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THE RENAISSANCE OF THE NEURON DOCTRINE: CAJAL REBUTS THE RECTOR OF GRANADA

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Abstract

The Spanish histologist Santiago Ramón y Cajal and the Italian anatomist Camillo Golgi, who were jointly awarded the 1906 Nobel Prize in Physiology or Medicine for their discoveries on the structure of the nervous system, are two of the most notable figures in neuroscience. It was the 'Golgi method' that enabled Cajal to gather evidence and defend neuronism (the contiguity of neurons as independent cellular units) against his chief rival's reticularism (the intracellular continuity of the cytoplasm among neurons in a widespread reticulum). Seven months after his Nobel lecture in Stockholm, Cajal wrote a powerful article which he titled 'El renacimiento de la doctrina neuronal' (the rebirth, revival, or renaissance of the neuron doctrine) as a response to an insurrection of reticularist ideas. This new wave of reticularism was instigated in Spain by the pathologist Eduardo García Solá, Rector of the University of Granada at the time, and stemmed from the interpretation of nerve regeneration experiments conducted by the German physiologist Albrecht von Bethe in Strassburg (today Strasbourg, France) and the Hungarian histologist Stephan von Apáthy in Kolozsvár (today Cluj-Napoca, Romania). Cajal's article was hosted by four different journals (three in Spain and one in Argentina). It constitutes an important testimony for the history of the neuron theory that has gone unheeded thus far. Therefore, we provide an English translation of Cajal's Spanish paper, placing it in the context of evolving notions during that first decade of the twentieth century crucial for neurobiology.

Keywords

• History of neuroscience • Neuron theory • Catenary theory • Reticularism
• Santiago Ramón y Cajal (1852–1934) • Eduardo García Solá (1845–1922)

Introduction

Santiago Ramón y Cajal (Figure 1) gave his Nobel Lecture in Stockholm on December 12, 1906 [1]. Seventh months later, he had to defend the neuron theory again, furnishing cogent arguments after an insurrection of reticularism. That rebuttal (Figure 2) was hosted by three different journals in Spain [2–4], and by the *Archives of Psychiatry and Criminology* in Argentina (the official journal of the Buenos Aires Society of Criminology), founded and edited by the philosopher and psychiatrist José Ingenieros (1877–1925) [5,6]. Cajal forcefully refutes the Rector of Granada, his friend Eduardo García Solá (1845–1922), who had spoken of the "decadence of the neuron" [7].

García Solá (Figure 1), a key figure in Spanish histopathology and microbiology and a proponent of laboratory medicine in the late 19th century, held the Chair of General Pathology in Granada from 1872 until his retirement in 1918 [8]. He published standard works, including a 'Textbook of General Pathology and Pathologic Anatomy' [9], which went through five editions over 30 years, a pioneering 'Manual of Clinical Microchemistry'

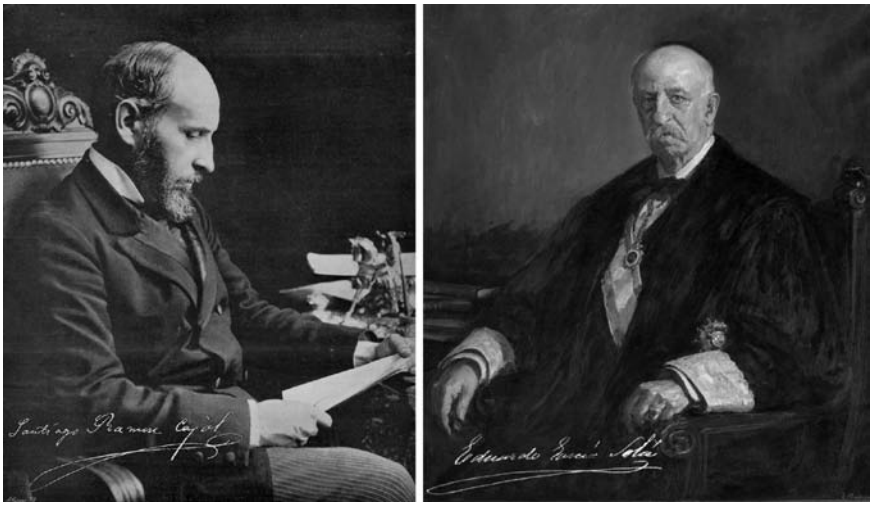

Figure 1. Santiago Ramón y Cajal (1852–1934), left, shortly after the announcement of the Nobel Prize award. Cover portrait in La Ilustración Española y Americana, Madrid, vol. 50, no. 42, November 15, 1906; signature from the Nobel volume [1] digitally etched onto the photograph. Eduardo García Solá (1845–1922), right, Professor at the Faculty of Medicine and Rector of the University of Granada from June 1891 to November 1909. Source: http://rectorado.ugr.es/pages/salon_rojo/rector_1891_egarciasola; signature from La Ilustración Española y Americana, Madrid, vol. 36, no. 38, October 12, 1892, digitally etched onto the painting.

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[10], and an 'Elementary Textbook of Normal Histology and Histochemistry' [11] based on original material from his tenure at the School of Medicine in Granada.

García Solá [12–14] and Ramón y Cajal [15,16] had earlier converged through their publications on the virulent bacillus and its treatment during the cholera outbreak in Valencia [8]. For his ground-breaking work on producing a vaccine, Cajal was presented with a Zeiss microscope by the provincial government of Zaragoza, which opened up entirely new horizons by enabling him "to attack the delicate problems of the structure of the cells without misgivings and with the requisite efficiency" [17].

Cajal and the neuron theory

Cajal, more than any other single investigator, contributed to our understanding of nervous system organization, laying the foundations of modern neuroanatomy, neuroembryology, and neuropathology [18]. He masterly chartered the microorganization of virtually every region of the central nervous system of vertebrates and compiled his results into the classic *Textura* [19]. He is rightfully recognized internationally as the father of modern neuroscience [20]. Thus, in the history of science and human thought, Cajal is viewed as the conceptualizer and founder, in 1889, of 'neural atomism' [21], *viz.* the Leucippus or the Democritus of the brain. (His groundbreaking discoveries on neural plasticity could also earn him the title of the Heraclitus of the brain [*Panta rhei*, 22].)

Two years later, Waldeyer [23] firmly supported Cajal's *neuronismo* and combined the objective evidence that had been adduced by His, Forel, Gowers, Kölliker, Retzius, van Gehuchten, von Lenhossék, Nansen, Cajal, as well as his brother Pedro Ramón y Cajal [24]. Waldeyer came up with the term *neuron* — a word first appearing in Homer's *Iliad* [25] — to denote what was, until then, called the 'ganglion cell' or 'nerve cell' and systematized the 'neuron doctrine' [1,26–32]. According to the neuron doctrine (Figure 3), or neuron theory today, nerve cells are viewed as polarized structures, contacting each other at specialized synaptic junctions, and forming the developmental,

Año cincuenta y cuatro. Madrid, 3 de Agosto de 1907. Núm. 2.799

EL SIGLO MÉDICO

SUMARIO

Madrid, 3 de Agosto de 1907.

EL RENACIMIENTO DE LA DOCTRINA NEURONAL

Por S. R. CAJAL

646 ARCHIVOS DE PSIQUIATRÍA

EL RENACIMIENTO DE LA DOCTRINA NEURONAL

POR S. R. CAJAL (DE MADRID).

Profesor en la Facultad de Medicina

Mi ilustre amigo el Dr. García Solá, en un artículo muy bien escrito y pensado, como todos los suyos, nos habla del *ocaso de la neurona*, dando por seguro, ó como muy probable, que las investigaciones de Apathy (un zoólogo) de Beethe (fisiólogo) y de Balfow Dohrn (naturalista), hayan minado los cimientos de la sólida y luminosa doctrina fundada por embriólogos é histólogos tan eminentes como His, Forel, Kölliker, Edinger, Retzius, V. Lenhossék, M. Duval, Waldeyer, Monakow, Bechterew, Lugaro, Tanzi, van Gehuchten, Schiefferdecker, Obersteirew, Marinesco, Langley, Dejerine y otros mil, todos los cuales (salvo los ilustres His y Kölliker, recientemente fallecidos) siguen defendiendo la bandera

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GACETA MÉDICA CATALANA

SUMARIO: El renacimiento de la doctrina neuronal, por S. R. Cajal. — La malaria y el mosquito. Anotaciones, por el Dr. Santos Rubiano. — Apuntes de Medicina legal: Muerte por estrangulación de una hernia intestinal diafragmática. Autopsia. Viabilidad del recién nacido en sus relaciones con los progresos de la cirugía. Desaparición de los vestigios profesionales, por el Dr. Bravo y Moreno. — Nota práctica sobre la técnica exacta de un parto según el método antiséptico, por el Dr. Just Lucas Championnière. — La psiquiatría: sus conquistas recientes y su elevada tendencia. Introducción al curso de la clínica de enfermedades nerviosas y mentales, por el Dr. Guillermo Mondio. — Los gérmenes invisibles y los ultramicroscópicos (conclusión), por el Dr. E. Bertarelli. — Revista crítica bibliográfica, por el Dr. Pérez Noguera. — Noticias científicas: Localizaciones cerebelosas. — Nuestra correspondencia con la prensa. — Objetos recibidos

El renacimiento de la doctrina neuronal

POR S. R. CAJAL

Mi ilustre amigo el Dr. García Solá, en un artículo muy bien escrito y pensado, como todos los suyos, nos habla del *ocaso de la neurona*, dando por seguro, ó como muy probable, que las investigaciones de Apathy (un zoólogo) de Bethe (fisiólogo) y de Balfow, Dohrn (naturalista), hayan minado los cimientos de la sólida y luminosa doctrina fundada por embriólogos é histólogos tan eminentes como His, Forel, Kölliker, Edinger, Retzius, V. Lenhossék, M. Duval, Waldeyer, Monakow, Bechterew, Lugaro, Tanzi, van Gehuchten, Schiefferdecker, Obersteirer, Marinesco, Langley, Dejerine y otros mil, todos los cuales (salvo los ilustres His y Kölliker, recientemente fallecidos) siguen defendiendo la bandera unitarista con más convicción y entusiasmo que nunca.

Figure 2. Title page of three variants of Cajal's 1907 'Renaissance' article [2,3,5].

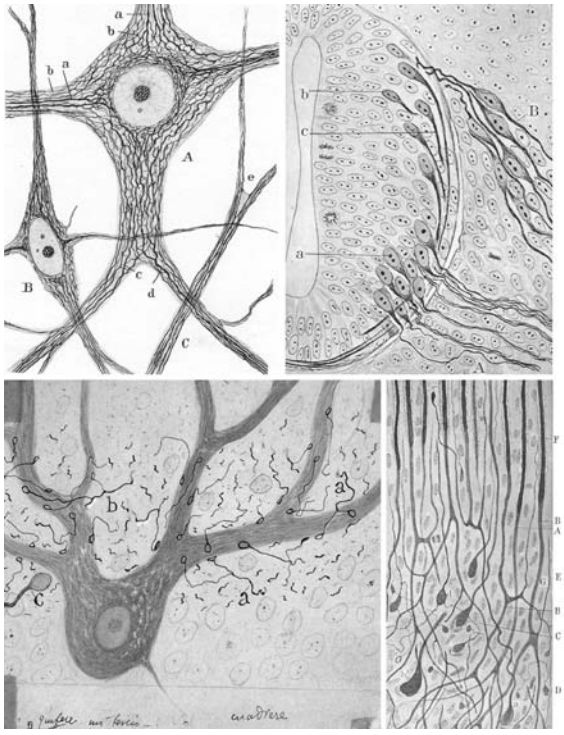

Figure 3. Three schemes from Cajal's 1906 Nobel lecture, and a drawing dated to 1907, in support of the neuron theory. Upper left: Spinal cord cells of a several day-old rabbit. Impregnation by the reduced silver nitrate procedure. A, large funicular corpuscle; B, small corpuscle; a, primary filament; b, secondary filaments; c, d, e, neurofibrillar anastomoses at the level of the dendritic divisions [1]. Upper right: Section from the spinal cord of a chick embryo at day 3 of incubation. Reduced silver method. A, anterior root; B, sensory ganglion and posterior root; a, motor neuroblasts; b, c, commissural neuroblasts whose axon terminates into a growth cone [1]. Lower right: Portion of the central end of the scar in the cut sciatic nerve of a one week-old cat sacrificed 3 days after the operation. A, B, non-myelinated portion of nerve tubes in the process of growth; F, old or myelinated segment of these tubes; C, growth bouton; D, small terminal bouton; G, fiber emitting retrograde branches; a, b, boutons making their way through the cut; c, free neurofibril ending in a ring; e, retrograde bouton; d, bouton from which emanate fine appendages that terminate in small boutons [1]. Lower left: A 1907 drawing by Cajal, depicting a Purkinje cell in the canine cerebellum, with the nerve terminals in a ring. India ink and water-diluted graphite on fine cardboard paper [60].

structural, functional, and trophic units of nervous systems [33].

Definitive proof of the neuron theory was attained half a century later, when the Argentinian cell biologist Eduardo De Robertis (1913–1988), in collaboration with the Uruguayan neurobiologist Clemente Estable (1894–1976), a former pupil of Cajal, put together and described at the ultrastructural level the separation of pre and postsynaptic membranes at the Biological Research Institute in Montevideo, in a Cellular Ultrastructure Department, which housed the first electron microscope in South America [34]. De Robertis carried on his work on synapses and synaptic vesicles with H. Stanley Bennett (1910–1992) in Seattle, studying the sympathetic ganglia of frogs and the nerve cord of earthworms dug from Bennett's own yard [35].

One of the most succinct assessments of the importance of the neuron theory and its implications for neuropsychiatry and biological philosophy, which has received little attention in the English bibliography, is a conference in Buenos Aires given by one of the foremost neuroanatomists of the twentieth century, the ingenious Christofredo Jakob (1866–1956), at a special session of the Society of Neurology and Psychiatry as an homage to Cajal the month after his death, on November 16, 1934. Here is an extract: "The keen eye and deft hand of Ramón y Cajal led us to the *economy of the invisible*, the impenetrability of which was lamented by Schiller. Cajal's powerful brain ousted the *ethereal fluid* of the *channeling systems of the brain* and placed us on the stable pedestal of *facts* in lieu of fancies. The clear mind of the great Spaniard was able to sum up anew a century's preparatory work, from Remak and Deiters to Golgi, Kölliker and Retzius, into the grandiose conception of the neuron theory, the quintessence of which rests on the most brilliant discovery by the astute scholar, i.e., the demonstration and exact interpretation of the function and organization of the axon. Cajal was the first to irrefutably demonstrate the free ending of its terminal ramifications, first in the cerebellum (pericellular baskets, climbing fibers) and subsequently in spinal and cerebral regions. Today this seems trivial, but back then it was the revelation of a new world, freshly leading ever since to our understanding of the principles of conduction, transformation and stabilization of nervous energy. Its philosophical importance rests with the elimination of the supposed immaterial fluids and the demonstration of the natural basis of all neuropsychic functions, whence the elaboration of a psychobiology became possible" [36].

The neuron theory and its repercussions for modern brain research have received a new round of extensive discussions on the occasion of the centennial of the Nobel Prize award to Cajal and Golgi [37–48].

The insurrection and the rebuttal

In his response [2–5], Cajal especially takes aim at the contentions of Albrecht von Bethe (1872–1954) and Stephan (István) von Apáthy (1863–1922), who had attacked the neuron theory [49–51] by insisting that nervous conduction takes place through small fibers passing from one cell into another, a thesis that eventually waned [52]. In particular, Bethe had conducted axonal regeneration experiments, which he interpreted as in line with Viktor Hensen's earlier 'catenary' or 'polygenic' theory of nerve fiber growth and regeneration that defended the fusion of multiple axon segments into a common stump, formed by the coalescence of linear chains of Schwann cells [53]. Cajal showed that this was not the case, and that the new fibers appearing in the distal stump of an experimentally dissected nerve emanated from the axonal sprouting at its proximal stump [20]. Cajal refuted such a resurfacing of reticularism by Bethe and Apáthy on more than one occasion [54,55]. He devised a reduced silver nitrate method, which he used to study the distribution of neurofibrils in the nervous system of vertebrates and invertebrates and their involvement in nerve regeneration [56], and concluded that neurofibrils are linear 'colonies' of particles constituting a dynamic internal skeleton of the neuron [57]. With his comprehensive reply to Apáthy [55], Cajal in effect ended the renewed reticularist campaign against the neuron doctrine [57], and eventually compiled his degeneration and regeneration studies into the classic monograph of 1913/1914 [58].

To our knowledge, this is the first English translation of *El Renacimiento de la Doctrina Neuronal* [2–5]. In brief, Cajal speaks firmly of the adversaries of the neuron doctrine, of the psychology and the vicissitudes of young investigators who, eager for fame and lacking in originality, often succumb to the unhealthy temptation to be negative and to discredit doctrines, even in dominions where science seems to have determined the formulations. Cajal patiently exposes and then rejects the 'arguments' made by anti-neuronists in order to inform those who ignore the actual phase of the problem, based on results from the preceding decade. For Cajal there is no fear: He follows the thinking about the neuron doctrine based on the work of van Gehuchten, Michotte, Donaggio, Tello, Schiefferdecker, Marinesco, Azoulay, Harrison, Neal, Münzer, Mott, Medea, Lugaro, Perroncito, Guido, Room, Krassin, Nageotte, and many others, skilfully refuting the arguments of reticularism and catenarism and arriving at an unmatched degree of solidity [59].

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TRANSLATION OF:

Santiago Ramón y Cajal (1907)
Professor in the Faculty of Medicine, Madrid

The renaissance of the neuron doctrine

El Siglo Médico 54: 479–485.
Gaceta Médica Catalana 31: 121–133.
Revista de Especialidades Médicas 10: 428–441.
Archivos de Psiquiatría y Criminología 6: 646–662.

(First English translation by A.M. Partsalis, P.M. Blazquez and L.C. Triarhou from the original Spanish text of *El Renacimiento de la Doctrina Neuronal*, dated by Cajal July 12, 1907).

My distinguished friend, Dr. García Solá, in a very well written and thought out article, as are all of his articles, speaks to us of the "decadence of the neuron" [1907] assuming for certain or quite probable that the research of Apáthy (a zoologist), Bethe (a physiologist) and Balfow, Dohrn (naturalists) have undermined the foundations of the solid and illustrious doctrine founded by embryologists and histologists as eminent as His, Forel, Kölliker, Edinger, Retzius, von Lenhossék, M. Duval, Waldeyer, Monakow, Bechterew, Lugaro, Tanzi, van Gehuchten, Schiefferdecker, Obersteiner, Marinesco, Langley, Déjerine, and a thousand others, all of whom (with the exception of the distinguished His and Kölliker, recently deceased) are today still defending the unitarist flag with more enthusiasm and conviction than ever.

Were I not afraid to offend my dear colleague's sensibilities, I would tell him that, influenced by the noisy flock of young anti-neuronists, he was alarmed too much and, above all, a little too late.

I cannot comprehend, given the mastery of the wise Rector of the University of Granada in the histology literature, why he does not credit in his article the fact that precisely over the past three years we have witnessed a compelling renaissance of the neuron doctrine, thanks to the recent histological works of van Gehuchten, Michotte, von Lenhossék, Donaggio, Tello, Schiefferdecker, Marinesco, Azoulay, Nageotte, Retzius, Athias, and ours; thanks to the histogenetic studies of Kölliker, Harrisson, Neal, Kehr, Gustwisch, Held, and ours; thanks to the histopathological studies (nerve regeneration) of Munzer, Langley, Mott, Halliburton, Medea, Lugaro, Perroncito, Guido, Sala, Marinesco, Krassin, Nageotte, and ours. Not only has the neuron doctrine dismissed the arguments of reticularism and catenarism, but it has also been enriched, thanks to improved tissue staining procedures, with valuable new morphological and histogenetic data, reaching a degree of solidity and prestige never previously attained.

I do not claim that the neuron concept lacks adversaries, and noteworthy adversaries at that. It has had adversaries since it emerged some 18 years ago, it has adversaries today, and will always have them, as long as the psychology of young investigators remains the same, (i.e., their eagerness for reputation). Finding the vein of originality too deep and difficult, they often fall for the unhealthy temptation of doing negative work, discrediting doctrines and tarnishing reputations, even in areas where science seems to have definitely established its principles, such that, with some honorable exceptions, anti-neuronists are not very modest or devoted to scientific truth. A thousand signs show this. Let me just mention one revealing fact of the arrogant egotism and anarchistic rebelliousness concealed in the depths of reticularism. Every anti-neuronist has his structural and dynamic model and defends it as if it were an intangible dogma. Apart from the simple and bright concept brought forth by His and Forel (which is not a theory, as is often said, but a pure and simple expression of facts from observation), there exist six or eight contradictory hypotheses. Thus, the nervous reticulum of Golgi and his disciples bears no resemblance to that of Nissl, Bethe and Apáthy, just as the concept of inter-protoplasmic mesh of Dogiel is not similar to that of Held and Wolff. Favoring imagination and caprice as the norm for their critics, rejecting selective methods for being too clear, and proclaiming the nonselective methods preferable, anti-neuronist schools have regressed to the times of Hence and Leydig, falling into the most deplorable confusion.

However, it is not now appropriate to show the contradiction and emptiness in which the protean phalanges of reticularism revolve and lose authority. I shall deal with such a pleasant and colorful theme in another manuscript. For now I shall examine, as a courtesy, the work of my distinguished friend Dr. García Solá, and I shall also inform those who, disregarding the present state of the subject, stick to the last little celebrity of 10 years ago, the true value and reach of the arguments employed by the most accredited anti-neuronists. These arguments are of three categories: structural, connective (or intercellular relationships), and neurogenetic.

Structural objections by Bethe and Apáthy

The body and expansions of nerve cells contain two factors: neuroplasm, whose sole function is nutritive, and a conductive factor, called the neurofibrils, which are delicate filaments, homogeneous and independent, placed in parallel bundles inside the dendrites and axon, spanning the cell body without ever ramifying or anastomosing. As these wise scientists perceive it, the soma or protoplasmic body is a simple point of crossing of independent nervous conductors; consequently, the neuron is an anatomic feature void of meaning, because the true morphologic and dynamic unit of the nervous system corresponds to the neurofibril.

As can be deduced from the above concept, this theory of Bethe and Apáthy leads to two postulates: the exclusive capability of these elemental filaments, excluding the cellular membrane and neuroplasm, and their perfect insulation inside the cellular body and its expansions.

(a) Independence of the neurofibrils. Leaving aside that the aforementioned wise men have already recognized, in certain cases, the existence of intracellular meshes of neurofibrils, the assertion of perfect and total individuality of the elemental threads loses supporters by the day. Unfortunately for the celebrated discoverers of the neurofibrils technique has advanced with giant steps since 1898. The precarious, difficult, and inconsistent methods used by scientists have been replaced by more perfect and consistent

methods, like those of Simago, Bielschowky, Cajal, Donaggio, DeRossi, Lugaro, etc. Armed with such methods, much more consistent and precise, many researchers have come out to compare their arms with those of the champions of anti-neuronism. And in the fervor created by the new analytical methods, an exuberant literature has sprouted — to which Spain has contributed more than 20 monographs — literature that does not deserve, by the way, the truly surprising silence and disdain of Dr. García Solá. Thanks to the clear and definitive revelations of modern impregnation methods, especially of my laboratory and that of Donnagio, it has been fully demonstrated that the neurofibrils form a complex mesh inside the cell body, instead of a plexus. And it has been clearly shown that the appearance of independent neurofibrils offered in Bethe's preparations were due to his imperfect use of the method, which stains exclusively the thicker filaments of the reticulum, eluding the finer secondary trabecular filaments, which are actually more abundant. This was the judgment, with small variations in interpretation, made by histologists such as van Gehuchten, Donaggio, Lenhossék, Marinesco, Michotte, Athias, Dogiel, Retzius, Azoulay, Nageotte, Legendre, Mahaim, Loudon, etc., the majority, in the end, of those who impartially studied the matter.

(b) Exclusive conductibility of neurofibrils. — This is an assertion for which no evidence exists. On the contrary, all we know on the morphology of neurofibrils suggests a conductive ability of the remaining elements of the protoplasm. I shall mention a few facts.

The first is the behavior of the neurofibrils at the level of the nerve terminations. Using the reduced silver nitrate method, I, as well as Dogiel, Loudon, Tello, and others, have provided objective proof that, in the motor plates and sensory endings, the neurofibrillar scaffolding within each branch forms meshes and complicated handles. From this it can be inferred that if, as Bethe and Apáthy maintain, the current flowed only through these threads, a paradoxical situation would occur wherein the motor nerve impulse would return, having reached the motor plate, to the source cell without discharging in the muscle.

In reality, the axon and its branches contain a reticular frame unified in all its parts. This fact, along with the demonstration recently offered by Retzius and Marinesco, that the neuroplasm is continuous at the level of the strangulations (Bethe maintained that the neuroplasm is interrupted at strangulations) have paved the way for the theory of Schiefferdecker, Wolff, and Verworn, for whom the neuroplasm, and not the neurofibrils, is the carrier of the nervous wave. Furthermore, that the neuroplasm and the cell membrane itself have conductive properties is supported by the fact that in the retina, olfactory bulb, cerebellum, etc., interneuronal relations are established by articulations, without it being possible to find any unifying filaments penetrating into the cell body.

Let me add an interesting datum: the dynamic concept of Bethe requires the firmness and stability of the neurofibrillar apparatus. Well, according to my observations, as well as those of Tello and García, confirmed and extended by Marinesco and Donaggio, the neurofibrillar reticulum, far from constituting a stable frame, represents an amoeboid scaffolding susceptible to great quantitative and qualitative transformations, depending on the physiological state (hibernation, effect of cold, fatigue, starvation, poisoning, infection etc.).

Thus, neither are the neurofibrils independent threads, nor do they conduct the nerve pulse individually, nor are they stable; recent structural findings do not contradict, in fact they graciously complete, as van Gehuchten has noted, the neuron doctrine.

Alleged intercellular anastomoses

The second argument derives from studies dealing with intercellular connections, first by Bethe and Apáthy and more recently by Bielschowky. This argument can be formulated thus: Around the nerve cell there exists, apart from the nerve terminations discovered by Cajal and confirmed by many savants, a very fine net of neurofibrils (pericellular net of Golgi — everyone credits Golgi for the discovery of this pericellular reticulated cortex, forgetting that a year earlier [Ramón y Cajal, 1897], I had already mentioned it when I used methylene blue in the nerve centers; the first communication of Golgi on the argument dates to 1898), which receives from an outside anastomosis of the nerve nest, being just a continuation of it, and from inside, bridges of union with the intraneuronal reticulum.

This theory, defended five or six years ago with great tenacity and perseverance by Bethe and his disciples and fervently discussed in schools, has crashed like the previous one against the final revelation of the neurofibrillar methods and the information, no less revealing, learned from the neuroplasm procedures.

I declare, of course, that such a flat pericellular reticulum is not of a nervous nature, nor is it related to the terminal arborizations of the axis cylinders. In fact Golgi, who colored and discovered this net using a modified silver chromate method independently of me, thought of it as a neurokeratin frame, destined to protect the cellular periphery; he never found any indications of communication with the nerve nests. Ehrlich's method, which in some cases stains this pericellular net exclusively and with great precision, according to the studies of Donaggio and ours, presents it as a membrane perforated with round holes and totally separate from both the exterior nerve fibers and the interior reticulum. Also Simarro, who stained this mesh with his method, considers it different from the fibrillar frame. On the other hand, Auerbach and Held share the same opinion. The latter author, who studied this reticulum in detail using a variety of techniques, considers it to be a neuroglial dependency, a view shared by Donaggio and others.

Finally, thanks to Bethe's kindness, we have had the opportunity to study the original specimens of this Strassburg physiologist, ascertaining these two important facts: (a) that the procedure of this author did not color the arborizations of nerve terminals: something which led him to wrongly interpret Golgi's net in his preparations as the pericellular nerve nests, completely invisible or insufficiently stained; (b) that the above specimens, carefully studied with better optics, only show a superposition between the pericellular net and the neurofibrils of the cell body, never the substantial contact predicted by the

reticularists. Additionally, the pure neurofibrillar methods (ours and Donaggio's), which lack affinity to non-nervous factors of the grey matter (neuroglia, blood vessels, intercellular cement, interstitial coagulated plasma), never reveal the aforementioned superficial net, while they constantly and admirably stain the intracellular neurofibrils, the nests and the rest of the nerve endings.

From all this it can be logically deduced that the nervous nature of Golgi's net, as well as its purported communications with intra- and extra-cellular neurofibrils, represents an anatomical hypothesis deprived of foundations.

So persuasive are the previous observations that the new reticularists, like Held, Holmgren, and Wolff have definitely abandoned the famous superficial net of Bethe, seeking the desired substantial communications (a true obsession for some spirits), not between this net and the neurofibrillar frame of the cell body, but between the terminal boutons of the pericellular nerve nests (Auerbach's boutons) and the previously mentioned protoplasmic scaffolding, an opinion which, *en passant*, represents another new precarious conjecture based on the misinterpreted results of our staining method (see the critiques by van Gehuchten, Michotte, Mahaisu, Schiefferdecker, Cajal, etc.).

Histogenetic arguments

Faced with the overwhelming headway of the concept of His and Forel, the anti-neuronists, uncertain in the morphological terrain, found refuge in neurogenetic arguments, as if this were an unconquerable bastion.

And this time they defended themselves with such zest and dexterity that, unexpectedly, panic spread among the defenders of the classical doctrine. I must confess that until 1903 most published work dealing with the problem of regeneration and embryonic neurogenesis found inspiration in the principles of polygenism. Dohrn, Büngner, Ballauce, Wieting, Durante, Marchand, Modena, Galeoti and Levi, Marinesco, Grasset, etc. fervently took communion in the new religion which was defined by Alfred Bethe, the most genial and ingenious of all of them.

This new reformatory movement dragged even such a clear and well-oriented spirit as van Gehuchten. Seduced by the ability and experimental genius of the physiologist of Strassburg, the scholar of Louvain, without relinquishing his neuronist faith, abandoned part of his previous convictions. In his opinion, the unity of the nerve cell, indisputable in the morphological terrain, would fail in the histogenetic terrain because axon formation could be the collaborative result of a great number of neuroblasts.

Let me formulate with precision the fundamental objection of anti-neuronists, transcribed by Dr. García Solá. The affirmative mode of this objection constitutes the hypothesis which, for brevity, I shall refer to as the *catenary hypothesis or theory.*

(a) The axis cylinders of the nerves of the embryo are not formed, as supposed by Kupffer, His, Kölliker, Cajal, Lenhossék, etc., by simple continuous growth and ramification of the expansion of a single neuroblast (the embryonic nerve cell of the spinal cord), but they derive, as argued by Dohrn, Balfour, Büngner, Bethe, etc., from the fusion and successive differentiation of several neuroblasts of the periphery, originally arranged in series, or as a chain extending from the cord to the nerve endings. The residual protoplasm of such neuroblasts would remain alongside the axis cylinders, forming the future Schwann cells of the myelin sheath.

(b) In accordance with this concept, when a nerve is cut in a young animal and the immediate reunification of the nerve fragments is prevented, the peripheral end, deprived of its trophic center, auto-regenerates; that is, once the old axons are destroyed, Schwann cells return to their embryonic phase, multiplying actively and forming a solid protoplasmic chain, in which the new nerve fibers sprout by differentiation and in a discontinuous fashion. Ultimately, in some cases, such conductors formed without the aid of trophic centers invade the scar and connect with the persisting central ends.

Such is the new theory that opposes the neurogenetic concept of His and Waller. To obtain experimental anatomopathological support, numerous authors, from Brown-Séquard to Bethe, working with the patience of a Benedictine monk, performed thousands of experiments (nerve transplants, root resection, displacement of the nerve stubs). At the same time, zoologists and histologists like Dohrn, Balfour, Sedgwick, Forel, Bethe, Fragnito, Levi, Capobianco, etc., strived to support it in the domain of neurogenesis.

It is sad to think about the sterility of such efforts and the great experimental ingenuity wasted in defending an error which was avoided by the first observers more than 30 years ago (Waller, Ranvier, Ziegler, Stroebe, etc.). However, I do not imply that the deductions of catenarists totally lack support from observations.

I must admit that there are a few dispositions of dubious interpretation that fertilize catenarism, like the appearance of new fibers in transplanted new segments, the regeneration of the peripheral stub displaced and separated from the central stub, the excitability of the peripheral stub with lack of excitability in the central stub, etc. But in their fervor to rapidly reach the prestige of unanimity, the catenarists committed two serious errors: They based their histological judgment on the results of the imperfect osmic acid method, capable of staining the new fibers only very late in the process when they already have a myelin sheath, and conceded major and almost exclusive importance to experimental physiological fallacies and the wish to resolve an anatomical problem. In vain did wise critics such as Munzer, Sangley, Mott, Haliburton, Purpura, and others, despite working with obsolete and unreliable methods, point attention to interpretation errors by Bethe and his followers. It also proved useless that, from the embryological perspective, Kölliker, Lenhossék, Harrison, Kehr, Gurwits, Neal, etc., actively rejected a doctrine that clashes with the best-demonstrated neurogenetic facts and particularly with the straightforward and unequivocal revelations of Golgi's method. Catenarists, disdainful of criticism, indignantly upheld their assertions, aggravating them with new paradoxes. The conflict would have continued if not for the enrichment of technique with a new procedure: The reduced silver nitrate method, born in Spain, and regularly employed throughout Europe today by histologists and anatomic pathologists.

To elucidate the problem, this method has the ability to perfectly stain, in a transparent coffee-brown color, the neurofibrils of the embryonic or young fibers, in embryos as well as in regenerating fibers, showing with perfect clarity the terminal ending, widened in the shape of a bouton, of the newly-formed, wandering axons of the scar. Provided with this new resource, many observers have joined in anatomic pathological experimentation during the last few years, submitting to sharp and severe criticism all the objective data and physiopathologic deductions that are the foundation and warranty of the catenary theory. In addition to us, Medea, Perroncito, Marinesco, Lugaro, Nageotte, Besta, Tello, Cl. Sala, using the silver nitrate method, and Purpura and Krassin, using the Ehrlich method, have shown beyond doubt that the fiery theory of discontinuous and polygenic development represents (with the exception of a few successes in secondary issues) the sad product of the imperfection of methods and neurogenetic and physiologic prejudices.

Lacking space, I cannot go into the details of the remarkable controversy between neuronists and catenarists over these past three years, nor can I point out the facts and arguments used by the defendants of the classic doctrine of His and Waller. Those wishing to inform themselves on this matter should consult published work by Perroncito, Marinesco, Ramón y Cajal [1905, 1906a, 1906b, 1906c] and Tello y Muñoz [1907].

Here I shall limit myself to recalling the following facts, detrimental to the catenary hypothesis and perfectly in agreement with the observations of Perroncito, Cajal, Lugaro, Marinesco, Medea, Krassin, Purpura, Tello, Mott, etc.

1. From the end of the axis cylinders of the central stub of a sectioned nerve one or more non-myelinated branches sprout early (2nd–4th day), before Schwann cells multiply and form strings,, which cross the scar and exit, ramifying profusely and finally reaching the peripheral stub. Thanks to the bouton or growth rod that crowns the ending of all young axons, and which gets perfectly stained by our method, the as yet impossible task of following the newly-formed axons from their origin to their termination has become easy.

2. Once these fibers reach the peripheral stub, they often ramify at the entrance, seize the old casings or Schwann sheaths, and in their exit towards the periphery they arrive (as was recently demonstrated by Tello) at the matrix plates where they reconstruct the old arborizations. Never in their development are they discontinuous, nor do they have any other relation to the cells of Schwann sheath apart from contiguity.

3. The early and active multiplication of Schwann cells of the peripheral stub is not intended to create new auto-regenerating fibers, but to form guide tubes, which get filled with a chemotactic substance meant to attract and steer the new fibers from the scar.

4. In those cases where, following artificial displacement of nerve fragments, there seemed to be, as catenarists envisioned, no sign of unifying fibers, the new staining method revealed a rich plexus of pale, unmyelinated fibers which establish the continuity between the axons of the central and the peripheral stub.

5. Finally, as my observations in embryos have demonstrated, even during the earliest phases, all the axons of the roots appear denuded and in continuation with the neuroblasts of His and not the slightest sign of the cellular chains described by Balfour, Sedgwick, Bethe, Fraquito, etc. exists. Held recently obtained similar results (with variations that do not apply here), successfully utilizing our procedure in the exploration of salamander and avian embryos.

In summary, the morphological arguments have not been confirmed; the anatomic pathological evidence has been refuted with the aid of methods superior to those used by the catenarists; in the field of embryonic development the recent data strongly support the neuron concept.

Everything announces the imminent and definitive victory. This is also evidenced by the doubts and perplexities of some catenarists, the indicative silence of others and the resolute defection of some of the most authoritative and committed individuals. Because in this scientific controversy a unique event has occurred: During the first skirmishes of the fight, and in view of the arguments made by Perroncito and myself, observers as prestigious as Marinesco, Levi, Medea, and Berta moved to my side. Even the illustrious Dohrn, the most formidable knight of catenarism, the reformer and almost founder of this doctrine, has just recognized his errors and is energetically proclaiming the verity of the neurogenetic doctrine of His. Recent observations of the stingray embryo have allowed him to confirm the centrifugal growth of cranial nerve axons, thereby abandoning opinions which he spiritedly held for a decade. Also ominous for the supporters of polygenism is the fact that Pochariski, a Russian doctor who has worked, with the aid of my method and that of Bielschowky's, in the laboratory of Marchand, one of the centers of catenarism and antineuronism in Germany, is reluctant and unwilling to defend the master's doctrine, but only in part and with great reservations. Finally, even the illustrious Bethe, who defined the school, has been influenced by the new findings. It is clear that the author of a voluminous book written in defense of the theory of discontinuity and reticularism cannot drastically change his opinion; but in his last work, where he tried to refute the serious objections to his theory put forth by Perroncito, Lugaro, Cajal, Marinesco, Mott, etc., he already appears much less exclusive, making the concession, among others, that the fibers of the scar and even those of the peripheral stub might stem from those in the central stub; as a consequence, today he does not even hold as true that the definite re-establishment of the paralyzed member's innervation is provided by Schwann cells of the distal stub.

Finally, before concluding this long and cumbersome article I would like to make some statements of personal character.

Among the colleagues that honor me showing interest in the reach and future of my ideas, there are two kinds: the good friends who, unaware of the majority of my works (unfortunately in Spain there are no more than two or three persons who have read them thoroughly) are afraid that, along with the neuron concept (which has been associated with my name by foreigners) my modest scientific work would sink, too; and those — fortunately very few — who, even more unaware of the value and reaches of my personal scientific contribution, seem to feel ineffable delight and frenetic exaltation

as soon as a Mr. Nobody foreign histologist, without prestige or authority, echoing perhaps some error of German origin, is permitted to contradict the neuron concept, or other arguments or deductions of mine. To this latter group of pious and affectionate colleagues undoubtedly belong certain persons who, now and again, and in the event of the alleged failure of the neuron — reported in some weekly French medical journal — send to me, believing it would bother me, anonymous letters full of raw insults and vulgar injustices.

It is not appropriate to answer those who attack with the visor down and hidden in the shadows. Nevertheless, I wish to calm both groups of compatriots. Neither do the former need be afraid, nor the latter rejoice. Understand once and for all that the neuron being a German idea, its possible failure would not affect my work, because my work is based on observations and facts, not theories.

The aforementioned concept (it is necessary to repeat, because as interesting as it might be, when the neuron declines, everybody attributes its paternity to me, and the reverse happens when it is on the rise) was formulated, although without proof, by His and Forel in 1887, as one of many conjectures or possibilities against the theories of Gerlach and Golgi, reigning at the time; however, neither His nor Forel could persuade anyone because in order to gain consent for these new ideas, it would have been necessary to objectively demonstrate the very last terminations of nerve fibers in grey matter. Only in 1888 and 1889 when, with the power of patience and perseverance, I described the true endings of the axis cylinders in embryos and young animals (which occur by gearings, pericellular nests, and climbing branches (i.e., by true articulations established between the soma and dendrites on one side and free nerve endings on the other) did the precarious and disdained hypothesis of His and Forel find scientific foundation, spread rapidly among schools, and, with incontestable impetus, overrun all rival theories. Innumerable morphological studies by Lenhossék, Kölliker, Retzius, van Gehuchten, Edinger, Lugaro, Sala, Harrison, Langley, Held, my brother, etc. confirmed and employed my fortunate findings, and the neuron concept, perfectly harmonizing with conjectures from physiology and pathologic anatomy, was elevated to the range of scientific dogma. Finally, Waldeyer, sheltering the new facts and observations under his high authority, had the merit to condense and popularize them in a brilliant synthesis, baptizing the new morpho-dynamic concept of the nervous system with the name *neuron*, which proved fortunate.

[Dr. García Solá, participating in a very common error in Spain, attributes to Dr. Waldeyer an experimental and observational contribution to the neuron doctrine, which never was. The learned anatomist from Berlin did not carry out any particular research on this point; he merely summarized in a German weekly my work and conclusions (as well as those of His, Kölliker, Lenhossék, Retzius, etc.), reproducing the most compelling figures and giving a name, popular today, to the doctrine. Of the three units implicated in it, the *genetic* was formulated by His, whereas the *morphological* and *physiological* is a logical consequence of my personal investigations.]

The neuron concept is, therefore, not mine; nevertheless, it was nourished by the morphological and neurogenetic facts provided by me; data which, confirmed by numerous wise scientists and various analytic methods, possess their own intrinsic and definitive value, whichever theory with which one interprets them, or whatever new complementary structural data the future may bring.

Let us suppose, as I recently noted in my conference in Stockholm (December 12, 1906), that a new method is discovered, one which reveals that within our nests and climbing nerve plexuses and the cell body, there exists a new system of most subtle unifying threads, hitherto inaccessible to current technique. Thanks to such a valuable discovery, my work would have been completed and perfected; in addition to the contacts I found in vertebrates, and Retzius and von Lenhossék found in invertebrates, we would need to admit that more intimate, heretofore unsuspected, ties between neurons in contact exist. The tenebrous cerebral and cerebellar jungle would become even more entangled. Between the swaying neuronal cups, a system of most delicate threads would entangle branches, creating a tight functional cohesion. But in such a case, would the branches, their roots and foliage cease to exist? And would the scientists who discovered them deserve falling into oblivion? In other words, in the improbable case of the definite abandonment of the notion of neuron individuality, how would this affect my own work and the work of many prominent histologists and embryologists, work essentially consisting of the direction and tracks of nervous pathways, encounters of bifurcations and axon collaterals, differentiation of neuronal populations, study of intercellular connections, determination of contacts, etc.? As far as I am concerned, it would all amount to no more than erasing a couple of paragraphs from some books and 180 monographs.

Only those alien to the morphological sciences and laboratory religion distrust the progress in histology and refer to histology as *celestial anatomy*. Impressed by the changeability of theories, they imagine that nothing is stable in histology, that anything can be overlooked because much is under discussion, when in fact there is discussion because there is advance. When histological images, revealing objects and substances in perfect clarity, present them distinctly and consistently in diverse orders of vertebrates; when, examined with various other complementary techniques, they are found to be well studied and described; when an austere observer with a critical stance eliminates personal bias, similar to what astronomers call *personal equation*, then histological facts represent a definite scientific achievement which should not be affected by the caprices of different schools and the fluctuations of speculation any more than the form or chemical properties of a muscle may be. In histology, as in all the natural sciences, doubts and controversies are not over the facts but over their dynamic interpretation.

This creed of preference for facts, as well as distrust for theories, was always the standard of my conduct. Aware of the fragility and volatility of my synthesis — always premature and based on incomplete and unilateral analysis — theories received only cautious accommodation in my books, and if anyone

doubts this, they should read the preface of my book on the histology of nervous centers, written in 1898, when neuronism was in full vogue, where regarding hypotheses and theories I wrote a doctrine that was considered excessively skeptical by more than one author.

Returning to the issue of neuronism, I am afraid that the neuron will be around for a while, and in my opinion the meritorious colleagues I alluded to should calm their nerves. Yes, dear colleagues: *la neurona* or *el neurona* will outlast us, and in its march toward the future the neuron will see new sunrises and sunsets. (Dr. García Solá prefers to say *el neurona*, because the French would write *le neurone*. So be it ... However, with that criterion, the Spanish should say *lo neurona*, because Waldeyer, who created the word, used the neutral gender and wrote *das Neuron*. Foreign usage should not impose on us; since the idea that is conveyed by the term, i.e., the concept of the 'nervous unit' *(la unidad nerviosa)*, is feminine in Spanish, let us use the feminine gender.) And in vain do the anti-neuronists hope for tranquility and unanimity. As I have made clear, new battles are beginning. The reticularist hypothesis of Held and others will replace that of Bethe and Apáthy, and the renewed controversy will only change its theater. It is so easy to destroy without creating! It is so difficult to create without destroying!

On my part, I would not hesitate passing to the reticularist camp, were I to be proven wrong. But it has to be proven with facts.

The good Sancho was willing to proclaim Dulcinea's beauty if only he were to be shown a portrait of hers of the size of a hempseed; I am likewise ready to confess the unmatched beauty of the reticularist doctrine, if only I were shown a constant, clear fact in its favor, not larger than a grain of mustard. But as long as the enthusiastic detractors of neuronism put forth, instead of demonstrations, anatomical hypotheses, and instead of precise and constant images, uncertain and incidental appearances, I shall remain faithful to the old and noble flag of unitarism. Because, although I am much concerned with the peace and tranquility of the spirit (not to be attained by me without renouncing the 'contact' doctrine), and although I sympathize with the ingenuous and romantic champions of reticularism, and although I have confessed that the neuron, as a scientific idea, has not been created by me — despite living persuaded that the positive facts provided by my modest work will sooner win than lose with the new speculative interpretations — there is something in me more powerful and captivating than the fancies and delights of the spirit: the sincere and impartial worship of the truth, wherever it may come from.

And for now ... still, the neuron is the truth, or so it seems.

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