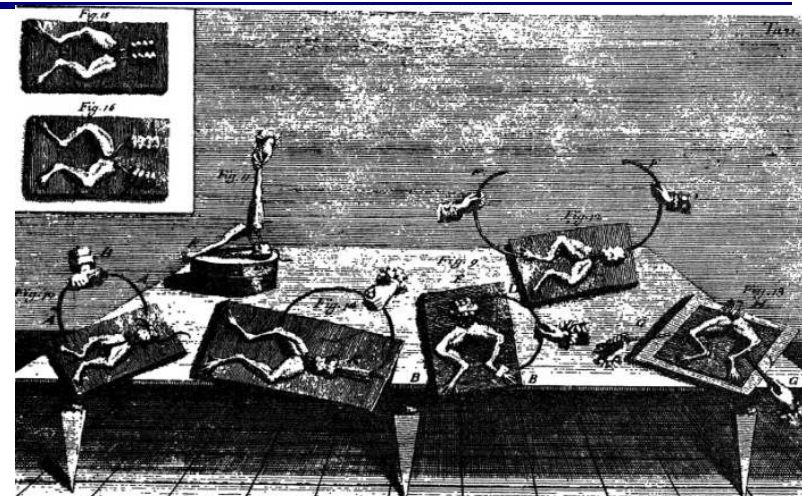
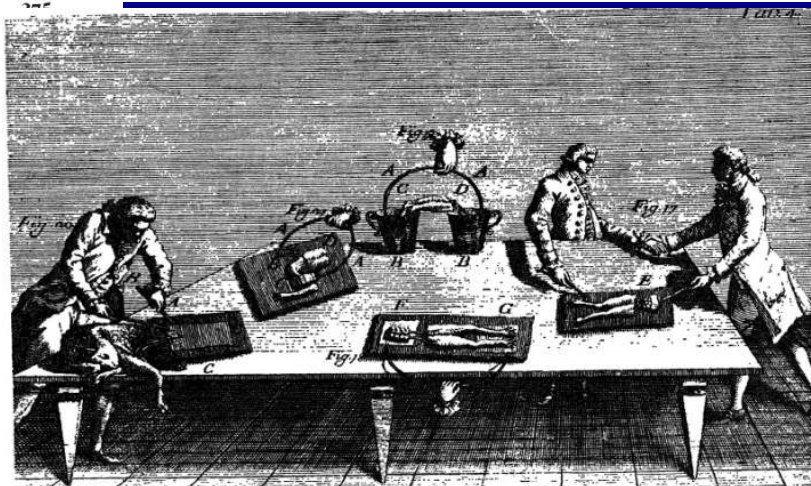
LUIGI GALVANI (1737-1798)

Italian physician and physicist. In 1762 he became a performer in anatomy on the University of Bologna. In 1775 he became here a Professor of Anatomy and Obstetrics. Galvani started his famous frog experiments in the early 1780's: the „animal electricity” was discovered with electrical stimulation of the frog nerve-muscle preparation. His scientific work is summarized in his book *De viribus electricitatis in motu musculari commentarius* (Commentary on the Effect of Electricity on Muscular Motion), published in 1791. His second work on animal electricity, *Trattato dell'Arco Conduttore* (Treatise on the Conducting Arc) was published in 1794. In 1796 Galvani was dismissed from his university positions because he refused to take a civil oath to the new Napoleonic republic for political and religious reasons.



LUIGI GALVANI (1737-1798)

Galvani can be regarded as the founder of electrophysiology. He made his experiments mainly on frogs, because their muscles kept on contracting for a long time after death. His famous experiment performed on the 26th January of 1781 is defined as Galvani's „first experiment”. He left a nerve-muscle preparation on the table with a friction machine. (at that time just static electricity was known, which changed soon with the invention of dynamic electricity by Volta) His assistant accidentally touched the nerve of the preparation with a scalpel exactly at the same time when the friction machine generated a spark. As a result the frog muscle contracted. This meant that electricity far from the nerve can also have an effect if a conductive medium is present (the assistant). The muscular contraction depended on whether the machine sparked or the contact was done with an insulated scalpel. Later they connected the friction machine with a metal wire to the frog leg: the contraction of the muscle appeared again as expected.



Galvani's frog experiments (L. Galvani: *De viribus electricitatis in motu musculari commentarius*, 1791)

LUIGI GALVANI (1737-1798)

In another experiment Galvani hooked up the frog legs on an insulated metal wire outside of the house. A storm was just to break out, and a lightning strike hit the conducting wire causing the contraction of all of the muscles of the preparations. This was the demonstration that natural electricity discovered by Benjamin Franklin (1706-1790) can also initiate muscular contractions.

Galvani developed one of the most modern laboratories in his own house: it was equipped with the best instruments for electrical research known that time. Electrostatic machines, Leyden jars, Aepinus' condenser and recently invented devices like the electrophorus could also be found in his lab.

LUIGI GALVANI (1737-1798)

The term „animal electricity” (also often referred as galvanism) comes from Galvani. He compared the muscle fibers to Leyden jars. According to his opinion, electricity is flowing from the brain through the nerves to every organ, so to the muscles too. The muscles store this electricity and when a stimulus generates an electric discharge, the excitable muscles contract.

This theory was attacked by his contemporary Alessandro Volta in 1792: a famous controversy began between the two scientists about the existence of „animal electricity”, which was continued by Galvani’s nephew Giovanni Aldini after his death in 1798. Volta claimed that the muscular contraction is just due to the interaction between two different metals, that generate a galvanic cell.

ALESSANDRO VOLTA (1745-1827)

Italian physicist. In 1774 he became Professor of Physics at the Royal School of Como and in 1779 he became Professor of Experimental Physics at the University Pavia. In 1775 he improved the electrophorus (invented by Johan Carl Wilcke in 1762), a device that produces static electric charge via the process of electrostatic induction. Volta discovered methane and studied the electrical capacitance. He became familiar with Galvani's „animal electricity” in 1791 and shortly observed that electricity is always flowing between two metals separated by an electrolyte. The frog preparation served as the electrolyte in Galvani's experiment, and because the muscle is an excitable tissue the electric current forced it contract. So according to Volta's findings there is no „animal electricity”.



ALESSANDRO VOLTA (1745-1827)

In 1800 Volta invented the voltaic pile, the first electric battery, and named it galvanic cell in honor of Galvani. The device consisted of two different metal discs (for example brass and zinc, but silver was also often used in place of brass), these were placed above each other in an alternating pattern with cardboards soaked in salt water between the metal pieces. The wet cardboards served as the electrolyte and the salt water could be replaced with sulphuric acid. The voltaic pile produced electric current continuously and for a long time contrary to the Leiden jar or the static electricity induced high-power, flash like discharges of electric condensation devices.

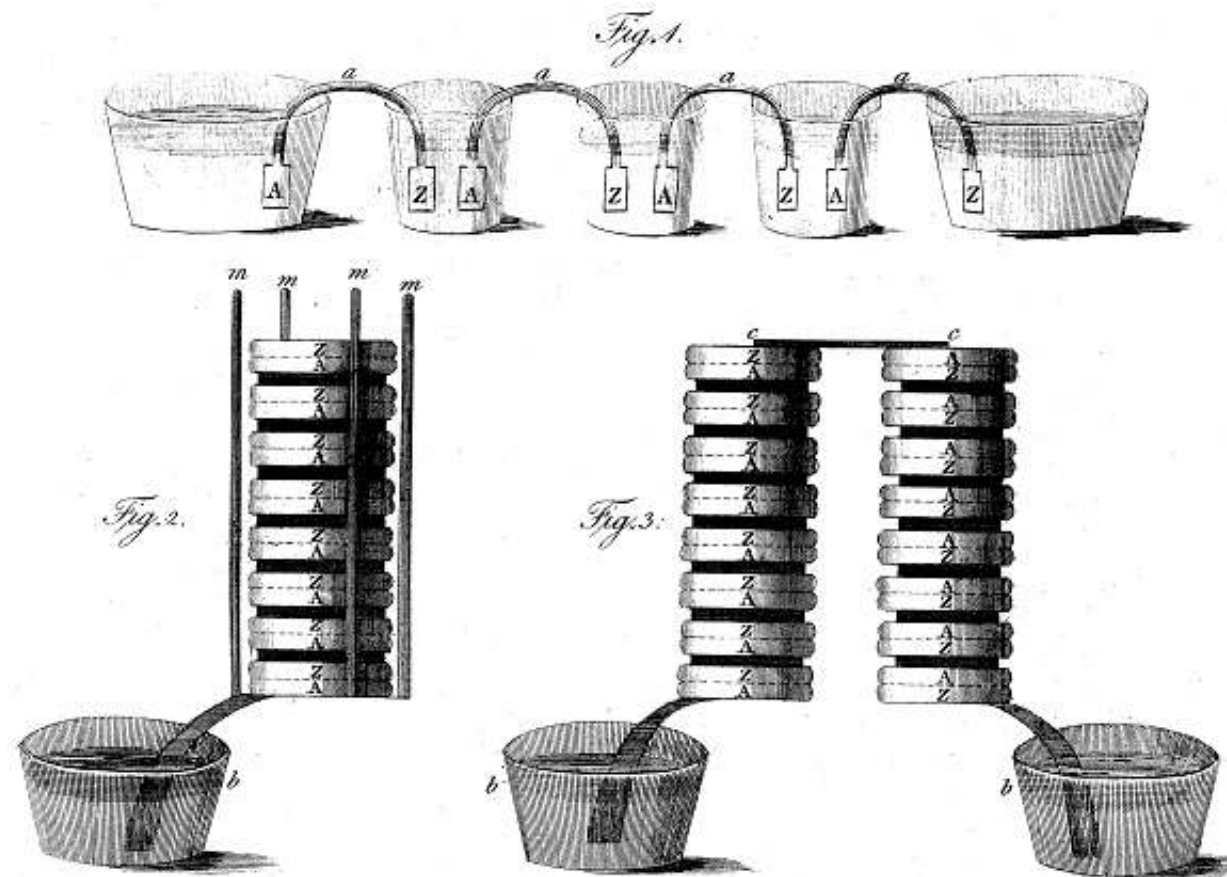
ALESSANDRO VOLTA (1745-1827)

So Volta figured out that two different metals in the presence of a wet medium, like the muscle of the frog, generate muscular contractions. In his opinion just two different metals and an electrolyte is needed to produce electricity. The muscle of the frog is only a wet media, which detects and reacts to electricity with contraction because of its excitability. The muscle itself does not generate electricity. There is no „animal electricity”, just the two metals are producing the electric current. This phenomenon is called bimetallic electricity.

Galvani's riposte: proved that „animal electricity” exists and is a real phenomenon. He cut through the spinal cord of frogs and put one of the prepared leg muscle to the lesioned end of the spinal cord. When the free end of the muscle touched the marrow, it contracted. With this experiment Galvani unwittingly discovered the phenomenon of the „lesion current”.

ALESSANDRO VOLTA (1745-1827)

Many experiments on electric stimulation of the brain were carried out with the voltaic pile at this time. Insects, frogs, and mammals were used to generate muscular contraction (Humboldt, Cabanis), but without success because the battery invented by Volta produced small currents, and probably the experimenter avoided the motor cortex and the other brain structures capable of evoking movements.



The voltaic pile (A. Volta, *On the Electricity Excited by the Mere Contact of Conducting Substances of Different Kinds*, 1800)

GIOVANNI ALDINI (1762-1834)

Italian physicist, nephew and assistant of Galvani. He became Professor of Physics in Bologna in 1798. Aldini carried out experiments where the principles of Galvani (animal electricity) and Volta (bimetallic electricity) were used together. He was the first who performed electric stimulation on the human brain. Continued the scientific debate between Volta and Galvani from the existence of „animal electricity” after Galvani’s death. Demonstrated that muscular contraction in frogs can be obtained with one metal only (he used purified mercury) or without the use of any metals. He treated and cured patients suffering from various mental disorders (like major depression) with the help of transcranial electric current administration.



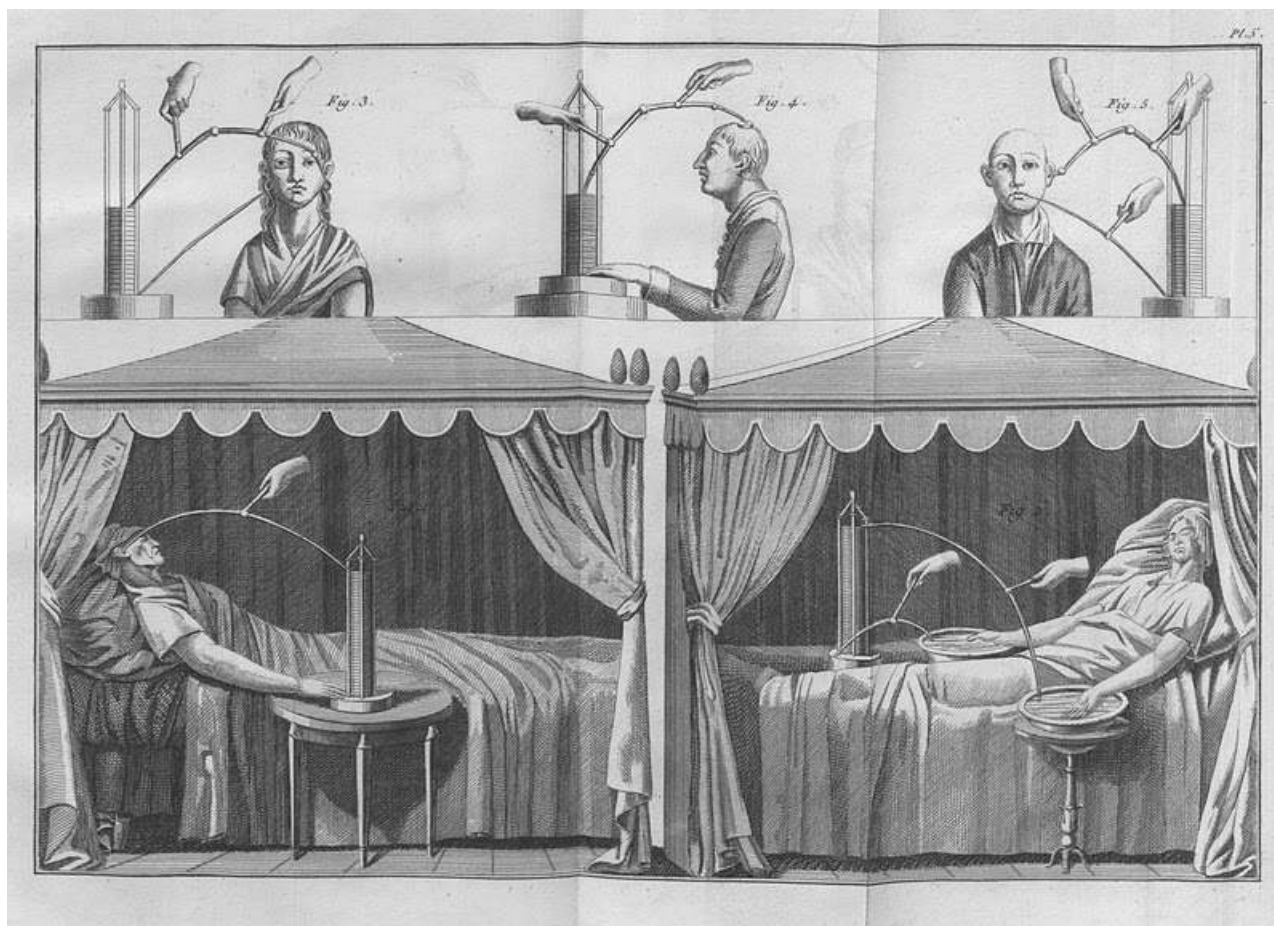
GIOVANNI ALDINI (1762-1834)

He made experiments on the heads and trunks of recently died cows, sheep, dogs and horses. Moistened the inside of the ears or the nasal cavity with salt water and put one of the metallic wires here and the other wire somewhere in the brain. Twitches of the facial muscles and the muscles of the extremities were observed during closing or opening the electric arc. He stimulated not just on the surface of the brain, but entered also to the deeper regions. Stimulating deep increased the amplitude of muscle movements. Carried out experiment on the heads and bodies of executed criminals: twitching of facial muscles or the convulsion of the corpse was visible. His most famous demonstration in 1803 on the executed murderer George Foster had very dramatic results: *“the jaw began to quiver, the adjoining muscles were horribly contorted, and the left eye actually opened.”* After placing one rod to the rectum, the movements of the dead body were *“so much increased as almost to give an appearance of reanimation.”*

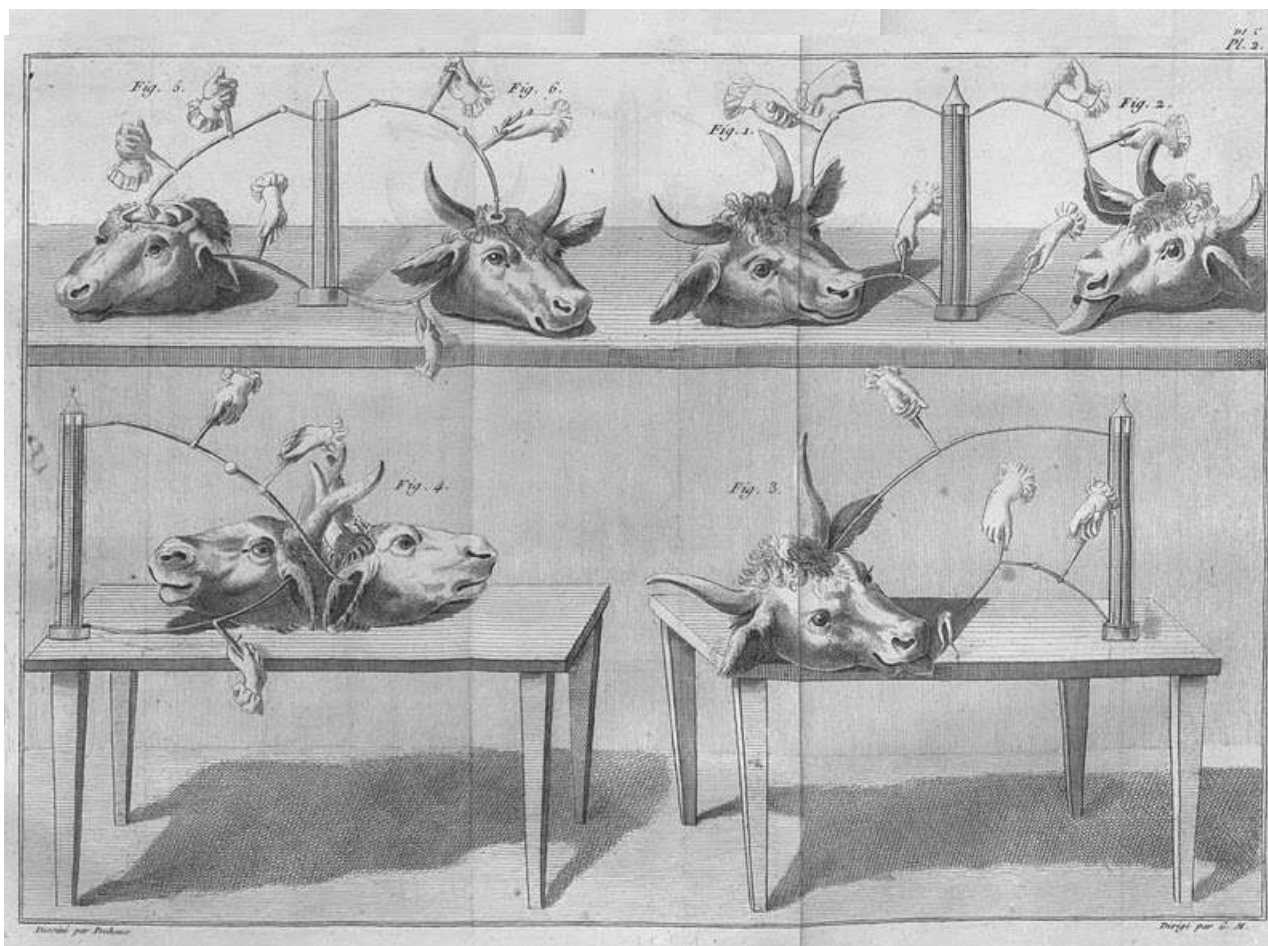
GIOVANNI ALDINI (1762-1834)

For his experiments he used voltaic piles which were constructed from copper and zinc disks. One of these galvanic cells consisted of 100 copper and zinc pieces. He proved that stimulating the left hemisphere leads to contralateral movements.

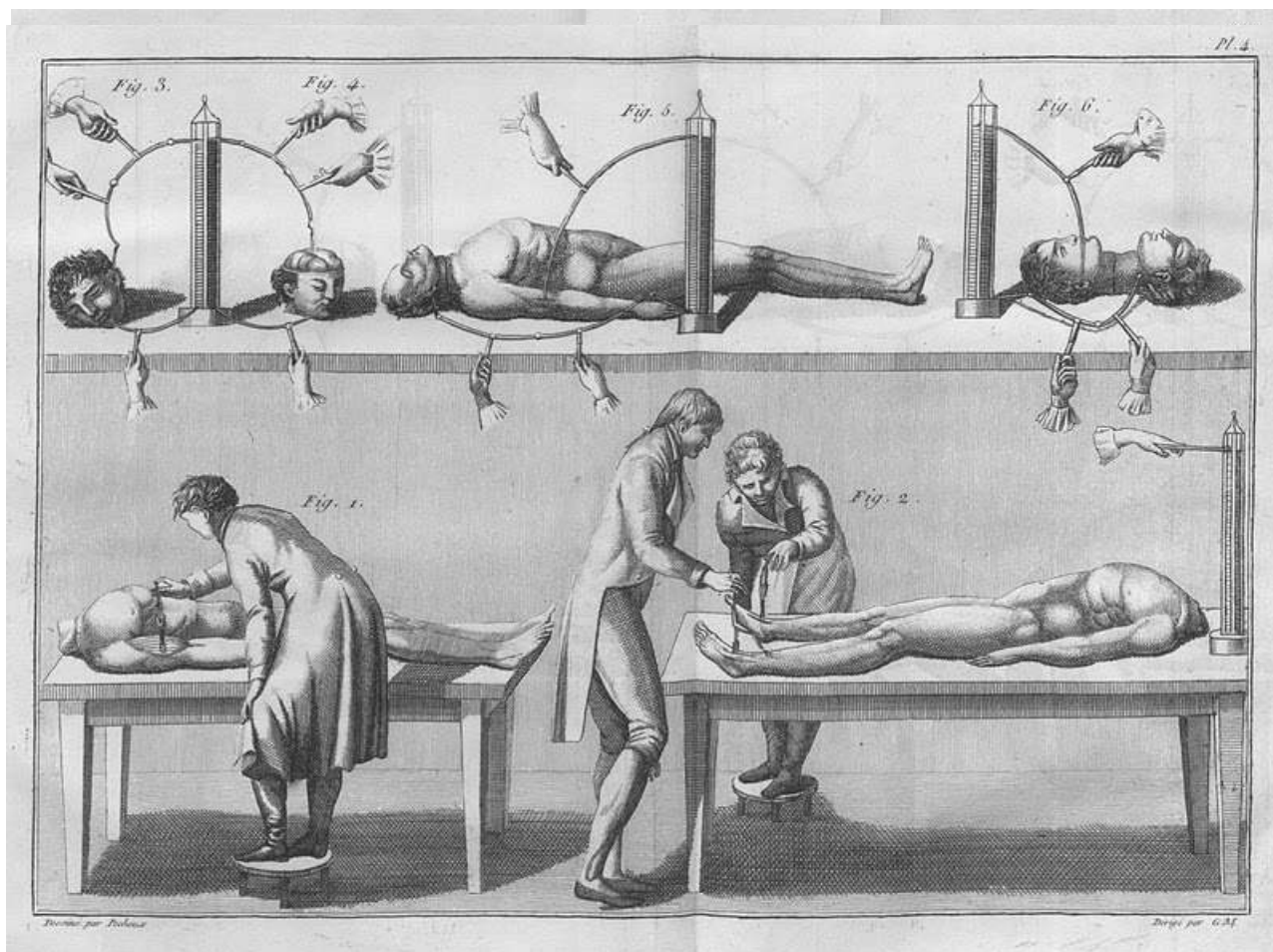
Travelled throughout Europe to popularize galvanism and the theory of „animal electricity” and also the usefulness of transcranial stimulation in medicine. In 1804 he published his book *Essai théorique et experimental sur le galvanisme* (Theoretical and experimental essay on galvanism) which contains the description of his experiments and 10 beautiful and informative plates drawn by Pecheux. Unfortunately his findings got lost or were ignored by the community, and his experiments were not continued by anyone. Electric stimulation of the brain were discovered again one century later by Gustav Fritsch and Eduard Hitzig.



Early „electrotherapy” by Aldini (Aldini J.: *Essai théorique et experimental sur le galvanisme*, 1804)



Animal experiments (Aldini J.: *Essai théorique et experimental sur le galvanisme*, 1804)



Experiments on executed criminals (Aldini J.: *Essai théorique et expérimental sur le galvanisme*, 1804)

EARLY ELECTRIC MEASUREMENT DEVICES

A galvanometer was an instrument for detecting and measuring electric current. Johann Schweiger built the first galvanometer in 1820: it was a compass with a coil of wires around it. This early devices were also called „multipliers” because of the multiple turns of wire. Later, galvanometers were constructed with two magnets, to become independent of the Earth’s magnetic field. This were called ‘astatic’ galvanometers. William Thomson (Lord Kelvin) invented the mirror galvanometer (patent in 1858), where the magnitude of the currents were calculated from the deflection of a light beam directed to a mirror moved by the magnets attached to it. The string galvanometer was developed by Willem Einthoven in 1901: the currents were detected with a thin and long silver coated quartz filament and the instrument was the first practical ECG. Another solution for measuring small currents was the capillary electrometer invented by Gabriel Jonas Lippman: this device could also be used for detecting the small currents of the heart.

CARLO MATTEUCCI (1811-1868)

Italian physicist and physiologist. Became the Professor of Physics at the University of Pisa in 1840. Matteucci followed the work of Galvani and his „animal electricity”. Started his electrophysiological experiments in 1830 and continued these until his death. Proved with a sensitive galvanometer invented by Nobili, that the injured tissue generates a continuously flowing electric current. Serial stacking of muscles, that form a „muscle pile” produce a greater current, than an individual muscle, same way as putting more metal disks to a voltaic pile generates bigger currents. He demonstrated sparkles by putting a torpedo fish between two metal plates. With his experiments he proved unequivocally, that the living organism can truly generate electric signals however it was not located to the central nervous system.



CARLO MATTEUCCI (1811-1865)

He used frog preparations to his examinations. In one of his experiments he touched the injured muscle of a frog nerve-muscle preparation with the nerve ending of another preparation. The muscle of the latter preparation contracted. He stated with the help of a galvanometer, that a current is flowing between the injured and uninjured surfaces of the muscle, later this phenomenon was called „current of injury”. The another frog preparation „sensed” this current and generated a muscular contraction. He called this frog preparation „rheoscopic frog” and used as an electric sensor in other experiments like in the demonstration of the presence of electric current in the heart at every heartbeat.

Matteucci wrote many papers on his electrophysiological investigations: for example the *Trattato dei fenomeni elettrofisiologici degli animali* (Treatise of electrophysiological phenomena of the animals) was published in 1844 and eleven memoirs can be found in the Philosophical Transactions from 1845-1861 with the title *Electro-Physiological Researches*.

JOHANNES MÜLLER (1801-1858)

German physiologist and comparative anatomist. Müller became a Professor of Physiology at the Bonn University in 1830, but soon went to the Humboldt University of Berlin (1833) also as a Professor of Physiology. He was the mentor of great scientists as Carl Ludwig, Emil du Bois-Reymond, Hermann von Helmholtz, Theodor Schwann and Friedrich Gustav Jacob Henle. Müller's famous work *Handbuch der Physiologie des Menschen* (Handbook of Human Physiology, 1833–1840) became the leading textbook in the subject. Contributed to many areas of physiology, especially to neurophysiology. He studied the cranial nerves, accelerated the understanding of hearing and speech, but his most important work was about the mechanisms of senses.



JOHANNES MÜLLER (1801-1858)

One of Müller's great experiments was that resulted in the distinguishing between sensory and motor nerves. By mechanically or electrically stimulating the anterior roots of frogs he observed movement in the extremities, which was not present in case of the stimulation of the posterior roots. He carried out another experiment that sensory and motor nerves are separate: cut through the posterior roots of nerves from a limb of frogs and dogs. The limbs became insensible, but movements were further observable. However the lesion of the anterior roots resulted in paralyzed limbs which have not lost their sensibility.

In 1844 Müller did the following statement: „*Probably we will never have the means to measure the speed of the nervous action, since we lack, in order to establish comparisons, these immense distances whereby we can calculate the speed of light, which, under this respect, has some relation with it.*” A few years later his pupil Hermann von Helmholtz measured the nerve conduction velocity of the frog nervus ischiadicus.

JOHANNES MÜLLER (1801-1858)

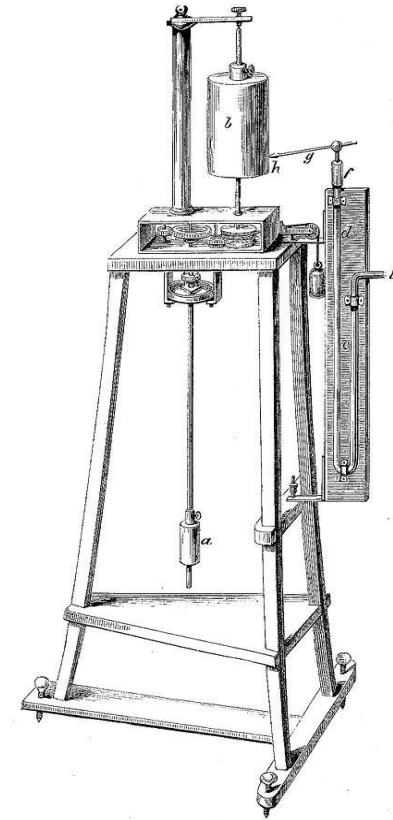
His researches about the senses and stimulation-sensation relationship resulted in the formulation of the „law of specific nerve energies”:

„The same cause, such as electricity, can simultaneously affect all sensory organs, since they are all sensitive to it; and yet, every sensory nerve reacts to it differently; one nerve perceives it as light, another hears its sound, another one smells it; another tastes the electricity, and another one feels it as pain and shock. One nerve perceives a luminous picture through mechanical irritation, another one hears it as buzzing, another one senses it as pain. . . He who feels compelled to consider the consequences of these facts cannot but realize that the specific sensibility of nerves for certain impressions is not enough, since all nerves are sensitive to the same cause but react to the same cause in different ways. . . (S)ensation is not the conduction of a quality or state of external bodies to consciousness, but the conduction of a quality or state of our nerves to consciousness, excited by an external cause.”

CARL WILHELM LUDWIG

(1801-1858)

German physician and physiologist. He became a Professor of Physiology in 1842 and a Professor of Comparative Anatomy in 1846. He invented the kymograph in 1847, a device used for recording the blood pressure. Later it was used by experimental physiologists for recording various time related events as response times, muscle contraction or tuning fork vibration. The kymograph consisted of a rotating drum holding a record sheet which was usually a smoked paper. A stylus contacted the sheet and recorded the signals.



Ludwig's kymograph (Élie de Cyon: *Methodik der physiologischen Experimente und Vivisectionen*, 1876)

HERMANN L. F. VON HELMHOLTZ

(1820-1894)

German physician and physicist. He became a Professor in Physics at the University of Berlin in 1871. Helmholtz worked on many areas of the modern science with significant results. He studied the vision and eye, and published the *Handbuch der Physiologischen Optik* (Handbook of Physiological Optics) in 1867 which became a fundamental reference work in the subject of vision and included theories on color vision (trichromatic theory of color vision), visual perception and spatial vision. Invented the ophthalmoscope, an instrument used to examine the human retina. He also contributed to the field of hearing with studies about the sensation of tone, the perception of sound and the organ of Corti. In physics the discovery of the law of conservation of energy made him widely known.



HERMANN L. F. VON HELMHOLTZ (1820-1894)

His main contribution to neurophysiology was the measuring of the nerve conduction velocity of the frog in 1850, which was stated impossible by his tutor Johannes Müller. The course of the interesting experiment was the following: Helmholtz stimulated the nervus ischiadicus of the frog with static electricity which resulted in the contraction of the gastrocnemius muscle. The muscle was tied up to the stylus of a kymograph so the contraction caused a deflection on the smoked paper. The rotation of the kymograph was started by a spring and a small device closed the electric circuit in the appropriate time, after the spring released the kymograph. The spring stopped the kymograph after one turn.

To measure the nerve conduction velocity, Helmholtz stimulated the nerve at two different points: first further from the muscle, than closer to it. When stimulation was carried out closer, the muscular contraction happened earlier and when stimulated further, a small delay was observable in the contraction.

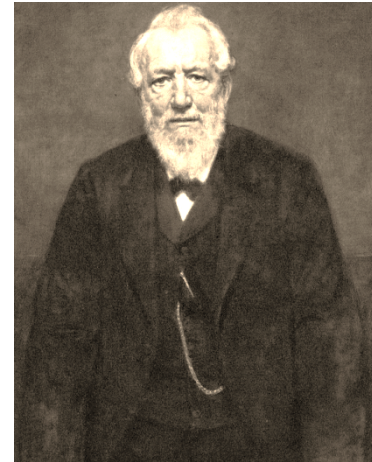
HERMANN L. F. VON HELMHOLTZ (1820-1894)

After that he had only to measure the distance between the two stimulation points and the time difference between the two contractions. The measuring of the time on the kymograph was achieved with the help of sine wave drawn by a 100 Hz tuning fork. This resulted in a 10 ms time scale. He got the conduction velocity by calculating the quotient of the distance and time. For the motor nerve of the frog this value was approximately 30 m/s. Later he measured the conduction velocity of the sensory nerves too, and a got a result around 50-100 m/s. He measured the conduction velocity also on human subjects. Another finding he made, that the conduction velocity depends on the temperature: cold decreases the values, heat increases it.

Publishing the results were not an easy task: neither Müller, nor Humboldt accepted his finding, but finally his friend Du Bois-Reymond helped him. Soon after Müller and also Humboldt admitted the accuracy of his measures, which roughly speaking, hold out nowadays too.

EMIL DU BOIS-REYMOND (1818-1896)

German physician and physiologist. He can be regarded as the founder of the experimental electrophysiology. Discovered the nerve action potential. His book *Untersuchungen über thierische Elektrizität* (Researches on Animal Electricity) appeared in 1848. He started his work on electrophysiology and bioelectricity after reading the essay of Carlo Matteucci got from his mentor Johannes Müller. He repeated Matteucci's experiments and confirmed some of his results, but in many cases du Bois-Reymond had proven that Matteucci was wrong. He improved the galvanometers used for measuring the currents of frog nerve-muscle preparations and used induced current for stimulation. The induction coil invented by Michael Faraday was used first in medical applications by du Bois-Reymond. This was called Faraday stimulation. The terms „electrotonus” and „stimulation” also comes from him.



EMIL DU BOIS-REYMOND (1818-1896)

Like Matteucci, he also discovered the „action current” or with another term the „current of injury”. (but the term comes from his student Hermann Ludmar) Du Bois-Reymond named this phenomenon, - where the harmed surface of the frog muscle was negative according to the unharmed surface - „negative variation” („Negative Schwankung”) He found this process also in nerves. This „negative variation”, which is actually the well-known action potential, travels through the whole nerve without energy loss, so they thought that this phenomenon is identical to the „animal electricity” discovered long ago. He measured the membrane potential from the harmed surface with macro methods.

He was the first who mentioned that some chemical process could be the reason of the delay of the action potential when advancing from the nerve ending to the muscle.

SIR VICTOR ALEXANDER HADEN HORSLEY

(1857-1916)

British scientist, physician and physiologist. Developed many practical neurosurgical techniques as the bone wax, the skin flap or the Horsley-Clarke apparatus. The latter was developed together with Robert H. Clarke in 1908 and was used to perform stereotactic surgery. With this method precise localization of each brain structure could be achieved with the help of numerical coordinates and a stereotactic brain atlas. The improved versions of the Horsley-Clarke apparatus, which are nowadays called stereotaxic frames, are widely used in animal experiments and in human neurosurgery. Horsley was also a very talented neuroscientist: he studied the brain functions of humans and animals, concentrating mainly on the cerebral cortex. He was the first who used intraoperative electrical stimulation of the cortex to localize the epileptic foci in humans.



EDUARD HITZIG (1839-1907)

GUSTAV FRITSCH (1838-1927)

Hitzig was a German neurologist and neuropsychiatrist and Fritsch a German anatomist and physiologist. More than a half century after Aldini's forgotten experiments they rediscovered the movements evoked with brain electrical stimulation. They studied the relationship between the electric current and the brain on the exposed cerebral cortex of unanesthetised dogs. They observed that the stimulation of certain parts of the cerebrum caused involuntary muscular contractions of specific parts of the dog's body. With this discovery they localized the motor cortex which is the brain area responsible for voluntary movements. They published their findings in the *Archiv für Anatomie, Physiologie und wissenschaftliche Medizin* with the title *Ueber die elektrische Erregbarkeit des Grosshirns* (On the Electrical Excitability of the Cerebrum) in 1870.



RICHARD CATON (1842-1926)

British physician and scientist. Caton became a Professor of Physiology in 1881 at the Victoria University. He was the first who recorded bioelectric signals from the cerebral cortex. To achieve this, he developed further the techniques of Du Bois-Reymond in 1875 and recorded electric potentials from the brain with Thomson's mirror galvanometer. For his experiments he used cats, monkeys and rabbits. After opening the skull and removing the dura, electrodes were clamped to the skull of the anaesthetized animals to avoid their displacement during movements. One electrode was placed over the area under study and the other somewhere on the surface of the brain or on the skull. After the surgery animals were allowed to recover consciousness. With the moving of the different body parts of the animals Caton could record electrical responses in the appropriate brain areas. He used David Ferrier's (1843-1928) map from the monkey cerebral cortex to determine the location of the electrodes.

RICHARD CATON (1842-1926)

The observed variation of potentials were independent from the heartbeat, respiration and from outer stimuli. In dying animals the degree of deflections decreased and soon later it ceased. According to him, the measured electrical potentials were generated by the electropositivity of the brain surface and by the electronegativity of the regions under the cortex.

He also recorded potentials shifts by giving strong stimulus to the animals. For example by illuminating the retina of the left eye with bright light he observed electrical potential changes in the posterior part of the right hemisphere.

Caton published his findings in the British Medical Journal in 1875 with the title *The electrical currents of the brain*. Two other publications followed this one and after these he stopped his studies on the brain and never continued it again. His discoveries did not became widely known, so many scientists rediscovered his findings a few years later.

BRAIN ELECTRIC POTENTIALS

In 1876 Vasili Yakovlevich Danilevsky (1852-1939) came to similar results independent from Caton, with experiments on dogs paralyzed with curare.

Adolf Beck (1863-1942) was also unaware of Caton's results and repeated them a decade later. He studied the spontaneous electric activity of the brain and observed that these spontaneous waves are not uniform, they can be separated in different groups. Beck stated that also human brain functions could be studied with electrodes placed on the scalp, but the necessary amplification technology was not yet available. Beck published his results in 1890 in the *Zentralblatt für Physiology*. Soon after his paper appeared, a sealed letter was opened on the Academy of Vienna sealed by Fleischl von Marxow in 1883. In the letter Marxow wrote that he already made a similar discovery about brain potentials years ago. He did not publish his observations, but with the letter he proved his priority. In 1891 Caton cleared the situation about the priority: he mentioned his report published in 1875 about brain electrical currents.

HANS BERGER (1873-1941)

Austrian psychiatrist. Berger became a Professor in Psychology in 1919 at the University of Jena. He recorded the first bioelectric signals from the brain of a human in 1924. His subject was his 15 year old son Klaus. He named the recordings Electroencephalogram (EEG). Published a paper about his findings in the *Archiv für Psychiatrie und Nervenkrankheiten* with the title *Über das Elektroencephalogramm des Menschen* in 1929. Discovered and named the first brain rhythms: the alpha activity appears in a relaxed, but alert state, when the eyes are closed. It disappears when counting or other mental activities are performed. The frequency range of the alpha rhythm is from 8 to 12 Hz and can be recorded with the best quality from the occipital region of the brain. He gave the name „alpha waves” because these were the first waveforms isolated from the human EEG, but for his honor alpha waves are also called Berger-rhythm.

HANS BERGER (1873-1941)

Beta waves have a lower amplitude but a higher frequency (12-30 Hz) compared to the Berger rhythm and are related to mental concentration and to startle reactions according to Berger.

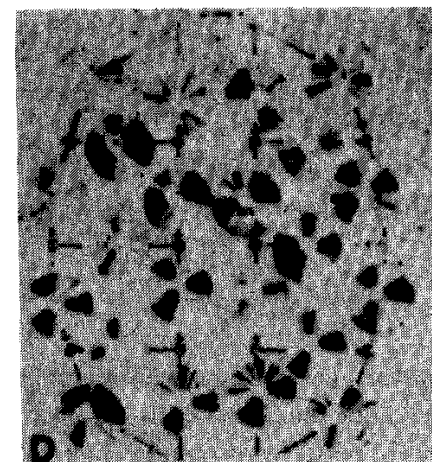
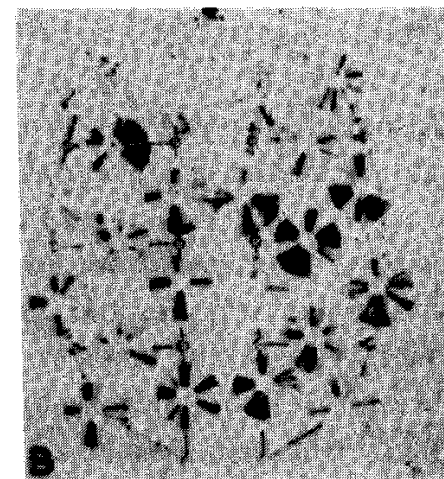
He used silver wires or silver foil electrodes placed on the scalp of the subjects, one electrode acting as a reference and the other as the active electrode. Usually one of the electrodes was placed at the front of the head (reference) and the other at the back over the occipital lobe. As a recording device he tried first Lippmann's capillary electrometer with poor results, after that he switched to the string galvanometer. Later he used a double coil Siemens galvanometer.

He studied the relationship of the EEG and brain diseases like epilepsy, Alzheimer's disease or sclerosis multiplex. In other experiments he found that alpha waves diminished during sleep or during general anesthesia.

In 1941 after tough times caused by the Nazis, Berger committed suicide.

WILLIAM GREY WALTER (1910-1977)

American neurophysiologist. Improved the EEG invented by Hans Berger, allowing Walter to detect many of the well-known brain waves from the alpha to the delta range. With this device he made a number of discoveries for example he could use the delta waves to locate brain tumors. In the 1960s he discovered the contingent negative variation (CNV) or readiness potential. Developed the first brain topography machine (also called toposcope) in collaboration with Harold W. Shipton, an electronic engineer. The toposcope displayed the spatial organization of the EEG activity in a new way. It consisted of an array of small cathode ray tubes connected to high gain amplifiers. He was also interested in robotics: the Machina Speculatrix was one of the first electronic autonomous robot, constructed by Walter.



INVENTIONS IN THE 20TH CENTURY

The discoveries on the electric phenomena of the brain came to a sudden stop at the end of 19th century, and needed the development of new technologies and techniques to produce new striking results. Here some examples of inventions which helped electrophysiology to regain its leading role in the field of science.

Karl Ferdinand Braun developed the cathode ray tube oscilloscope in 1897. Lee de Forest invented in 1906 the vacuum tube, which could amplify the weak bioelectric signals of brain. The first transistor was developed by John Bardeen and Walter Brattain in 1948 at the AT&T's Bell labs. The field effect transistor (FET) made it possible to build miniaturized, reliable, portable and much cheaper instruments. Later, with the invention of the MOS (metal oxide semiconductor) transistor and the integrated circuit technology, the EEG machines and other scientific devices became affordable by smaller laboratories too.

NOBEL PRIZES IN ASSOCIATION WITH BIOELECTROMAGNETIC PHENOMENA

Year	Name	Nationality
1901	<u>Jacobus van't Hoff</u>	The Netherlands
1903	<u>Svante Arrhenius</u>	Sweden
1906	<u>Camillo Golgi</u> <u>Santiago Ramón y Cajal</u>	Italy Spain
1920	<u>Walther Nernst</u>	Germany
1924	<u>Willem Einthoven</u>	The Netherlands
1932	<u>Edgar Douglas Adrian</u> <u>Sir Charles Sherrington</u>	Britain Britain

NOBEL PRIZES IN ASSOCIATION WITH BIOELECTROMAGNETIC PHENOMENA

Year	Name	Nationality
1936	<u>Sir Henry Hallet Dale</u> <u>Otto Loewi</u>	Britain Britain
1944	<u>Joseph Erlanger</u> <u>Herbert Spencer Gasser</u>	U.S. U.S.
1949	<u>Walter Rudolf Hess</u>	Switzerland
1961	<u>Georg von Békésy</u>	U.S.
1963	<u>Sir John Eccles</u> <u>Alan Lloyd Hodgkin</u> <u>Andrew Fielding Huxley</u>	Australia Britain Britain

NOBEL PRIZES IN ASSOCIATION WITH BIOELECTROMAGNETIC PHENOMENA

Year	Name	Nationality
1967	<u>Ragnar Arthur Granit</u> <u>Haldan Keffer Hartline</u> <u>George Wald</u>	Finland U.S. U.S.
1968	<u>Lars Onsager</u>	U.S.
1970	<u>Julius Axelrod</u> <u>Sir Bernard Katz</u> <u>Ulf von Euler</u>	U.S. Britain Sweden
1981	<u>David Hunter Hubel</u> <u>Torsten Nils Wiesel</u> <u>Roger Wolcott Sperry</u>	U.S. Sweden U.S.

NOBEL PRIZES IN ASSOCIATION WITH BIOELECTROMAGNETIC PHENOMENA

Year	Name	Nationality
1991	<u>Erwin Neher</u> <u>Bert Sakmann</u>	Germany Germany
2000	<u>Arvid Carlsson</u> <u>Paul Greengard</u> <u>Eric Kandel</u>	U.S. U.S. U.S.

CAMILLO GOLGI (1843-1926) S. RAMÓN Y CAJAL (1852-1934)

They received the Nobel Prize in Physiology or Medicine in 1906 for their studies on the structure of the nervous system. This was the first shared Nobel Prize.

Golgi invented the silver-staining, an impregnation method, which randomly stains cells in the nervous tissue. The traced black neurons were well separable from the yellow background. Golgi discovered the Golgi tendon organ and Golgi apparatus in the cells. The Golgi cells in the cerebellum were named also after him.

Cajal was a great supporter of the neuron doctrine, which stated that the neuron is the functional unit of the nervous system, that builds up from these discrete, individual cells. Golgi's silver-staining was a very good proof to the theory, nonetheless that Golgi held opposed views: he thought that the nervous system is a huge network, where continuity is between every part of the system.

WILLEM EINTHOVEN (1860-1927)

Einthoven received the Nobel Prize in Medicine in 1924 for inventing the first practical electrocardiogram (1903). First electrocardiograms based on Lippmann's capillary electrometer were very inaccurate and had very little clinical significance. Einthoven's ECG recorder used a string galvanometer which was much more sensitive than the capillary electrometer, but was far not so comfortable than modern ECGs: the subjects had to immerse their hands and legs into containers of salt water. The ECG was recorded from the salt solutions.

Einthoven named the deflections of the ECG: the letters P, Q, R, S, T were assigned to the waves. He described the electrocardiographic features of a number of cardiovascular disorders.

EDGAR DOUGLAS ADRIAN (1889-1977)

SIR CHARLES SHERRINGTON (1857-1952)

They won the Nobel Prize in Physiology for their work on the function of neurons in 1932.

Adrian studied the properties of the propagating electric impulses on frog nerve-muscles with the help of a capillary electrometer and a cathode ray tube, which amplified the bioelectric signals. He investigated the sensory and the motor nerves and found that the strength and quantity of the stimulus is expressed not in the increase of the voltage of the response but in the number of evoked nerve impulses. He also observed the adaptation of the sensory organs to prolonged stimuli.

Sherrington worked on the reflex arcs of the spinal cord and investigated the distribution of the segmented skin fields. Discovered that not just motor but also sensory nerve fibers exist in the muscles, and found two sensory apparatus in the muscle: the muscle spindle and the Golgi tendon organ.

SIR HENRY HALLETT DALE (1875-1968)

OTTO LOEWI (1873-1961)

Dale and Loewi received the Nobel Prize in Physiology for discovering the neurotransmitter acetylcholine and their work in the chemical transmission of nerve impulses.

Dale synthesized acetylcholine from ergot and studied its effects on living organisms. At this time two contrary theories existed about the nature of signaling at the synapse: one group of scientists believed that the signaling was chemical, and the others thought that the transmission at the synapse has an electrical nature. Dale supported the chemical view. Later it was proven that most of the synapses are chemical, but there are some that are electrical.

Dale originated a scheme used to differentiate neurons according to what neurotransmitter they release. The *Dale's principle* states that each neuron releases only one type of neurotransmitter. Later this rule has been shown to be false.

SIR HENRY HALLETT DALE (1875-1968)

OTTO LOEWI (1873-1961)

Loewi identified the first chemical neurotransmitter in the nervous system. The discovery of acetylcholine happened with the help one of his dreams:

„The night before Easter Sunday of that year (1920) I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at 6 o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. The next night, at 3 o'clock, the idea returned. It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered 17 years ago was correct. I got up immediately, went to the laboratory, and performed a single experiment on a frog's heart according to the nocturnal design., (Loewi,O.(1953). From the work shop of discoveries. Lawrence: Univ. Of Kansas Press.)

He named the substance Vagusstoff because it originated from the vagus nerve.

JOSEPH ERLANGER (1874-1965)

HERBERT SPENCER GASSER (1888-1963)

They won the Nobel Prize in Physiology in 1944 for their work on the functions of nerve fibers.

Erlanger built the sphygmomanometer for measuring the impulse-propagation of the heart. He worked out modern analysis methods of neuroscience with the help of Gasser. Erlanger and Gasser studied nerve impulses with the help of cathode ray tubes. They could record the time course of nerve impulses for the first time. They confirmed that axons of large diameter transmit nerve impulses more quickly than thin axons. They classified the nerve fibers to three groups according to their properties: A, B, C. The three groups were further subdivided into subgroups: A alpha, A beta, A gamma, A delta. C group also has got subdivisions called dorsal root fiber and sympathetic fiber. The fastest conducting fibers are the A fibers.

WALTER RUDOLF HESS (1881-1973)

Hess awarded the Nobel Prize in Physiology or Medicine in 1949 for mapping the areas of the brain involved in the control of internal organs.

Hess first carried out chronic experiments on cats where electrodes were inserted in the diencephalon of the animals. During his studies of the hypothalamus he found areas of this brain region where electric stimulation caused an increase in the blood pressure, rise of the frequency of heart beating and faster respiration. Stimulation on another sites decreased the blood pressure, the pulse rate and resulted in a slower respiration. He could also evoke increased or decreased urinating, defecation and bowel movements. Stimulating other places could induce salivating, vomiting or a change in the thermal regulation. He could also elicit complex emotional responses like rage. By low frequency stimulation of the thalamus he induced natural like sleep with slow EEG activity.

GEORG VON BÉKÉSY (1899-1972)

Békésy received the Nobel Prize in Physiology or Medicine for his research on the function of the cochlea in 1961.

He worked at Hungarian Post Office during the time of his discoveries as an engineer and had to solve problems related to long distance telephone transmission. To manage the telecommunication tasks, he wanted to understand the mechanism of hearing. So Békésy developed a method for dissecting the inner ear of human cadavers and studied the cochlea. He observed that the basilar membrane moves like a surface wave when stimulated by sound. Different frequencies of sound caused the maximum amplitudes of the waves to occur at different places on the basilar membrane along the coil of the cochlea. He theorized that the placement of each hair cell along the coil of the cochlea corresponds to a specific frequency of sound (tonotopy). Békésy also developed a mechanical model of the cochlea later.

SIR JOHN ECCLES (1903-1997)

ANDREW FIELDING HUXLEY (1917-)

SIR ALAN LLOYD HODGKIN (1914-1998)

They won the Nobel Prize in Physiology or Medicine for their work on the synapse and action potentials in 1963.

Eccles investigated synaptic transmission using the stretch reflex as a model. Because this reflex consists only of a sensory and a motor neuron, it could be easily studied. He observed EPSPs (excitatory postsynaptic potential) or IPSPs (inhibitory PSP) during electrical stimulation of particular muscles.

Huxley and Hodgkin investigated the behavior of the cell membrane on the giant axons of the Atlantic squid with the help of the voltage clamp technique. They hypothesized the existence of ion channels and gave an accurate mathematical model of the activation processes and propagation of the action potentials. (Hodgkin-Huxley model)

RAGNAR ARTHUR GRANIT (1900-1991) GEORGE WALD (1906-1997) HALDAN KEGGER HARTLINE (1903-1983)

They received the Nobel Prize in Physiology for their studies on the neurophysiological and chemical mechanisms of vision in 1967.

Granit developed a microelectrode what he inserted in the retina of cats and recorded the first electroretinogram. He studied what happens in the rods, cones, ganglion cells and nerve fibers. Discovered the two types of receptores (rods and cones) and the three cones sensitive to different colors of the light. So the Young-Helmholtz theory of trichromatic color vision was finally proven.

Wald discovered the relationship between vitamin A and the photopigment rhodopsin and showed that vitamin A was essential in retinal function.

Hartline recorded the electrical activity from the retina crabs and frogs and discovered the receptive fields in the eye and that areas next to activated photoreceptores are inhibited.

SIR BERNARD KATZ (1911-2003) JULIUS AXELROD (1912-2004) ULF SVANTE VON EULER (1905-1983)

The Nobel Prize was awarded to them in 1970 for their work on neurotransmitters, chemical transmission and the mechanisms related to them.

Katz studied the biochemistry and action of acetylcholine, and found that there is always a defined number of neurotransmitters in the vesicles at the neuromuscular terminal. From these vesicles a quantum of neurotransmitters are released to the synaptic cleft during the exocytosis after the influx of calcium ions.

Axelrod's major work was on the release, reuptake, and storage of the neurotransmitters epinephrine and norepinephrine. Later he carried out researches on the pineal gland.

Euler discovered the substance P and the noradrenalin (norepinephrine). Substance P is a peptid that is found in the brain and spinal cord, and is associated with inflammatory processes and pain.

DAVID HUNTER HUBEL (1926-) and TORSTEN NILS WIESEL (1924-) ROGER WOLCOTT SPERRY (1913-1994)

They received in 1981 the Nobel Prize in Physiology or Medicine for their researches related to the information processing in the visual system.

Hubel and Wiesel inserted microelectrodes into the primary visual cortex of anesthetized cats and categorized the responsive neurons. They also discovered the ocular dominance columns in the visual cortex and made important studies related to cortical plasticity.

Sperry made researches on patients with untreatable epilepsy, who underwent callosotomy, where the corpus callosum was cut through to separate the two hemispheres of the brain. He made interesting experiments to examine the differences between the right and left hemisphere. His studies contributed greatly to understanding the lateralization of brain functions.

ERWIN NEHER (1944-) BERT SAKMANN (1942-)

They were awarded the Nobel Prize in Physiology or Medicine in 1991 for the development of the patch-clamp technique and for their studies on the function and behavior of single ion channels in the cell membrane.

With the help of a micropipette they could isolate a tiny area of the cell membrane in different ways (Cell-attached patch, whole patch, inside-out patch, outside-out patch) and record the molecular events of ion channels located here and to measure the transmembrane current. Shortly after inventing the patch-clamp technique, researches on the structure of the ion channels increased to understand their function.

ARVID CARLSSON (1923-) ERIC KANDEL (1929-)

PAUL GREENGARD (1925-)

They received the Nobel Prize in Physiology or Medicine in 2000.

Carlsson studied the neurotransmitter dopamine and its effects in Parkinson's disease. He developed a method for measuring the amount of dopamine in brain tissues and showed that dopamine levels in the basal ganglia are high. Basal ganglia is a brain area important for movement organization. He could reduce the symptoms of Parkinson's disease with L-dopa, which is the precursor of dopamine.

Kandel did research on the physiological basis of memory storage in neurons. He used a simple animal model the *Aplysia californica* (California sea hare).

Greengard's experiments focused on events inside the neuron caused by neurotransmitters: he studied the behavior of second messenger cascades that transform the docking of a neurotransmitter with a receptor into permanent changes in the neuron.

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REVIEW QUESTIONS

What was the electroscope used for?

How stored the leyden jar the electric charges?

Which theory wanted Swammerdam to prove with his experiments? What was the point of his experiments?

What was Galvani's „animal electricity”?

What was the structure of the first battery, the voltaic pile?

Who stimulated first the human brain electrically?

Name some early electrical measurement devices!

Who measured the nerve conduction velocity first? What was his experimental set-up?

What was the Horsley-Clarke apparatus used for?

Who invented the electroencephalogram? What was the first brain rhythm he discovered?