

OCCASIONAL PAPER

The discovery of the pyramidal neurons: Vladimir Betz and a new era of neuroscience

Sergiy V. Kushchayev,¹ Vitaliy F. Moskalenko,² Philip C. Wiener,¹ Vitaliy I. Tsymbaliuk,^{3,4}
Viktor G. Cherkasov,⁵ Irina V. Dzyavulska,⁵ Oleksander I. Kovalchuk,⁵ Volker K. H. Sonntag,¹
Robert F. Spetzler¹ and Mark C. Preul¹

1 Division of Neurological Surgery, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

2 Department of Social Medicine and Organization of Health Protection, Bogomolets National Medical University, Kiev 01601, Ukraine

3 Department of Reconstructive Neurosurgery, State Institute of Neurosurgery, Kiev 04050, Ukraine

4 Department of Neurosurgery, Bogomolets National Medical University, Kiev 01601, Ukraine

5 Department of Anatomy, Bogomolets National Medical University, Kiev 01601, Ukraine

Correspondence to: Mark C. Preul, MD,
Division of Neurological Surgery,
Barrow Neurological Institute,
350 West Thomas Road,
St Joseph's Hospital and Medical Center,
Phoenix, AZ 85013, USA
E-mail: mark.preul@chw.edu

As a consequence of nascent technology, the 19th century witnessed a profound change in orientation to the nervous system. For example, improved microscopy in the first half of the 19th century allowed high magnification without blurring. The subsequent observation of nucleated cells led to the identification of individual brain cells. Philosophical changes in approach to the natural sciences took their lead from those applied to physical observations. The Ukrainian anatomist and histologist, Vladimir Alekseyevich Betz (1834–94) played a pivotal role in reshaping scientific and philosophical approaches to the brain, connecting cerebral localization, function and brain microstructure. Betz revolutionized methods of cell fixation and staining. Sometimes his efforts yielded enormously complicated technological improvements. Betz's greatest contribution, however, was connecting his discovery of the function of giant pyramidal neurons of the primary motor cortex ('cells of Betz') with the cortical organization. Considering cortical cytoarchitectonics in relation with physiological function, Betz recognized this organization in two areas: motor and sensory. He defined a functional area on histological grounds and thereby opened the way to study precise cortical areas. Betz participated in the scientific transformation of cytoarchitectonics based on macro- and microscopic studies of the cortical surface, enabling him to view the paths of nerve cells in the brain. Betz's influence allowed systemization of scattered scientific findings. The discovery of pyramidal cells was a turning point in the prevailing philosophical and scientific approach to the brain, linking cytoarchitecture, neurophysiology and cerebral localization.

Keywords: Vladimir Betz; pyramidal cells; cortex; Betz cells

Introduction

For the person who, after me, will enter a temple where, according to Sylvius, 'Death is glad that even it contributes to life,' this essay should be a guideline on the following: Anatomy should not be considered a completed descriptive or the only applied scientific discipline having the honor to serve medical practice; it is a thing described by a well-known speech of Hamlet to Horatio: 'There are more things in heaven and earth, Horatio, Than are dreamt in your philosophy.' (Vladimir Betz, 1887 *Morphology of Osteogenesis*).

In this article, we present a detailed biography of Vladimir Betz (1834–94), who has gone largely unheralded, documenting his contributions and impact upon the nascent neuroscience (although the term 'Betz cell' has become widely known, Betz was not included among Haymaker and Schiller's *Founders of Neurology*, and there is no mention of him in the over 450 pages of Clarke and Jacyna's *Nineteenth Century Origins of Neuroscience Concepts*). We also show for the first time color photomicrographs of his own histological preparations—the brain cells named for him, the Betz cells, or the giant pyramidal cells. After four centuries of investigation of the brain, Betz was the nexus of three separate lines of neurological sciences. His contribution played a seminal role in the emergence of the modern system we recognize as 'neuroscience'. The discovery of and insight into the pyramidal cells, i.e. 'the cells of Betz', allowed scattered scientific facts and findings to be systematized and became the basis for neurohistological works of Cajal, Golgi, Lewis, Campbell and Brodmann as well as neurophysiological and surgical studies of Broca, Horsley, Sherrington, Cushing and Penfield.

Neuroscience at the turn of the 19th century

Radical changes in philosophical outlook impacted explorations in biology and medicine in the 19th century. Such explorations had been, up until this time, really Galenism revisionist schemes. This was an age influenced by such people as Auguste Comte (Comte, 1844) and the metamorphosis of vitalistic approaches of Naturphilosophie or romantic philosophy into more empirical, observational and reductionistic methods in the physical and biological sciences (Karenberg, 2000; Gardner and Martin, 2000).

Important discoveries resulted in significant progress in fixation, cutting, staining and studying brain tissue. Neuroanatomists, such as Johann Christian Reil, Francisco Gennari, Felix Vic d'Azyr, Luigi Rolando and Richard Ladislaus Heschl, began to focus their studies on smaller parts of the brain, likely made possible by the improved means to preserve tissue (Gennari, 1782; Vicq d'Azyr, 1784; Reil, 1809; Rolando, 1829; Heschl, 1855). Notable advances in neurohistology reflected more versatile and reliable staining techniques such as those used by Gabriel Valentin (1836) and Theodor Schwann (1839).

Refinements in technology permitted investigations of brain microscopic organization and corresponding physiological activities (Jacobson, 1993). As early as 1833, Christian Gottfried Ehrenberg,

using a simple microscope and unstained material, described cortical slices with fibres in the white matter that were continuous with those of the spinal cord and those from the periphery (Ehrenberg, 1833). The origin of these fibres, however, was unknown. However, the neuron theory had not yet been formulated so that the relationship of nerve to grey matter was still obscure. The introduction of the achromatic microscope in the 1820s (Quekett, 1848; Ratcliffe, 2009) with high magnification and resolution without blurring permitted observation of nucleated cells, resulting in the ability to identify individual brain cells. Joseph Lister's work with microscopes led him to conclude that almost all of the previous microscopic observations of histological structure were invalid because of gross optical aberrations produced by earlier lenses (Lister, 1830; Bracegirdle, 1977).

Although soon discredited, phrenological theories were an impetus for the concept of cerebral localization and became a focus of philosophical, scientific, and clinical observations over the next decades (Gall and Spurzheim, 1809, 1810; Simpson, 2005). The outlook that cell types must have some teleological underpinning became a focus of critical investigation, led by the theories of such people as Henri Milne-Edwards (Milne-Edwards and Foster, 1841; Jacobson, 1993). Ideas that the cerebral cortex was composed of histologically distinct areas began to take root.

Mid-19th century achievements

Observations of cellular spatial regularity was the impetus for investigations of cytoarchitectonics (Jacobson, 1993; Clarke and O'Malley, 1996). In 1840 Jules Gabriel Francois Baillarger described the layers of the cerebral cortex and connecting white matter fibres (writing that the six alternating layers of grey and white substance resembled a Voltaic pile) (Baillarger, 1840). In 1858 Rudolph Berlin reported the arrangement of cortical nerve cells in a regular layered order and, importantly that there were recognizable cell types occupying stereotypical positions. In addition to layers, Berlin observed various types of carmine stained cells that he described as spindle cells, granule cells and pyramidal cells (Jacobson, 1993). Theodor Hermann Meynert described cortical layers and formulated the idea of an 'organologie' of the cortex, basing his description of variations of five cortical laminae (Meynert, 1872). Despite Meynert's careful studies of the cerebral cortex, which involved a search for variation in cells and their arrangement, he overlooked one of the most characteristic cortical cells: pyramidal or motor cells (Clarke and O'Malley, 1996).

Meanwhile, clinical observations began to be systematically correlated to altered or diseased brain states through the work of Pierre Paul Broca (1861), Hughlings Jackson (1866) and Henry Charlton Bastian (1869). Gustav Fritsch and Eduard Hitzig (1870) demonstrated that discrete areas of the dog's cortex gave excitomotor responses to galvanic stimulation. Based on such investigations, the surface of the cerebrum began to be considered as a functional area, although these numerous important findings lacked a systematic integration. However, Vladimir Betz

(Fig. 1) was part of a new epoch in the history of brain philosophy that integrated cerebral localization, function and brain microstructure.

Vladimir Betz: early life

Vladimir Alekseyevich Betz was born on 14 April 1834 in Ostra, a small town in northern Ukraine, which at that time was a part of the Russian Empire. A child of a noble, relatively wealthy family that may have had origins in Germany (Karev, 1999), the adolescent Vladimir was sent to the Second Kiev Gymnasium, well known for its educational rigor, to continue his education. In 1853 he entered the Faculty of Medicine of St Vladimir University in Kiev where he was an excellent student and enjoyed his studies.

The Faculty of Medicine of St Vladimir University opened in 1840, with the Department of Anatomy headed in 1844 by Alexander Valter, a student of the famous surgeon, Nikolay Pirogov. Valter enthusiastically developed the department; he introduced the Anatomical Museum where he collected

anatomical specimens and built the new facility to house the Department of Anatomy (Betz, 1884). The level of professional teaching was extremely high, supported by Valter's logistical organization for acquiring anatomical material for the theatre. During this period, the anatomy department purchased hundreds of cadavers annually (Betz, 1884; Ikonnikov, 1884). Valter took note of the young Betz, who displayed a proclivity for anatomy and physiology, inviting him to continue his career at the department.

After he graduated in 1860, the young doctor Betz was appointed a prosector's aide in the St Vladimir Department of Anatomy (Kachaturyan, 1950; Kukuev, 1950). Because of the German pre-eminence, the best researchers from the Russian Empire were often sent west for postgraduate training. Thus Betz was sent to Germany and Austria to work with anatomist Josef Hyrtl and physiologists Ernst Brücke and Carl Friedrich Wilhelm Ludwig. He also studied with Robert Wilhelm Eberhard Bunsen, Rudolph Albert von Kölliker, Hermann Ludwig Ferdinand von Helmholtz and Gustav Robert Kirchhoff (Kachaturyan, 1950). In Vienna, Betz worked in research laboratories and published the results of his studies in the leading European journals.

Early research: focus on the liver

Betz returned to the Ukraine and in 1863 obtained a Doctor of Sciences degree with his thesis *On the Mechanism of Circulation in the Liver*. In this work, he showed himself to be a qualified specialist not only in anatomy but also in physics. Among the seminal contributions of Betz's thesis were his descriptions of the pressure differences between the hepatic portal system and hepatic artery, the relationships of the gall ducts to hepatic venous flow, and the degenerative changes that occur in the liver as a result of manipulations of the hepatic artery (Betz, 1863, 1864; Lauth, 2007). Betz also published on hydraulic aspects of the liver circulation (Hermann, 1883).

Betz performed anatomical and histological investigations of the suprarenal glands, lungs and bone. He discovered a chromaffin reaction of the adrenals and contributed some of the earliest accounts of osteogenesis and bone development (Betz, 1864, 1887). As Betz began his studies of the brain, he discontinued studies of other organ systems. At the end of his professional career, however, Betz again studied systems other than the brain (Kachaturyan, 1950). Betz was a comprehensive researcher and often lectured on chemistry and physics (Kachaturyan, 1950; Kukuev, 1950). His studies on the suprarenal gland appear to have profoundly influenced his leanings toward microanatomy, where his combined knowledge of chemistry, physics, histology and anatomy was essential (Bobrik, 2010).

Interest in the brain

In the early 1860s, Betz began to concentrate on studies of the brain. The writings of the Russian physiologist, Ivan Mikhailovich Sechenov, *Reflexes of the Brain* published in 1863, were an



Figure 1 Photograph of Vladimir Betz, his Cyrillic signature below 'Prof. V.A. Betz.' [sic], contained in his self-published Atlas of the Human Brain, 1879. Photograph courtesy of the Vladimir Betz Museum at the Department of Anatomy Bogomolets National Medical University, Kiev, Ukraine.

impetus in this line of work (Sechnov, 1863; Bobrik, 2010). For several years, Sechenov had studied and worked in Europe in many of the same laboratories as Betz. In an 1870 lecture in St Petersburg, Betz recounted the origins of his interest in studying the brain:

Any business is difficult but the specific investigation of such a dark and tangled section of science such as the brain is much more complicated. It requires a lot of time and resources. It requires not only the comprehensive investigation according to current tasks but also reconsideration of all previous work to date to make the correct conclusions. The difficulty and insufficiency in the study of the brain are well accepted by all the anatomists. Hyrtl said that he regarded the anatomy of the Brain as a book sealed with numerous stamps and that humanity will open it, will read it, and only during the last day of all existence will humanity understand all of the truths comprised within it (Betz, 1871, p. 2).

From 1864 to 1867, Betz lectured on anatomy and histology at St Vladimir University, rising to the rank of Extraordinary Professor in 1868. Vladimir Tomsa, who presented Betz as a candidate to this position wrote: 'Betz is specialized in the part of the descriptive anatomy (central nervous system) that represented an insurmountable difficulty for anatomists and remained almost untouched. The difficulty of this study have been overcome by his hard work, mechanical dexterity and clear understanding of the problems' (The Journal of the Ministry of the Education, 1868, p. 401). In 1869 Betz was promoted to Head of the Department of Anatomy, and in 1870 he was elected as Ordinary Professor. In 1871 he also began to practise neurology in the St Cyril Hospital in Kiev (today known as Ivan Pavlov Kiev City Psychoneurological Hospital Number 1).

Betz believed his histological science could aid in explaining neurological diseases, and thus he approached clinical medicine using science: 'It is up to the scientists and psychiatrists to research more thoroughly these centers in the brain and especially anteriorly.... This could possibly throw light on the sudden occurrence of temporary paralysis of cerebral origin; on eclampsia of pregnancy; or epileptic convulsions, hysterical laughter, and finally it could, in a great area, explain the appearance of partial or total aphasia' (Betz, 1950c, p. 228; this reference contains Betz's lectures in Russian published in 1950 and unfortunately does not cite specifically the original date of the lecture. Based on the topic, it is likely that the original date is the middle portion of the 1870s).

A new method of investigating the central nervous system

Betz's revolutionary methods of fixation and staining were the result of his motivation to improve histological technique and to exploit the latest microscope technology. As described in his 1870 paper *Die Untersuchungsmethode des Centralnervensystems beim Menschen* (translated 3 years later into English as *Methods of Investigating the Central Nervous System in Man*), many of his

methods were enormously complicated (Betz, 1873). Betz significantly improved Reil's method of brain tissue fixation with ethanol by adding ether and chloroform, potassium bichromate, and iodine (Betz, 1950b). He established certain fixation solutions and methods for fixing every specific brain structure.

To give the preparations a certain degree of firmness, I placed them first in a solution of iodine in alcohol, and afterwards in aqueous solution of potassium bichromate. The different parts of the nerve-centers, viz. the spinal cord, the medulla oblongata, the pons Varolii, the cerebellum, and the cerebrum, require various times and various degrees of concentration of both these solutions, as well as some mechanical preparation (Betz, 1873, p. 343).

It is likely that Betz carefully noted different preservation techniques in the western European centres he visited, however, there can be no doubt that he was an intrepid explorer involved in often arduous chemical experimentation that would improve the appearance and observation of his sections. Betz's unique method allowed him to fixate even deep brain structures, vastly improving the ability to harden the entire brain. With old techniques, the cortex was hardened first and deep areas of the brain often were not penetrated nor preserved well for fixation. 'By this process, I have succeeded in hardening complete cerebral hemispheres, even after they have been removed from the body three or four days after death; but in such cases, longer time and more concentrated solutions are required' (Betz, 1873, p. 346). Betz's tissue preparation allowed him to examine the white matter tracts of the brain in exquisite detail: 'My method of the brain fixation... Gives me a chance to make casts directly from the brain' (Betz, 1950b, p. 127).

Betz's method allowed him to cut extremely thin brain sections (Fig. 2). He had specific instructions for cutting and invented a system that minimized friction and allowed tissue to be cut smoothly:

The construction of the knife used is a matter of great importance. The chief evils to be guarded against are friction in drawing the knife along and adherence of the knife to the mass from which the section is made, or of the section itself, to the upper surface of the blade. Consideration of these points has led to the idea that the preparation of large and thin sections is wholly a matter of individual skill and dexterity. By my plan, any person will be able, with a little practice, to cut large sections, and always in the same plane. Using a razor, which is convex on its upper surface and concave on the lower surface, attains this desired result.... it is possible to keep a layer of fluid both above the place of section and under the section as it is made, by which all friction is avoided. In order to keep an excess of fluid on the surface, which is especially necessary in making large sections, water must be kept continually flowing. The apparatus, made by connecting an Indian-rubber tube to the mouthpiece of a chemical wash-bottle, gradually blew air in while the section was prepared. For very large sections a wash-bottle with three jets may be used. In order to know the arrangements of the nervous elements, series of successive sections must be studied without any interval. Such a series cannot be

obtained by mere freehand cutting, since the surface of a section always becomes, after a time, concave, and a screw section machine must be used. A mixture of wax and oil is used to imbed the preparation in the section machine, and alcohol used to wet the knife (Betz, 1873, p. 346).

Until Betz's time, unsuccessful staining of brain sections had been a limiting factor for examination. 'Various colouring matters, which have been of late years recommended for tinting microscopic preparations—such as indigo, aniline colors and various vegetable dye-stuffs—are not suitable for preparations of the nervous centers. Some of them are imperfectly absorbed, and others are washed out by the process of depriving the preparations of water' (Betz, 1873, p. 348).

Carmine, or, as some call it, ammonium carminate, introduced by Gerlach, still remains the best, and perhaps the only coloring material for these preparations. I think I can confirm Deiters's statement, that if it is necessary to color nerve preparations at all, the use of carmine for this purpose leaves nothing to be desired.... It tints all microscopic preparations very rapidly, but especially those of the nerve-centers. Half an hour, or an hour at most, is enough to impart the most perfect and intense coloring to preparations of any size.... With a more dilute solution some parts can be colored, others left uncolored; and in this way beautiful and instructive preparations showing the grouping of the grey matter are obtained (Betz, 1873, p. 348).



Figure 2 'A perfectly hardened brain permits very large and thin sections to be made. I have preparations of the whole pons Varolii with the corpora quadrigemina, which are thin enough to be examined with immersion lenses, and I have lately obtained complete transverse sections through the whole of the hemisphere. Very thin sections are obtained from the cord and medulla oblongata, e.g. of one twelfth or one twentieth of a millimeter in thickness.' (Betz, 1873). For these purposes Betz invented a special guillotine-like cutting machine that yielded excellent brain sections.

Betz's specimen collection

Betz created a massive collection of 8941 brain and spinal cord specimens, including samples of healthy and mentally ill humans, infants, monkeys, dogs and rats (Ikonnikov, 1884). '...These preparations open the door to identify the laminar distribution of the grey and white matter in a hemisphere; this topic, as is known, comprises a rather important and, at the same time, rather difficult part of descriptive anatomy—almost no researchers focused on this direction in their studies' (Moskalenko *et al.*, 2010). He received many honours and awards for his work, including medals at the All-Russian Manufacturing Exhibition in 1870 in St Petersburg, and with the success of this exhibition, Betz received many invitations to lecture. His lectures were later subsequently published in collected form (Ikonnikov, 1884) (Fig. 3).

Betz received a personal invitation to present his specimens at the Vienna World Exposition of 1873, where he was awarded a

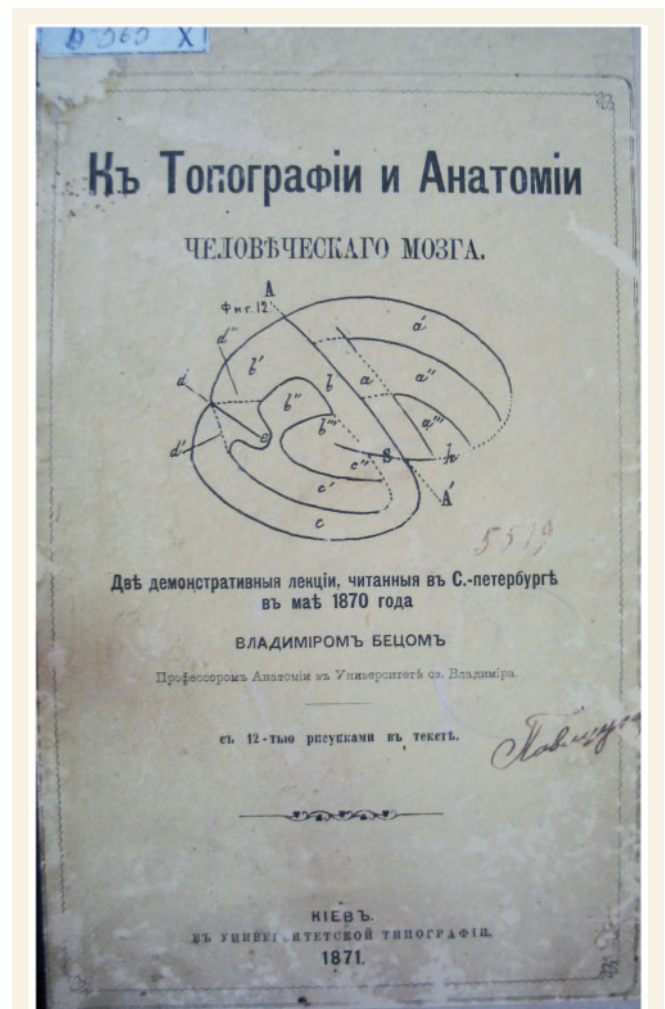


Figure 3 Betz lectures published as a book: *On Topography and Anatomy of the Human Brain – Two demonstrative lectures given in St-Petersburg in May 1870* (Betz, 1871).



Figure 4 Certificate announcing the 'Fortschritts Medaille' presented to Betz at the Vienna World Exposition of 1873. Photograph courtesy of the Vladimir Betz Museum at the Department of Anatomy Bogomolets National Medical University, Kiev, Ukraine.

'Fortschritts Medaille' (Fig. 4). A contemporary review by a Viennese medical journal stated:

Betz's sections surpassed all that has been performed earlier. Their delicacy and clarity allow understanding of the connection of parts with a confidence that has been missing in earlier investigations. Important discoveries from Betz's work concern the optic nerve fibers for teaching about neuroretinitis which has been tremendously important. Betz's demonstration and preparations were acclaimed by attendees and the chairperson with applause, and with this believe that the presenter (Betz) demonstrated the most important discovery in anatomical techniques. They called upon him to exhibit a collection of his preparation in the next year (University News, 1873, p. 20).

Josef Hyrtl, serving as an expert commission member for the Exposition, wrote as follows:

In the ninth volume of the archives of microscopic anatomy Professor Betz published a new method of examining the central nervous system. This method teaches us the possibility of hardening large brain matter in a relatively short period of time such that the most delicate sections can be prepared of which the microscopic examination has yielded instructive and unexpected information about the fibrousness of the brain. This has resulted in a true and important service to the field of brain anatomy the practical usefulness of which is improved by the fact that by applying the Betz Method the brain can be hardened inside the skull itself and hereunto serve for preparation of plaster casts which reveal the individual differences of the gyri and furrows depending on age, gender, and acquired or inherited states of the brain and which

allow most readily for comparative anatomic examinations of the surface of the brain in great numbers.

My own examination of the Betz specimens has confirmed the above against all objections. The excellence of these specimens (of which he brought more than 2,000 to Vienna for which there was space only for a few 150 in the Russian exhibit) shows so far that they can be photographed at higher magnifications and yield images which leave nothing to be desired in sharpness and clarity of detail. I have to say that no anatomist has advanced the knowledge of brain structure as much as Professor Betz.

I therefore consider it my duty to recommend the unequalled accomplishment of my Russian colleague for special consideration by the jury and to apply for the awarding of the medal of progress for Professor Betz with the epigraph: for his exquisitely beautiful and most instructive human and comparative anatomic brain specimens. Entirely identical to the original of my report.

Prof. Jos. Hyrtl

Vienna, August 4, 1873' [*sic*] (University News, 1873, p. 21).

After Betz's success in Vienna, the German Society of Anatomists and Carl Ludwig offered him 7000 Austrian Guildens for his collection (a massive amount for the time). However, Betz refused the sale and instead gave the collection as a gift to the medical faculty of St Vladimir University (Ikonnikov, 1884; Kachaturyan, 1950).

Discovery of 'Giant Pyramids'

Betz's most significant contribution was to connect cerebral organization and function with specific, unique histological evidence. 'The sulcus of Rolando divides the cerebral surface into two parts; an anterior in which the large pyramidal nerve cells

predominate.' 'They are predominantly in the fourth cortical layer and are from 0.05–0.06 mm wide and from 0.04–0.12 mm long.... Undoubtedly these cells have all the attributes of so-called "motor cells" and definitely continue as cerebral nerve fibres' (Betz, 1874, pp. 578–80, 595–9). Betz wrote that he discovered these cells, which he called 'giant pyramids', in Meynert's fourth cortical layer (i.e. next to the deepest layer) of the precentral gyrus. Since that time the layers have been refined, and today the Betz cells are defined as being found in the fifth cortical layer. As well as in the human precentral gyrus, Betz found these cells in

the same location in dogs, chimpanzees, baboons, and other primates (Fig. 5) (Betz, 1874).

His discovery of giant pyramidal neurons in the fifth layer of the primary motor cortex, correlated to and elaborated by insight into cortical function, was formulated in the landmark article *Anatomischer Nachweis Gehirncentra* (Betz, 1874). For such an important article, it did not have an especially auspicious beginning. The article was less than eight pages long and due to a printer's error, another unrelated article was printed in the midst of Betz's article. Its style was dense and the article was packed with

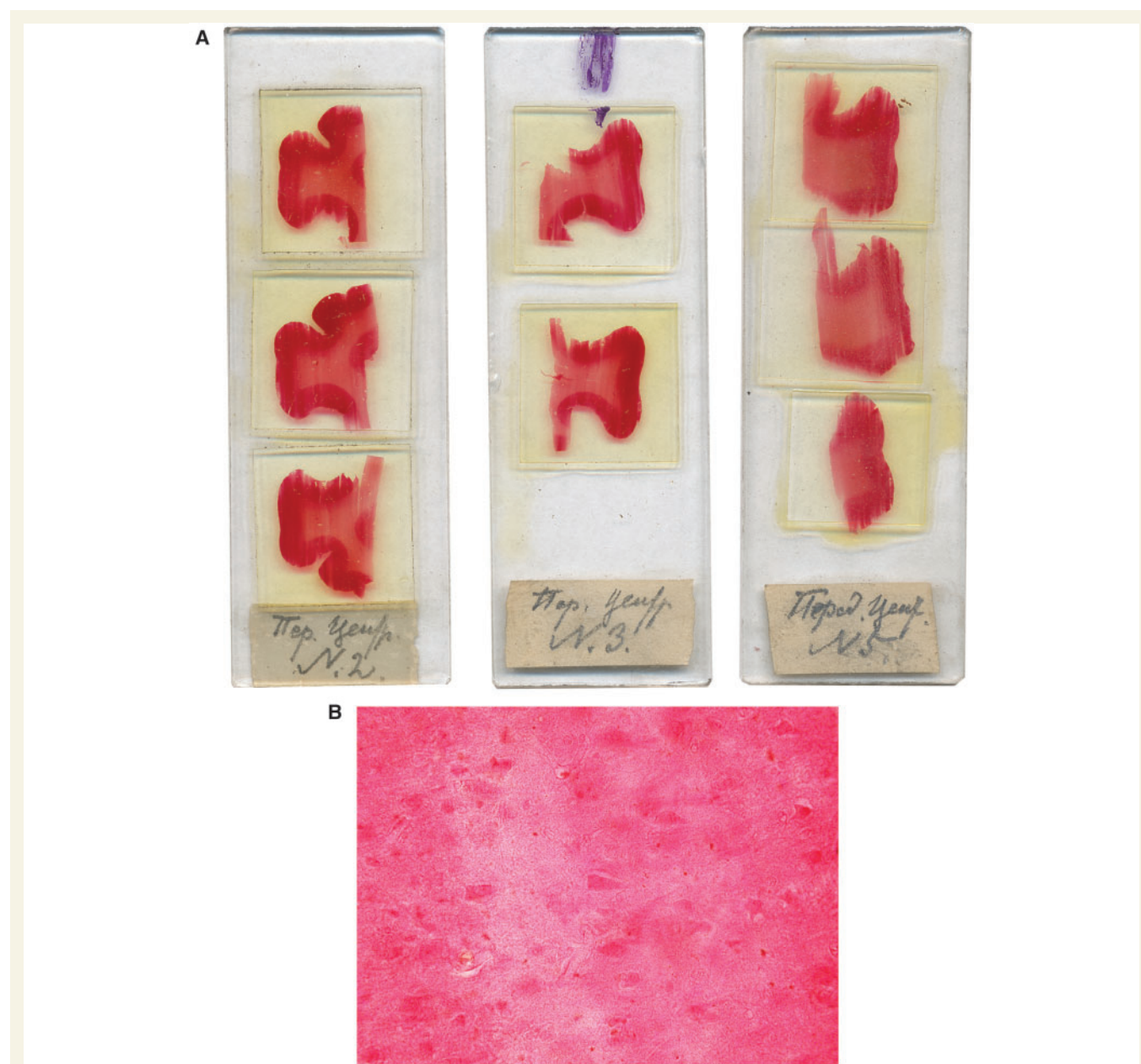


Figure 5 (A) Betz's original microscope slides showing the brilliant carmine staining from Betz's technique. Each slide is labelled by Betz in abbreviated Russian 'Ant. Centr.' with the number of the slide. (B) A modern photomicrograph of one of Betz's slides reveals the pyramidal cells of the cortex. Although not as revealing as staining techniques might be today, Betz was nevertheless able to interpret the cells and their processes. This is the first time Betz's sections have been published in colour. Photographs courtesy of the Vladimir Betz Museum at the Department of Anatomy, Bogomolets National Medical University, Kiev, Ukraine.

facts. Typical for Betz, he published first in a local journal in Russian and then in German. Subsequently, his most important works were translated and republished in English (Fig. 6) (Betz, 1875, 1950c).

Betz's descriptions of the processes of pyramidal cells began to explain Ehrenberg's findings that fibres in brain white matter were continuous with those of the spinal cord and those from the periphery (the terms 'cells', 'dendrites' and 'precentral' were added by the authors to make the quote more comprehensible):

Each of them (cells) has two main processes, and 7 to 15 secondary protoplasmatic processes (dendrites) which in turn branch out into smaller ones. At its origin, one of the main processes is thick, as is the case in the pyramidal cells of the cortex. It then tapers as it proceeds to the periphery of the cortex and, in its course, gives off branches. The other process, however, is thin; it starts in the nucleus of the cell, and proceeds directly into the axis cylinder, which becomes thicker after a short distance and acquires a nerve sheath; it thus undoubtedly continues as a nerve. The cells of this anterior cortical region do not form a continuous layer but rather are imbedded as nests of one, two, three, or more cells. These nests are from 0.3–0.7 mm. distant from each other. In such a nest one may find at times as many as five cells of different sizes and of the dimensions stated above. Furthermore, these cells are sparser in the lower half of the anterior central (precentral) convolution but more plentiful and closer together in its upper end and in the part on the medical surface of the hemisphere (Betz, 1874, pp. 578–80, 595–9; Clarke and O'Malley, 1996).

With his usual attention to methodological detail, Betz sought to identify the characteristics of his giant pyramid cells and their processes in young and old human brain specimens:

In young individuals and in an eleven-year-old brain I found fewer nests; the cells were smaller and also had fewer protoplasmic

processes. In very old brains (seventy years old and slightly younger) these cells acquire a seemingly special nucleus, which consists of yellow granules that are resistant to carmine dye. In children and young individuals these cells have a uniform protoplasm which can be evenly stained with carmine and in which no derangement can be shown. These cells are more numerous and apparently large in the right hemisphere than in the left.... These giant pyramids occur in the stated areas in every human brain, in the idiot, in the chimpanzee, in the gray, brown, small Persian Pavian, and in the green monkey (Betz, 1950b, p. 225; Clarke and O'Malley, 1996).

Perhaps most importantly for the functional significance of the pyramidal cells, Betz linked them not only to the results of Fritsch and Hitzig, but investigated their existence in the same species in which Fritsch and Hitzig had done their work:

Such consistency in the region where these cells can be found, manifested as a very definitive cortical layer, as well as in a specific cerebral convolution, prompted me to devote my attention to that particular part of the animal brain, mainly the dog's, in which Fritsch and Hitzig achieved such brilliant physiological results, i.e. the lobe which borders the cruciate sulcus. I now found such cells of the same shape and in exactly the same position in nests in the dog, precisely in the lobe just mentioned. So in the dog, as well as in man, they are imbedded in the fourth cortical layer and occur only in this lobe and in the anterior half of the posterior (postcentral) convolution bordering it. In the dog, they are somewhat smaller, but nevertheless are the largest in its entire nervous system. They also possess two large and many small processes, and the inner process runs into a genuine nerve filament. In the area where they are found there are also many axis cylinders visible in the white substance, which run in the same direction as in the human. Undoubtedly these cells have all the attributes of the so-called 'motor cells' and very definitely continue as cerebral nerve fibres (Betz, 1874, pp. 578–80, 595–9; Clarke and O'Malley, 1996).

Considering cortical cytoarchitectonics in relation with physiological function, Betz recognized this organization in two areas: motor and sensory. 'Based upon the present findings, it may be asserted that there are two cerebral areas which may be designated as two centers, one motor and the other sensory' (Betz, 1874, pp. 578–80, 595–9; Clarke and O'Malley, 1996).

Betz described functional areas on histological grounds and thereby opened the way for study of the precise relationships between cells and cortical areas. His work laid the foundation for the modern doctrine of cytoarchitectonics based on macro- and microscopic studies of the cortex surface that enabled him to view the paths of nerve cells in the brain. By linking cytoarchitecture, neurophysiology, and cerebral localization, the discovery of pyramidal cells was a momentous event in philosophical and scientific approaches to the brain. Betz coupled his discovery with experiments on electrical stimulation of the motor centres of the brain. He not only studied the morphology of the pyramidal cells, but he also postulated their function by relating his findings to the best neurophysiological and phenomenological evidence of the

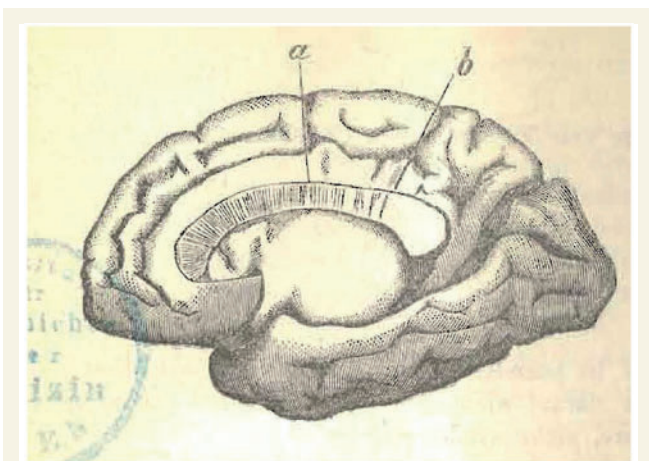


Figure 6 Identification of 'motor' zone by Betz from his first publication on giant pyramidal cells of the cortex, translated into German and published as 'Anatomischer Nachweis zweier Gehirncentra' in the journal, *Centralblatt für die medizinischen Wissenschaften* in 1874 (Betz, 1874).

day: 'Previous investigations of anatomists and histologists did not find proper anatomical background for explaining the results of Fritsch and Hitzig's experiments. In 1874, I published investigation of the human and monkey cortex where I showed a specific unknown before nervous cells discovered by me which I called, giant pyramides' (Betz, 1950d, p. 229).

In his work *Über die feinere Struktur der Gehirnrinde des Menschen* (*On Details of the Cerebral Cortex Structure in Man*) published in 1880, Betz provided an architectonic division of the brain cortex and 'arranged (the material) in topographical order'. Clearly identifying five cortical layers, as opposed to the mere lines visible to Gennari and others in fresh unstained brains, Betz found evidence for structural specialization that he believed correlated with specific functions and described the giant pyramidal cells in more detail.

The general structure of the human cortex is the following. It consists of five different layers, one after another from outer layer to inner one.... The fifth layer is a layer of special fusiform cells. This five-layer structure of the human cortex can be considered as a fundamental pattern. So far specific particularities of the cortex structure depending on the location were found only in a few areas. Meynert showed that the cortex around the fissurae calcarinae does not contain the third pyramidal layer, but it has two granular layers, divided by the layers of neural fibres.... And finally according to my investigations the cortex of the anterior central gyrus and paracentral lobuli contains the giant cells (giant pyramidal cells) that are localized as nests' (Betz, 1950d, pp. 230–1).

The anteriorcentral gyrus, beginning from the upper border of the lower one-third of its length, demonstrates in the upward direction the following peculiarities. First, large cells (giant pyramidal cells) appear in this region in the superficial part of layer V; these cells appear as single units or pairs, and these pairs are localized at considerable distances from each other. Then, in the upward direction, these cells are grouped in clusters containing three or four units, and the spacing between these clusters decreases. In more upward parts, these clusters include greater numbers of the cells, at least four, but sometimes five or even seven. From the former site, i.e. the superficial part of layer V, these clusters enter layer III and are localized in the latter as an interconnected stratum, and single cells enter layer II and also layer IV and an upper part of layer V. In the paracentral lobe, this stratum is again divided into clusters, and, within the above lobe per se, these cells are localized either as layers, one above another, or as clusters occupying different positions (Betz, 1950d, p. 232).

Betz and brain comparative cytoarchitectonics

Betz believed he could elucidate the details of organization of the pyramidal cells in a comparative nature, as well as in normal and diseased states: 'The gender difference in the brain's structure consists of the following. The frontal lobe of (female humans) contains a thinner and rarer third layer. The same can be said about the anterior frontal gyrus. There are smaller forms of

pyramids and giant pyramids are smaller and rare. But the third layer occipital and posterior part of the parietal lobe contain more cells and these are larger in size' (Betz, 1950a, p. 154).

Betz held a systematic, fundamental approach that was essential for understanding disease: 'There is need for a precise notion on the organization of the brain; such a notion, which can be understood by every physician, is being enhanced every day. A psychiatrist, when discussing changes in the density, color, and weight of the brain and other distinct features of this organ, will be unable to formulate and precise conclusion until an anatomist shows him the pathways where things should be searched and in what manner' (Betz, 1872, 1873, 1950b; Moskalenko *et al.*, 2010). He investigated the cellular elements of the cortex in cases of mental diseases, and in at least one family there appear to have been definitive structural abnormalities especially as noted in the giant pyramidal cells:

'All disabled persons from one family have similar brain structure, but for persons from different families, comparison of anatomy shows differences in the structure of the brain.' (Betz, 1950a). 'As for cortex of underdeveloped persons so called idiots.... The cortex of the Morey (the family) has the following particularities. The frontal lobe consists of narrow but large pyramids without appropriate order, so it is not possible to distinguish the fifth layers: the giant cells of the central gyrus and the cells from the area that corresponds to paracentral lobule are narrow and curved with the small amount of thick proto-plasmatic processes (dendrites), I was not able to find the major process (axon)' (Betz, 1950d, pp. 227–38).

The Viennese Moritz Benedikt (known for describing the midbrain-alternating syndrome) was one of the founders of criminal anthropology and a pioneer in electrotherapy. He believed that morality was nothing more than a kind of sense organ whose neurophysiological substrate was located in a specific part of the human cortex. Betz assisted Benedikt with his research on the brains of criminals and performed investigations of the anatomical background of criminal behaviour (Verplaetse, 2004). Betz believed that criminal behaviour originated in the defective development of certain parts of the brain, and could be differentiated on an anatomical basis compared with normal people. This subsection of Betz's specimens was presented as a part of his collection at the Vienna World Exposition in 1873. In appreciation of Betz's assistance, Benedikt dedicated his 1880 text *Anatomical Studies upon the Brains of Criminals* (Benedikt, 1881) to Betz:

First of all, I must here express my warmest thanks to Professor Betz, of Kiev, who was at the same time a spur, a guide, and a support to me. It was only the greatest confidence in his authority and special knowledge in this branch that encouraged me to continue my studies in spite of the great distrust which they encountered, and to conquer the subjective fear of hopelessly wandering around a source of error; a fear which must necessarily possess everyone who stands isolated with his facts (Benedikt, 1881, p. v-vi).

As a scientist and practicing physician and whether exactly correct or not, Betz clearly understood the important relationships among anatomy, development, disease, physiology and behaviour. 'Between 20–40, the brain obtains the maximum of its development and all of its function uses the maximum amount of its energy' (Betz, 1950a, p. 154). On 22 September 1870, in a lecture on anatomy in Kiev, he commented on the unknown of the brain:

If physiology is not the anatomy-based branch of science, any theory that tries to explain one physiological phenomenon or another falls to the ground in the face of the first anatomical term...The anatomy of the brain requires the systematized collection of data, a more detailed explanation, and interpretation of many earlier known things, but it has single things that stand like a milestone with no inscription... (Moskalenko *et al.*, 2010, p. 2).

Betz's 'Atlas of the Brain' and the art of printing

In 1879, Betz published an *Atlas of the Human Brain* (Betz, 1879; Fig. 7) after already deciding earlier that decade to print the book himself. In 1872, after examining the collection of preparations presented by Betz at the Congress of Naturalists and Physicians in Leipzig, Ludwig proposed to publish an atlas of figures made from these specimens at the expense of the Dresden Academy of Sciences. Betz, however, rejected this proposal because he wanted the book published in his homeland.

While staying in Vienna, the physiologist Ernst Wilhelm von Brücke (a pupil of Johannes Müller) suggested that Betz investigate acquiring his own photographs. In Vienna, Betz bought a cliché printing system and took it back to Kiev. He acquired photography equipment at the anatomical department and prepared the cliché from 1873 to 1874. However, he was unable to locate anyone in Kiev who could satisfactorily publish the format. Therefore, Betz went to St Petersburg where he found two publishers proposing work for sums of 18 000 and 7000 rubles. The expense (e.g. the monthly salary of a pressman was 35 rubles) motivated Betz to apply to the Russian Academy of Sciences for financial support, but he was denied. Likewise, he was turned down at the Ministry of Education. Undaunted, he purchased a printing machine in 1876, learned press techniques, hired two pressmen and published his own atlas with exquisite quality (Ikonnikov, 1884). When the administration at St Vladimir University saw the quality of the book, Betz received some financial support for further publication. The first sample of his atlas, the first and finest of its kind, was printed in June 1879 (Hines, 1934). Moreover, after mastering the art of printing, Betz helped Benedikt to publish his book. Even the organizers of the anthropological conference in Kiev, after searching for the best polygraphists, asked Betz to publish their materials (Ikonnikov, 1884). His achievements in photography and printing were so noteworthy that Betz was elected chair of the Photography Section of the Kiev Technical Society for several terms (Ivanov, 1894).

Betz and Broca

Two months after receiving the first copy of his atlas in August 1879, Betz travelled to Moscow to participate in the First Meeting of Russian Empire Society of Naturalists, Anthropologists and Ethnographers, where he was elected a member. Pierre Paul Broca, with whom Betz kept a scientific relationship and correspondence, was one of the organizers of the meeting. On his return to Paris, Broca visited Kiev to see Betz's collection. There, Betz and Broca speculated on the role of the olfactory lobe in humans and its differences compared with other animals (Kachaturyan, 1950; Kukuev, 1950). After returning to Paris, Broca sent the results of a preliminary olfactory study to Kiev (Bobrik, 2010). Excited about the findings, Betz prepared 5000 new specimens of olfactory lobes and found 11 types of histological patterns within the anatomical structure.

Unfortunately, for what might have been an extraordinary collaboration, Broca died suddenly in 1880. Subtly, but perhaps fittingly as a tribute to Broca, in a review of his own work (Betz, 1881), Betz laid the foundation for what appears to be a description of a novel concept, the columnar cellular organization of the central motor region. Subsequently, he presented the results of his research on olfactory lobes at the Meeting of Natural Scientists in Odessa in 1883. It is likely that Broca was interested in Betz's work because both had accomplished much in the way of comparative anatomical studies, both were interested in cerebral localization and structural foundation of function, both had published on cerebral topography, and both were involved in elucidating scientific bases for disease. Unfortunately, we know little of the subjects of their conversations, but Betz appears to have been as captivated by anthropological studies as was Broca.

Ukrainian patriotism

In 1883 Betz and Vladimir Antonovich, Professor of History from St Vladimir University, decided to publish a book titled, *Historical Public Figures of South-Western Russia* in three volumes (the term South-Western Russia referred to Ukraine). The first volume included descriptive portraits of hetmans of Ukrainian Cossacks (e.g. Sagaidachnyi, Khmel'nitskii) and described prominent political and military historical figures of the Ukraine (hetman was the highest military title in Ukraine's Cossack Hetman as well as the head of state and was in common usage from the 15th–18th centuries. The involvement of Betz in the creation of this historical publication may have been the result of strong feelings for some of his ancestors who were descended from Zaporozh'ye Cossacks in southern Ukraine). Reaction to Betz's book was sharp; he received published criticism for this work, both from public figures in Kiev and from the Russian Empire (Shubinsky, 1883; Moskalenko *et al.*, 2010). This criticism may have significantly exacerbated the long-standing tension between Betz and the administration of St Vladimir University (Shubinsky, 1883; Moskalenko *et al.*, 2010).

In 1884 during the official celebration of the 50-year anniversary of St Vladimir University, and at an occasion when several of the university's most famous members were elected Honorary Professor, Betz was not included in the programme. In 1890 the

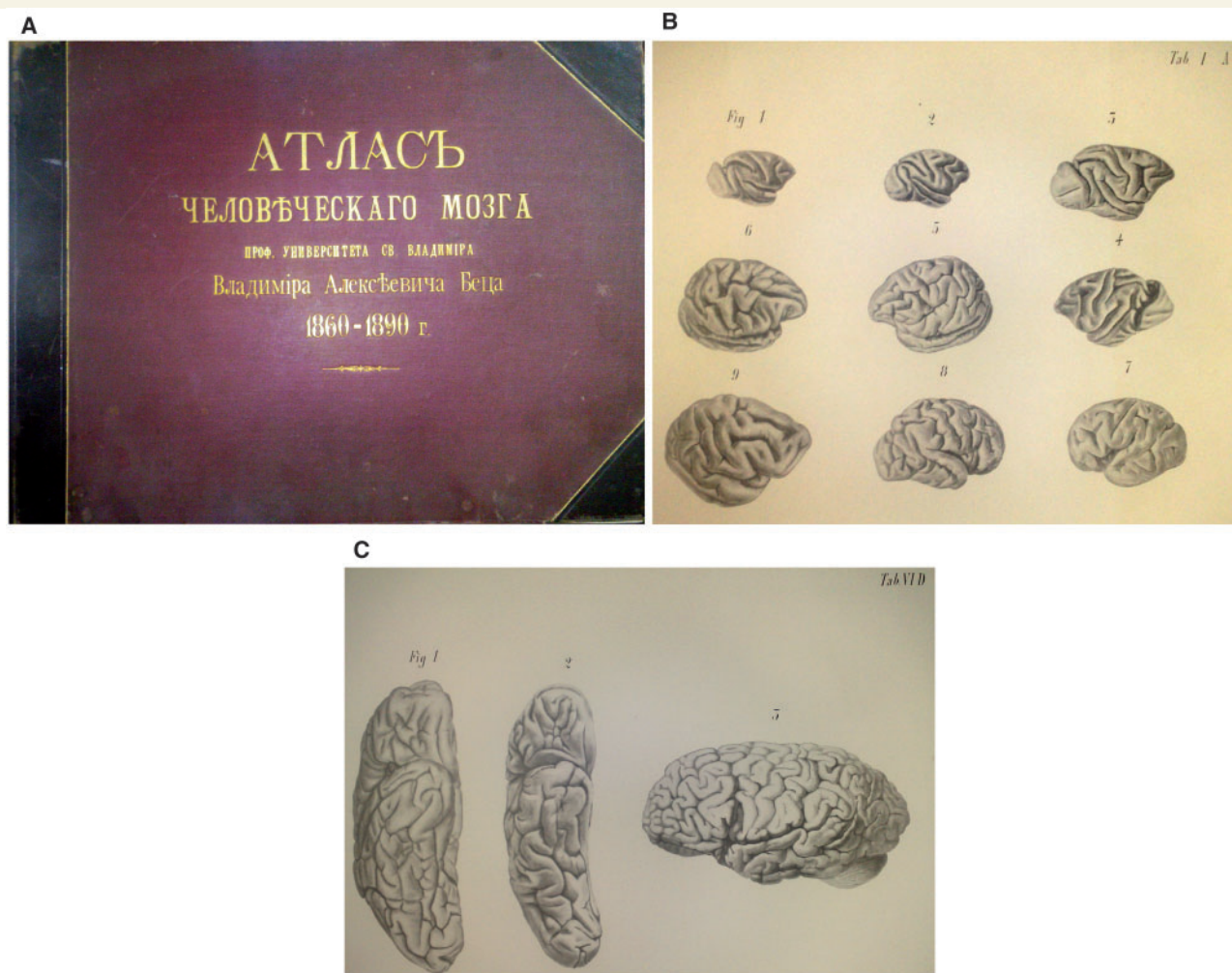


Figure 7 (A) *Atlas of Human Brain* published by Betz in 1890. When the administration at St Vladimir University saw the quality of the book, Betz received some financial support for further publications. The first few copies of his atlas, the first and finest of its kind, were hurriedly printed in June 1879 so that Betz could take them on his trip to Moscow, mainly to show Broca (Ikonnikov, 1884; Hines, 1934). Among the many photographs from the atlas, Betz was particularly interested in those that revealed brain development and disease or asymmetries, such as in (B) showing surface topography of the left and right cerebrum at the different stages of human development, and (C) showing variability of the surface topography of the cerebrum. Moreover, after mastering the art of printing, Betz helped Benedikt to publish his book. Even the organizers of the anthropological conference in Kiev, after searching for the best polygraphists, asked Betz to publish their materials (Ikonnikov, 1884). His achievements in photography and printing were so noteworthy that Betz was elected chair of the Photography Section of the Kiev Technical Society for several terms (Ivanov, 1894). Photographs courtesy of the Vladimir Betz Museum at the Department of Anatomy, Bogomolets National Medical University, Kiev, Ukraine.

disagreement with the university became more overt when he refused to cooperate to announce his upcoming vacancy as department head. He left the university at age 56, at what should have been the height of recognition and prominence after 30 years of visionary and practical scientific work. He continued his clinical work at St Cyril Hospital and was appointed as a principal physician of the South-Western Russian railway.

Betz's personality

There is limited information about Betz's personal life or his personality. Two books published in Russian in the Soviet Union in

1950 depicted Betz as a near hero with no character flaws (Kachaturyan, 1950; Kukuev, 1950). Russian 19th century documents accessible in the post-Soviet era help to reconstruct a personal view of Betz (The Journal of the Ministry of the Education, 1868; Ikonnikov, 1884; Tsymbaliuk, 2009). He was highly educated and motivated; fluent in Russian, Ukrainian, German and Latin; and was fond of reading the Greek philosophers in their original language (Kachaturyan, 1950). His contemporaries described him as lively, principled and punctual (Kachaturyan, 1950; Kalita, 2010). Apparently, he was a bright lecturer and able to explain extremely complicated subjects with relatively simple language, and would frequently comment on the social and moral impacts of science. Betz insisted on a thorough and

complete understanding of medicine beyond mere memorization of facts; few students passed his anatomy examinations on their first attempt (Kalita, 2010). An obituary stated that 'Vladimir Betz and his lectures were like a compendium of the wisdom of medical science. His lectures often leave the limits of the topic, and included a large amount of information from other areas of life and science. Moreover Betz was able to present any lecture as the old masters did with great variety, with witty phrases and jokes that were often picked up and learned by the students' (Ivanov, 1894). Vladimir Tomsa stated that: 'Betz gave private classes for the doctors who were preparing to obtain the degree of Doctor of Medicine. It is well known that people more readily take the private classes with teachers from whom they can gather the most information within the shortest time' (The Journal of the Ministry of the Education, 1868, pp. 401–2). But it also appears that Betz had a rather peevish disposition and was easily irritated (Kachaturyan, 1950; Kukuev, 1950). In 1861 while Betz was a student and travelling to various famous European centres, he published 'A Letter from Vienna' in the journal *Modern Medicine* (Russian language) in which he criticized the methods and results of major figures and laboratories in which he had recently been working. He was very demanding of himself and of others as exemplified by his enormously difficult methods of brain tissue preparation and undertaking the assembly of a collection of almost 9000 brain specimens, plus 5000 for Broca. His articles were usually dense informational works; in fact, using his huge collection to describe the giant pyramid cells resulted in only six terse pages.

Betz received two awards from Russian Emperors: The Order of Saint Vladimir third degree in 1879 and the Order of Saint Stanislaus first degree in 1888. Having come from a wealthy family and remaining financially comfortable throughout his life perhaps explains why he did not sell his specimen collection and engaged himself in purchasing printing equipment and publishing his own texts. However, Betz never had a family and lived alone. Certainly, few women of the time would have happily agreed to a complete printing press operation in their home!

Betz seems to have held that science should have a practical and beneficial influence on the human condition. In his lecture on anatomy in 1870, during the Franco–Prussian War, he expressed hope for a more enduring use of human industry, using the analogies of government manipulations, desires, and war as a backdrop for the study of human health, social, and moral states:

Ladies and gentlemen! At the time when the people in western Europe who have reached a high level of civic consciousness are physically beating each other, making barbarism worthy of (the) primitive stages (of human development), we Russians, remaining behind the times in civic consciousness, gathered here together to start the fight against these social prejudices that from the cradle till the grave clog man's mind. They obscure the direct and clear observance of nature itself, its phenomena and laws. The fight between Germany and France is caused by material demands, hunger for profits, and mercenarial interests of the nations' leaders. We will be fighting for world domination of the

sensible notions of nature and humankind. Instead of needle guns, Krupp steel cannons, nitroglycerin bombs and buckshots, we will come to you against your prejudices with microscopes, chemical reactants, the devices of physics, and anatomical samples.

Yes, man is a complicated machine and there innumerable advantages of the knowledge of that machine: in your practical activity, in your home life, in your care for yourself and people close to you, and in your command of these things, with you rests the faith of your subordinates, in management of which rests your responsibilities for the lives of millions and the faith of the people for whom you are responsible. You can say that in disciplining children, in managing of your subordinates, in management of the provinces one should know and learn the laws of moral life. But moral life depends on the material aspects of life; the material diseases lead to moral diseases; decline of social morality is an indication of the decline of social health. You would not be cheating yourself by observing the dashing appearance of soldiers whose tightened collars bulge their eyes from their skulls and who faint not because of lack of energy, but because of compression of the superficial neck veins. You would not put onto the soldier two satchels filled with sand and put on an additional four rifles until the blood gushed out from his mouth because you know that the human body cannot bear that without harm for his health (Kachaturyan, 1950, p. 14)

Vladimir Betz died from heart disease on 14 October 1894 at the age of 60 and was buried at the Vidubicheskiy Monastery in Kiev in accordance with his will (Fig. 8).

Legacy of Vladimir Betz

The results of the clinical and experimental works of Broca, Jackson, Fritsch, Hitzig and others became related to structure through Betz's histological investigations, which elucidated the structural differences of the various cortical areas. His histological demonstration that the motor cortex corresponds to the distribution of giant pyramid cells, led to acceptance that the central fissure divides the cortex into anterior motor and posterior sensory regions. In 1878, Bevan Lewis confirmed that the 'motor area' described by Betz contained giant pyramidal cells. Interestingly the studies of Betz and Lewis attracted relatively little attention at first. Lewis wrote:

In an article contributed to the 'Centralblatt' for August 1874, Professor Betz has given the details of an extensive examination of the cerebral cortex, which proved a valuable addition to our knowledge of its histology, as he therein advanced several original observations indicating the existence of certain definite regions hitherto unnoticed amongst the list of those characterized by a dissimilar lamination. With a few exceptions and misstatements, this article was a really fresh addition to existing knowledge of cerebral topography. In the March number of the same journal for the present year there appears an account of a still more extended inquiry into the diversified structure of the human cortex cerebri (Lewis, 1881, p. 238).



Figure 8 The grave of Betz in Kiev at the Vidubicheskiy Monastery (built in A.D. 1077) adjacent to the west bank of the Dnieper river. The panoramas from the grave and monastery befit the scientific vision of Vladimir Betz. According to Ukrainian tradition, to be buried in a monastery is to have achieved a life of service and honour for humanity.

In 1875 as the subject of his annular course on Pathological Anatomy, Jean-Martin Charcot launched a series of lectures on cerebral localization and contemporaneously used Betz as the example to illuminate the great transition in philosophy that had recently occurred regarding the brain. The pyramidal tract, which is a major pathway of voluntary movements, was a focus of Charcot's great clinical interest: '...Lastly, there are the so-called pyramidal giant cells, which were carefully described by Betz and Mierzejewsky. They sometimes attain a diameter of '040 to '050 mm, that is to say, a diameter equal to that of the large ganglionic or motor cells in the anterior grey cornua of the spinal cord' (Charcot and Hadden, 1883, p. 192).

Moreover, it has long been known that certain regions of the cortex differ, as regards structure, in a very remarkable manner. But the most recent and most valuable researches on this subject are those accomplished by Betz, the results of which were published in the 'Centralblatt' of last year. Betz made it his purpose to study the textural modifications presented by the grey matter, convolution by convolution. From this standpoint, we must distinguish, according to him, on the surface of the hemispheres two fundamental regions, which are as nearly as possible bounded by the fissure of

Rolando. In front of this fissure, the cortex is characterized by the predominance of the large pyramidal cells over the globular cells (Charcot and Hadden, 1883, p. 26).

During Betz's time, concomitant technological advances permitted surgery of the brain to gain practicality using cerebral topographic methods for relatively accurate, precise surgery of the cortex and to begin to understand the cellular basis of neurological disease (Reis *et al.*, 2008). However, the Betz cells held great intrigue until well into the 20th century. The elucidation of motor and sensory phenomena did not become completely clear until the work of Sherrington, Cushing and Penfield. It was especially important for neurosurgeons to identify and establish exact borders of the different functional areas to predict the effect of neurosurgical manipulations in the brain. Although Betz identified motor (anterior to the Rolandic sulcus) and sensory areas (posterior to the Rolandic sulcus) according to histological patterns, his findings required confirmation and more detailed functional exploration.

In 1887 Victor Horsley published his maps of the human brain based on his own experiments on monkeys and, to some extent, on observations in humans (Horsley, 1887). His maps showed an area of motor representation similar to that found by David Ferrier. The motor area extended both in front of and behind the Rolandic fissure and was rather broad. In the same year, William W. Keen became the new editor of *Gray's Anatomy*, and he added a section entitled 'Cerebral Localization and Topography' (Keen, 1903; Uematsu *et al.*, 1992). At that time, American surgeons in the Philadelphia area were stimulating the brains of their patients with focal epilepsy and observed the excitability of motor cortex in response to electrical stimulation. In 1889, American casualty surgeon J. Morrison wrote the following:

'The revolution of a decade has so completely modified the position of this subject (lesion localization), that the localization of encephalic functions may no-longer be spoken of as a question: it has entered the domain of fact; though in matters of detail a vast amount of work still remains to be accomplished... We owe to Betz the valuable discovery that in the cortex of the Rolandic area, and in this region alone, are found giant ganglionic cells analogous to the large anterior cornual cells of the spinal cord. This is highly suggestive of motor function.... These relations explain some phenomena of hemiplegia' (Morrison, 1889, p. 193).

A series of physiological and anatomical studies performed by Charles Sherrington and Alfred Campbell (Grünbaum and Sherrington, 1903; Leyton and Sherrington, 1917; Uematsu *et al.*, 1992) on the Rolandic cortex in the early 1900s further elucidated the distribution of the giant pyramidal Betz cells (Campbell, 1905; Lord Cohen of Birkenhead, 1958; Eccles and Gibson, 1978). From 1900 to 1903 Campbell examined brain specimens from higher apes that Sherrington had given him after completing stimulation studies (Campbell, 1905; Eccles and Gibson, 1978; Uematsu *et al.*, 1992). In 1903 Sherrington presented the final cytoarchitectural studies to the Royal Society of London, and Campbell published his work in 1905 (Campbell, 1905). Campbell's published work described 17 regions of the

cortex, each tied to specific functions such as vision, sensation, and olfaction (Campbell, 1905). Campbell's work seems to have directed Sherrington's thoughts on cerebral mapping toward distinguishing the pre-Rolandic motor cortex functionally from the post-Rolandic area of the sensory cortex. Campbell held that there were no motor cells (Betz cells) in the cortex behind the Rolandic fissure; instead, the area was rich with small granular cells. Furthermore, he believed that the arrangement of the post-Rolandic fibres was more indicative of a sensory centre (Horsley, 1887; Campbell, 1905; Uematsu *et al.*, 1992).

Along with Campbell in the beginning of the 20th century, several neuroanatomists, (Grafton Elliot Smith, Korbinian Brodmann, Cécile and Oskar Vogt), set out to study the microanatomy of the human cerebral cortex using the new Nissl staining technique (Geyer, 2011). This cartographic approach ushered in what has been described as an 'era of feverish map-making' (Zeki, 2005). In 1909 Korbinian Brodmann published his findings in a comprehensive monograph entitled *Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues* (Treatise on Comparative Localization in the Cerebral Cortex) where he identified 47 histologically distinct regions further developing the concept of the relationship between histology and function (Brodmann, 1905). Brodmann wrote concerning the functional anatomy of the brain that 'since the first pioneering research of Meynert and Betz, a continuous stream of workers has studied the cellular lamination of the cerebral cortex and its specific modifications in man and in individual animals. It would, therefore, be reasonable to expect that there would now be a solid basis of knowledge and understanding, at least as far as the essential elements are concerned.' However, he stated there 'were major contradictions, not only in interpretations, but also in observations' while there was 'complete terminological confusion...making interpretation quite impossible' (Brodmann, 1905). He cited Betz as having provided reliable evidence on which to develop the connection between cellular pattern and function:

W. Betz, provided an important, and perhaps the only lasting, advance in this direction in the oldest work on cortical localisation that we, at least, possess. Already in 1874, he showed that two different 'anatomical centres', one anterior and one posterior, were separated by the sulcus of Rolando on the brain surface. The anterior domain, that Betz termed 'motor centre' is characterized, as he described, by the presence of unusually large cells, grouped into clusters, the so-called 'giant pyramids', that were completely absent in the posterior 'sensory centre' (Brodmann, 1905, p. 6).

Cushing confirmed Sherrington's functional stimulation findings in patients and claimed that his results were in exact accord with Sherrington's findings in anthropoids and with Krause's and Frazier's findings in humans (Cushing, 1909; Uematsu *et al.*, 1992). In 1906 Cushing drew a map of the human brain. The drawing showed the Rolandic fissure as an undisputed dividing line, with the motor cortex in front of it and the sensory area behind it. The drawing was made for the chapter *Surgery of the Head* in W.W. Keen's surgical text (Cushing, 1907; Fulton, 1946; Uematsu *et al.*, 1992). In 1909 Cushing summarized his

observations of two patients, concluding that stimulation of the postcentral convolution elicited a definite sensory response. The location of the central fissure was determined by obtaining characteristic motor responses from the precentral area (Cushing, 1909):

One of the most important steps in our progress toward a more exact localization of function in the cerebral cortex was taken when, by a method of unipolar faradization, Sherrington and Grünbaum accurately delineated the confines of the so-called motor area. Their circumscription of this electrically excitable strip of cortex in the ape to the anterior wall of the fissure centralis (Rolandi) and to the adjoining surface of the precentral gyrus, has received confirmation through the more recent studies of myelination, and through investigations into the finer histology of the cortex, which has shown that this area corresponds with the distribution of the Betz cells (Cushing, 1909, p. 44).

The most detailed correlations of histology, function and organization of the central area in humans, however, were performed by Wilder Penfield, initially with the help of Edwin Boldrey beginning in the mid-1930s. Boldrey's 1936 thesis, *The Architectonic Subdivision of the Mammalian Cerebral Cortex* was a compendium of cytological and functional correlations from stimulation and mapping studies of the brains of operated patients, (Boldrey, 1936) and led to Penfield's text, *The Cerebral Cortex of Man* (Penfield and Rasmussen, 1950). Penfield continued to remark upon and illustrate the organization, distribution and function of the Betz cells until well into the 1950s, basing most of the work upon Campbell and Sherrington. The Betz cells held special interest for Penfield also since Betz had found pyramidal cells in the hippocampus ('cornu Ammoni') in a unique, close arrangement he termed 'glomeruli corticales'. It has long been suspected that this pyramidal neuron organization plays a role in susceptibility and propagation of hippocampal seizures, and furthermore, these hippocampal neurons appear to be involved in formation and disorders of memory (Kandel and Spencer, 1961).

On a singular level, Betz's work demonstrated the importance of appropriate preparation and staining of brain samples. Later, more conclusive histological techniques were developed by Camillo Golgi and Santiago Ramón y Cajal, allowing anatomists to examine elements in the nervous system with considerably greater precision. The discovery of and insight into the pyramidal cells (i.e. 'the cells of Betz') allowed scattered scientific facts and findings to be systematized. Betz's contribution toward the modern system of histology, cerebral localization, and neurophysiology that we recognize today as 'neuroscience' has been relatively overlooked. Perhaps this has been because there has been little access to his work, lectures, archives, and books originally written in Russian. As well, the period of the Soviet Union was restrictive in access to information and historical sources. Cajal wrote of Betz:

In reality, our knowledge of the structure of motor region did not advance much until the publication of the work of Betz, who noted as characteristic of the motor region, the existence of giant pyramids at the level of fourth layer of Meynert, these are absent from the rest of the cortex...In such manner, the cerebrum becomes

reduced to two poles, motor and sensory, like the grey matter of the spinal cord, where, according to belief of Betz, the anterior horn is motor and the posterior sensory (Cajal, 1899, p. 190).

Today Betz's collection, including microscope slides, human and animal brain sections, brain models, instruments, and various other artefacts, is maintained in the Department of Anatomy of the Bogomolets National Medical University in Kiev. Most of the preparations have withstood the test of time. After nearly a century and a half, the gross brain specimens and the microscope slides with carmine-stained brain slices appear vibrant and fresh. These priceless items survived the cataclysms of the 20th century, including the October revolution of 1917 and the subsequent Russian Civil War. At that time, the museum was not owned by anyone and sometimes was even left without security and subjected to occasional looting. During the German occupation of Kiev during World War II, the museum was again left without security. Notwithstanding, most of the samples survived from what Betz's obituary referred to as the 'lobus paracentralis Betzii'. With this article, we are humbled and honoured to show Vladimir Betz's pyramidal cells to the world in the glorious colour in which he meant them to be seen, juxtaposed to a history of his life and his profound contribution to neuroscience.

Acknowledgements

Dr Kushchayev was awarded the Vesalius Prize from the Section on History of Neurological Surgery by the American Association of Neurological Surgeons in 2010 for his historical work on Vladimir Betz.

Funding

The Newsome Family Endowed Chair of Neurosurgery Research at the Barrow Neurological Institute (to M.C.P., in part).

References

- Baillarger J. Recherches sur la structure de la couche corticale des circonvolutions du cerveau. *Mém Acad R Méd* 1840; 8: 149–83.
- Bastian HC. On the various forms of loss of speech in cerebral disease. *Brit Foreign Med-Chirurgical Rev* 1869; 43: 209–492.
- Benedikt M. Anatomical studies upon brains of criminals. A contribution to anthropology, medicine, jurisprudence, and psychology. New York: William Wood & Company Publishers; 1881.
- Betz W. The circulation within the liver, especially that of the hepatic artery. *Zeitschrift fuer rat Med* 1863; 18: 44–60.
- Betz V. Some notes on microscopical structure of suprarenal glands. *University News of St Vladimir University (Kiev) (in old Russian)* 1864; 6: 48–60.
- Betz V. On topography and anatomy of the human brain (two demonstrative lectures given in St Petersburg in May 1870) (in old Russian). Kiev: Empire Saint Vladimir University; 1871.
- Betz W. Die Untersuchungsmethode des Centralnervensystems beim Menschen. *M Schultze's Arch f micr Anatom* 1872; IX: 101–17.
- Betz W. Methods of investigating the central nervous system in man. *Q J Microsc Sci* 1873; s2–13: 343–50.
- Betz W. Anatomischer Nachweis zweier Gehirncentra. *Centralblatt für die medizinischen Wissenschaften* 1874; 12: 578–80, 595–99.
- Betz W. Distinction of two nervecentres in the brain. *Q J Microsc Sci* 1875; 15: 190–2.
- Betz V. Atlas of the human brain (in old Russian). Kiev, 1879.
- Betz V. Sur la structure de l'écorce cérébrale. *Revue d'anthropologie* 1881; 3: 426–38.
- Betz V. Anatomical theatre of St Vladimir university. In: Ikonnikov V, editor. Historical and statistical notes on scientists and research-auxiliary organizations of Empire Saint Vladimir University. (in old Russian) Kiev: Empire Saint Vladimir University; 1884. p. 246–87.
- Betz V. Morphology of osteogenesis (in old Russian). Kiev: Kulzhenko Publishing; 1887.
- Betz V. Anatomy of the brain surface. In: Kachaturyan AA, editor. V.A.Betz. Anatomical and histological investigations. Selected works (in Russian). Moscow: Medgiz; 1950a. p. 139–222.
- Betz V. A new method of investigating the central nervous system. In: Kachaturyan AA, editor. V.A.Betz. Anatomical and histological investigations. Selected works (in Russian). Moscow: Medgiz; 1950b. p. 105–28.
- Betz V. Distinction of two nervecentres in the brain. In: Kachaturyan AA, editor. V.A.Betz. Anatomical and histological investigations. Selected works (in Russian). Moscow: Medgiz; 1950c. p. 223–8.
- Betz V. On particularities of the structure of the brain cortex. In: Kachaturyan AA, editor. V.A.Betz. Anatomical and histological investigations. Selected works (in Russian). Moscow: Medgiz; 1950d. p. 229–40.
- Bobrik II. Anatomist that opened the way for the neurology and psychiatry. *Mistetsvo Likuvannya (The art of treatment) (in Russian)* 2010; 4: 10–14.
- Boldrey EB. The architectonic subdivision of the mammalian cerebral cortex thesis in partial fulfillment of the requirements for the degree of Master of Science. Montreal: McGill University; 1936. p. 206.
- Bracegirdle B. J. J. Lister and the establishment of histology. *Med Hist* 1977; 21: 187–91.
- Broca PP. Remarques sur le siège de la faculté du langage articulé, suivie d'une observation d'aphémie (perte de la parole). *Bull Soc Anat* 1861; XXXVI: 330–57.
- Brodman K. Beiträge zur histologischen Lokalisation der Grosshirnrinde. Dritte Mitteilung: Die Rindenfelder der niederen Affen. *J Psychol Neurol Lpz* 1905; 4: 177–226.
- Cajal CR. Studies on the human cerebral cortex II: structure of the motor cortex of man and higher mammals. *Revista Trimestral Micrográfica* 1899; 4: 117–200 and 1900; 5: 1–11.
- Campbell AW. Histological studies on the localisation of cerebral function. Cambridge: Cambridge University Press; 1905.
- Charcot JM, Hadden WB. Lectures on the localization of cerebral and spinal diseases. London: The New Sydenham Society; 1883.
- Clarke E, O'Malley CD. The human brain and spinal cord: a historical study illustrated by writings from antiquity to the twentieth century. San Francisco: Norman Publishing; 1996.
- Comte A. "Discours préliminaire sur l'esprit positif," *Traité philosophique d'astronomie populaire*. Paris: Carilian-Goeury; 1844.
- Cushing H. A note upon the faradic stimulation of the post-central gyrus in conscious patients. *Brain* 1909; 32: 44–53.
- Cushing HE. A discussion of some immediate and some remote consequences of cranial injuries based on three clinical histories, which illustrate the extradural, subcortical and intermeningeal types of intracranial hemorrhage. *NY Med J* 1907; 85: 160–5.
- Eccles JC, Gibson WC. Sherrington, his life and thoughts. New York: Springer International; 1978.
- Ehrenberg CG. Nothwendigkeit einer feineren mechanischen Zerlegung des Gehirns und der Nerven vor der chemischen, dargestellt aus Beobachtungen. *Annalen der Physik und Chemie* 1833; 28: 449–73.

- Fritz G, Hitzig E. Ueber die elektrische Erregbarkeit des Grosshirns. *Archiv für Anatomie, Physiologie und wissenschaftliche Medicin* 1870; 37: 300–32.
- Fulton JF. Harvey Cushing, a biography. Springfield, IL: Charles C. Thomas; 1946.
- Gall FJ, Spurzheim G. *Recherches sur le système nerveux en général et sur celui du cerveau en particulier*. Paris: Schoell; 1809.
- Gall FJ, Spurzheim G. *Anatomie et physiologie du système nerveux en général et sur celui du cerveau en particulier*. Paris: Schoell; 1810.
- Gardner EP, Martin JH. Coding of sensory information. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Principles of Neural Science*. 2000. p. 1414.
- Gennari F. *De Peculiari Structura Cerebri Nonnul-lisue Eius Morbis*. Parma, Italy: Ex Regio Typographeo; 1782. p. 72–5.
- Geyer S, Weiss M, Reimann K, Lohmann G, Turner R. Microstructural parcellation of the human cerebral cortex – from Brodmann's post-mortem map to in vivo mapping with high-field magnetic resonance imaging. *Front Hum Neurosci* 2011; 5: 19.
- Grünbaum ASF, Sherrington CS. Observations on physiology of the cerebral cortex of some of the higher apes. *Proc Roy Soc* 1903; 72: 152–209.
- Hermann L. *Handbuch der Physiologie*. Leipzig: Verlag Von F.C.W. Vogel; 1883.
- Heschl R. *Compendium der allgemeinen und speciellen pathologischen Anatomie*. Wien: Wilhelm Braumüller; 1855.
- Hines M. Cytoarchitecture of cerebral cortex in man. *Proc Assoc Res Nerv Ment Dis* 1934; 13: 26.
- Hinton J. Report on physiology. In: Hinton J, Handfield J, Windsor, editors. *A year-book of medicine, surgery, and their allied sciences, for 1863*. London: The New Sydenham Society; 1864. p. 17–18.
- Horsley V. Remarks on ten consecutive cases of operations upon the brain and cranial cavity to illustrate the details and safety of method employed. *Br J Med* 1887; 1: 863.
- Ikonnikov V. Historical and statistical notes on scientists and research-auxiliary organizations of Empire Saint Vladimir University. (in old Russian). Kiev: Empire Saint Vladimir University; 1884.
- Ivanov P. Vladimir Alekseevich Betz (obituary). *The Word of Kiev*. 1 October 1894. (in old Russian).
- Jackson JH. Clinical remarks on the occasional occurrence of subjective sensations of smell in patients who are liable to epileptiform seizures, or who have symptoms of mental derangement, and in others. *The Lancet* 1866; 659–60.
- Jacobson M. *Foundations of neuroscience*. New York: Plenum Press; 1993.
- Kachaturyan AA. V.A.Betz. Anatomical and histological investigations. In: Kachaturyan AA, editor. *V.A.Betz. Anatomical and histological investigations. Selected works (in Russian)*. Moscow: Medgiz; 1950.
- Kalita V. Among the people he was called “holy doctor”. *Health of the Ukraine (in Russian)* 2010; 6: 42–4.
- Kandel ER, Spencer WA. The pyramidal cell during hippocampal seizure. *Epilepsia* 1961; 2: 63–9.
- Karenberg A. The schwann cells. In: Koehler PJ, Bruyn GW, Pearce JMS, editors. *Neurological eponyms*. Oxford: Oxford University Press; 2000.
- Karev VM. *The Germans of Russia (Die Deutschen Russlands)* (in Russian). Moscow: ERN; 1999.
- Keen WW. Topography of the brain in its surgical relations. In: Keen WW, White JW, editors. *An American textbook of surgery for practitioners and students*. Philadelphia: W.B. Saunders Co.; 1903. p. 548–54.
- Kukuev L. V.A. Betz. Anatomical and histological investigations. *Selected works (in Russian)*. Moscow: Medgiz; 1950.
- Lautt WW. Regulatory processes interacting to maintain hepatic blood flow constancy: vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. *Hepatal Res* 2007; 37: 891–903.
- Lewis WB. Critical digests and notices of books. *Brain* 1881; 4: 238–46.
- Leyton A, Sherrington C. Observations on the excitable cortex of the chimpanzee, orang-utan and gorilla. *Q J Exp Phys* 1917; 11: 123–222.
- Lister JJ. On some properties in achromatic object-glasses applicable to the improvement of the microscope. *Phil Trans R Soc Lond* 1830; 130: 187–200.
- Lord Cohen of Birkenhead. Sherrington, physiologist, philosopher and poet. Springfield, IL: Charles C Thomas; 1958.
- Meynert T. *The brain of mammals. Human and comparative histology*. London: S. Strieker; 1872. p. 367.
- Milne-Edwards H, Foster J. *Outlines of anatomy and physiology*. Boston: Little & Brown; 1841.
- Morrison JTJ. On the localization of intracranial lesions. *Birmingham Med Rev* 1889; 25: 193–218.
- Moskalenko VF, Cherkasov VG, Vasilenko DA. The world-renowned Ukrainian neuroanatomist Prof. Vladimir A. Betz (on the 175th anniversary of his birthday). *Neurophysiology* 2010; 42: 3–9.
- Penfield W, Rasmussen T. *The cerebral cortex of man. A clinical study of localization of function*. New York: Macmillan; 1950.
- Quekett J. *A practical treatise on the use of the microscope*. London: Hippolyte Bailliere Publisher; 1848.
- Ratcliffe MJ. *The quest for the invisible - microscopy in the enlightenment*. Farnham, Surrey, England: Ashgate Publishing; 2009.
- Reil JC. *Untersuchungen über den Bau des grossen Gehirns im Menschen*. *Arch Physiol* 1809; 9: 136–46.
- Reis CV, Sankar T, Crusius M, Zabramski JM, Deshmukh P, Rhoton AL Jr, et al. Comparative study of cranial topographic procedures: Broca's legacy toward practical brain surgery. *Neurosurgery* 2008; 62: 294–310.
- Rolando L. *Della Struttura degli Emisferi Cerebrali*. Turin: Memorie della Regia Accademia delle Scienze di Torino 1829; 35: 103–45.
- Schwann T. *Mikroskopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen*. Berlin: Verlag der Sander'schen Buchhandlung; 1839.
- Sechnov IM. Reflexes of the brain (Russian). *Meditsinsky vestnik*. (in old Russian) 1863; 47–8.
- Shubinsky S. Critique and bibliography. *Istoricheskiy Vestnik* (in old Russian) 1883; 12: 693–4.
- Simpson D. Phrenology and the neurosciences: contributions of F. J. Gall and J. G. Spurzheim. *ANZ J Surg* 2005; 75: 475–82.
- The news on activity and current status of our institutions *Journal Ministry Educ (St Petersburg)* (in old Russian). 1868; 139: 387–461.
- The Protocol of Council Meetings. *University News of St Vladimir University (Kiev)* (in old Russian). 1873; 11: 1–29.
- Tsybaliuk VI. Professor Betz Volodymyr Oleksiyovich (on the 175th anniversary of his birthday). *Ukrainian Neurosurgical Journal (in Ukrainian)* 2009; 1: 70–1.
- Uematsu S, Lesser RP, Gordon B. Localization of sensorimotor cortex: the influence of Sherrington and Cushing on the modern concept. *Neurosurgery* 1992; 30: 904–12.
- Valentin G. *Ueber den Verlauf und die letzten Enden der Nerven*. Nova Acta Acad Caes Leop-Car nat cur 1836; 18.
- Verplaetse J. Moritz Benedikt's (1835–1920) localization of morality in the occipital lobes: origin and background of a controversial hypothesis. *Hist Psychiatry* 2004; 15: 305–28.
- Vicq d'Azyr F. *Recherche sur la structure du cerveau, du cervelet, de la moelle allongée, de la moelle épinière; & sur l'origine des nerfs de l'homme & des animaux*. *Hist Acad Roy Sci Paris* 1781/1784; 1784: 495–622.
- Zeki S. Introduction: cerebral cartography 1905–2005. *Philos Trans R Soc Lond B Biol Sci* 2005; 360: 651–2.