



Commentary

A Tale of Two Brains – Cortical localization and neurophysiology in the 19th and 20th century

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Abstract

Introduction: Others have described the importance of experimental physiology in the development of the brain sciences and the individual discoveries by the founding fathers of modern neurology. This paper instead discusses the birth of neurological sciences in the 19th and 20th century and their epistemological origins.

Discussion: In the span of two hundred years, two different conceptions of the brain emerged: the neuroanatomical brain, which arose from the development of functional, neurological and neurosurgical localization, and the neurophysiological brain, which relied on the neuron doctrine and enabled pre-modern electrophysiology. While the neuroanatomical brain stems from studying brain function, the neurophysiological brain emphasizes brain functioning and aims at understanding mechanisms underlying neurological processes.

Conclusion: In the 19th and 20th century, the brain became an organ with an intelligible and coherent physiology. However, the various discoveries were tributaries of two different conceptions of the brain, which continue to influence sciences to this day.

Relevance: With modern cognitive neuroscience, functional neuroanatomy, cellular and molecular neurophysiology and neural networks, there are different analytical units for each type of neurological science. Such a divide is a vestige of the 19th and 20th century development of the neuroanatomical and neurophysiological brains.

🔍 history of medicine, history of neurology, cortical localization, neurophysiology, neuroanatomy, 19th century

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Introduction

In this narrative review, I will explore the birth of cortical localization and the anatomo-clinical method in the 19th century and the revolutionary neuron doctrine in the early 20th century. These themes will be approached thematically rather than chronologically. While other authors have elegantly placed neurophysiology within the broader context of experimental physiology, I will argue that in the span of two hundred years, two different brains: the neuroanatomical brain, exemplified by cortical localization and the anatomo-clinical approach, and the neurophysiological brain, exemplified by the neuron doctrine and electrophysiology. I will distinguish between brain function, understood as the attribution of physiological functions to discrete anatomical structures, and brain functioning, understood as an approach to nervous system functioning and physiology that emphasizes mechanisms. I will argue that the current state of neuroscience, with the various different levels of understanding, represents the heritage of this very particular historical development.

Discussion

The brain as a physical entity: localization of function and the anatomo-clinical approach

For a most of human history, the brain has been an element of fascination. As early as 1600 BC in Ancient Egypt, the famous Edwin Smith Surgical Papyrus in Ancient Egypt described several brain lesions and reported on spinal cord injuries. However, it is in Greece, in the 5th century BC, that a first true model of the brain arises.

Aristotle (384-322 BC) was the most influential Greek physician and argued strongly for the use of animal dissection to unravel the mysteries of human nature. This emphasis on the empiric study of the human body along with some very specific political conditions led to the widespread use of human dissection in Alexandria in the 3rd century. Indeed, Herophilus and Erasistratus, two famous Alexandrian anatomists, provided the first descriptions of the cerebrum, the cerebellum and the cranial nerves¹.

¹ Aristotle's emphasis on the empiric study of the human body along with some very specific political conditions led to the widespread use of human dissection in Alexandria in the 3rd century. Please see Lloyd G. Alamaeon and the Early History of Dissection." *Sudharch Sudhoffs Archiv* 59, no. 2, 1975, 113-47 p.p. for a detailed review of the early history of dissection.

² Hippocrates et al., *Hippocrates* (Cambridge, Mass.; London: Harvard University Press; W. Heinemann, 1923), 139-79.

³ As Geoffrey Lloyd, "Alamaeon and the Early History of Dissection," *sudharch Sudhoffs Archiv* 59, no. 2 (1975). demonstrates, it is quite clear that their physiological constructs were never empirically verified and that dissection played little if any role in their vision of the brain.

Hippocratic doctors, on the other hand, emphasized rejection of the supernatural and emphasized clinical examination^{2,3,4}. The epitome of medicine and neuroscience in the Antiquity is Galen's masterful combination of careful anatomical experimentation and clinical reasoning. In synthesizing Hippocratic and Alexandrian medicine, Galen was able to explain why patients undergoing goiter surgery often suffered from aphonia; indeed, he famously successfully reproduced this finding by vivisectioning a dog's recurrent laryngeal nerve.^{5,6} This newly found interest in neuroanatomy did not translate into any change in explanations of physiology; Galen still attributed the function of the brain to a vital spirit⁷ and Hippocrates's four humors doctrine would go on to be the dominant theory of disease until the Renaissance. For the several centuries following Galen, knowledge of brain structure changed very little and debates revolved around metaphysical questions. Despite Vesalius's publication of *Fabrica* in 1543, which included a new level of neuroanatomical detail, the 16th century did not challenge classical Galenic physiology. For both Greek and Renaissance thinkers, brain function and brain functioning were regarded as theoretical questions that were best solved through reasoning rather than experimentation. If they did not willfully emulate Greek and Renaissance scientists, proponents of cortical localization and the anatomo-clinical approach in the 18th and 19th centuries certainly owe the description of countless neuroanatomical structures and the introduction of many anatomical terms to the work of these great anatomists. This section will explore the birth of cortical localization, the anatomo-clinical approach and functional neurosurgery.

It is in 1664 that Thomas Willis published his seminal paper *Cerebri anatome*. In many ways, this work marked a transition between the philosophical approach to brain function and the emergence of functional anatomy. Influenced by William Harvey's discovery of circulation, Willis based his theories on comparative anatomy and clinical cases rather than *a priori* theories about the mind. Thus, it was his observation that lesions to the cerebral hemispheres affected the ability of patients to recall⁸ that guided his theory of memory being assigned to the cerebral gyri.⁹

⁴ *ibid.*, 131.

⁵ A. Karenberg, "Chapter 5: The Greco-Roman World," *Handbook of clinical neurology* 95 (2010).

⁶ Stanley Finger, *Minds Behind the Brain : A History of the Pioneers and Their Discoveries* (Oxford ; New York: Oxford University Press, 2000), 43-44.

⁷ *Origins of Neuroscience : A History of Explorations into Brain Function* (New York: Oxford University Press, 1994).

⁸ Finger S. *Minds behind the brain : a history of the pioneers and their discoveries.* Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

⁹ Finger S. *Origins of neuroscience : a history of explorations into brain function.* New York: Oxford University Press; 1994. xvii, 462 p. p.

Likewise, his classical description of the brain's arterial supply and of the eponymous Circle of Willis was based on careful experimentation¹⁰ and skillful dissection.¹¹ As a clinician, Willis gave the first description of myasthenia gravis¹² and narcolepsy¹³, in addition to coining the words *neurology* and *psychology*. In trying to correlate structure, function and clinical deficits, one can argue that Willis planted the seed for what would become the anatomico-clinical approach.

If neuroanatomy and clinical neurology continued to evolve throughout the end of the 17th and the beginning of the 18th century, Franz Joseph Gall and Paul Broca's paradigm-changing theory of cortical localization the advent of functional neuroanatomy. In 1792, Franz Joseph Gall, having examined hundreds of skulls from individuals with over- or underdeveloped faculties,¹⁴ (6) became convinced that the cerebrum was composed of discrete organs responsible for the brain's faculties and that these could be inferred by looking at cranial morphology.¹⁵ He termed his doctrine organology (or phrenology), and it became extremely popular both amongst scientists and in popular culture by the early 19th century. However, as the movement became part of popular culture, it started losing scientific credibility and more and more scientists rejected the idea that examining the cranium could allow for any understanding of the brain.^{16,17,18} The use of phrenology by proponents of eugenics and the subsequent antislavery movement in the United States also contributed to its demise.¹⁹

In hindsight, if some its premises were wrong, the basic idea of cortical localization of function was correct. However, it took growing evidence,^{20,21} as well as the reputation of the famous neurosurgeon Paul Broca, to revive it. Broca, a respected figure in French medicine²², was examining the brain of a patient who

had lost the ability to speak when he noticed a "chronic and progressive softening, which was centered in the third frontal convolution of the left hemisphere."²³ He presented his findings to the Société d'Anthropologie in 1861. This single case is perhaps the most important in the history of neurology; it convinced most neuroscientists that function can indeed be ascribed to specific cortical areas.²⁴ John Hughlings Jackson, the father of British neurology, was one of those.²⁵ Indeed, the physiologist expanded on Broca's discoveries, noting that the right hemisphere appeared to mediate spatial perception²⁶ after seeing a man incapable of recognizing both his surroundings and his family.²⁷ Later, Jackson would observe that seizures often "march" from one limb to another, a finding which could only be explained by the motor cortex having different regions corresponding to various body parts.²⁸ This new concept of cortical localization of function had two very important consequences. First, it sparked the scientific community's interest in functional anatomy. Second, it paved the way for Jean-Martin Charcot's anatomico-clinical approach.

In 1870, Gustav Fritsch and Eduard Hitzig published several experiments showing that the dog cortex was electrically excitable and that stimulating an area near the front of the cerebrum led to movement of the hindpaw. Wilder Penfield, along with Edwin Boldrey and Theodore Rasmussen, expanded on this new technique and famously used electrical stimulation to map the motor cortex and develop the cortical motor homunculus (Figure 3B and 3C).

David Ferrier was a physician who, seeing Jackson as his scientific mentor, set out to prove his theory. In 1873, he successfully demonstrated that stimulation of

¹⁰ Willis T, Feindel W, Pordage S. The anatomy of the brain and nerves. 2014. He notably injected dyes inside the arteries to demonstrate this significant anastomosis.

¹¹ Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

¹² Keynes G. THE HISTORY OF MYASTHENIA GRAVIS. Med Hist Medical History. 1961;5(04):313-26.

¹³ Lennox WG. THOMAS WILLIS ON NARCOLEPSY. Arch NeurPsych Archives of Neurology And Psychiatry. 1939;41(2):348.

¹⁴ Ackerknecht EH, Vallois HV. Franz Joseph Gall, inventor of phrenology and his collection. Madison: Dept. of History of Medicine, Univ. of Wisconsin Medical School; 1956.

¹⁵ Temkin O. Gall and the phrenological movement. Bulletin of the history of medicine. 1947;21(3).

¹⁶ Jefferson G. Selected papers. [London: Pitman; 1960.

¹⁷ Flourens P. Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertébrés. 1842.

¹⁸ Flourens P. Examen de la phrénologie. 1851.

¹⁹ McCandless P. Mesmerism and Phrenology in Antebellum Charleston: "Enough of the Marvellous". The Journal of Southern History. 1993; 58 (2), 211.

²⁰ Bouillaud J-B. Recherches expérimentales sur les fonctions du cerveau en général, et sur celles de sa portion antérieure en particulier. J Heb Méd. 1830;6 : 527-70.

²¹ Aubertin E. Sur le volume et la forme du cerveau. Bull Soc Anthropol. 1861;2.

²² Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364

²³ Broca P. Remarques sur le siège de la faculté du langage articulé; suivies d'une observation d'aphémie (perte de la parole). Bulletins de la Société Anatomique.

1861;6:330-57, 98-407. Reprinted from Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press;

2000. xii, 364. This would of course later be called Broca's area. Carl Wernicke would subsequently describe the receptive aphasia associated with temporal lobe lesions.

²⁴ Berker EA, Berker AH, Smith A. Translation of Broca's 1865 report. Localization of speech in the third left frontal convolution. Archives of neurology.

1986;43(10):1065-72. Broca subsequently realized that language was restricted to a dominant hemisphere

²⁵ Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364

²⁶ Jackson JH. Hemispherical coordination. Medical times and Gazette. 1868;2:208-9.

²⁷ Jackson JH. Case of disease of the brain-left hemiplegia-mental affection. Ibid. 1872;1:513-4.

²⁸ Jackson JH. A study of convulsions. London: Odell & Ives; 1870.

various areas of the brain of small mammals led to purposeful movements.^{29,30} After exploring the function of various other brain regions, including the sensory cortex and the frontal lobes, the experimental physiologist summarized his findings in his famous book *The Functions of the Brain*³¹. He subsequently published its clinical counterpart *Localization of Cerebral Disease*³² and founded the scientific journal *Brain*. Several other scientists after him would continue investigating the function of the cerebrum, with more and more sophistication and ingenuity.

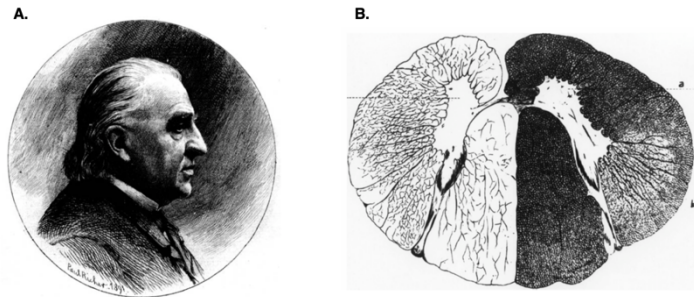


Figure 1 - A. Portrait of Jean-Martin Charcot. From Kumar, Jean-Martin Charcot: the father of neurology, 2011 B. Cross-section of the spinal cord in the superior cervical region in a patient with ALS from Charcot and Joffroy's 1869 report in the Archives de Physiologie Normale et Pathologique. We can appreciate the sclerosis of the lateral columns (a) and the debris in the anterior horn cells (b). From Charcot, 1869

While Ferrier and Penfield exemplified the influence of cortical localization on experimental physiology, it is Jean-Martin Charcot who first used localization of function in clinical neurology. The French neurologist's entire medical system aimed to link neurological presentations with specific neuroanatomical lesions. The first step Charcot undertook was therefore a detailed clinical documentation, including not only the patients' signs and symptoms, but also drawings and tracings of tremor patterns.³³ Subsequently, he carefully examined the brain and spinal cord of these patients with a microscope and correlated the

pathological findings with their clinical presentations (Figure 1A and 1B). The story of amyotrophic lateral sclerosis (ALS) best illustrates Charcot's revolutionary method. At La Salpêtrière hospital, the neurologist noticed that some patients had weakness along with contractures³⁴, while some other patients had weakness with no contractures³⁵. When examining the spinal cord of the patients that had both weakness and contractures, Charcot noted that "on both sides in the lateral areas, there are two brownish-gray streak marks produced by sclerotic changes".³⁶ On the other hand, in patients with weakness in the absence of contractures, the lesion was limited to the anterior horns. These observations were of enormous significance. Not only did they allow Charcot to give the first description of ALS in 1874, they also suggested that the motor system was organized in two-parts and they firmly anchored clinical neurology in neuroanatomy.

As discussed above, cortical localization gave rise to functional localization with the physiologists and neurological localization with the anatomo-clinical approach. The first documented case of the use of cortical localization in surgery comes from Rickman Godlee, who successfully removed a tumor from a patient's motor cortex in 1885 using functional maps.³⁷ In 1908, Horsley and Clarke published a seminal paper in *Brain*, describing the use of a coordinate system to target specific areas of the brain³⁸, which they called stereotaxy. Similar to how Charcot linked post-mortem lesions to clinical deficits, stereotaxy allowed surgeons to link areas of the brain with specific functions and gave rise to neurosurgical localization. In 1947, two neurosurgeons, Spiegel and Wycis injected alcohol into the globus pallidus and the thalamic dorsomedial nucleus of a patient with Huntington's disease, using stereotactic surgery on a human patient for the first time³⁹. The implications were two-fold: not only was it now possible to operate on patients without leaving them with severe neurological impairments, but

²⁹ In fact, Ferrier was also following up on experiments done by Fritsch and Hitzig, two German scientists, who showed in 1870 that stimulation of different parts of the frontal cortex led to movement of different in dogs and that injury to this region impairs purposeful movements. These experiments are reviewed in 1. Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

³⁰ Ferrier D. The Localization of Function in the Brain. [Abstract]. Proceedings of the Royal Society of London. 1873;22:228-32.

³¹ Ferrier D. The functions of the brain. 2011.

³² Ferrier D. The localisation of cerebral disease; being the Gulstonian lectures of the Royal College of Physicians for 1878. London: Smith, Elder; 1878.

³³ While René Laennec and his predecessors were the first to emphasize the importance of correlating anatomy and pathology³³, Charcot took the approach to an entire new level. See Goetz CG. Visual art in the neurologic career of Jean-Martin Charcot. Archives of neurology. 1991;48(4):421-5. for more details.

³⁴ Charcot J-M. Sclérose du cordons lateraux del la moelle épiniere chez une femme hystérique atteinte de contracture permanente des quatres membres. Bull de la Société

Méed des Hôpit de Paris. 1865;2:24-35. Contractures would now be best described as hypertonia.

³⁵ Charcot J-M, Joffroy A. Deux cas d'atrophie musculaire progressive : avec lésions de la substance grise et des faisceaux antéro-latéraux de la moelle épinière. Archives de physiologie normale et pathologique. 1869:629-49.

³⁶ Charcot J-M. Sclérose du cordons lateraux del la moelle épiniere chez une femme hystérique atteinte de contracture permanente des quatres membres. Bull de la Société Méed des Hôpit de Paris. 1865;2:24-35.

³⁷ Godlee RJ, Bennett H. THE EXCISION OF A TUMOR FROM THE BRAIN. The Journal of Nervous and Mental Disease The Journal of Nervous and Mental Disease. 1885;12(2):247.

³⁸ Horsley V, Clarke RH. THE STRUCTURE AND FUNCTIONS OF THE CEREBELLUM EXAMINED BY A NEW METHOD. Brain Brain. 1908;31(1):45-124.

³⁹ Spiegel EA, Wycis HT, Marks M, Lee AJ. Stereotaxic Apparatus for Operations on the Human Brain. Science. 1947;106(2754):349-50.

neuroscientists now had access to precise neurophysiological recordings, expanding the scope of functional neuroanatomy from serendipitous patient injuries to deliberate neurosurgical interventions. In the late 20th and early 21st century, functional neurosurgery continued to expand. From treatment of Parkinson's disease with precisely implanted deep-brain stimulators to thermal ablations for treatment-resistant epilepsy, the neuroanatomical brain and localization of function are still alive and well in neurological surgery.

It is clear from this discussion that cortical localization enabled the development of functional anatomy, anatomo-clinical neurology and functional neurosurgery. However, this picture of the physical brain lacked any physiological insight; its proponents were interested in *what* the brain did as opposed to *how* the brain did it. Of course, one can argue that the lack of technical infrastructure prevented early 20th century scientists from investigating brain function. However, this would be an oversimplification; the whole field of cognitive neuroscience is, even in the 21st century, interested in localization of function. The tools used by cognitivists are based on neurophysiology, but the object they study is function, not functioning. In fact, these two brains very much coexisted in the 20th century and continue to coexist to this day. Such an emphasis on macroscopic anatomical function in addition to the more traditional physiology is rather unique to the brain. While macroscopic cardiac inotropy and chronotropic are certainly fundamental to our understanding of the cardiovascular system, they are directly derived from the study of ion channels and traditional physiology. Conversely, macroscopic brain function is not readily explained by cellular physiology and stands as a separate field of study. There are multiple reasons for this. For one, the complexity of the brain is ten-fold that of any other organ in that its function is not merely maintenance of homeostasis. Therefore, studying the mechanisms behind various neurological functions is hampered by the sheer number of actions the brain performs and by their level of abstraction. However, the brain also allows for a remarkable accuracy when correlating lesions and function. Damaging parts of the liver will not lead to clinical manifestations that are readily correlated with

hepatic function, but neurology is different. Charcot himself remarked that “[he] do[es] not think that elsewhere in medicine, in pulmonary or cardiac pathology, greater precision can be achieved”⁴⁰. Perhaps there lies the reason for neurology's 200-year-old interest in cortical localization.

The brain as a physiological entity: the neuron doctrine and electrophysiology

Unlike brain anatomy, brain physiology was largely a debate of philosophers throughout Antiquity and the Middle Ages. Indeed, Galen's vital spirit⁴¹ and Hippocrates's *four humors* doctrine remained the dominant theory of disease until the Renaissance. The late 17th and 18th century, with their plethora of technological advances, would serve to challenge classical and medieval conceptions of the brain, while setting the stage for the advent of the neuron doctrine and electrophysiology.

While Thomas Willis is considered as one of the first experimental physiologists⁴², he and his contemporaries had a fundamental problem. Without the tools to study microscopic brain function, investigating brain functioning was challenging. Therefore, early 17th century experimental physiologists focused on neuroanatomy, while a physiological understanding of brain functioning was achieved only in the 18th century and the 19th century. Etymology illustrates this lag very well: while some neuroanatomical terms were introduced by Galen and Vesalius, it is Wilhelm His, in 1890,⁴³ and Albert Kölliker, in 1896,⁴⁴ who were the first to introduce the concepts of “dendrites” and “axons”.

In the late 17th century, Anthony van Leeuwenhoek and Robert Hooke developed the first microscopes, thereby allowing for the first time the study of tissues and cells. At a time when most physiologists still believed in the existence of a Galenic “animal spirit” traveling through nerves, van Leeuwenhoek, examining cow optic nerves, reported in 1675 that he “could find no hollowness in them”.⁴⁵ In 1755, Albrecht von Haller's further challenged Galen and Descartes when he elegantly showed that “by intercepting the

⁴⁰ Charcot JM, Blin EdE, Charcot J, Colin H. Lecons du mardi à la Salpêtrière. Paris: Claude Tchoud; 2002.

⁴¹ Finger S. Origins of neuroscience : a history of explorations into brain function. New York: Oxford University Press; 1994. xvii, 462 p. p.

⁴² Thomas Willis and his contemporaries in the early 17th century are considered experimental physiologists in that they used experimentation to understand body function. However, they could not study brain functioning (due to lack of tools) and were interested in the neuroanatomical brain rather than the neurophysiological brain. In this text, brain functioning (neurophysiology) is defined as an approach that emphasizes mechanisms, rather than the broader definition used in standard medical history texts. Therefore, the historical term “experimental physiologists” here serves

to highlight the revolutionary introduction of experimentation in explanations of brain function, but it should not be interpreted as suggesting that the first experimental physiologists were studying neurophysiological brain. They were, in fact, primarily interested in cortical localization of function.

⁴³ His W. Die Neuroblasten und deren Entstehung im embryonalen Marke: Hirzel; 1890. 363 p.

⁴⁴ Kölliker A, Ebner V. Handbuch der Gewebelehre des Menschen. 6th ed. Leipzig: Engelmann; 1896.

⁴⁵ Antonie van Leeuwenhoek, “A study of bovine optic nerve” (Philos Trans R Soc, 1675) in Finger S, Boller F, Tyler KL. History of neurology. Edinburgh ; New York: Elsevier; 2010. xviii, 952 p. p.

communication between a part and its nerve, [...] it is thereby deprived of sensation".⁴⁶ In doing so, he established that nerves are excitable and not merely the inanimate cylinders described by Descartes. If these remarkable achievements were not sufficient to generate a new understanding of brain physiology, old Galenic ideas were nonetheless challenged. If animal spirit was not traveling through hollow nerves⁴⁷, what was the basis for nerve function?

It is therefore in this new neurophysiology, free of Galen and Descartes influences, that Luigi Galvani discovered what he called "animal electricity"⁴⁸ in 1780. Technical advances in electrical engineering, including the invention of the Leyden jar in 1745, allowed Galvani to demonstrate that nerves can be electrically stimulated, and that this electrical stimulation is intrinsic to the nerve fibers. These experiments provided the last fatal blow to Galenic and Cartesian theories of transmission of information, while also pioneering the discipline of neurophysiology. The brain, however, was far from the only organ whose physiology was becoming more clear. Indeed the early 19th century, notably under the influence of François Magendie and Claude Bernard, was dominated by experimental physiology. Magendie, whose earlier work was focused on pharmacology, was himself interested in neurophysiology and in 1822, along with Charles Bell⁴⁹, recognized that the ventral and dorsal spinal roots were respectively motor and sensory^{50,51,52}. This was one of the first experimentally-verified insights into nerve function.

Around the same time, microscopy, which had been abandoned by most physiologists due to concerns over its reliability, rose to prominence again thanks to technical advances in optics, tissue preparation, and staining.⁵³ In 1837 famous histologist Jan Evangelista Purkinje described the now famous cerebellar Purkinje cell, an event which marked the genesis of what would come to be known as the *neuron doctrine*. This was

followed by Theodor Schwann's cell theory and discovery of the myelin sheath.⁵⁴ These discoveries propelled neurohistology to the forefront of neurological research. It culminated in 1889 with the famous Spanish histologist Santiago Ramón y Cajal, who, in 1889, used Camillo's Golgi's stain to examine the retina, the olfactory bulb and the cerebellum (Figure 2).⁵⁵ This experiment convinced him that neurons were indeed the functional unit of the brain and thus no different from other cells in the human body.⁵⁶ Hence, as neuroscience was increasing its spatial resolution to include tissues and cells, an entirely different analytical unit arose: the neuron. Scientists would now be able to study not only brain regions, but individual brain cells as well. This afforded scientists the possibility of studying diseases such as epilepsy, which had frustrated eminent neurologists, including Charcot, because of their lack of lesion-based pathophysiology.^{57,58}

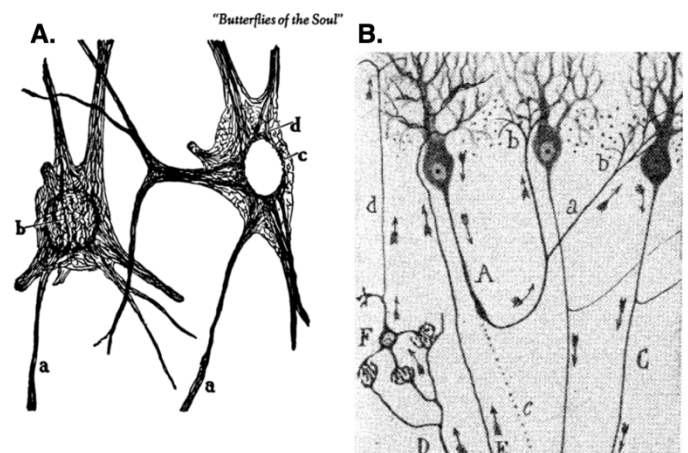


Figure 2 - A. Section stained by Cajal's reduced silver-nitrate method from Canon, Explorer of the human brain, 1949 B. Scheme that shows the path of the impulses in the cells of Purkinje from Cajal, Cajal's degeneration and regeneration of the nervous system, 1991

Charles Scott Sherrington, who was awarded the Nobel prize in medicine in 1932, was perhaps the first

⁴⁶ Haller Av, Temkin O. A dissertation on the sensible and irritable parts of animals. Baltimore: The Johns Hopkins Press; 1936. 1 p., 49 p. p.

⁴⁷ That nerves are hollow tubes carrying pneuma or animal spirit was suggested by Hunayn

⁴⁸ Luigi Galvani, *De viribus electricitatus in motu muscularis* (Tomus Septimus, Bologna, 1791) in Finger S, Boller F, Tyler KL. History of neurology. Edinburgh ; New York: Elsevier; 2010. xviii, 952 p. p.

⁴⁹ Bell C, Shaw A. Reprint of the "Idea of a New Anatomy of the Brain," with Letters, &c. Journal of Anatomy and Physiology. 1868;3(Pt 1):147-82.

⁵⁰ Magendie F. Expériences sur les fonctions des racines des nerfs rachidiens. Journal de Physiologie Expérimentale et Pathologie. 1822;2:276-9.

⁵¹ Finger S. Origins of neuroscience : a history of explorations into brain function. New York: Oxford University Press; 1994. xvii, 462 p. p.

⁵² There is some controversy as to who the discovery should be attributed to. While Bell did not publish his results in a leading journal and was not clear on the sensory function of posterior nerve roots, Magendie used the words "more specifically related to sensation", which have been seen as equivocal as well.

⁵³ Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

⁵⁴ Schwann T, Smith H, Schleiden MJ, Westleys & Clark, Sydenham Society. Microscopical researches into the accordance in the structure and growth of animals and plants. London: Printed for the Sydenham Society; 1847. xx, 268 p., 6 leaves of plates p.

⁵⁵ Finger S. Minds behind the brain : a history of the pioneers and their discoveries. Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

⁵⁶ Ramón y Cajal S. Trabajos escogidos : (1880-1890). Barcelona: Antoni Bosch Editor; 2006.

⁵⁷ Charcot JM, Bourneville. Leçons sur les maladies du systÈme nerveux faites à la Salpêtrière. Paris: A. Delahaye and E. Lecrosnier : Aux Bureaux du ProgrÈs mÉdical; 1884.

⁵⁸ Charcot would venture a few hypotheses about epilepsy in the above lectures given at La Salpêtrière. Specifically, he distinguished between hysterical epilepsy and regular epilepsy and he thought that temperature was the fundamental difference between the two conditions.

experimental physiologist to use the neuron as his analytical unit (Figure 3A). While he was initially interested in cortical localization^{59,60} and neuroanatomy, his interests shifted to function⁶¹, with a particular interest in the spinal cord. This change in focus is most interesting, because it illustrates that even in the early 20th century, there were already two different types of brains: a neuroanatomical and a neurophysiological one. Sherrington's decision to study the spinal cord is also significant; while ascribing specific functions to lesioned areas of the brain requires no particular understanding of physiology; the spinal cord has a physiological complexity that requires the study of neuronal transmission and interactions. This study led Sherrington to describe the physiological basis for reflex action, which he explained in his book *The Integrative Action of the Nervous System*⁶². He was also the first to realize the importance of inhibitory neurons in the function of the nervous system.⁶³ The fact that Sherrington introduced the concept of the *synapse* to explain one-way nerve transmission and the fact that reflexes were slower than nerve conduction velocities⁶⁴ embodies the neurophysiological brain. Indeed, the synapse was not an anatomically observable structure at the time, yet, it was essential as a theoretical construct to explain transmission of information between neurons. Interestingly, Wilder Penfield, who was a student of Sherrington at Oxford, was primarily interested in cortical localization of function. However, and perhaps because of Sherrington's influence, in his study of seizure-induced cerebral vasospasm, he made commendable efforts to utilize both localizationist and physiological explanations for epilepsy and to integrate all available neuroscientific knowledge concerning its pathophysiology.^{65,66,67}

While all these discoveries were of interest to neurologists, they had but a few clinical applications. The neurophysiological brain really only became clinically important with the advent of neurodiagnostics, including electroencephalography and electromyography. Edgar Douglas Adrian was perhaps the most important force behind the development of clinical neurophysiology. In 1935, he showed that information was transferred between neurons via trains of electrical activity, which varied in

frequency based on the intensity of the stimulus. As he uncovered more and more rules of neuronal transmission, Adrian also became interested in psychiatrist Hans Berger's claim that one could record the electrical activity of neurons using electrodes placed on the scalp. His interest was so great that he set out, over the next decade, to prove that neurons formed the basis of electroencephalography.⁶⁸ This marked the advent of electrophysiology and was nothing short of revolutionary for clinical neurology. Gibbs, Davis and Lennox would first describe the spike-and-wave pattern seen in absence seizures, while Denny-Brown and Pennybacker, inspired by these results, would go on to describe fibrillation potentials using the new electromyography technique. With neurodiagnostics, the neuron doctrine and the physiologic brain finally had clinical relevance. EMG, EEG and continue to spark advances in neuroscience and neurology to this day.

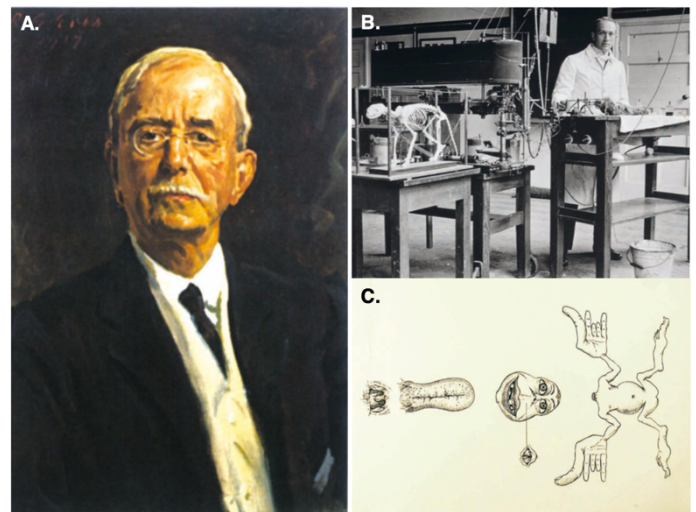


Figure 3 - A. Portrait of Sherrington by R.G. Eves, 1927 B. Penfield in Sherrington's laboratory in Feindel, *The Physiologist and the Neurosurgeon*, 2007 C. Penfield's first motor homunculus in Penfield, *Somatic Motor and Sensory Representation*, 1937

Conclusion

In essence, the two hundred years extending from the 1660s to the 1930s represent one continuous, slow paradigm shift. From an inanimate, physical entity inhabited by an immortal soul, the brain became an organ with a physiology that could be understood.

⁵⁹ Sherrington CS, Grünbaum ASF. An address on localization in the 'motor' cerebral cortex. . *BJM*. 1901;2:1857-9.

⁶⁰ Sherrington CS, Grünbaum ASF. A discussion on the motor cortex as exemplified in the anthropoid apes. . *BMJ*. 1902;2:784-5.

⁶¹ Finger S. *Minds behind the brain : a history of the pioneers and their discoveries*. Oxford ; New York: Oxford University Press; 2000. xii, 364 p. p.

⁶² Sherrington CS. *The integrative action of the nervous system*. 2012.

⁶³ Sherrington CS. Reflex inhibition as a factor in the co-ordination of movement and postures, *Quarterly Journal of Experimental Physiology*. 1913;6(3):251-310.

⁶⁴ Hermann Helmholtz was able to accurately measure nerve conduction velocities

⁶⁵ Feindel W, LeBlanc R. *The wounded brain healed : the golden age of the Montreal Neurological Institute, 1934-1984*. 2016.

⁶⁶ Penfield W, Erickson TC. *Epilepsy and cerebral localization; a study of the mechanism, treatment and prevention of epileptic seizures*. Springfield, Ill.; Baltimore, Md.: C.C. Thomas; 1941.

⁶⁷ Penfield W. *No man alone : a neurosurgeon's life*. Boston: Little, Brown; 1977.

⁶⁸ Adrian ED, Matthews BHC. The interpretation of potential waves in the cortex. *TJP The Journal of Physiology*. 1934;81(4):440-71.

However, unlike other organs, we saw the emergence of two different brains: the neuroanatomical brain, the result of cortical localization and the anatomo-clinical approach, and the neurophysiological brain, the result of the neuron doctrine and neurodiagnostics. Of course, the two brains were not mutually exclusive entities. After all, electrophysiology, whose very existence depends on neurons, was used by Penfield to map the motor cortex (Figure 3B and 3C).⁶⁹ However, it is the function, the *what*, that is interesting to localizationists.

The *how*, the functioning, is another question altogether, one that is best answered by studying neuronal interactions. Therefore, if applications in neurophysiology were useful to functional anatomists, these two visions still represent two very different levels of understanding, two models whose functional unit differs in scale and whose scientific question differs in nature. Unlike Thomas Kuhn's concept of scientific paradigms, the advent of neurophysiological brain did not, by any means, mark the demise of the neuroanatomical brain. Both scientific programmes, to use Lakatos' epistemology, are empirical, successfully anticipate the result of pathological alterations and are not mutually exclusive. Rather, they evolve as parallel entities, mutually benefiting and enabling each other, as exemplified by Penfield's discovery of the motor homunculus, but fundamentally differing in their scientific question. Akin to the Feyerabendian idea that there is no single scientific method, they both contribute to the modern understanding of the brain, and of neurological disorders.

Nowadays, with behavioral and cognitive neuroscience, functional neuroanatomy, cellular and molecular neurophysiology and neural networks, the challenge will be to bridge these various levels of understanding. Just like electrophysiology was able to link the neuron doctrine to functional anatomy, neuroscientists will need to emulate Penfield by moving from description to integration, a task that is both difficult and essential.

“If it seems to neurologists today that our present understanding of the brain and the mind of man is hardly more than a beginning of science, it may be reassuring to recall that our task is the ultimate one. The problem of neurology is to understand man himself [...]. This may be the most difficult, and surely it is the most important, task of all.”⁷⁰

Wilder Penfield, MD

⁶⁹ Penfield W, Jasper HH. *Epilepsy and the functional anatomy of the human brain*. Boston: Little, Brown; 1954.

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⁷⁰ Wilder Penfield in Willis T, Feindel W, Pordage S. *The anatomy of the brain and nerves*. 2014.