ARIADNA'S THREAD IN THE LABYRINTH OF NERVE ACTION OR SANTIAGO RAMÓN Y CAJAL'S LAW OF DYNAMIC POLARIZATION

JOSÉ LUIS GONZÁLEZ RECIO

ABSTRACT. After presenting the theory on the free termination of the neuron in 1888, Cajal tried to establish the principles to which the activity of the nervous cell was subjected. In the writings published to that purpose, between 1889 and 1897, a simultaneous interest in the morphological and functional aspects which the explanation of neuronal conductivity possesses becomes evident. These aspects were combined in the discovery of the *dynamic polarization law*, without doubt the founding principle of neurosciences. The present study is an analysis of the conceptual, methodological, epistemological and historical keys of that discovery.

KEY WORDS. Ramón y Cajal, neuron, dendrite, axon, polarization, morphology, neurohistology, neurophysiology, empirical problems, conceptual problems, methodology, epistemology.

INTRODUCTION

In 1906, Santiago Ramón y Cajal (1852-1934) received the Nobel Prize for Physiology and Medicine, sharing the award with the Italian scientist Camillo Golgi. The contributions of the Spanish researcher to descriptive anatomy, histology and neurophysiology were granted international recognition by the awarding of this prize, though recognition had already occurred. He had previously been named *doctor honoris causa* by Cambridge University (1894) and confirmed at the International Medical Congress in Paris (1900), where the city of Moscow awarded him its prize for the most relevant work in the field of biomedical research carried out over the preceding three years. Before receiving the Nobel Prize, Cajal dedicated over twenty years of his life studying the morphology and the functional dynamic of the neuron, at a time when the structure and the activity of the nervous cell was not yet well defined. The results of these studies led to the formulation of two theories that will have major conse-

Departamento de Filosofía I, Facultad de Filosofía, Universidad Complutense, 28040 – Madrid, España. / e-mail: jolgonza@filos.ucm.es

quences regarding the knowledge of the architecture and the functions of the nervous system: the *theory of the neuron* and the *theory of dynamic polarization*. Both were published over a nine-year period between 1888 and 1897. The work carried out and the approach taken show that simultaneous attention to the organic form and to the processes which take place in connection with this is essential. The morphological hypothesis on the free termination of the neuron had been illuminated, indeed, by the possible function which the protoplasmic prolongations might perform; at the same time, the idea of a dendrite-axon orientation, as a via of the *nervous impulse*, was developed on the basis of decisive and accurate microanatomical data. The theory or dynamic polarization law concludes this stage in Cajal's life, and the following pages are devoted to this period; their purpose is to clarify both the scientific features of the neurophysiological research carried out, and some of its historical, methodological and epistemological keys.

Between 1884 and 1887, Ramón y Cajal was professor of anatomy in Valencia. His work there led to the presentation of the theory of the neuron, which was the foundation for the research which would culminate in the physiological hypothesis on the mode of transmission of the nervous currents. Cajal obtained the Chair of Descriptive and General Anatomy in Valencia after applying without success for equivalent positions once in Saragossa and twice in Granada. The Valencia period of his intellectual life represents a major turning point in the scientist's career, since this is when he begins to direct his research towards histology and leaves behind the years devoted to descriptive anatomy [1]. At that time, the School of Medicine that Cajal joins as a professor is a centre open to the orientations and supposed innovators working at other European universities:

> ...it boasted [...] already there a teaching staff which in the main followed the so-called "laboratory medicine," a current of medical thought clearly founded on experimental research, and in which, among others, the following stood out: Ferrer y Viñeta, rector of the university and a surgeon who pioneered antiseptic surgery along with Aguilar y Lara, the internist Crous y Casellas, author of a treatise on normal and pathological neurophysiology, Amalio Gimeno, who promoted experimental pharmacology and, also, in a very noteworthy way, professor Peregrín Casanova, who held the other Chair of Anatomy with Cajal and who introduced Darwinian evolutionism in Spanish anatomical teaching. At the time when Cajal accepted the Chair of Anatomy in Valencia the anatomical museum was still being run by Elías Martínez Gil, whom Cajal's father no doubt also knew and who in 1883 published a treatise on "Anatomy of the Humours," where we may see the micrographic activity of the histology cabinet at the Valencia faculty before Cajal's arrival [2].

Valencia was where the future Nobel Prize winner would begin to become familiar with Golgi's chromoargentic coloring technique, which he learned from Luis Simarro, the most prominent figure in neurophysiology in Spain. Since 1884, he publish in installments, in Valencia, his *Manual of Normal Histology and Micrographic Technique* [3], he join the Royal Academy of Medicine and become a member of the Valencia Medical Institute, where he chair the History and Philosophy Section, which he succeeded in directing towards biological and experimental research [4].

At that time, European neurohistology owed its theoretical underpinnings largely to the work of Otto Deiters *Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugethiere* (1865). In this work, a basic morphological organization had been defined for the cells of the nervous system which comprised: the cellular body with its nucleus; the *protoplasmic prolongations,* and the nervous expansion (cylinder-axis or axon), which Wilhelm His was to name shortly afterwards *dendrite* and *neurita* respectively. With regard to the disposition of the cells in the nervous tissue—a subject which I shall return to in the next section—there were two main currents: one was characterized by Kölliker, His and Forel, who claimed that limits existed between cellular units and considered the latter as independent elements; the second, sustained by von Gerlach and Golgi, inclined towards interpenetration and fusion either of dendrites among themselves or with collateral ramifications of neurites (von Gerlach), or exclusively, between the terminal and collateral beams of the axons (Golgi) [5]. It could thus be admitted that, in accordance with the opinions and data defended by von Gerlach and Golgi, nervous tissue possessed a singular make-up which made it different from the rest of tissue formations, or one might conjecture that an analogy existed between its structure and other tissues, defend the general validity of the cell theory and seek the necessary empirical evidence that His and Forel's observations and research had yet to provide. Cajal chose the second way, which would lead him to the formulation of the theory of the neuron and the hypothesis of dynamic polarization.

TOWARDS THE HYPOTHESIS OF DYNAMIC POLARIZATION

In 1888, Ramón y Cajal, now professor of histology at the University of Barcelona, publishes two articles—"Structure of the nervous centers of bird" and "Structure of the cerebellum [6]"—in which he presents his theory of the neuron. Employing the coloring method with silver chromate, created by Golgi, he established beyond doubt that, like all other tissues, nervous tissue was formed also by real independent cellular units. The empirical evidence supplied by the Spanish histologist was not compatible with the reticular theory that had been defended by von Gerlach and

Meynert, and which even Golgi had given its definitive formulation: *the nervous substance constituted a diffuse network; the last branches of the axons interpenetrated and composed a mesh in which it was not possible to delimit real differentiated cellular structures* [7]. The neuronal *network* hypothesis not only meant taking a standpoint regarding to the microanatomy of the nervous tissue but, as it may easily be imagined, also included implicit consequences for neurophysiology. In such a representation of the nervous elements, it was difficult to understand how neuronal activity was established by defining selective routes, directions or vias. For this reason the theory of free termination of the neuron, proposed by Cajal, acquired a precise functional significance, besides the direct and primary significance it possessed for the morphological configuration of the nervous system; a structural disposition that its promoter summarized in the following principles:

1. The collateral and terminal ramifications of the cylinder-axes do not end by creating a diffuse network: it is rather through free arborizations.
2. These small branches of the axons are applied—Cajal claimed—to the body and the dendrites of the other nerve cells producing a relation by contact.
3. Taking this disposition into account, it may be surmised that the dendrites participate in the chain of conduction of the nervous impulse—in contrast to Golgi's opinion, who saw in protoplasmic expansions channels for the circulation of nutrient elements.
4. The nervous impulse is also transmitted by contact, as in the articulations of electric conductors, or by some kind of induction [8].

The physiological consequences of these findings, with reference to descriptive anatomy, were presented by Ramón y Cajal in two papers which must be seen as milestones in the historical development of neurosciences. The first paper appeared in 1891 and was titled "Physiological importance of protoplasmic and nerve expansions of grey matter cells," the second, "Laws of morphology and dynamism of nerve cells," was published in 1897 [9]. Throughout the nine years that passed between the publication of these articles in which the theory of the neuron was established, and the paper in which Cajal concludes what he decided to call *law* or *theory of dynamic polarization*, the different aspects of his research offer the science historian and philosopher an extremely stimulant area for reflection. The distinguished histologist sets out with such subtlety and detail the methodological requirements with which he works, elaborates on the problems that microscopic observation confront him, and reveals the effort of conceptual creation involved in the research activity, that his work reflects a lucid simultaneous attention to relevant questions both for the science

constructed in the laboratory and for the theory of science. Cajal is as meticulous in the design of the preparations which he will place on the microscope slide and in the assessment of the observational evidence it can provide, as he is in the analysis of the fundamentals and the expression of the conjectures or deductions which he offers. The difficulties of coloring, the demands of strict observation, the need to back up neurohistological findings with the cellular conception of all tissues, or the secrets of micrographic technique, are communicated to us in the same pages where experiments, data and ideas, which are constantly being revised, finally lead to the discovery of a basic neurophysiological law: *the cellular body and the protoplasmic expansions represent an apparatus for the reception of currents, which always go towards the axon or cylinder-axis, to be distributed through the terminal and collateral ramifications of the latter over the protoplasm of other neurons* [10]. It is a physiological principle that is so elementary today that we can overlook the value and the importance it had when it was first formulated. It was to define, in fact: a) the dynamic primary outline in which any future investigation on the activity of the nervous system would have to be situated; b) it depended on the structural autonomy of the neuron and was thus tied to the cellular theory; c) it had relevant heuristic scope; d) it ruled out assumptions widely accepted by the function scientific community—such as the trophic function of protoplasmic expansions; e) it was in harmony with well-known facts and processes of embryogenesis, and f) it illuminated the philogenetic course of important neuroanatomical formations. However, as I have just pointed out, the writings that contain the course of the research, up until the new law is formulated, are also full of metascientific considerations explicitly stated by the author. The role of induction, the impositions or demands of experimental reasoning, the epistemological battle between realism and instrumentalism, the ontological considerations of scientific knowledge, the dynamic of theories, and in general a large number of the empirical and conceptual problems examined today by the theory of science have a place and are evaluated in the totality of contributions which led Cajal to posit the theory of dynamic polarization of the neuron.

GENERAL CONNECTION OF NERVE ELEMENTS

Only one year after publishing the two articles in which the theory of the neuron is formulated, Cajal begins to evaluate the consequences entailed by the first physiological conjectures he had put forward in the 1888 papers. He collects these first observations and reflections in the study entitled "General connection of nerve elements" (1889). In his opinion, the purpose of the protoplasmic branches is to establish transmission contacts, both with the dendrites of analogous cells such as nerve fibers (axons) of

different origins. He believes that such a function is obvious in the olfactory glomeruli or in the Purkinje cells, and probably in the ganglial cells of the retina and the pyramidal cells of the brain [11]. Nevertheless, he believes that, in the light of the data provided at that time by histology, it is still too early to define the physiological specificity of both expansions. Prudently, he stresses that the activity of the neuron and the nerve tissue demands a research that can deal equally with morphological and dynamic aspects. The hypothesis of the trophic role of the protoplasmic prolongations had long been ruled out for Cajal, but he was still unable to assign specific and exclusive actions either to the cylinder-axes or to the dendrites. He suggests that the different length of the protoplasmic expansions is related to the distance at which the receiving elements are located from the excitation. In a truly functional sense, therefore, one must not speak of differences between the little prolongations and what constitutes the nerve fiber. As far as the connection is concerned, all the neuronal elements possess identical significance: they serve to relate contiguously histological units through the model of electrical conduction: "The only difference is that the role of the cylinder-axes is to carry the nerve action to distant territories, and thus are long conductors; while the protoplasmic expansions transmit it to nearby elements [12]."

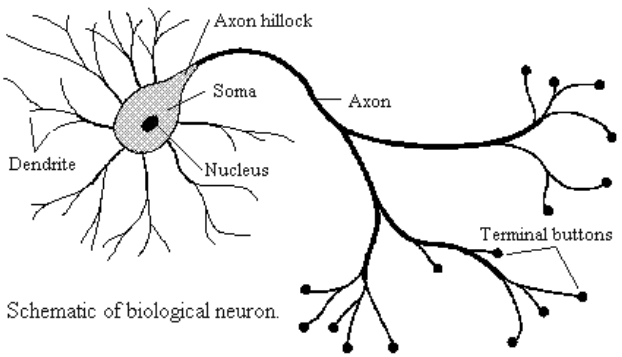
In a period of only two years, however, these initial assumptions would be profoundly modified. Cajal, meanwhile, could avail with the result of his brother Pedro's research, who, in his doctoral thesis of 1890, confirms the existence of axons in mammals' retinal neurons which had heretofore been difficult to observe [13]. As I have mentioned above, in 1891 the following paper is published: "Physiological importance of nerve and protoplasmic expansions of grey matter cells." Cajal recognizes here that he has for some time been convinced that passage of current takes place by means of multiple contacts between the final arborizations of the nerve fibers, and the body and the protoplasmic branches of the contiguous cells. The problem was to determine the *direction* of the currents which traverse these structures. And this is the objective that he believes he has accomplished in the 1891 article. The possibility of establishing a criterion to determine the aforementioned direction existed: those nerve organs such as the retina, the olfactory bulb or the motor nerves—where the starting point of excitation is known—might be explored. If it could be proved, without exception, that the protoplasmic arborizations function as a receiving apparatus and the nerve expansion as an application apparatus, it would be feasible to formulate a hypothesis which might be evaluated by future observations, both in organs similar to those mentioned and in central cells [14].

In the next pages of the article, Cajal presents, first of all, all the evidence endorsing the idea of a dendrite-axon polarity for nerve stimulation: in the olfactory bulb; in the retina; in the cones, and in the optic nerve. His

intention is to subsequently carry out a generalization to the central vias. The argument is always the same: as we know the place of excitation and the anatomical architecture of the linked nerve elements, it is not difficult to conjecture what the direction of the current that circulates along the dendrites and cylinder-axes may be. Inside the retina, for example, the contact between the ramifications of the fiber of the cones and the ascendant branches of the bipolar cells may be appreciated as well as, subsequently, the contiguity between the terminal branches of the axons of the latter and the dendrites of the cells that form the ganglial layer. The nerve impulse then continues its course until it reaches, by the fiber of the neurons of the ganglial layer, the protoplasmic branches of the cells which integrate the geniculated bodies and the quadrigeminal bodies [15].

A limited number of conclusions may therefore be established to synthesize the 1891 article and summarize what may now be called the *Law of dynamic polarization of the neuron*:

1. The role which—according to Cajal—the protoplasmic expansions play contradicts the purely vegetative function that Golgi and his disciples assigned them.
2. Transmission of the nerve movement takes place from the protoplasmic branches and the cellular body to the nerve expansion.
3. Every cell possesses a receiving apparatus (body and protoplasmic expansions), a conduction apparatus (cylinder-axis) and an application apparatus (terminal arborization of the cylinder-axis).
4. The functional role—motor or sensitive—is subordinated to the connections that the cylinder-axis and protoplasmic expansions possess. Sensitive will be every cell whose protoplasmic expansions terminate in cutaneous or mucous free surfaces. Motor will be those whose cylinder-axis fixes on muscular corpuscles [16].



Schematic of biological neuron.

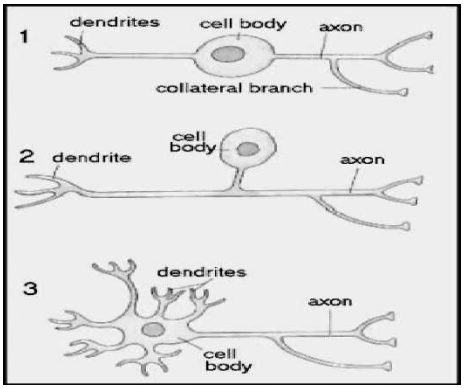
LAWS OF MORPHOLOGY

In the 1897 article, "Laws of the morphology and dynamism of nerve cells," Cajal starts by claiming authorship of the discovery of the dendrite-axon polarization, which the Belgian histologist van Gehuchten also seeks to be credited with [17]. He remembers that before 1891 he had already conceived the *cellulipete* conduction hypothesis, and that, when van Gehuchten alludes to it, he formulates it without accepting it, considering it as truly a physiological principle only after reading Cajal's study on the connection of the other nerve elements [18]. Indeed, they had both come to share the defense of the functional schema that I have just described: the current would always go from the protoplasmic expansions to the cellular body, and from the latter to the cylinder-axis, until it reached its terminal arborizations.

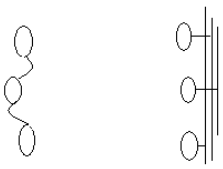
Nevertheless, in a somewhat theatrical and dramatic way, Cajal surprises us at the very beginning of the paper with the following declaration: "The formula that van Gehuchten and I have given of this hypothesis is not, however, correct. Strictly applied it relates only to sensitive bipolar corpuscles and all central neurons whose functional expansion sprouts from the cellular body [19]." The reason is that on many occasions the cellular body moves away from the cylinder-axis or the latter proceeds from a protoplasmic branch. So the completely correct formulation of the dynamic polarization law, without exceptions and of a truly general character, must be as follows:

> The cellular body and the protoplasmic expansions represent a current reception apparatus, which always go towards the axon to be distributed by means of the terminal and collateral ramifications of the latter over the protoplasm of other neurons; the current, therefore, is not always cellulipete in the protoplasmic expansions nor cellulifuge in the nerve expansions; rather in the former—dendrites—it is constantly axipete, that is, it goes towards the axon and dendrifuge in the latter—cylinder-axis. The expansions and cellular body represent, consequently, a system of converging currents; the cylinder-axis a flow of parallel currents, and the terminal nerve arborization a source or beam of diverging currents [20].

Cajal had obtained very relevant data from comparative anatomy. In some invertebrates, such as worms and crustaceans, the dendrites—receivers of currents—join the axon directly through peripheral expansion. It is not to be understood, thus, that with protoplasmic prolongations the current is *always cellulipete*—since occasionally it does not traverse the cellular body—nor *universally cellulifuge* in the cylinder-axis, for the same reason.



He soon substantiates, however, that such a structural disposition exists also in the rachidial ganglia of many vertebrates, with the result that, beyond all doubt, the new claim in which he wishes to summarize the polarization law may be accepted as a general principle. Both from the philogenetic point of view and the ontogenetic, monopolarity seems to be truly a functional victory. Cajal is persuaded that evolution and development advance from bipolarity to monopolarity. It expresses nature's tendency towards economy regarding time, material and space. In the reformulated hypothesis it is clear that the necessity of passage of the *axipete* excitation through the soma is excluded. The tendency to monopolarity constitutes an ingenious disposition which considerably abbreviates conduction time of sensitive stimulation, as it makes straight a route which in previous states of philogeny or development was winding [21].



RACHIDIAL GANGLIA

For Cajal, it is beyond all doubt that when a physiological principle—such as the one he proposes—is not only borne out by available experience, but also suggests rules applicable to new phenomena, it is then a hypothesis whose degree of legitimacy increases considerably. This is what occurs with the dynamic polarization hypothesis, once purged of the error which made intervention of the cellular body necessary for the transmission of all currents provided by the dendrite prolongations. The hypothesis helps, certainly, to explain many singular morphological facts which had not

been possible to interpret properly. It justifies why in crosier cells the functional expansion originates in the higher part of a protoplasmic prolongation, or it proves the same fact in the cerebellum grains and in many cerebral corpuscles. The reason is always the same in Cajal's opinion: it originates in the value which the *economy of protoplasm*, *material*, possesses "of a useless route, either of the axis, its terminal branches, or of the dendrite expansions [22]." To the claims regarding economy of time and material, yet another may be added: the *saving of space*: "the law of saving—he maintains—regulates also the disposition and direction of the protoplasmic expansions, which always go as straight as possible towards the terminal arborizations with which they must maintain a relation [23]."

The 1897 article ends with two questions which the author leaves unanswered, both of great interest to understand the conceptual and theoretical context within which he works. Cajal situates both on a philogenetic horizon, making organic forms dependent on evolution. However, his words seem to suggest that he is not leaving cellular microanatomy exclusively in the hands of natural selection. Perhaps the principles which keep the energies traversing the neurons in balance cooperate with it:

> ¿Could the aforementioned imbalances of tensions have brought about, acting over long periods of philogenic evolution, all those dispositions which we see in neurons with regard to the emergence and advance of the axon? In a word, might not cellular morphology and the very laws regulating it be mere results of protoplasmic dynamism, something akin to effects of the balance of the energies circulating around nerve cells [24]?

CONCLUSIONS

Starting from the overview set out here, I believe it is possible to establish a series of conclusions summarizing the origin, character and scope of the research carried out by Ramón y Cajal, between 1888 and 1897, on nerve activity.

1. The road to the definitive dynamic polarization hypothesis touched on three stages which correspond with the three articles whose content I have synthesized. In the first, although Cajal denies the trophic function of the dendrites and the axon, he is unable to postulate physiological differences attributable to each type of prolongation. The 1891 paper includes two new ideas of great relevance: a) the presence of the cylinder-axis as a constant morphological element within the nerve cell, which Cajal dares to generalize after his brother Pedro's research on the existence of axon in the retinial cells of vertebrates, and b) the first version of the law, which assigns to what he calls the *nerve movement* an invariable trajectory, that goes from the protoplasmic branches to the cellular body and from here to the nerve expansion. However, it is a formulation he must correct,

since between 1891 and 1897 he has succeeded in verifying that the passage of the nerve impulse through the soma does not constitute a universal fact; on occasions, the cellular body moves away from the axon and may even proceed from a dendrite expansion. It is expressed thus in the "Laws of morphology and dynamism of nerve cells."

2. The work carried out by Cajal, up to when he provided neurophysiology with the nucleus of a research program that would prove enormously fertile, amounted to a process of trial and error in which both *empirical* and *conceptual* problems were evaluated. The discussion with von Gerlach, Golgi, Meynert or van Gehuchten was restricted to criteria of validation dependent on the methodological conceptions and theoretical assumptions which were active at that time. One may speak therefore of a rationalizing reference framework, within which the evidence provided and the echo caused by this evidence take on their role. If we understand the theory of the neuron in a morphological-dynamic sense, it must be admitted that to arrive at it demanded a labor of adjustment between theoretical expectations, observation and hypothesis which lasted over ten years; that it was subjected to scrutiny by the existing patterns of scientific rationality and that it was judged, also, for the capacity it showed to connect with the basic principles included in the cytology of the end of the nineteenth century. The conceptual make-up of the dynamic polarization law shows traits, in short, that would allow it to be interpreted as the nucleus of a Lakatosian program emerging from the heart of neurohistology, but which is clearly connected to a vaster program depending on cellular theory. As I explained elsewhere some time ago, the consolidation of cytology as a scientific discipline needs to be interpreted also from Lakatos's methodological model, and proves unintelligible from a Kuhnian perspective [25]. Nevertheless, Laudan's distinction between the empirical problems and conceptual problems that face research traditions becomes inevitable in this episode in the history of science [26].

3. The theory of the neuron, presented in the 1888 papers [27], resolved a basic conceptual problem: that of the perfect homogeneity of the notion of *cell*, threatened until then by the alleged singular nature of the *substance* or *nerve tissue*. Since the mesh hypothesis, it was very difficult to understand the way in which the selective routes of the nerve action were established. Cajal showed that the neuron, like the other tissue units, possessed morphological limits; was a differentiated histological entity that established transmission contacts with other neurons. Once the microanatomical structure of the nerve cell had been settled, it was necessary to determine its function and how this was fulfilled. In other words: the neuron concept did not yet possess all the theoretical weight which was to turn it into a concept generating functional explanations. The principle of polarization defined the nexus between the cellular form and its func-

tion: it gave neurophysiology a theoretical term—*neuron*—which was a vehicle of both anatomical and dynamic notes. As is often the case, the concept was *constructed* in a complex dialogue with the observations, the methodological assumptions, the tacit theoretical assumptions and the categorial expectations it needed to meet. The apparent non-existence of axons in certain cellular formations represented another conceptual problem, in which solution the work of Pedro Ramón y Cajal was crucial in order to arrive at the unified law on the transmission of the nerve impulse. Besides all of this, the defense in the 1897 paper, of the *laws* relating to economy of material, time and space highlights Cajal's great preoccupation to achieve a wide theoretical coverage for the polarization principle. Indeed, they constituted postulates which lent clear conceptual strength as they were connected with philogenic or developmental facts, at a time when the laws of recapitulation were very much taken into account. In fact, the term *neuron* was drafted with basic notions from cytology, histology, descriptive anatomy, comparative anatomy, physiology, embryology, the theory of evolution and even with the propagation of electrical currents model, to which the Aragonese scientist alluded when he referred to transmission of the *nerve impulse*. In another respect, Cajal's work illustrates well the idea that morphology and physiology are two complementary fields of research, which have reciprocal heuristic value and clarify each other. If it is true that anatomical architecture tells about the possible potential activities, and no less true that the physiological dynamic makes the structural organization and its teleonomic efficiency intelligible. In fact, the specific orientation and direction of nerve activity either in sensitive vias or in motor vias, added data of value—as Cajal himself admits—for an interpretation of the way in which the nerve cells appeared connected and the role played by the dendrites and the cylinder-axis. In short, the dynamic polarization law could claim credit for a high rate of conceptual problem resolution which justifies its relatively rapid acceptance.

4. The language employed in Cajal's three articles might seem to hint at an epistemological position inclined towards positivism. I believe, however, that such an assessment would be excessive, lacking in nuance and probably even false. On the one hand, Ramón y Cajal evinces from his youth a conscious and explicit rejection towards metaphysical systems. So explicit that at times he gave voice to it expressly in an article [28]. On the other, his stalwart defense of observation and the lessons to be learnt from it ought to be understood as appropriate for an ingenuous empiricist, an enemy of hypotheses and an even greater enemy of the capacity of scientific terms to achieve mastery of the essential constitution of natural or biological entities. With regard to this issue, I think the following considerations are essential. Like other relevant scientific figures of the

time—Claude Bernard would be a prominent example—Cajal rules out the possibility of a scientific theory becoming a metaphysical system or the pretext for uncontrolled speculation without observational backing. However, not only does he trust the validity or consistency of the cellular theory and the theory of the neuron; he also understands them as vehicles of a knowledge which pierces the authentic constitution of living beings. The dynamic polarization law acts within a parallel epistemological anchor. Its explanatory capacity is linked to the form of the neuron and its topological articulation with the adjacent neurons, that is to say, it is tied to a tacit acceptance of the aptitude inherent to spatial realism so as to provide vias of intelligibility which put us in contact with the real organization of physiological processes. Such a dependence on the geometrical order is evident, in addition, in the specific functional schemas for the sensitive routes and motors of nerve action, both subject to a realistic evaluation of spatial orientation. I think, therefore, that Cajal maintains a firm commitment to scientific realism, without implying an essentialist adherence of a metaphysical nature: his scientific work rests upon the ontological rooting of the theoretical terms he works with, although this is not to be confused with a the intention to construct with them an ontology of life.

5. In the methodological terrain, the commentary regarding the assumptions admitted, the principles expressed and the real scientific practice must be even more detailed. Despite frequent calls for attentive observations at the outset of scientific work, Cajal shows himself at times as a lucid defender of the basic mission of hypotheses in research, while at other moments he slips unconsciously towards ingenuous inductivism. On December the fifth of the same year in which he published the last of the articles we have analyzed (1897), he delivers his inaugural address to the *Academia de Ciencias Exactas, Físicas y Naturales* [29]. He states here:

> Having observed the facts, one must observe their significance, as well as the relations that link the new truth to totality of Science's postulates. In the presence of a strange phenomenon, the first movement of the mind is to imagine a hypothesis which will explain and subordinate it to one of the known laws. Experience will decide subsequently on the credibility of the conception.
>
> Meditating on the nature of good hypotheses, he realizes that most of them represent happy generalizations or risky inductions, in whose virtue the recently discovered fact is considered provisionally as a particular case of a general principle or as an unknown effect of a known cause...
>
> To create the hypothesis we must take the following rules into account:
>
> 1. the hypothesis must be obligatory, that is, that without it there is no discretion to explain the phenomena;
> 2. it must be, besides, possible to check or test ...;

> 3. it must be easily imaginable, that is, translatable into the language of physics-chemistry...;
> 4. fleeing from hidden properties and metaphysical essences, it must tend to resolve issues of quality in problems of quantity;
> 5. it must suggest, if possible, [...] new and happier conceptions ...
> And, at all events, the explanation rejected as false will always have one advantage: it restricts, by exclusion, the field of the imaginable, by eliminating unacceptable solutions and causes of error [30].

The fragment is, no doubt, of inestimable value. Cajal moves away from any position that might be confused with the attempt to establish an ontology of life, as I said above. A reader and deeply knowledgeable of Bernard's methodological theses [31], he shares with him: the assignation of a decisive role to hypotheses, to the possibility of falsifying them, to their formulation in the clarifying setting of the language of physics-chemistry, to their explanatory capacity and, finally, to their guiding power. Claude Bernard was never the positivist that some physiology historians have wished to portray [32], and Ramón y Cajal—although his way of expressing himself might cause misunderstandings—was even less so. May the following blunt words, taken again from the paper where his methodological convictions are expressly synthesized, serve as a sample:

> Claudio Bernard seems to us to exaggerate somewhat when, by way of providing examples to support his theses, claims that "we shall never know why opium has a soporific effect, or why from the combination of hydrogen and oxygen a body springs so diverse in physical and chemical properties as water." This impossibility of reducing the properties of bodies to laws of position, form and movement of atoms (today we would say ions and electrons) is real, but it does not seem to be so in principle and forever [33].

Assuming a position which again may well be interpreted from a Laudanian perspective, the University of Barcelona professor defends the explanatory scope—and not merely descriptive—of the physiological laws, draws the theoretical boundaries which they must respect—the physical-chemical—and, most important, is sure of being able to link them with the *basic entities* which associate with the theoretical terms of the *tradition* in which he works: the *cell* and its *organelles, molecules*, *atoms* and even *ions* and *electrons*. Nobody was as aware as he was of the interdependency of the aforementioned *basic entities* and the *methodological requirements* that they imposed—from coloring techniques to the future support of much more powerful microscopes.

The conduct of hypotheses as research guides is recognizable, then, in many places in his writings. We discover a Cajal who stresses the guiding function of theories and points out the preponderance of these in the

theory-experience relation. His attention—summarized above—to conceptual problems and to the links neurohistology should forge with cytology, microanatomy, embryology, general physiology or the theory of evolution seem to indicate that he was conscious that science's future direction is not settled only in the sphere of observation, established phenomena and induction. However, there is no lack of fragments where the role of experiment is hypostasized, the possibility of well-established generalizations is given as certain, and it is claimed that facts may become *fixed* definitively. The permanent double attention to descriptive anatomy and comparative anatomy, on the one hand, and neurophysiology, on the other, explains this interesting ambivalence. Indeed, Cajal supposes that fertile hypotheses are those that mark the route to observation, but he is incapable of perceiving that theories or theoretical expectations enter our interpretation of experience, or in the articulation of experimental designs and the evaluation of the findings:

> Before the phenomena that march around the sensory organs, the activity of the intellect may only be truly useful and fecund by modestly shrinking so as to observe them, describe them, compare them and classify them, according to their analogies and differences, in order to arrive subsequently, by induction, at the knowledge of their determining conditions and empirical laws [34].

> ... there they are, immutable and defying well-observed facts of anatomy and physiology, chemistry and geology... "Give me a fact—said Carlyle—and I shall bow down before it [35]".

The dynamic polarization law depended, it is true, on well-established facts. It demanded advances in microscopic observation which were essential to define the general structure of the neuron and, especially, the permanent presence of the cylinder-axis. Observation triggered, in addition, the discovery that *nerve currents* did not always traverse the soma, since in monopolar neurons the nerve impulse reached the axon from the dendrites. They were morphological data which defined the framework of the possible plausible physiological hypotheses. Cajal had to pay heed, naturally, to such facts and assign therefore a primary function to experience. Even so, he was not aware that his observations made sense or that they made up as such the complex framework of the optical laws implied in microscopy, coloring techniques, the principles of cytology already admitted, the concepts of comparative anatomy or the interpretative program of philogeny linked to the hypothesis of natural selection. His new neurophysiological law could be formulated by the concurrence of detailed observations and hypotheses with growing explanatory capacity. It is not strange, therefore, that in the 1897 address he hesitates on assessing the leading role which induction and the formulation of conjectures

merit in scientific research. It is obvious, at any rate, that he trusts in the possibility of reaching the naked facts, of an uncontaminated experience, capable of acting as unappealable judge in the validation of scientific knowledge.

6. Cajal's double attitude shows, besides, a relevant aspect of the options at stake within science methodology. The nineteenth century was one of continual debate between inductivists and deductivists; in Great Britain, for example, was thoroughly developed in the writings of Whewell, Herschel and Mill [36]. Throughout *Reglas y consejos sobre la investigación científica* (*Rules and Advice Concerning Scientific Research*), Cajal quotes often from Descartes, Bacon, Comte, Bernard or Mach, among many other writers who had defended precise methodological conceptions. What seems to me most noteworthy, however, is that the Spanish scientist depends for his standpoints with respect to the *method*—more than on any national tradition or faithfulness to distinguished names within the disciplines he cultivates—on the demands imposed by the basic entities and fundamental processes on which he is working: descriptive microanatomy invites him to meticulous observation and generalization; neurophysiology leads him to the formulation of hypotheses and experimental verification. It is, as I have suggested, a theory-experience interaction where scientific realism, as a background epistemological posture, enables well-known methodological consequences to be established for the basic ontology from which the scientist views the world.

I believe, in conclusion, as I have already said, that the structure and the dynamic proposed by Larry Laudan for the traditions of scientific research are corroborated in some of their most specific features by the mode in which Ramón y Cajal's contribution to histology came about.

NOTES

1 With reference to the years spent by Cajal in Valencia, besides from his autobiography, I use the data and the careful narration of events which Francisco Vera Sempere carried out in "Cajal, catedrático de Anatomía en Valencia", *Rev. Esp. Patol.*, 35(2002), 395-408. I have also made use of José M. López Piñero's splendid introduction to *Cajal* (Barcelona, Península, 1986, pp. 5-59).

2 Vera Sempere, F.: *l.c.*, p. 398.

3 Ramón y Cajal, S.: *Manual de Histología Normal y Técnica Micrográfica*, Valencia, Librería de Pascual Aguilar , 1884 -1888.

4 Cfr. Vera Sempere, F.: *l.c.*, p. 400.

5 Cfr. López Piñero, J.M.: *o.c.*, pp. 7-8.

6 Ramón y Cajal, S.: "Estructura de los centros nerviosos de las aves", *Revista Trimestral de Histología Normal y Patológica* 1(1888), 1-10; "Estructura del cerebelo", *Gaceta Medica Catalana*, Tomo XI, Nº 15, 15 August 1888.

7 Golgi, C.: *Sulla fina anatomia degli organi centrali del sistema nervoso*, Reggio, Tip. di Stefano Calderini e figlio, 1884 (Milan, 1885, 1886).

8 Cfr. Ramón Y Cajal, S.: *Recuerdos de mi vida: Historia de mi labor científica*, Madrid, Alianza, 3ª edición, 1981, p. 68.

9 "Significación fisiológica de las expansiones protoplasmáticas y nerviosas de las células de la sustancia gris," Report read at the First Regional Medical-Pharmaceutical Congress in Valencia (Session of 24 June 1891). The paper was published the same year in Barcelona by the printer's "La Academia", which was owned by the Widow and Sons of E. Ullastres. This is the edition I have used and which I will quote from as SFEP. Three years later, the Report was published by the printer's Domenech de Valencia within the minutes of the Congress (pp. 70-85). The second article, "Laws of morphology and dynamism of nerve cells," appeared in the first number of (March 1897) of the *Revista Trimestral Micrográfica*. I shall refer to it heretofore as LMDCN. Nevertheless, as is reflected in the claims in which he summarised his theory of the neuron—reproduced above—in 1888 Ramón y Cajal had already begun to propose hypotheses on the functional value of dendrites; attempts which took even more solid form in a 1889 study, "General connection of nerve elements", which appeared on 2 October in *La Medicina Práctica*. I have consulted it in the reprint for the *Trabajos Escogidos* (*Selected Works*) (Tomo I, Madrid, Jiménez Molina, 1924, pp. 479-487), and which I will refer to as CGEN.

10 LMDCN, pp. 1-2.

11 Cfr. CGEN, pp. 484-485.

12 CGEN, p. 480.

13 Ramón Y Cajal, P.: *Memoria leída ante el Claustro de la Facultad de Medicina de la Universidad Central en el Solemne Acto de Graduarse de Doctor por el Licenciado D. Pedro Ramón y Cajal, Director de trabajos anatómicos en la Facultad de Medicina de la Universidad de Zaragoza,* Madrid, Imprenta Colonial, 1890. Pedro Ramón y Cajal refers, indeed, in his Report, to the invariable existence of nerve ramification in the neurons of the retina and holds with the theory advanced a year previously by his brother Santiago with respect to the function of dendrites: "...we shall say that the retinas of mammals, birds, saurians, batrachians, fish, etc., offer a notable structural accord... We may conceive protoplasmic ramifications as the relation organs of the nerve cells. These ramified appendices gather the energies transmitted now by the nearby corpuscles (synergic transmission), now that brought about by the conduc-

ting fibres". Moreover it offers each nerve corpuscle a filament or cylinder-axis, the conductive via of its specific activity. (*L.c.*, pp. 41-43).

14 SFEP, pp. 1-3.

15 SFEP, p. 6.

16 SFEP, p. 15.

17 Initially, Van Gehuchten had opposed the physiological schema conceived of by Cajal: "It seems to us difficult to admit Cajal's hypothesis, although very ingenious, according to which the peripheral prolongation of the sensitive ganglial cells would be a protoplasmic prolongation, while the central expansion would represent a true axon. Ramón y Cajal arrived at this hypothesis by comparing, for example, the bipolar elements of the olfactory mucous with the elements of the spinal ganglia. The idea of considering the peripheral prolongation as protoplasmic is ingenious in the sense that it easily a functional difference between protoplasmic and nerve expansions. The protoplasmic prolongations would have *cellulipete* conduction and would serve to transmit to the cellular body the nerve commotions coming from the neighbouring elements; while the cylinder-axis would offer *cellulifuge* conduction, destined to put the nerve element from which it comes in relation with the others. But to admit this hypothesis it would be necessary to completely modify the idea we have of the protoplasmic prolongations, and admit that one of these prolongations may become the cylinder-axis of a nerve corpuscle, which seems to us difficult to accept" (Gehuchten, A. van.: "La moelle epinière et le cervelet", *La Cellule*, 7(1891), quoted in Ramón y Cajal, S.: *Recuerdos de mi vida. Historia de mi labor científica*., Madrid, Alianza, pp. 117-118). However, the Belgian scientist modifies his opinion in a very short time, and comes out in favour of the polarization law in a 1892 article: "Nouvelles recherches sur les ganglions cérébro-spinaux", *La Cellule*, t. VII, fasc. 2.

18 Cfr. LMDCN, pp. 1-2.

19 *Ibid.*

20 *Ibid.*

21 Cfr. LMDCN, p. 4.

22 LMDCN, p. 15.

23 LMDCN, p. 19.

24 LMDCN, p. 25.

25 Cfr. González Recio, J.L.: "Elementos dinámicos de la teoría celular", *Revista de Filosofía*, 8(1990), 83-109. También: González Recio, J.L.: "El racionalismo crítico y la reconstrucción racional de la historia de la citología". Minutes of the *Congreso Filosófico Internacional Karl Popper*: *Vigencia y Transformación de su Pensamiento*. Facultad de Humanidades y Artes (UNR) Rosario, Argentina, 3-5 June 2004.

26 Cfr. Laudan, L.: *Progress and Its Problem. Towards a Theory of Ccientific Growth*, Berkeley, University of California Press, 1977. The first three chapters are of special interest.

27 See note 1.

28 Ramón Y Cajal, S.: "Los actos reflejos y la filosofía del inconsciente", *La Clínica*, 201(1881), 265-267.

29 I quote from the twelfth edition of the text, published by Espasa Calpe (*Reglas y consejos sobre investigación científica. Los tónicos de la voluntad.* Madrid, Espasa Calpe, 1991). The work was reprinted in 2005 in an edition by Leoncio López-Ocón (*Los tónicos de la voluntad. Reglas y consejos sobre investigación científica.* Madrid, Gadir Editorial, 2005).

30 *O.c.*, pp. 127-128.
31 Cfr. *O.c.*, p. 24.
32 Cfr. González Recio, J.L.: "Who killed histological positivism? An approach to Claude Bernard's epistemology", *Ludus Vitalis*, 22 (2004), 61-82.
33 *Reglas y consejos sobre investigación científica. Los tónicos de la voluntad.* Madrid, Espasa Calpe, 1991, p. 24.
34 *Ibid.*
35 *O.c.*, p. 101.
36 Cfr. Whewell, W.: *History of the inductive sciences*, Londres, Frank Cass, 1967; Herschel, J.F.W.: *A preliminary discourse on the study of natural philosophy*, Chicago-Londres, The University of Chicago Press, 1987; MILL, J. S.: *A system of logic ratiocinative and inductive : being a connected view of the principles of evidence and the methods of scientific investigation*, Londres, Longman, 1970.

BIBLIOGRAPHY

Albarracín, A. (1983), *La teoría celular*, Madrid: Alianza.
Castro, F. de (1981), *Cajal y la escuela neurológica española*, Madrid: Editorial Complutense.
Golgi, C. (1884), *Sulla fina anatomia degli organi centrali del sistema nervoso*, Reggio: Tip. di Stefano Calderini e figlio.
González Recio, J.L. (1990), "Elementos dinámicos de la teoría celular", *Revista de Filosofía* 8: 83-109.
González Recio, J.L. (1992), "Anotaciones epistemológicas a la teoría celular", *Uroboros. Revista Internacional de Filosofía de la Biología* I (2): 67-84.
González Recio, J.L. (2004), "El racionalismo crítico y la reconstrucción racional de la historia de la citología". *Actas del Congreso Filosófico Internacional Karl Popper: Vigencia y Transformación de su Pensamiento*. Facultad de Humanidades y Artes (UNR) Rosario, Argentina, 3-5 June 2004.
González Recio, J.L. (2004), "Who killed histological positivism? An approach to Claude Bernard's epistemology", *Ludus Vitalis* XII (22): 61-82.
González Recio, J.L.(2004),"El acto reflejo y la recusación de la metafísica. Reflexiones sobre la epistemología del joven Ramón y Cajal", *Revista de Historia de la Psicología* 25 (4): 13-22.
González Recio, J.L. (2004), *Teorías de la vida*, Madrid: Síntesis.
Herschel, J.F.W. (1987), *A Preliminary Discourse on the Study of Natural Philosophy*, Chicago-Londres: The University of Chicago Press.
Laín Entralgo, P. (1949), *Dos biólogos: Claudio Bernard y Ramón y Cajal*, Buenos Aires: Espasa-Calpe.
Laudan, L. (1977), *Progress and Its Problems. Towards a Theory of Scientific Growth*, Berkeley: University of California Press.
López Piñero, J.M. (1986), *Cajal*. Madrid: Península.
Mill, J. S. (1970), *A System of Ratiocinative and Inductive Logic: Being a Connected View of the Principles of Evidence and the Methods of Scientific Investigation*, Londres, Longman.
Ramón y Cajal, P. (1890), *Memoria leída ante el Claustro de la Facultad de Medicina de la Universidad Central en el Solemne Acto de Graduarse de Doctor por el Licenciado D. Pedro Ramón y Cajal, Director de trabajos anatómicos en la Facultad de Medicina de la Universidad de Zaragoza*, Madrid: Imprenta Colonial.
Ramón y Cajal, S. (1881), "Los actos reflejos y la filosofía del inconsciente", *La Clínica* 201: 265-267.
Ramón y Cajal, S. (2001), *Discurso de doctorado y trabajos de juventud*. Edición a cargo de Ángel Merchán, Madrid: Universidad Europea CEES.
Ramón y Cajal, S. (1888), "Estructura de los centros nerviosos de las aves", *Revista Trimestral de Histología Normal y Patológica* 1: 1-10.
Ramón y Cajal, S. (1888), "Estructura del cerebelo", *Gaceta Medica Catalana* XI (15), 15 August 1888.
Ramón y Cajal, S. (1924), "Conexión general de los elementos nerviosos", en *Tratados Escogidos*, Tomo I, Madrid: Jiménez y Molina, pp. 479-487.
Ramón y Cajal, S. (1891), *Significación fisiológica de las expansiones protoplasmáticas y nerviosas de las células de la sustancia gris*, Barcelona: La Academia.
Ramón y Cajal, S. (1897), "Leyes de la morfología y dinamismo de las células nerviosas", *Revista Trimestral Micrográfica* 1: 1-25.
Ramón y Cajal, S. (1981), *Recuerdos de mi vida: Historia de mi labor científica*, Madrid: Alianza, 3a edición.
Vera, F. (2002), "Cajal, catedrático de anatomía en Valencia (1884-1887)", *Rev. Esp. Patol.* 35: 395-408.
Whewell, W. (1967), *History of the Inductive Sciences, London: Frank Cass.*