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COMMENTARY

120 years of Hippocampal Schaffer Collaterals

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ABSTRACT: Károly Schaffer (1864–1939) was a Hungarian neurologist who distinguished himself through original discoveries in human neuropathology. At the beginning of his scientific carrier, he described the cellular and fiber structure of the hippocampus, earning him a high reputation in neuroscience. Schaffer (1892) described the so-called ''collateral fiber system'' that connects the CA3 and CA1 regions of the hippocampus, known today as Schaffer collaterals. To decipher the history of this well-known eponym, we review Schaffer's original German publication and follow the impact of his research in the contemporary literature. © 2012 Wiley Periodicals Inc.

KEY WORDS: CA3; CA1; connectivity; cell types; interneurons

INTRODUCTION

Károly Schaffer (Fig. 1), son of a sculptor, completed his medical studies in Budapest in 1888 (Baran et al., 2008). József Lenhossék, the director of the Institute of Anatomy in Budapest, encouraged Schaffer's ambition in research and admitted him to his Institute as a research assistant in 1883. This position provided the young doctor with the opportunity to learn the methods of histology, including the Golgi impregnation, which was known since 1873. Schaffer was only a 24-year-old medical student when he published his first scientific work on the histopathology of spinal cord lesions caused by rabies (Schaffer, 1888). He assumed, correctly, that the rabies virus traveled from the bitten body part by way of peripheral nerves to the corresponding segments of the spinal cord, where the most severe cellular infiltration and necrosis could be found. On the basis of this finding, he proposed a novel theory of virus propagation along the peripheral nerves. The article was introduced to the Hungarian Academy of Sciences by Endre Hőgyes, who initiated the anti-rabies immunization in Hungary. Between 1887 and 1895, Schaffer worked in Budapest with Károly Laufenauer at the St. Rókus Hospital. Laufenauer was the first university professor of psychiatry in Hungary, and he supported Schaffer's neuropathological research.

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Schaffer's scientific career coincided with the era of feverish discussions on the nature of neuronal communication, initiated by Santiago Ramón y Cajal. The "reticularis camp," lead by Camillo Golgi (1843–1926), promoted the idea that the cytoplasm of one nerve cell was continuous with the cytoplasm of other nerve cells. However, Ramón y Cajal could not find evidence for the continuity among neurons, and instead, he argued that nerve cells were independent elements establishing connections by contiguity, i.e., only touching each other (Finger, 1994). The neuron doctrine debate was fully blooming after von Waldeyer-Hartz's (1856–1921) imposing review on the subject in 1891. After this publication, the continuous reticular network hypothesis of Golgi no longer appeared tenable, although the Hungarian István Apáthy remained a strong defender of the continuity hypothesis (Benedeczky, 1995), fuelled largely by his own observations in 1897 (Apáthy, 1897). Ramón y Cajal wrote a critical remark on the publication of Apáthy (Ramón y Cajal, 1908), defending his contiguity view. Traces of this remarkable conflict in neuroscience history persist (cf., Sotelo, 2011).

Mihály Lenhossék (the son and successor of József Lenhossék in the chair of the Institute of Anatomy in Budapest), a friend and supporter of Schaffer, was aware of the importance of Ramón y Cajal's work and joined the defenders of the neuron doctrine against the reticularists' agenda (DeFelipe, 2002; Fischer, 1889; Lenhossék, 1935). In this debate, Schaffer was convinced by the contiguity character of communication between neurons and rejected the continuity hypothesis.

In 1891, Schaffer spent a few months in the laboratory of Karl Weigert (1845–1904) in Frankfurt-am-Main, Germany, where he got acquainted with Ludwig Edinger (1855–1918), who at that time studied the pathways of pain and heat sensation. In 1894, he visited Hyppolite Bernheim (1840–1919) in Nancy, France, and Edward Brissaud (1852–1909) in Paris, where he attended lectures on hypnosis.

Károly Schaffer began to investigate the structure of the Ammon's horn of the rabbit and newborn pig in 1889, leading to his classic German publication in 1892. For this work, he used the copper lacquer-method of Golgi, Ramón y Cajal, and Weigert; later,

FIGURE 1. Portrait of the 70-year-old Károly Schaffer.

he modified the original Nissl cell staining by utilizing both methylene blue and magenta red for better visualization of the cells (Schaffer, 1893). The article "Beitrag zur Histologie der Ammonshornformation" (Contribution to the Histology of the Cornu Ammonis) was published in the "Archiv für mikroskopische Anatomie" (Schaffer, 1892). Before its appearance in print, the content of the article was presented to the Hungarian Academy of Sciences by Viktor Mihalkovics (on February 15, 1892). The article contains several hand-drawn microscopic pictures of the typical cells and the schematic view of the hippocampus (Fig. 2).

The concise novel message of the work, which survives to this day, is that the large pyramidal cells in the regio inferior of the hippocampus give rise to axons that course in the dendritic layers of the smaller pyramidal cells of the regio superior. In today's parlance, the axons of CA3 pyramidal cells innervate the dendrites of CA1 pyramidal neurons. Schaffer's description of the collaterals and the bifurcation of the axons of the large pyramidal cells, his fundamental observation, can be found on page 615 (Suppl. Note 1.): "The small and the large pyramids send their protoplasmatic projections (i.e., axons in today's nomenclature) principally into two directions. Those at the base (he refers here mainly to CA3c pyramidal cells, see Fig. 2) approach the alveus like the roots of a tree, giving rise to numerous branches. Others approach the apical dendrite (Spitzenfortsatz), forming a bundle in the stratum radiatum. These emerge from the cell body, run for some distance, and then bifurcate to give rise to small branchlets, which turn toward the lamina medullaris involuta" (likely referring to the perforant path, which carries fibers mainly from the entorhinal cortex).

These few sentences secured a place for Károly Schaffer in the history of hippocampus research. He correctly pointed out that CA3 pyramidal cells innervated both the basal dendrites (the alveus/oriens bundle) and the apical dendrites (the radiatum bundle) of pyramidal neurons. According to Figure 2, the parental cell bodies of these collaterals emerge largely from pyramidal cells of the CA3b subregion. He thought (incorrectly) that these fiber bundles originate from different cell groups (as is clear from the separate axons emanating from CA3b and c in Fig. 2). Later axon tracing and intracellular axon reconstruction experiments established that CA3 pyramidal cells in all subregions give rise to bifurcating (Schaffer) collaterals, which target both the apical and basal dendrites of both CA3 and CA1 pyramidal cells (Ishizuka et al., 1990; Li et al., 1994). Axons of CA3 pyramidal neurons do not invade the molecular layer of the subiculum, nor do they project to other retrohippocampal structures (entorhinal area, parasubiculum, presubiculum, and postsubiculum). Thus, the branchlets he implied enter the "lamina medullaris involuta" (in Fig. 2) likely do not exist. Nevertheless, Schaffer's description of the intrahippocampal CA3-CA1 connections has set the stage for future anatomical and functional studies.

In his article, Schaffer referred to the "the ingenious researcher Ramón y Cajal" who dealt with the structure of cerebral cortex of mammals. On page 627, Schaffer used the original French text of Ramón y Cajal (Sur la structure de l'écorce cérébrale de quelques mammifères, 1891) to validate his own observations (Suppl. Note 2.) "Les collateralés des cylindre-axes des grandes pyramides sont trés nombreuses. . ." in English: "The axons of the large pyramid cells have abundant collaterals. These run generally in a horizontal or oblique direction; they retain their straight pathways and ramify once or twice. Oftentimes, it can be observed that those at the inferior position give rise to branches, which can be followed until they approach the molecular layer. In some cases, it could be observed that two or three collaterals were originating from one short common trunk." Schaffer followed the nomenclature of Ramón y Cajal to label the various layers of the hippocampus. In today's terms, there is no molecular layer (stratum moleculare) in the CA1 region. In Schaffer's figure (Fig. 2), the molecular layer appears to refer to the zone of the distal apical dendrites, adjacent to the hippocampal fissure, and above the stratum granulosum. In current nomenclature, the layer of the distal apical dendrites is known as the stratum lacunosum-moleculare, and the zone between this layer and the cell body layer is known as the stratum radiatum. Although Schaffer referred to the radiatum bundle of the CA3 collaterals, in Figure 2, the bundle is marked by an arrow as stratum lacunosum. Thus, while there is a bit of confusion with the terminology, Schaffer correctly drew the CA1-bound collaterals above the stratum lucidum (i.e., the fiber bundle of the dentate mossy fibers). Figure 2 also contains several putative interneurons with locally

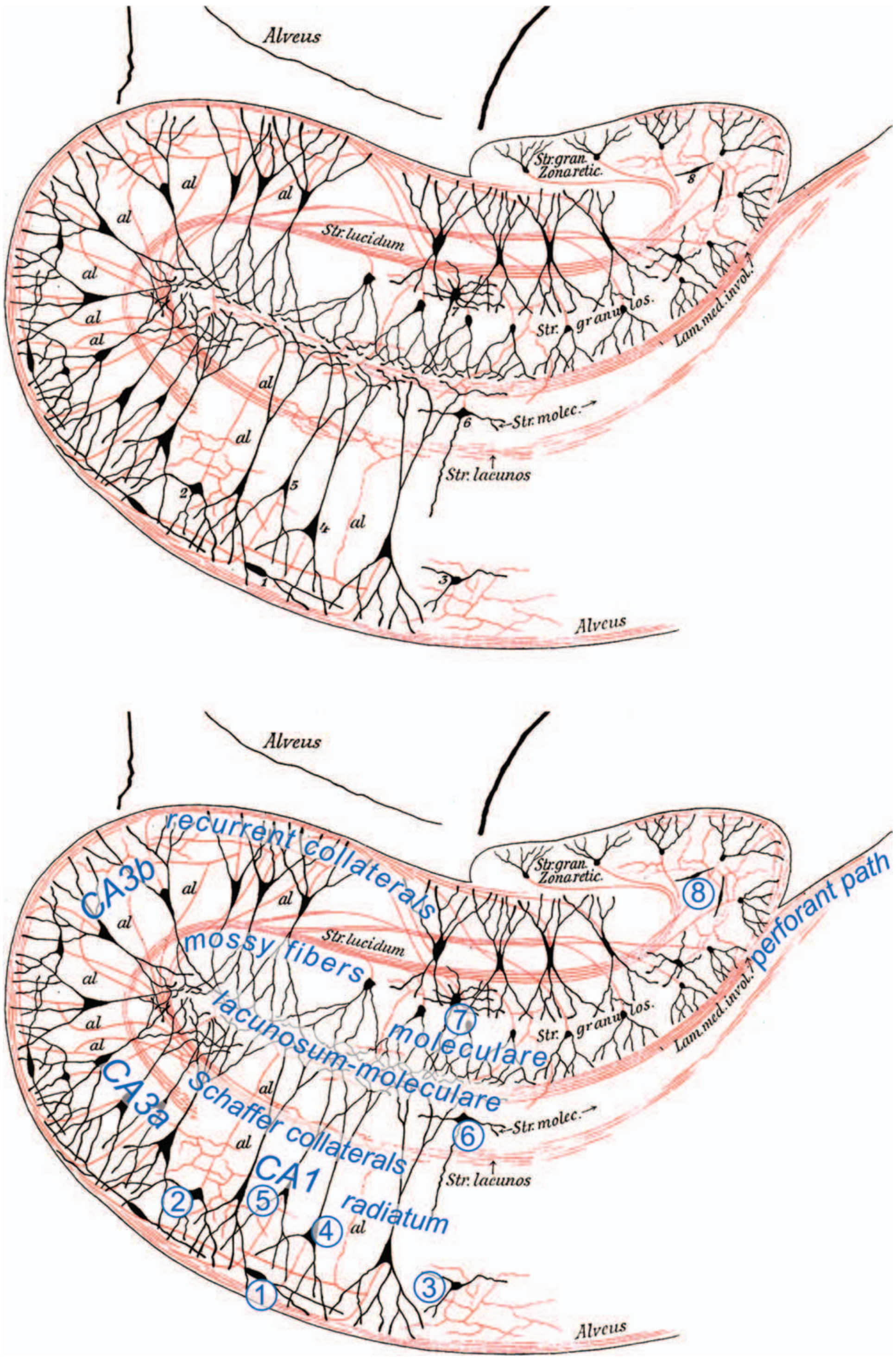

FIGURE 2. Upper part: Schaffer's original hand drawing of the main cell types and the basic structure of the rabbit hippocampus (1892, Fig. 15, page 632, Suppl. Note 11.). 1, Fusiform nerve cell; 2, polymorph nerve cell; 3, Golgi's nerve cell; 4, giant pyramidal cell; 5, small pyramidal cell; 6, nerve cell of the molecular layer; al, ascending collaterals of the pyramidal cells—and partially also some polymorphic cells—which are passing altogether in the stratum lacunosum; 7, polygonal nerve cell of the fascia dentate; 8, fusiform cell at the same place. Lower part: the same figure labeled with today's anatomical nomenclature. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

arborizing axon collaterals (cells 1, 2, 3, 6, 7, and 8), indicating that Schaffer was aware of the existence of the diversity of other neuron types besides the more uniform pyramidal cells.

Károly Schaffer also extensively cited the article of Luigi Sala who described the histoanatomy of the hippocampus (Zur feineren Anatomie des grossen Seepferdefusses, 1891). Sala was a coworker of Golgi and a supporter of the reticularist concept of his master. Below, we translate those paragraphs from the original German text of Sala, which concern the fiber system of the hippocampal white matter (Sala, 1891):

- Page 40, point 3 (Suppl. Note 3.): "...the gray convolution layer is composed by giant pyramidal and spindle-shaped cells; their axons are preferably directed toward the alveus. Most of the fibers of the alveus and nearly all of the lamina nuclearis (i.e., the pyramidal layer—added by the authors) take their origin from these cells."
- Page 41, point 6 (Suppl. Note 4.): "In the organization of lamina nuclearis, not only the dense neural net of the gray convolution layer participate but also the fibers from the superficial white substance which are running from the fascia dentata toward the alveus and the fimbria."
- Page 41, point 7 (Suppl. Note 5.): "...most fibers composing the superficial white matter take their origin from the neural net of the globoid cells; additional fibers join these fibers from the branch of the lamina nuclearis and head toward the alveus and the fimbria from the fascia dentata." Sala thus described only branches of pyramidal cells heading toward to the white matter of the alveus and fimbria but failed to notice the collaterals heading toward the apical dendrites of CA1 pyramidal cells.

Thus, concerning cells and their connections, Schaffer found disagreement between the statements of Sala and his own. On pages 630 and 631 of his article, Schaffer formulated some cautious reservations about Sala's (1891) findings (Suppl. Note 6.): "Sala does not describe nerve cells with ascending axons. Also, I searched in vain for a definitive statement on cells of the molecular layer. He also thinks that the alveus is formed by the axon-cylinders of the pyramidal cells; likewise, he thinks that nearly all fibers of the "Kernblatt" (lamina medullaris externa; i.e., alveus—added by the authors) take their origin from the giant pyramidal cells. According to my observations, the final endings of pyramidal cell apical dendrites distribute in the lamina involuta. However, the latter is also composed of the ascending axon-cylinders of the subpyramidal nerve cells and the processes of cells in the molecular layer (i.e., stratum lacunosum-moleculare; added by the authors). I have also mentioned that the protoplasmic endings of the nerve cells of the stratum granulosum extend to the periphery of fascia dentata, albeit I could not clarify their connections with the glial cells. I fully agree with his opinion that the stratum lucidum is composed of the axons of the granule cells of the stratum granulosum. However, whereas Sala adds that the fibers of stratum lucidum (he does not use this term) are directed to the alveus and to the fimbria, I observed that these axon endings terminate at the apical dendrites of pyramidal cells in the Ammon's horn, where they eventually join the neuronal-net below and above the pyramidal cells. Concerning his statement that between the fascia dentata and the Ammon's horn a transition exists, composed by neuronal fibers, I am in full agreement, since I mentioned such a structure when describing the lamina medullaris involuta. Sala did not mention any other formations apart from the spindle-shaped neurons of the dentate gyrus, whereas I described polygonal nerve cells that send their protoplasmic branches to the fascia cortex (outer molecular layer—added by the authors). It is highly probable that I did not see those rare superficial neurons due to problems of impregnation but which can be visualized by the Nissl method and which, according to Sala, give rise to functional processes oriented towards the superficial layer." These paragraphs illustrate Schaffer's confidence (and correctness) about the courses of axon branches, including those of the dentate granule cells.

The following sentences (page 626) reflect the sophisticated style of Schaffer (Suppl. Note 7.): "If I compare my own observations to those of Cajal's findings, I miss only those nerve cells which have several axons and until now have been described only by him in mammals in the stratum moleculare (i.e., stratum lacunosum-moleculare) of the rabbit. By this remark, I would not deny the existence of such elements in the Ammon's horn; it is highly probable that by using other impregnation methods they might be found." These comments of Schaffer illustrate his sincere trust in Ramón y Cajal as well as his awareness of the irregular nature of the Golgi impregnation method.

Santiago Ramón y Cajal confirmed the observations of Schaffer and cited him in several of his papers (1893, 1894, 1899–1904, 1909–1911). In his book (Histologie du systeme nerveux de l'homme et des vertébrés. 1909–1911; translated to French by his friend Leon Azoulay), Ramón y Cajal mentioned Schaffer's observations for the first time (page 752): "Schaffer pense que tous les cylindres-axes desune fois parvenus aux grandes cellules pyramidales du hile, se mettent á serpenter, soit au-dessus de ces neurones et se portent ainsi en avantn c'est-á-dire vers la region de la corne d'Ammon, qui est placée sons la fimbria;...." This text was translated from French to English by Swanson and Swanson (1995, page 617): "Schaffer believes that after arriving in the region of large hilar pyramidal cells, all granule cell axons begin...to curve rostrally toward parts of the Ammon's horn near the fimbria. At this point, they curve rather abruptly to form a longitudinal bundle superficial to the large pyramidal cells, in a region that might be referred to as vacuolar because of the many spaces revealed in carmin or hematoxylin preparations. This suprapyramidal region already had been noted by earlier workers, and corresponds to Honegger's stratum lucidum." Ramón y Cajal's view can be read on the same page: "Our observations which are based on hundreds of excellent preparations, agree completely with those of Schaffer. In addition, despite the alternate view of Sala who thought that some mossy fibers behave like short axons, we believe that all such fibers descend to the large pyramidal cell layer without dividing."

Ramón y Cajal repeated several statements of Schaffer also in the book "Les Nouvelles idées sur la structure..." which appeared in Paris in1894. (English translation by Swanson and Swanson: "New ideas on the structure..., 1990). Concerning the fiber system of the alveus and the polymorph cell layer the following can be found on page 74: "The cells of this layer were noted by Sala and described perfectly by Schaffer, who also clarified the course and other features of their axon." Also the subtypes of cells in the polymorph layer were confirmed by Ramón y Cajal in the same chapter: "The cells with ascending axon were discovered and drawn by Schaffer, who distinguished two subtypes based on the way in which their axon behaves." On page 78, Ramón y Cajal wrote "Schaffer discovered that the thick axon of inferior or giant pyramidal cells gives rise to one or occasionally two thick collaterals that ascend to the stratum lacunosum and then course horizontally through the entire length of the regio superior, where they ramify to contact the apical bouquet of small pyramidal cells. Ascending collaterals do not arise directly from the axon of superior cells, at least along their descendant course." Under the subtitle of middle subzone (stratum lacunosum or lacunar layer; page 80) we can read "... the horizontal bundles consist of fibers that stretch from the inferior region of Ammon's horn to the vicinity of the subiculum. As Schaffer noted, the majority of such fibers are ascending collaterals derived from the axons of large pyramidal cells in the inferior region of Ammon's horn." Furthermore on page 83: "...the bundles of axons derived from granule cells are organized just as those drawn and described by Schaeffer" (sic).

Ramón y Cajal himself never used the term "Schaffer collateral." However, he cited and popularized Schaffer's findings abundantly. In the legend of the well-known original sketch of the hippocampus in his book (Schema de la structure... 1909–1911, Fig. 479; page 753) he did not mention the Schaffer collaterals. Instead, the corresponding fiber system was referred to as "collaterales ascendantes des grandes cellules pyramidales." In the English translation of the "Nouvelles idées sur la structure du systéme nerveux chez l'homme et chez les vertebrés" (Ramón y Cajal, 1894, 1990), Ramón y Cajal did not mention Schaffer's name, although the collaterals are well portrayed in Fig. 22 (p. 84, H: bundle of the large ascending collaterals). Interestingly, in the English version of the original "Textura del Sistema Nervioso del Hombre y de los Vertebrados" (Ramón y Cajal, 1899–1904), translated by Swanson and Swanson (1995) one can read in the legend of Fig. 479 on page 619: "... recurrent collaterals of pyramidal cells to the stratum lacunosum of Ammon's horn (Schaffer collaterals)..., ascending (Schaffer) collaterals of large pyramidal cells." We can only assume that the translators added Schaffer's name to assist the present-day reader.

In this same translated text by Swanson and Swanson (Ramón y Cajal, 1899–1904, 1995), readers can find the abbreviations CA1 and CA3 (e.g., p. 618, and in the legend of Fig. 479). However, these terms (CA = cornu Ammonis) were introduced only decades later by Lorente de Nó (1934). Although the CA classification of specific anatomical areas in the cornu Ammonis made it easier to describe the cellular regions and their interconnections, compared with the previously used regio inferior and regio superior, Ramón y Cajal certainly did not use these terms.

Although Ramón y Cajal popularized Schaffer's original findings, it was Rudolf Albert von Kölliker (1817–1905), the German physiologist and anatomist from Würzburg who introduced the term "Schaffer collateral" into the literature. Kölliker accepted the neuron doctrine when he became acquainted with Ramón y Cajal's works and he even studied Spanish to translate Ramón y Cajal's book to German. The term "Achsencylinder" (or Axencylinder as was always written by Schaffer) was replaced by "axon," presumably by Kölliker (Finger, 1994). It is likely that Kölliker became familiar with Schaffer's findings when he personally met Ramón y Cajal and read his work on the anatomy of the Ammon's horn. Four years after the publication of Schaffer's paper Kölliker referred to the fiber system as "Schaffer'sche Collateralen" in his influential anatomy book ("Handbuch der Gewebelehre des Menschen," 1896, page: 748) (Suppl. Note 8.): "The axons of these giant pyramidal cells show a peculiar nature, first mentioned by Schaffer and later explicated by Ramón y Cajal. They divide after a short run into two branches or, better to say, deliver strong collaterals. The actual axons are collectively converted into a nerve fiber of the "fimbria" but a collateral also branches to the upper parts of the "stratum oriens," climbs up through the "stratum radiatum" to the "stratum lacunosum," after giving off one or two small collaterals. The horizontal fibers form a myelinated nerve fiber. In essence, these fibers run in the direction to the "subiculum," give off fine collaterals into the "stratum radiatum" and the "stratum lacunosum" and terminate with free endings, which contact the ascending dendritic bundles of the typical giant pyramids. If one investigates the layers described up to now with "Weigert" preparations, similarly to Ramón, one will find that the myelination of the axons of many of the pyramidal cells begin in the "stratum oriens." Furthermore, not only do the ascending parts of the axons of cells with ascending nerve-extension have myelin sheaths but the trunk and the thick horizontally running branches of the axon cylinders of cells with horizontal axons as well. There is also a dense nerve network of fine unmyelinated collaterals of all axon cylinders. The ascending collaterals of the thick "Schaffer-collaterals" (Schaffer'schen Collateralen Markscheiden), which are in the region of the giant pyramidal cells of the "cornu Ammonis" have myelin sheaths, whereas myelin is absent from the smaller fibers of the anterior region of the "cornu Ammonis."

Lorente de Nó also refers to the fibers connecting CA3 and CA1 regions as Schaffer collaterals in his landmark paper about the study of the ammonic system (1934, page 131). Forty-two years after Schaffer's publication, Lorente de Nó's opinion regarding the axon collaterals of the CA3 region was different from Schaffer's opinion. However, he does not question the significance and originality of Schaffer's discovery (Lorente de Nó, 1934; page 131): "While the old authors (Schaffer, Cajal, Kölliker) accepted that all giant pyramids have a Schaffer collateral..., my preparations show that this is not true. In CA3c, almost all the pyramids have Schaffer collateral. In CA3b only about half and CA3a almost none. Those pyramids, which do not have Schaffer collateral, give rise to one or two collaterals, which ascend to the Str. radiatum and constitute immediately above the Str. pyr. of CA2 and CA3a a powerful (hitherto undescribed) association path which runs parallel to the axis of the Ammon's horn." Subsequent reconstructions of the axon collaterals of single pyramidal cells from the different subregions support Lorente de Nó's observations regarding the different projection patterns of the CA3 subregions (Li et al., 1994).

In his 1892 publication on the hippocampus, Károly Schaffer also described that two sublayers are juxtaposed in the pyramidal layer. The corresponding German text of this statement can be found on page 615 of Schaffer's article (1892) (Suppl. Note 9.): "The pyramidal cell layer has an interesting appearance. First of all, it is divided into two layers: one consists of giant pyramidal cells which follow the subpyramidal layer, and the other consists of small pyramidal cells directed towards the stratum radiatum." These are illustrated by neuron 4 and 5 in Figure 2, respectively. On page 626, after citing Ramón y Cajal's opinion on the cellular layers of the Ammon's horn, Schaffer wrote this personal comment (Suppl. Note 10.): "One gets the impression that the Ammon's horn might be a uniquely built, but to a certain extent compressed, cortex." Slomianka (2011) remarked recently that "Looking at cell types, Schaffer (1892) understood the pyramidal cell layer as the merger of two layers that also characterize the adjacent subiculum: a deep layer containing large pyramidal cells and a superficial layer composed of small pyramidal cells." The physiological significance of the sublayer organization of the pyramidal cells, conceived by Schaffer 120 years ago, has been recently demonstrated (Mizuseki et al., 2011).

After 1895, Károly Schaffer discontinued his work on the anatomical connections of the hippocampus and turned his attention to the histopathological research of syphilis and storage diseases (Schaffer, 1901, 1905). His important contribution to neuropathology was the discovery of swollen neurons that accumulate chemically unidentified lipid substances in Tay-Sachs disease. The cellular deposits were later proposed to be named as "Schafferscher Zellprozess" by Bielschowsky (Miskolczy, 1940). Schaffer thought that the "amaurotic familial idiocy" (i.e., Tay-Sachs disease) was caused by selective lesion of ectodermal constituents of the nervous system. Subsequently, it has been shown that the condition is an autosomal recessive disorder, caused by the absence of an essential enzyme that breaks down a substance called ganglioside, present mainly in the nervous system. Schaffer (1927) also recognized the independent pathology of neuroglia in several diseases. Based on further investigations of primary neuronal degenerations, he suggested that the heredo-neurodegenerative diseases could be characterized by a three-fold selectivity: they have ectodermal origin (germ layer selectivity), are located at a well-defined level of the nervous system (segment selectivity), and affect the nervous system (system selectivity). To demonstrate the validity of this theorem, the familial amyotrophic lateral sclerosis has proven to be the best example (Schaffer, 1936). During those scientifically productive years, Schaffer and his colleagues assembled a very large collection of histological slides. Some of these specimens were on display at the 1899 World Fair in Paris, and Schaffer won a silver medal (Leel-Őssy, 1996).

Acknowledging Schaffer's scientific merit, the University of Budapest established the "Interacademic Brain Research Institute" (IBRI) in 1912 under his leadership, where Schaffer taught neuroanatomy and neuropathology. At the age of 61, Schaffer was appointed to the chair of the Psychiatry and Neurology Clinic of the University in Budapest (today's Semmelweis University). He reluctantly accepted this honor with the condition that he could move all his specimens and equipment to the Clinic. Schaffer's international reputation was signified by the fact that he was invited to write the chapter about amyotrophic lateral sclerosis and spinal paralysis in the handbook of Bumke and Förster in 1936.

In his later years, research on the morphological basis of specialized talents was among Schaffer's favorite topics. He analyzed the macroscopic and microscopic characteristics of the brains of persons with outstanding skills in language, music, and arithmetic (1932).

Ramón y Cajal died in 1934 at the age of 82. Schaffer (1935) wrote Cajal's obituary in German with highest admiration.

Károly Schaffer exerted strong influence on his pupils and successors. On the basis of his scientific achievements, he is considered the founder of Hungarian neurology. Because of his authority, he determined not only the scientific direction but also the scientific ethics of his pupils and their followers. Schaffer published 243 articles, most of them in German. The majority of the publications in the field of neuropathology appeared in the prestigious journal "Zeitschrift für die gesamte Neurologie und Psychiatrie." The Springer publisher collected these articles in 19 volumes under the title: "Hirnpathologische Beiträge" and donated the omnibus volumes to the author Schaffer (see Környey, 1976). In the 18th volume, Schaffer summarized his histopathological studies on neurons (Schaffer and Miskolczy, 1938).

On the occasion of the 40th anniversary of Schaffer's scientific carrier (1887–1927), his eldest student, Dezső Miskolczy collected the publications of Schaffer and his coworkers in a volume (see Miskolczy, 1973, Leel-Őssy, 1996). Ramón y Cajal wrote the introductory appraisal to this book, describing the character of Schaffer as someone with a painstaking judgment and deep knowledge in neurological sciences, and he listed two rare and admirable qualities of Schaffer: "...sobresaliente para la investigacion personal, y maravillosa capacidade adaptacion a los progresos doctrinales y técnicos, cualquiera que sea el pais de donde procedan" (in English: "... outstanding ability for substantive research and excellent accommodation to the progress of modern science and technique that might originate from any country of the world."). Professor Max Nonne (1934), the famous German neurologist from Hamburg emphasized at the occasion of Schaffer's 70th birthday in the journal Klinische Wochenschrift: "the readers of this weekly journal ... know his work on the histology of hippocampus; this work was one of the first that governed the interest to this region of the brain, which induced later multiple directions of research." When Károly Schaffer suddenly died in 1939 at the age of 75, due to an unrecognized obstruction of his intestine (ileus), he left two manuscripts for publication on his desk (Baran et al., 2008).

Finally, we remark that in the scientific literature, Károly Schaffer's name is frequently misspelled as Schaeffer, Schäffer or Schaefer, as it can also be found in some of the cited translations. This might lead to misidentification of Károly Schaffer as Edward Albert Schäfer (1850–1935), the challenger of David Ferrier, who described the Schäfer-sign, a pathologic reflex of the lower limb caused by the lesion of the corticospinal tract. We emphasize that in all of his original papers Ramón y Cajal spelled Schaffer's name correctly.

In his entire scientific career, Károly Schaffer contributed a single thesis to the hippocampus when he was only 28 years old. However, this magnificent work became a landmark paper in our understanding of the intrinsic organization of the hippocampus. In the footsteps of Ramón y Cajal, he described an essential link in the organization of the "trisynaptic circuit" of the Ammon's horn. A new era of hippocampus research began with novel aspects of functional anatomy by Lorente de Nó. The works of Ramón y Cajal, Schaffer and Lorente de Nó paved the way to our current knowledge of the functional properties of the hippocampus and its role in behavior, learning and memory.

Supplementum

Note 1.:

"So die kleinen als die grossen Pyramiden senden hauptsächlich in zwei Richtungen ihre protoplasmatischen Fortsätze aus. Die basalen streben gleich den Wurzeln eines Baumes zum Alveus, wobei sie zahlreiche Nebenzweige entsenden; der Spitzenfortsatz, welcher eigentlich das Strat. Radiatum bildet, entsteht aus der Zelle als zumeist dicker Strang, welcher nach einem gewissen Verlauf unter spitzwinkeliger Gabelung in zahlreiche Zweige und Zweichen sich auflöst, die insgesamt in die Lam. med. Involuta umbringen." (Schaffer, 1892)

Note 2.:

"Les collatérales des cylindre axes des grandes pyramides sont trés nombreuses.... La direction que suivent les collatérales est ordinairement horizontale on oblique; elles conservent communément leur rectitude et se dichotomisent une on deux fois. Il n'est pas rare d'observer que les plus hautes prennent un cours ascendent, se ramifient et s'entendent par leurs ramilles jusque prés de la zone moléculaire; en certains cas ou remarque que deux ou trois collatérales procédent d'une petite tige courte d'origine." (Ramón y Cajal, 1891)

Note 3.:

"3) dass die graue Windungschicht aus Riesenpyramiden- oder spindelförmigen Zellen gebildet wird, deren funktioneller Fortsatz sich vorzugsweise gegen den Alveus richtet, Aus diesen Zellen nehmen grösstentheils die Fasern des Alveus und fast alle der Lamina nuclearis ihren Ursprung." (Sala, 1891)

Note 4.:

"6) dass an der Bildung der Lamina nuclearis außer den dem ausgebreiteten Nervennetze der grauen Windungschicht entstammenden Fasern auch andere oberflächlichen weißen Schicht und jenem Bündel angehörige Fasern sich betheiligen, welche sich aus der Fascia dentata zum Alveus und zur Fimbria begeben." (Sala, 1891)

Note 5.:

"7) dass der grösste Theil der die oberflächliche weisse Schicht bildenden Fasern aus dem kugeligen Zellen entstammenden Nervennetze seinen Ursprung nimmt; zu diesen Fasern treten noch andere, welche der Lamina nucnearis und jenem Bündel angehören, das sich aus der Fascia dentata zum Alveus und zur Fimbria begiebt." (Sala, 1891)

Note 6.:

"Sala beschreibt Nervenzellen mit ascendirendem Axencylinder gar nicht. Ebenso suchte ich vergeben nach einer ausdrüchlichen Angabe von Zellen der moleculären Schicht. Den Alveus lässt auch er aus den Axencylindern der Pyramiden entstehen; ebenso sollen fast alle Fasern des Kernblattes aus den Riesenpyramiden ihren Ursprung nehmen. Nach meinen Angaben verbreiten sich die Endausläufer der Pyramidenspitzenfortsätze in der Lam. involuta; doch wird letztere ferner noch durch die aufsteigenden Axencylinder der subpyramidalen Nervenzellen, ferner durch die functionellen Fortsätze der Zellen in der moleculären Schicht gebildet. Dass die Protoplasmafortsätze der Nervenzellen des Str. granulosum bis zur Peripherie der Fascia dentata reichen, erwähne auch ich, doch konnte ich eine Verbindung derselben mit den Gliazellen nicht constatieren. Darüber sind wir einig, dass das Str. lucidum aus den Axencylinder der kugeligen Zellen des Str. granulosum gebildet wird; doch während Sala angibt, dass die Fasern des Str. lucidum (diesen Nahmen gibt er nicht an) zum Alveus und zum Fimbria gehen, fand ich, dass dieselben an den Spitzenfortsätzen der Pyramiden in's Ammonshorn ziehen, um sich schliesslich jenem Nervennetze anzuschliessen, welche ober- und unterhalb der Pyramiden sich befindet. Seinem Ausspruche, dass zwischen Fascia dentata und Ammonshorn ein Uebergang von Nervenfasern stattfindet. Schliesse ich mich vollkommen an, da ich einen solchen bei der Besprechung der Lam. med. involuta erwähne. Ausser den spindelförmigen Nervenzellen des Nucleus fasciae dentatae erwähnt Sala keine anderen Gebilde, während ich noch polygonale, mit ihren Protoplamafortsätzen in die Fasciarinde dringende Nervenzelle beschreibe. Es liegt wohl einzig nur in der Imprägnation, dass ich unter dem oberflächlichen weissen Bündel der Fascia dentata nicht jene spärlichen—mit der Nissl'schen Methode zwar sichtbar gemachte—Nerverzellen sah, über welche Sala angibt, dass der funktionelle Fortsatz zur oberflächlichen Schicht zieht." (Schaffer, 1892)

Note 7.:

"Vergleiche ich meine Befunde mit jene von Cajal, so vermisse ich einzig die bei Saugethieren bisher nur vom ihm beschriebenen Nervenzellen mit mehreren Axencylinder, welche es im Strat. moleculare des Kaninchens antraf. Damit will ich aber nicht die Existence solcher Elemente für das Ammonshorn absprechen, denn es ist möglich, dass bei weiteren Imprägnationen solche sich finden lassen." (Schaffer, 1892)

Note 8.:

"Die Axonen dieser Riesenpyramiden zeigen eine von *Schaffer* zuerst ervähnte und von S. Ramón weiter verfolgte Eigentümlichkeit (meine Fig. 791 vom Menschen). Dieselben theilen sich nach kurzem Verlaufe in zwei Aeste oder geben, wie man vielleicht besser sagen könnte, eine starke Collaterale ab. Der eigentliche Achsencylinder geht in eine Nervenfaser der Fimbria über, die Collaterale dagegen steigt, nachdem sie den oberen Theilen des *Stratum* oriens ein oder zwei Aestchen abgeben hat, durch das *Stratum radiatum* zum *Stratum lacunosum* herauf, wird hier horizontal und gestaltet sich zu einer markhaltigen Nervenfaser desselben; als solche verlaufen dieselben in der Richtung auf das *Subiculum* zu, geben freie Collateralen in das *Stratum radiatum* und *lacunosum* ab und enden mit freien ausgebreiteten Verästelungen, die die aufsteigenden Dendritenbüschel der typischen Pyramiden mit den Riesenpyramiden verbinden. Untersucht man die bisher beschriebenen Lagen an *Weigert*-schen Präparaten, so ergiebt sich nach *S. Ramón*, dass die Markscheiden der Axonen der Pyramidenzellen bei vielen erst im *Stratum oriens* beginnen. Fernen besitzen Myelinhüllen die aufsteigenden Theile der Axonen der Zellen mit aufsteigendem nervösen Fortsatze, ferner der Stamm und die dicken horizontal verlaufenden Aeste der Achsencylinder der Zellen mit horizontalen Axonen. Marklos sind dagegen die feinen Collateralen aller eben genannten Achsencylinder und der dichte Nervenfilz der Pyramidenzone. Von den aufsteigenden Collatralen haben die dicken in der Region der Riesenpyramiden des Ammonshorns vorkommenden Schaffer' *schen* Collateralen Markscheiden, während die feineren der ersten Region des Ammonshornes solcher entbehren." (Kölliker, 1896)

Note 9.:

"3) Sehr interessante Verhältnisse bietet die Schicht der Pyramidenzellen dar. Vor allem sei erwähnt, dass die selben in zwei, übereinander liegende Lagen zu trennen sind: die auf die subpyramidale Schicht folgende Lage besteht aus sog. Riesenpyramiden, auf welche einwärts gegen das Str. radiatum eine Schichte von kleineren Pyramiden folgt." (Schaffer, 1892)

Note 10.:

"Man gewinnt den Eindruck, als wäre das Ammonshorn eine typisch gebaute, doch gewissermassen comprimierte Rinde." (Schaffer, 1892)

Note 11.:

Schaffer's original legend of Fig. 15. (page 632): "Schema des Ammonhornes. 1. fusiforme, 2. polymorphe, 3. Golgi'sche Nervenzelle, 4. Riesenpyramide, 5. kleine Pyramide, 6. Nervenzelle der moleculären Schicht, et al. ascendierende Collateralen der Pyramiden, welche (theils auch jene der polymorphen Zellen) insgesamt in das Strat. lacunosum übergehen, 7. polygonale Nervenzelle der Fascia dentata, 8. daselbst fusiforme Zelle." (Schaffer, 1892)

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