A Short History of European Neuroscience
- from the late 18th to the mid 20th century -

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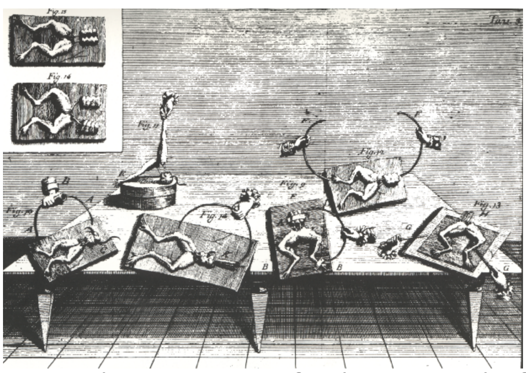
Neuroscience, as a discipline, emerged as a consequence of the endeavours of many who conspired to illuminate the structure of the nervous system, the manner of communication within it, its links to reflexes and its relation to more complex behaviour. Neuroscience emerged from the biological sciences because conceptual building blocks were isolated, and the ways in which they can be arranged were explored. The foundations on which the structure could be securely based were the cell and neuron doctrines on the biological side, and morphology and electrophysiology on the functional side. The morphological doctrines were dependent on the development of microtomes and achromatic microscopes and of appropriate staining methods so that the sections of anatomical specimens could be examined in greater detail. Electrophysiology provided the conceptual modern framework on which the notion of the nervous function was envisioned as depending on an ongoing flux of electrical signals along the nervous pathways at both central and peripheral levels. These aspects of the history of neuroscience will be explored under headings of electrical excitability, the neuron, glia, neurotransmitters, brain function and localization, circuits and diseases. A general account of developments in neuroscience up to 1900 can be found in the FENS supported project at http://neuroportraits.eu/, while the *Neuroscience by Caricature in Europe throughout the ages* – another FENS funded project – illustrates a history of Neuroscience through the use of caricature on facts and people.

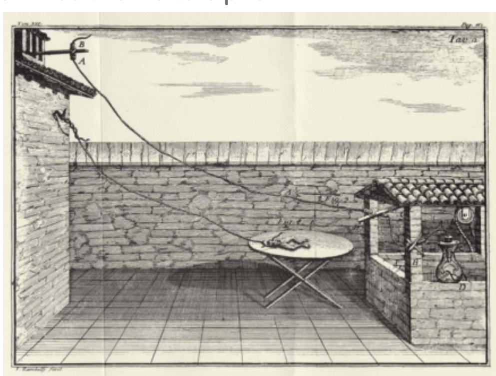
A presentation of historiography of neuroscience in Romania during 1870-1970 and the biography of János Szentágothai alongside with his legacy for neuroscience in Hungary and worldwide were realized thanks to FENS history grants. Likewise, a History of French neuroscience presenting remarkable French scientists who contributed to the development of neuroscience can be consulted on the History of Neuroscience Club webpage.

1. Electrical excitability

It was the Italian Luigi Galvani (1737 – 1798) who introduced the concept that electrical current could initiate responses in nerve and muscle in 1791. He studied medicine and philosophy and was appointed lecturer in anatomy at the University of Bologna. Using the Leiden jar he was able to generate voltage and discovered that the production of a spark caused muscles to contract. The animal he used was the frog which has then become a favorite animal model in physiology. His opponent at that time was Alessandro Volta (1745 – 1825) who repeated Galvani's experiments and started a major controversy.Volta's studies led also to the discovery of the battery using alternating disks of zinc and copper, which is known as the Voltaic pile.

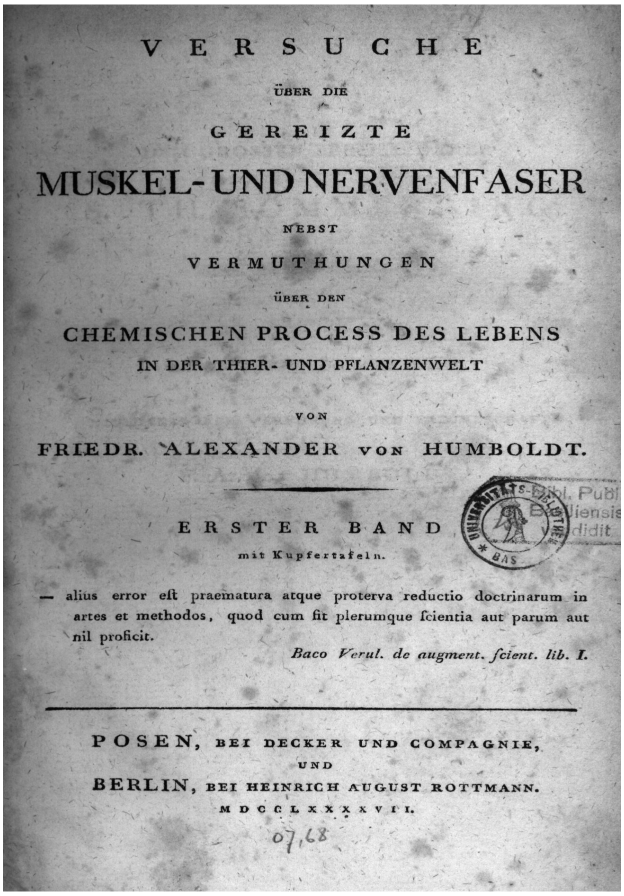


Experimental arrangement of Galvani, note the frog legs and the electrodes for excitation (1791)



Electrical charges during thunder storms can excite the frog muscle (1791)

A strong supporter of the concept of animal electricity and contemporary of Galvani and Volta was Alexander von Humboldt (1769-1859) who published his extensive series of experiments on 300 different animal species in 1797 (*Experiments on the excited muscle- and nerve fiber including assumptions of the chemical process of life in the animal and plant world*) before he departed to his first major journey to South, Central and North America. After his return he also published a paper on the electric eel which he caught in the Amazon.



VERSUCHE

ÜBER DIE

GEREIZTE

MUSKEL- UND NERVENFASER

NEBST

VERMUTHUNGEN

ÜBER DEN

CHEMISCHEN PROCESS DES LEBENS

IN DER THIER- UND PFLANZENWELT

VON

FRIEDR. ALEXANDER VON HUMBOLDT.

ERSTER BAND

mit Kupfertafeln.

— alius error eſt praematura atque proterva reductio doctrinarum in artes et methodos, quod cum fit plerumque ſcientia aut parum aut nil proficit.

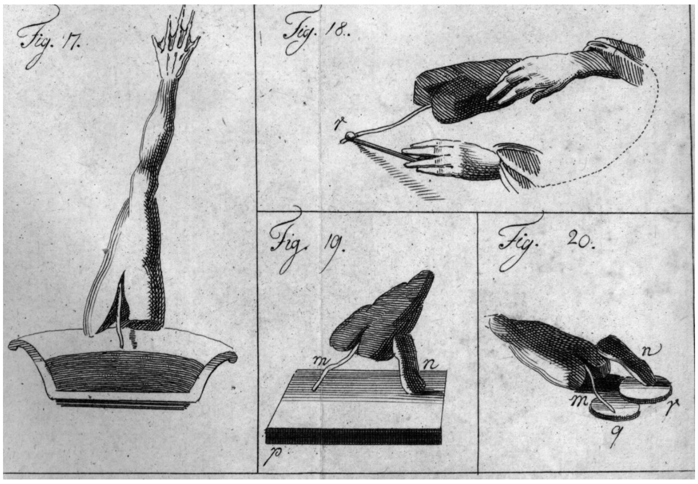
Baco Verul. de augment. ſcient. lib. I.

POSEN, BEI DECKER UND COMPAGNIE,

UND

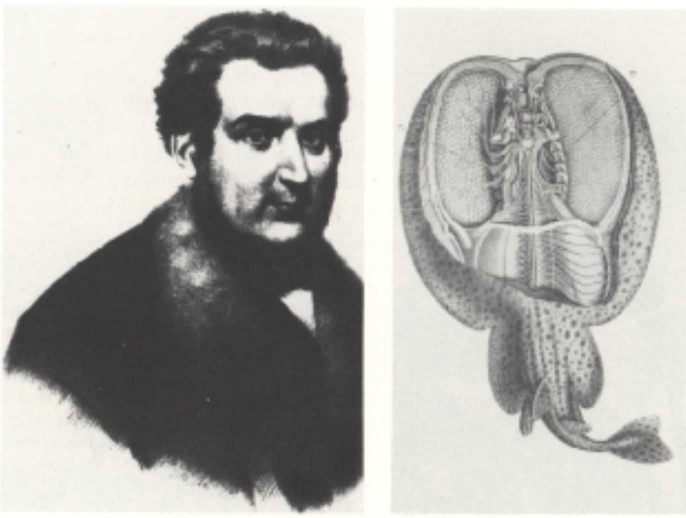
BERLIN, BEI HEINRICH AUGUST ROTTMANN.

MDCCLXXXXVII.

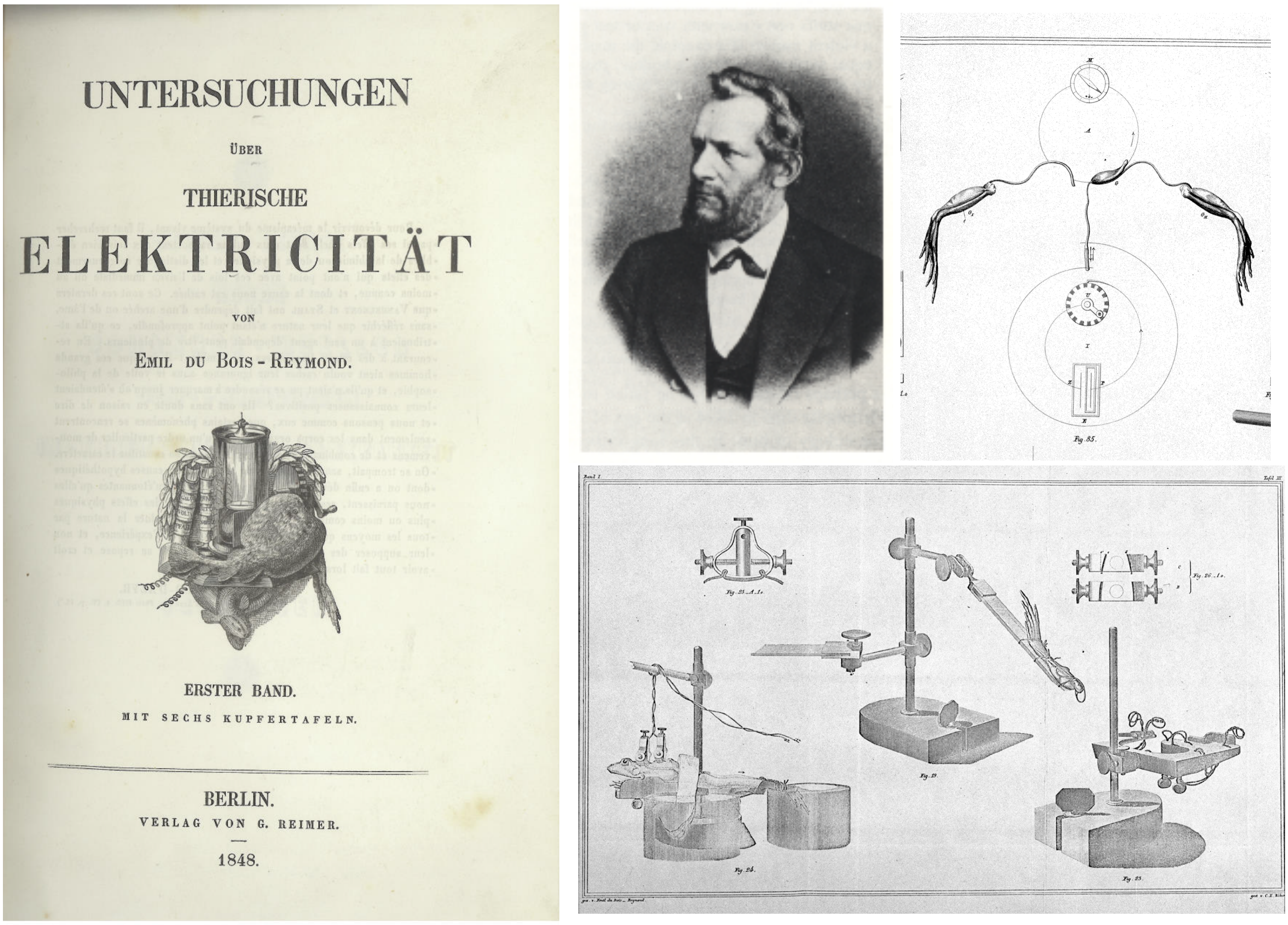


Experimental arrangements of the electrical stimulation by Alexander von Humboldt

The next advance was made by Carlo Matteucci (1811-1868), a professor of physics in Pisa. He studied the electric organ of the ray. He found that there was a difference in the electric charge between the interior and the exterior of a muscle fiber and that could generate currents. As a readout for the current he used the sciatic nerve of the frog. One of the major problems of that time was the lack of proper instrumentation to measure these highly sensitive and small electrical currents. This changed with the discovery of electromagnetism and the development of an instrument based on this phenomenon to measure current. This was achieved by Hans Christian Oersted (1777 – 1851) in Copenhagen at 1820. The first instruments to measure animal currents based on Oersted's concept were built by Matteucci and Emil Du Bois-Reymond (1818 – 1896). During his doctoral thesis at the Berlin University he built the equipment with the help of mechanics Werner Siemens and Georg Halske (later founding the Siemens&Halske telegraph company) which allowed him to unequivocally measure the currents generated by muscle and nerves. Matteucci used a galvanometer with 3000 turns of copper wire while Du Bois-Reymond's instrument contained over 5 km of wire and consisted of 24 000 turns. His major experimental animal was also the frog but he was



Portrait of Carlo Mateucci and his experimental animal, the electric ray able to show that such currents were actually also generated by humans.Du Bois-Reymond also introduced the inductorium for stimulating nerves. At this time it became clear to the scientific community that nerve and muscle can not only be stimulated by electricity but they themselves generate electrical currents. However, the mechanism how this current is generated was quite unclear at that time.

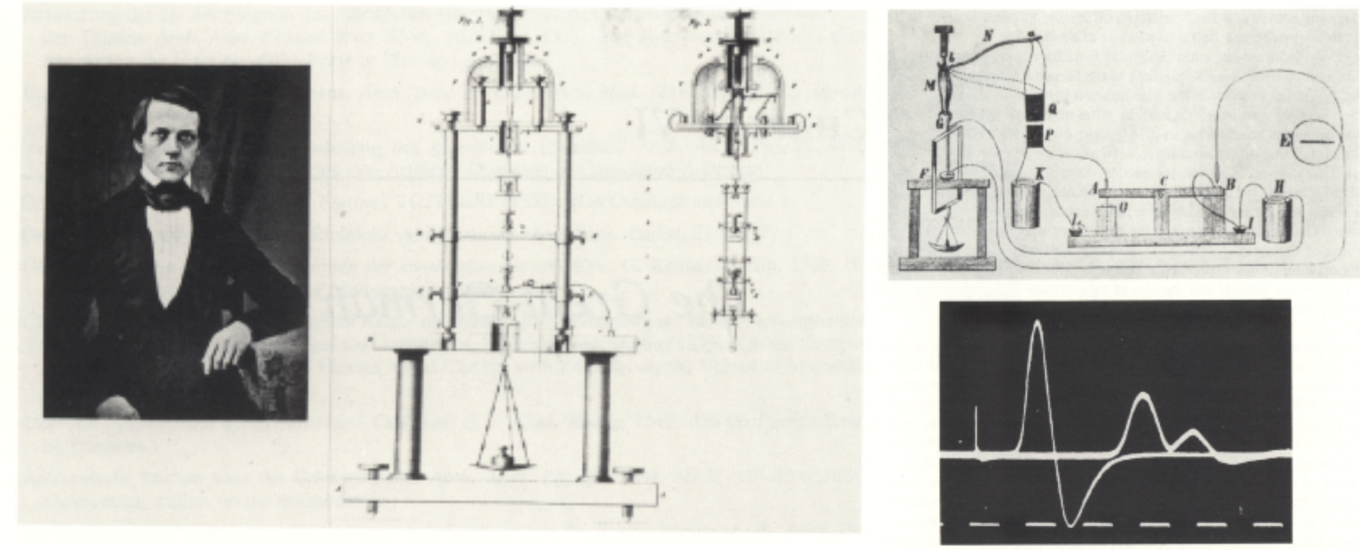


Experimental arrangement by Emil Du Bois-Reymond to record currents from frog muscle and nerve

Another landmark experiment of that time was done by the young Hermann Helmholtz (1821 – 1894) in Berlin. While building a highly complex instrument he was able to determine the electrical impulse velocity traveling along a 4cm segment of frog nerve. The estimation of the speed was up to 30m/s which is a realistic value.

Another important step was put forward by Julius Bernstein (1839 – 1917) in Halle who suggested that the resting potential across the cell membrane is dominated by the permeability for potassium. In applying an equation developed by the German physical chemist Walter Nernst (1874 – 1941, Nobel Prize 1920) P= RT/F ln $[K^+]_{out}$/ $[K^+]_{in}$, he formulated the concept for the resting membrane potential.

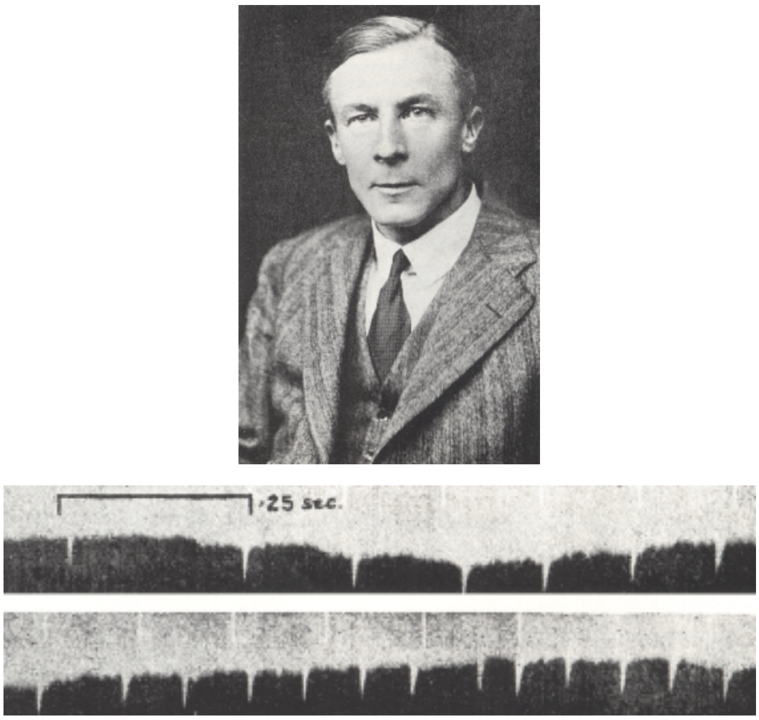
While the German school of physiologists had dominated this field in the second part of the 19th century subsequently the focus shifted to Britain. Keith Lucas (1879-1916) and Edgar Douglas Adrian (1889-1977, Nobel Prize 1932) developed equipment to measure impulses from peripheral nerves at the Cambridge physiology laboratory. Adrian continued this work after Lucas' death in World War II as an airplane pilot. Their recordings of single unit activity using string galvanometers was the pathway to modern electrophysiology. Based on his experiments he was reconstructing the time course of an action potential. An important advance was the development of powerful amplifiers.



Experimental arrangement by Hermann von Helmholtz to measure the conduction velocity of nerves (1852)

In Germany at that time period a completely different breakthrough in electrophysiology took place. Hans Berger (1873-1941) from Jena made the first recording of electrical activities from the human skull in 1924. These EEG recordings are now a standard tool in clinical neurophysiology.

Portrait of Charles Scott Sherrington (right)

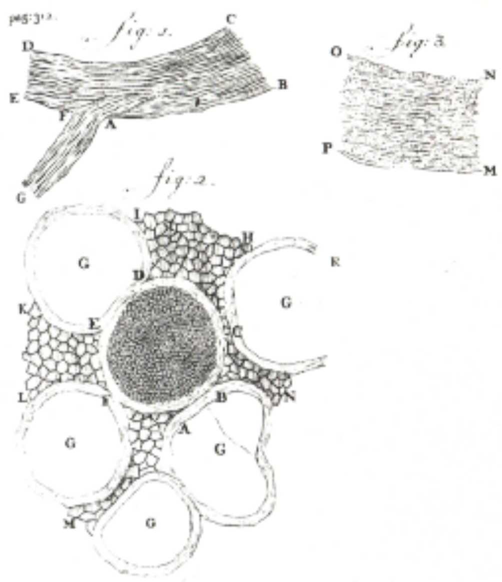


Portrait of Edgar Douglas Adrian and recordings of action potentials from the peripheral nerve

Until the outbreak of World War II the ionic nature of the action potential was still an enigma. It was the pioneering work of Alan Lloyd Hodgkin (1914-1998) and Andrew Fielding Huxley (1917-2012) in Plymouth that unraveled the mechanisms of how action potentials are generated. Using the giant axon of the squid as a preparation and voltage clamp recordings as a method they formulated the basis of what is today written in neurophysiology textbooks about the action potential being composed of a sodium and potassium current. This seminal work was published in a series of core Journal of Physiology papers. Alan Hodgkin and Andrew Huxley were awarded the Noble prize in Physiology or Medicine in 1963.

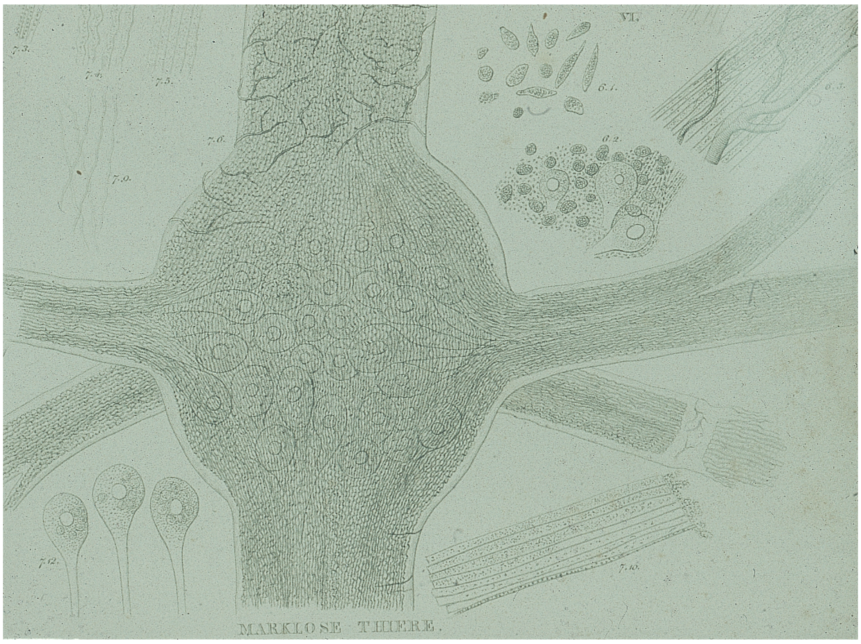
2. The Neuron

Antoni van Leeuwenhoek (1632 – 1723) in Delft described elements in cells (the name given by Robert Hooke, 1635-1703, to tissues seen under a microscope because they reminded him of the cells of monks) and he was a pioneer in the use of microscopes to inspect biological specimens. The focus of neuroscientists until the early 19th century, however, was rather on the gross anatomy of human and animal nervous systems. The pioneer in introducing microscopes to university research was Christian Ehrenberg (1795-1876) in Berlin. He was the first to publish an image of a nerve cell in his publication with the interesting title *Observations of a so far unknown structure of the organ of the soul of human and animals* (1836). While the pictures of nerve cells of vertebrates were not as convincing as his image of neurons from the ganglion of a leech, which catches the features of a neuron. Shortly after Jan Evangelista Purkinje (1787 – 1869) - at that time based in Breslau (today's Wroclaw) - was the first to publish an illustration of an mammalian neuron, namely the Purkinje cell in the cerebellum of the cow. This image was published in the proceedings of the German natural scientists and Medical Doctors meeting (Deutsche Naturforscher und Ärzte) in Prague in 1838, the city to which Purkinje returned later.

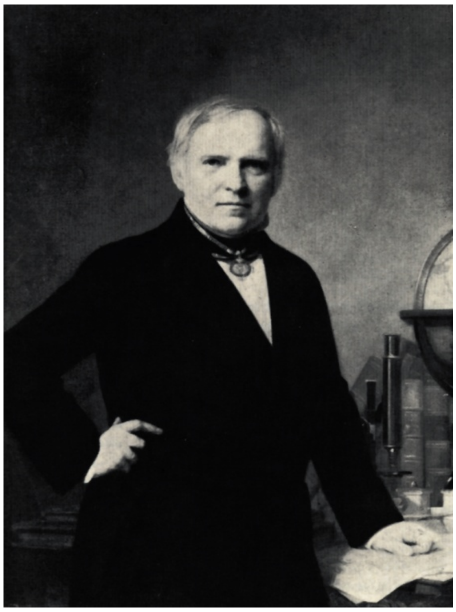


Portrait of Antoni van Leeuwenhoek and drawings from preparations of nerve

The use of the first dyes in histology (carmesin red) by Joseph Gerlach (1820-1896) from Erlangen and Albert Kölliker from Würzburg (1817-1905) yielded clearer pictures of the different nervous elements of different brain regions. The most convincing picture of a nerve cell in that early period was delivered by Otto Deiters (1834 – 1863) from Bonn in a book published after his very early death in 1863 being only 27 years old.

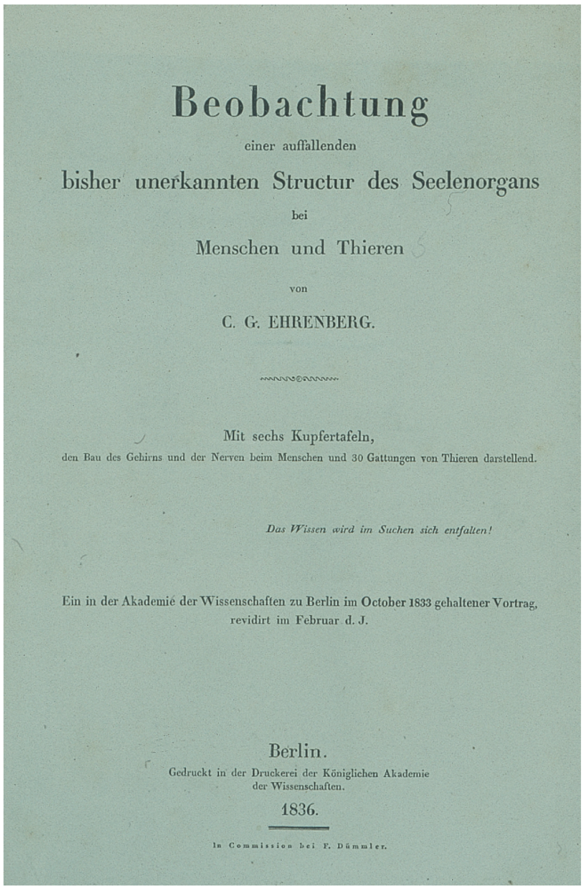


First image of a neuron in leech ganglion by Christian Ehrenberg



Christian G. Ehrenberg (1795-1876)

Subsequently, the revolution came from Italy. The development of the silver impregnation by Camillo Golgi from Pavia (1843-1926, Nobel Prize 1906) in 1871 yielded pictures of nerves (and also glial cells) with a clarity and complexity previously never achieved (see also our FENS history project *Golgi Revealed at* http://musei.unipv.it/musei/en_2_coll_6_PG.html). This staining method boosted anatomy and histology of nervous tissue and was used by scientists world wide. Particularly it was used by Santiago Ramon y Cajal (1852–1934) in Madrid who was the most influential neuroanatomist of the time (if not all times). His book, *The histology of the nervous system*, is one of the greatest landmarks in neuroscience. The *Nobel Prize* in Physiology or Medicine 1906 was awarded jointly to Camillo *Golgi* and Santiago Ramón y *Cajal* *"in recognition of their work on the structure of the nervous system".* But they were not on good terms which each other since Golgi opposed the view of Cajal that neurons are structurally isolated elements. During the visit of Cajal to Berlin, Wilhelm Waldeyer-Hartz (1848 – 1890) was inspired to write a booklet in which he coined the term neuron. He writes: “The nervous system is composed of numerous nerve units (neurons) which are anatomically as well as genetically independent. Each nerve unit is composed out of three parts: the nerve cell, the nerve fibre and the dendritic tree. Physiological propagation can promote from the cell to the dendrite and also in opposite direction. The motor pathways run only in direction from the cell to the dendrite, the sensory ones in one or the other direction.”



Beobachtung

einer auffallenden

bisher unerkannten Structur des Seelenorgans

bei

Menschen und Thieren

von

C. G. EHRENBERG.

Mit sechs Kupfertafeln,

den Bau des Gehirns und der Nerven beim Menschen und 30 Gattungen von Thieren darstellend.

Das Wissen wird im Suchen sich entfalten!

Ein in der Akademie der Wissenschaften zu Berlin im October 1833 gehaltener Vortrag, revidirt im Februar d. J.

Berlin.

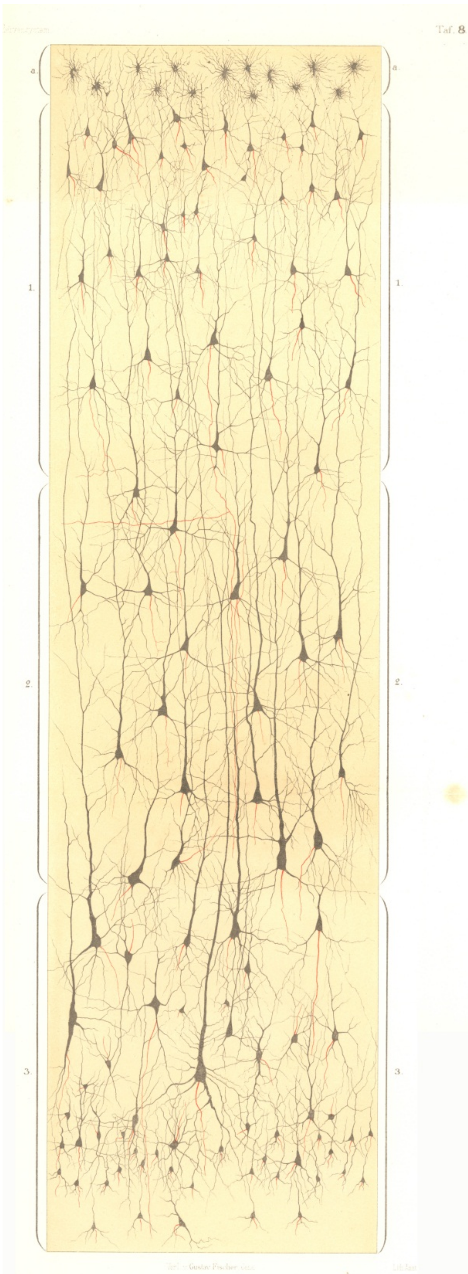
Gedruckt in der Druckerei der Königlichen Akademie der Wissenschaften.

1836.

In Commission bei F. Dümmler.

3. Glia

The concept that the brain contains a second population of cells besides neurons was promoted by Rudolf Virchow (1821 – 1902) from Berlin in his seminal book *Cellular Pathology* published in 1858. He, however, had coined the term two years earlier in a comment on one of his previous publications. The term is from the Greek word which means clue or puddy. However, glial cells were even recognized earlier, but not named. Heinrich Müller (1820-1864) from Würzburg had published the image of radial cells in the retina, which were later named after him. Even earlier Robert Remak (1815-1865) in 1838 and Theodor Schwann (1810 - 1882) in 1839 recognized cells in the peripheral nervous system, which are today known as Schwann cells. The first network of astrocytes in the cortex was published by Friedrich Merkel (1845 – 1919) and Jacob Henle (1809-1885) in 1869 in Göttingen. Henle is the same scientist who also discovered the loops in the kidney.



Network of neurons in the cortex by Camillo Golgi

The first convincing image of an oligodendrocyte was recognized by Camillo Golgi and published in his famous Atlas in sections through white matter tracts. It was the Hungarian Mihály or Michael von Lenhossek (1863 – 1937) at that time working in Germany who coined the term astrocyte, however, without distinguishing them from other types of glial cells. It was not until 1919 that the different types of central nervous system glia were defined. It was a student of Ramon y Cajal, Pio del Rio Hortega (1882-1945) who made this seminal definition while working in Madrid. He coined the terms oligodendrocyte and microglia and distinguished both cells from the astrocytes. This was described in a series of papers published in Spanish. The English-speaking world was introduced into this topic when Hortega summarized his findings in English in the landmark book by Wilder Penfield, *Pathology and Cellular Pathology of the Nervous System* (1932).

Downloads of seminal papers on the history of glia you can find on the homepage of Network Glia.

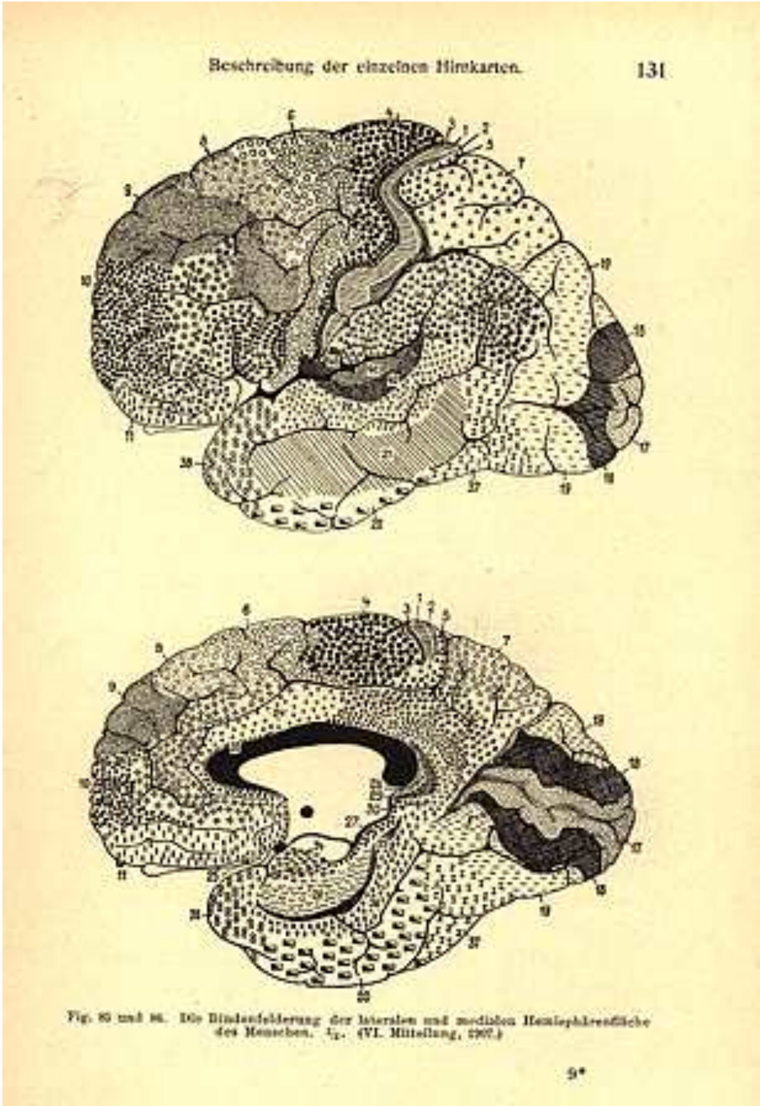
4. Neurotransmitters

Otto Loewi (1873-1961)

The nature of the chemical which mediates synaptic transmission remained a miracle until Otto Loewi (1873-1961, Nobel Prize 1936) a professor of pharmacology at the University in Graz did his pioneering studies by stimulating the vagus nerve and recording the heart's beating rate. When he transferred the solution in which a vagus nerve was stimulated to another heart he observed a changing frequency. He concluded that the nerve releases a substance which acts on muscle. This first neurotransmiter he named it

Vagusstoff (Vagus substance). This was later identified by Henry Dale (1875-1968, Nobel Prize 1936) at the National Institute for Medical Research in Hampstead, London as acetylcholine. Wilhelm Feldberg (1900-1993), a refugee from Nazi-Germany, was Dale’s collaborator in establishing this concept.

5. Brain function and localization



Landscape of the brain as published by Korbinian Brodman

Franz Josef Gall (1758-1828) introduced the concept of brain localization. Despite the fact that he was an excellent anatomist publishing on the histology of the nervous system his misconception was that he assumed that brain function would have an impact on the skull morphology. This created a pseudo science called phrenology (see also our FENS history project *“The Rise and Fall of Phrenology in Edinburgh”* (http://www.phrenology.mvm.ed.ac.uk/Home.html). He summarized his findings in 1810 in the publication *Anatomy and Physiology of the nervous system in general and the cerebrum in particular*. New insights into the localizing brain functions came from studies of patients with brain lesions. John-Baptiste Bouillaud (1796 – 1881) from Paris found that patients had impaired speech after damage of the anterior lobes. This concept was consolidated by Paul Broca (1824 – 1880) in Paris. In a patient he studied in 1861 he found that loss of speech (aphonia) coincided with the lesion at a defined site in the third frontal convolution of the left hemisphere. Another area was discovered by Carl Wernicke (1848-1905) who found that sensory aphasia is associated with the damage to the left temporal lobe. These human studies were paralleled by studies on animals with defined electrical stimulations. Gustav Fritsch (1838-1927) and Eduard Hitzig (1838-1907), both assistants at the physiology department in Berlin headed by Emil Dubois-Reymond - identified the motor cortex in 1870 by electrical stimulation while observing defined movements in dogs. The work of Fritsch and Hitzig was extended by David Ferrier (1843-1928) in London and published in his book *The functions of the brain* (1876). In 1909 Korbinian Brodmann (1868-1918) in Berlin published a map of the brain defining areas related to different functions, which are today known as the Brodmann areas.

Portrait of Korbinian Brodman

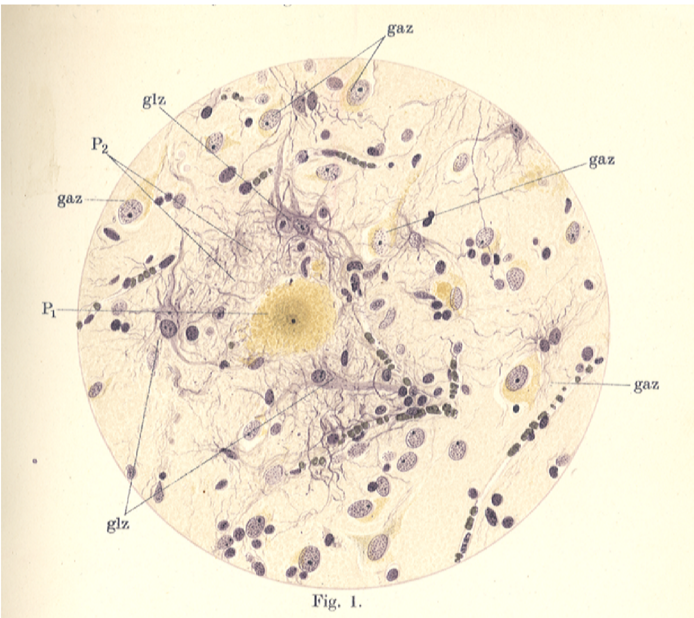
6. Circuits

It was in the early part of the 19th century that it was recognized that the spinal cord received its sensory information via the dorsal nerve roots while the fibers activating the muscles projected via the ventral roots. This was pioneered by studies from Francois Magendie (1783–1855) in Paris and Charles Bell (1774–1842) from London. While the reflex arc was known it was Charles Scott Sherrington (1857-1952, Nobel Prize 1932) in Oxford who studied the details of this phenomenon, and formulated the concept of excitatory vs. inhibitory states. While studying nerve fibers terminating on muscles he coined the term motor unit. Ramon y Cajal had visited Sherrington in 1904 and inspired him to define the synapse proposing a small gap between a nerve fiber and the next nerve cell (see also our FENS history project "*Neuroanatomical Histology – A historical repository at the University of Oxford*": https://history.medsci.ox.ac.uk/). He also argued that an excitatory synapse should lead to membrane depolarization while inhibition should stabilize the membrane potential.

7. Diseases

In the beginning of the 19th century asylum hospitals converted from pure maintenance stations to clinics of Neurology and Psychiatry. In this time period, the majority of brain diseases were described and defined according to their symptoms.

- James Parkinson (1755-1824), London, Parkinson´Disease, 1817
- Jean-Martin Charcot (1825–1893), Hôpital de la Salpêtrière in Paris, ALS and Multiple Sclerosis, around 1880
- Georges Gilles de la Tourette (1857-1904), Paris, Tourette-Syndrom, 1885
- Eugen Bleuler (1857-1939), Zürich, Schizophrenia (Morbus Bleuler), 1911
- Alois Alzheimer (1864–1915), Frankfurt, Alzheimer´s disease, 1909
- Alfons Maria Jakob (1884-1931) and Hans-Gerhard Creutzfeldt (1885-1964), Hamburg, Creutzfeldt Jakob Disease, 1920



The first histopathological image of an Alzheimer Disease brain

Further reading

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