“Anatomical mechanism of consciousness: Astroglia, amoeboidism and the theory of neuronal avalanche in the cortex of the cerebral hemispheres.”

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«Ανατομικός μηχανισμός της συνείδησης: Αστρογλοία, αμοιβαδοειδισμός και η υπόθεση της χιονοστιβάδας της νευρικής αγωγής στον φλοιό των εγκεφαλικών ημισφαιρίων»

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Abstract

The purpose of this thesis is two-fold: firstly, to preserve, in updated English translations, two theoretical papers written by Santiago Ramón y Cajal (1852–1934) in 1895 and 1896 under the titles, “Conjectures on the anatomical mechanism of ideation, association and attention” and “Conjectural interpretations of certain points in neurological histophysiology”; and secondly, to set some of the ideas proposed by Cajal in a modern perspective. In his “Conjectures,” Cajal ventured to explain the mechanisms of perception, association and attention in cellular terms. He introduced the term “impression unit,” which would propagate, leading to conscious act via an “avalanche of conduction.” Additionally, he attributed mental repose and sleep to morphological variations of neuroglia; at times of relaxation, astrocytes would grow appendices that penetrated among nerve cell connections and blocked the conduction of the “nervous current”; in energetic contraction, such glial “pseudopodia” would shrink, allowing neuronal processes to come into contact again. In the sequel to the “Conjectures,” Cajal presented strong arguments defending the neuron theory against the reticular theory. Moreover, he discussed the functional differentiation of spinal motor neurons and cortical pyramidal cells, which respectivly subserve movement and consciousness, despite their morphological similarity.

Keywords:

Neuron theory

Cerebral cortex

Neuronal amoeboidism

Glial amoeboidism

Santiago Ramón y Cajal (1852–1934)

Pedro López-Peláez y Villegas (1863–1903)

Σύνοψη

Ο σκοπός αυτής της διπλωματικής είναι διττός: Πρώτον, να διατηρηθούν, σε ενημερωμένες αγγλικές μεταφράσεις, δύο θεωρητικές εργασίες του Santiago Ramón y Cajal το 1895 και το 1896 αντίστοιχα, υπό τους τίτλους: “Conjectures on the anatomical mechanism of ideation, association and attention”, και, “Conjectural interpretations of certain points in neurological histophysiology”, και, δεύτερον, να τεθούν ορισμένες από τις ιδέες που πρότεινε ο Cajal σε μια σύγχρονη Νευροεπιστημονική προοπτική.
Στις “Conjectures” του, ο Cajal, προσπάθησε να περιγράψει τον μηχανισμό της αντίληψης, του συσχετισμού των ιδεών και της προσοχής, εισάγοντας τον όρο "μονάδα εντυπώσεων" (“impression unit”) που θεώρησε πως διαδίδεται στον εγκέφαλο ως "χιονοστιβάδα αγωγιμότητας" (“avalanche of conduction”). Επιπλέον, πρότεινε ότι η διανοητική ανάπαυση και ο ύπνος, με φυσικές ή τεχνικές μεθόδους, οφείλονται στις μορφολογικές παραλλαγές της νευρογλοίας. Πιο συγκεκριμένα ότι, σε περιόδους χαλάρωσης, αναπτύσσονται αποφυάδες που διεισδύουν στις νευρωνικές συνδέσεις και εμποδίζουν την αγωγή του «νευρικού ρεύματος», ενώ σε περιόδους ενεργητικής συστολής, τα ψευδοπόδια συρρικνώνονται επιτρέποντας να έλθουν σε επαφή οι νευρωνικές αποφυάδες.
Σε μια συνέχεια των ”Conjectures”, ο Cajal παρουσίασε ισχυρά επιχειρήματα για την υπεράσπιση της νευρωνικής θεωρίας ενάντια στην δικτυακή επηρεάζοντας μεταγενέστερους αλλά και σύγχρονους ερευνητές. Επιπλέον, συζήτησε τη λειτουργική διαφοροποίηση των κινητικών νευρώνων του νωτιαίου μυελού και των φλοιικών πυραμιδοειδών κυττάρων, τα οποία αντίστοιχα υποστηρίζουν τους μηχανισμούς της κίνησης και της συνείδησης παρά την μορφολογική τους ομοιότητα.

Λέξεις-Κλειδιά:

Νευρωνική θεωρία

Φλοιός των εγκεφαλικών ημισφαιρίων

Νευρωνικός αμοιβαδοειδισμός

Γλοιακός αμοιβαδοειδισμός

Santiago Ramón y Cajal (1852–1934)

Pedro López-Peláez y Villegas (1863–1903)

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Contents

1. Introduction

Santiago Ramón y Cajal (1852–1934) began his scientific career by studying the pathogenesis of inflammation for his doctoral thesis. He continued by focusing on the microbiology of cholera, and cellular structure in general. His early contributions remained unknown because of Spain's relative isolation from the remaining of continental Europe at the time. Nevertheless, his ingenious studies on the nervous system were meant to shape the future of Neuroscience.

During his years in Valencia, from 1884 to 1887, enchanted by the experiments of Jean-Martin Charcot (1825–1893), Ambroise-Auguste Liébeault (1823–1904), Hippolyte Bernheim (1840–1919) and Henri-Étienne Beaunis (1830–1921) on hypnotic suggestion, Cajal decided to devote some of his time to explore the potential of hypnosis, both as a therapeutic method and as a tool for altering consciousness in healthy individuals. The preoccupation with hypnosis became a source of enjoyment and relaxation: "The artistic and philosophical sulci of my brain were also employed … In the guise of relaxing agents for neurons in danger of hardening from disuse, I developed two kinds of amusements: picture-taking excursions, and the experimental study of hypnotism" (Cajal, 1988). Cajal organized a "Committee for Psychological Research" and his domicile was soon "streamed by the most remarkable kinds of hysterics, neurasthenics, maniacs and even accredited spiritualistic mediums."

In the summer of 1889, Cajal published "Pains of labor considerably attenuated by hypnotic suggestion" (Cajal, 1889), a case study that may carry more interest for neuroanatomists and neuroscience historians studying the spectrum of his diverse career, rather than a landmark contribution to the evolution of psychiatry (Stefanidou et al., 2007). Incidentally, that was also the year when the Swiss neuroanatomist and psychiatrist Auguste Forel (1848–1931) published his book on "Hypnotism, Its Meaning and Application" (Forel, 1889). Cajal was surprised by the effects of hypnosis on healthy individuals, and further observed the outset of cataplexy, analgesia, hemorrhages, hallucinations, amnesia, and the abolition of free will. He completed his experimentation with hypnosis and abandoned what might have been a lucrative practice, just before moving to Barcelona: "Having satisfied my curiosity, I dismissed my patients" (Cajal, 1988).

With great clinical intuition, Cajal (Fig. 1) continued to explore the inner mechanisms of mental acts in his pursuit of an integrative psychology (Marijuán, 2001; Nieto, 2009). Seven years after evolving his key code of the principles that govern the morphology and connections of the nervous system, and six years after publishing his paper on hypnotic suggestion, Cajal, constantly driven by a desire to combine his morphological discoveries with their functional implications (Sotelo, 2003), attempted to explain the cellular processes that may alter consciousness and form the basis of hypnotic phenomena. Thus, he put together two theoretical constructs, the "Conjectures on the

anatomical mechanism of ideation, association and attention" (Cajal, 1895a), and the "Conjectural interpretations of certain points in neurological histophysiology" (Cajal, 1896).

In 1895 Cajal was Professor of Histology in the Faculty of Medicine of the University of Madrid. The first of these papers (Fig. 2) was deemed of such interest that a German version appeared in the scientific press as well, with the author's consent (Cajal, 1895b). Commenting on the German version of "Conjectures" (Cajal, 1895b), the psychiatrist and comparative neuroanatomist Theodor Ziehen (1862–1950), then working in Jena (where he attended Nietzsche among his other patients), summarized the main points and praised Cajal for acknowledging the totally hypothetical nature of the essay (Ziehen, 1897).

The "Conjectures" were favorably enfolded by psychologists: "The Spaniard of Barcelona, of such world-wide reputation, has with perfect right ventured over the line of strict anatomy into the provinces of psychology. The invasion is a welcome one. Such scientific incursions are like that of the spies into Canaan — they bring back rich and exceedingly good fruit" (Allin, 1896). G. Stanley Hall (1846–1924) of Clark University in Massachusetts earmarked Cajal's hypothetical retraction and relaxation of perivascular neuroglia in the cerebral cortex, their isolating properties and the regulation of capillary contraction and blood flow as underlying physical bases of mind associations, the imperative rapidity of words or thought, stagnation and forgetfulness, the monoideistic concentration of attention, vehement action, fatigue, confusion, and other mental acts (Hall, 1897).

In a remarkable convergence, 1895 was the year that also saw the light of Sigmund Freud's "Project for a Scientific Psychology" (Freud, 1966). Thus, the two eminent physicians independently conceived hypotheses on the biology of the mind (Triarhou and del Cerro, 1985).

The English translations of Cajal's two complete texts that follow are revised and improved versions of those included in the book on the writings of Cajal on psychology, art, and education (Triarhou, 2015; Walusinski, 2017). The text has been annotated with modern terminology. For example, the word "axon" is used in place of Cajal's "nervous arborization," and the word "dendrite" in place of "protoplasmic appendage."

2. Conjectures on the anatomical mechanism of ideation, association and attention [1895], by S. Ramón y Cajal (English translation)

2.1. Is each perception subserved by one or by multiple nerve cells?

Research in recent years on the structure of the nervous system revealed that there is a fixed chain of conductors or neurons between the sense organs and the nervous centers, whereby the impression gathered by a single sensory cell in the periphery is propagated toward the brain as an "avalanche of conduction" (*avalancha de conducción* in Spanish, *lawinenartige Leitung* in German), i.e., through an increasing number of cells.

Any reader needing more information about the anatomical facts on which I base my analysis should read my "New Ideas on the Structure of the Nervous System" (Cajal, 1894a), and my conference on the connections of nerve cells read before the Royal Society of London as "The Croonian Lecture" (Cajal, 1894b).

Let me cite some examples of this principle, already suspected by Golgi, but which was fully demonstrated only after the surprising results on the true nerve terminations in the cerebrospinal axis were obtained.

In the fovea centralis of the retina, where visual acuity is the highest, a cone struck by light leads its commotion to a bipolar cell; this cell then conducts it to a subjacent nerve cell (of the ganglion layer), whose functional process, neatly ramified in the superior colliculus, disseminates the motion over a large group of cells; ultimately, the axons of this cellular group terminate in the occipital region of the cerebral cortex, where, by their ramifications, they touch the terminal tufts of countless pyramidal cells. Thus, the "impression unit" (*unidad de impresión* in Spanish, *Eindruckseinheit* in German) gathered by a single cone has succeeded in influencing hundreds and perhaps thousands of nerve cells in a cortical center. (I define the "impression unit" as a simple motion gathered during the sensory impression by a single retinal cone or rod, or by a hair cell of the cochlea. Therefore, each retinal image comprises as many impression units as the number of photoreceptor cells that are simultaneously excited).

The same explanation applies to the acoustic apparatus. One or two hair cells of the organ of Corti transmit the impression to an auditory nerve fiber (cell of the spiral ganglion of the cochlea), which in turn conducts it to the ventral acoustic ganglion of the medulla. There, thanks to a bifurcation (von Kölliker, Held, and others) and the emission of numerous collaterals, every acoustic root fiber propagates the motion to many nerve cells. Each of the conductors or axons of the cells of the ventral ganglion run up from the trapezoid body of the pontine tegmentum, thanks to their numerous collaterals, in a chain of conduction into a new series of adjacent neurons in the nucleus of the trapezoid body, the superior olive, the preolivary nucleus, the inferior colliculus, and so forth. Lastly, the excitation arrives at the cerebral cortex, where it presumably diffuses to a still larger group of pyramidal cells.

The avalanche of conduction in the olfactory apparatus, in sensory nerves, and so on, is also rather evident, and has been confirmed by several histologists who recently studied the structure of the olfactory bulb and the spinal cord (Golgi, Cajal, von Lenhossék, van Gehuchten, von Kölliker, Retzius, and others).

From what was exposed it follows that, for the scarce number of sensory cells that are stimulated, the excitation propagated to the cerebrum puts in commotion an extraordinary number of cortical pyramidal cells. Consequently, it is rational to infer that the sensation or perception is not the result of the work of a single nerve cell, but of many.

It is equally likely that the same cell group, generating in the physiological order a specific sense, is also responsible for the preservation, in a latent state, of this same perception; in other words, the same pleiad of cortical pyramidal cells involved in the perception of a sound or a visual image will also, under volitional solicitation, elaborate the recollection of such sensations.

The phenomenon of the avalanche of conduction described above, and the small number of sensory cells (cones of the fovea centralis, auditory cells, and so forth) that must collect all the numerous impressions to which our senses are

susceptible requires us to admit that each sensory cell, as well as each subordinate group of cerebral pyramidal cells, successively intervene in the production of distinct images. Beneath the anatomo-physiological aspect, a perception will be distinguished from other senses belonging to the same sensory order through the number and respective position of the cortical pyramidal groups which are put into motion.

Let me give an example: when, after looking at a luminous circle placed at a small enough distance such that its entire image is impressed on the fovea centralis and does not affect more than a circular line of cones, we examine under comparable circumstances a square or a hexagon of a size equal to the circle, it becomes evident that some cones will be activated by both images; others will not be activated by either, and some will receive the impression of only one of them. Therefore, I think, given of course the fixation of the afferent conducting apparatus, that the same variations would occur in the corresponding area of the cerebral cortex: groups of pyramidal cells that enter into commotion during the perception of the first image will repose in the second, and vice versa; whereas other cell groups will be excited in both perceptions.

From the above one may infer that the cortical sensory centers represent a true amplified or dilated projection of the receptive surfaces of the sensory organs, thereby positing the existence, as some authors have supposed, of a retina and an organ of Corti centrally. However, one must add that in the cerebral cortex each sensory cell is represented not by one, but by a group of pyramidal cells.

I also consider it likely that each group of pyramidal cells, which is anatomically connected to a sensory cell, maintains the various images, or “impression units,” that each cell has communicated at different times, in a latent state. Such latent images can be seen as discontinuous layers (spread over a large number of pyramidal cell groups) of a certain state of potential energy, which can be easily converted to actual energy, i.e., a very special vibration (the apperception or secondary perception), under the stimulus of the volition or at the mercy of other conditions.

However, not all sensory pyramidal cell groups retain such latent impressions effected by a few auditory or retinal cells, but only those which, by virtue of repetitive attention, reach the necessary level for registration. Therefore, attention operates as a selective mordant dye of the image, fixing and reinforcing the color at specific points. This explains why a remembered sensation is always different from that brought about by the corresponding sensory organ. In reality, the recollection represents a form of integration of these points of the image that are attended to with sufficient intensity; similarly to composite or family photographs, the memory only presents the essential features as most apparent, while many details remain vague, uncertain, and sometimes even totally obscured.

Another legitimate induction appears to be the supposition that many identical objects project their images on the fovea or excite other sensory nervous surfaces, thereby condensing their latent images in them or in very immediate groups of cerebral pyramidal cells. In relation to the auditory sensations, this supposition seems highly likely: the same note (ignoring the harmonics that follow other routes) must reside, as a memory concept, in the same path of cortical cells. For visual sensations, this supposition is, at first sight, somewhat risky, because the same object seen at different distances must necessarily impress different retinal cones and thus different groups of pyramidal cells. However, such a difficulty partially vanishes if we recall that, out of habit, we distinctly place each object that we want to see at the same distance and in the same position; thus, at each repetition of the impression, the same or the most proximal cones, and therefore the same pyramidal cell groups will be excited (recall that we instinctively place ourselves at a nearly constant distance from an object during the acts of reading, writing, looking at a picture, talking to a person, and so on).

If we accept this thought, we can conceive exactly why the repetition of the same perception under similar conditions leaves a deep and thorough memory; it comes from within the same pyramidal group as successive forces of attention accumulate to create the latent image. For the same reason, an object is poorly remembered or not remembered at all if it were only perceived once or without the ordinary conditions of a distinct perception.

It is also possible that the analogy that we subjectively establish between two representations is somatically linked to

the number of common pyramidal groups which intervene in its production; the dissimilarity would depend on the small number of cell groups common to two successive representations; thus, opposition would result from a total mismatch of the pyramidal groups engaged in each perception.

It is impossible to proceed further in my analysis of the mechanism of cerebral activity, were I to ignore the mental motion and the form by which a direct perception becomes latent in order to be converted into a memory. The issue is not less obscure and inaccessible when it is reduced to the histological process of association. I would only dare conjecture that the so-called associations of space, time, analogy and contrast (principles of Wundt) that correspond to the same order of sensations have as their substrate the connections established between nerve collaterals and the dendrites of cells residing in the same cerebral center, and where the Martinotti cells with the ascending axons and the multipolar cells of the first cortical layer may play an important role; the associations effected between images of a distinct sensory order (e.g., a gustatory apperception evoking a visual one, an auditory memory giving rise to an idea of form or color) would be driven by the so-called association and callosal cells of the cerebral hemispheres. Thanks to these cells, the groups of adjacent pyramidal cells in the visual centers would activate those belonging to the auditory, tactile and gustatory cortical areas, among others, thereby establishing a vast system of intercortical connections by virtue of which, from a first apperception, the entire complex registry of sensory memories could run.

2.2. Hypotheses on the histological mechanism of association, sleep and wakefulness

The impression on the sensory organ on its transmission to the cerebrum and its storage in specific groups of cells are fixed, necessary phenomena that we can neither suppress nor modify. As our eyes open and see, the image of the object is registered in the cerebrum. It is up to our volition to attend or not to such representations. However, given the anatomo-physiological conditions of the sensory execution, once initiated, the activation of all the neurons that come between the connection of a cone and a group of cerebral cells cannot be impeded. This fixation of the mechanism of the impression, the transmission and the perception of the sensory image forces us to widely accept the afferent chain of visual, auditory, sensory neurons, and so forth, as a fixed and invariable assembly.

This does not apply from the moment that the image has been recorded in the sensorium; at this point, the direct perception has been converted to a reflexive or secondary perception.

The arrival of the nervous motion at the cerebral cortex, even if it is of equal intensity and nature, does not inevitably follow the same route. According to Forel (1894), the energy of the afferent currents is often absorbed by the cerebrum, thereby being transformed into ideas, judgments, and volitions; although, in certain cases, they appear to be reflected almost entirely in the form of a motor reaction. With respect to the association of ideas, everyone knows that a primary visual perception, for example, leads to auditory images in certain cases, to gustatory representations in other cases, while in even further cases it may not provoke any secondary representation. On the other hand, the association process seldom follows the same order (for example, the order of analogy, coetaneity, space, and contrast), and the circle of the evoked ideas does not consistently achieve the same radius. Experience proves that speech occasionally becomes difficult, memory becomes clumsy, the association of certain senses quite impossible. At times, the laboriously sought idea suddenly emerges in the mind, as if the continuity of a broken conductor was restored or the obstacle which was impeding the contact between axonal branches and somata or dendrites was removed.

All this appears to indicate that the architecture of the sensory centers of the cerebrum, as well as the association pathways, are not absolutely fixed; there is perhaps a variable histological factor to which the infinite mutations of mental labor can be ascribed.

I am aware that such variations may be related, to a certain extent, to the inhibition of certain cerebral areas, to interference of the currents, to increases in the resistance of the conductors on the occasion of changes in the chemical

composition of the nerve fibers or the interstitial matrix. In other words, such variations may be related to mere physicochemical disarrays without a concomitant anatomical or histological modification of the cerebral plot. However, such hypotheses are not based on any foundation and, even if accepted, could not explain all the numerous facts of dynamic variation that come into play in the cerebral cortical theater.

I am hardly satisfied with the ingenious histological hypothesis of Duval (1895), conceived by that scholar to account for sleep and the cerebral rest induced by narcotics. Based on my demonstration that the terminal nerve branches are completely free and establish contact with the soma and dendrites of nerve cells in the nervous centers, Duval supposed that such a connection could become more or less intimate by means of the amoeboid retraction of the nerve arbors in question. During sleep, either natural or induced, the nervous ramifications become retracted, thereby moving away from the cells and disrupting the passage of the currents; in the waking state, the reverse phenomenon would occur, and the arborizations mentioned would once again contact the cell soma, resulting in currents being communicated unimpeded from the fibers to the nerve cells. A similar hypothesis was put forth, although with some differences, by Rabl-Rückhard (1890), which raised many difficulties, some recently discussed by von Kölliker (1895). The latter scholar noted that it is in fact impossible to distinguish the minor amoeboid variation in the nerve fibers and terminal arborizations that are susceptible and to observe them throughout life (motor plates, sensory nervous ramifications et cetera, of salamander larvae, and so on).

On my part, I shall add the following facts, which are contrary to the hypothesis of Duval:

Firstly, the terminal nerve arborizations of the cerebellum, the olfactory bulb, the central acoustic ganglia, and the optic lobe, among others, constistently manifest the same expansion, form, and degree of proximity to the cell body, regardless of the mode of death of the animal (exsanguination, chloroform, curare, strychnine or other means).

Secondly, the terminal nerve branchlets of the retina and the optic lobe of reptiles and amphibians (the only animals that I have attempted to experiment on) exhibit the same appearance when the organs are at rest (death after prolonged darkness) or when they are active (death after exposure to the sun for many hours). These last experiences, performed a few months ago to identify the morphological variations that correlate with the resting or the active state of the nerve cells, convinced me that at least the sensory organs and their primary receptive stations of the centers, and also the axons and dendrites maintain a constant disposition.

In contrast, my studies on the cerebral cortex led me to suspect that the morphology of some neuroglial cells varies during mental work. In the grey matter of the same brain, neuroglial cells sometimes retract and other times are equipped with short and stout appendages; at other times these cells exhibit long and abundant expansions that bristle with countless secondary and tertiary branchlets (the cells of penniform expansions of Retzius). In fact, all of the transitions between the retraction state and the relaxed state can be observed.

These diverse phases of the neuroglial cells of the grey matter were undoubtedly observed by Andriezen (1893a, 1893b), Retzius (1894), and others, although they were believed to be fixed, i.e., mere morphological varieties of the typical cell of Deiters.

The more I reflect on the meaning of neuroglial cells, the more convinced I become that scholars, influenced by the prejudice begotten at a time when the structure of the neuroglia was elusive, confuse under the same designation cellular elements of very different physiological assets. In my view, it is necessary to distinguish the neuroglia of the white matter from that found in the grey matter. In addition, it is necessary to disregard the infantile hypotheses which allege that the task of the Deiters cells is to sometimes provide nutrition to nervous tissue and, at other times, to support the cells and fibers. I do not understand what nutritive benefit the nerve cell may obtain from the plasma before it reaches it by traversing the density of neuroglial cells, which would ultimately have to steal a part of the nutrients. Moreover, would not this plasma reach more easily through the liquid or semiliquid amorphous material that serves to cement the nerve cells?

This is in fact the path taken by nutritive juices through the grey matter, because neuroglial cells only reside in a few spots of the grey matter, which precisely correspond to the localities with less abundant cell bodies.

The supporting role that some scientists attribute to the neuroglial cells is no less trivial or complimentary. Can the tiny cellular corpuscles, isolated, flexible, much more delicate and smaller, support the nerve cells themselves? Why do many nerve cells lack such a mode of support, whereas the white matter, which is much firmer and less in need of support than the grey, contains neuroglia in large quantities?

For the sake of brevity, and setting aside other considerations, I shall next discuss my conjecture on the importance of the diverse classes of neuroglia.

At least three classes of cells are mistakenly included under the designation "neuroglia": the neuroglial cells of the white matter, the perivascular cells well described by Golgi, and those of the grey matter, known above all through the work of Retzius (1894).

(a) *Neuroglial cells of the white matter* are fixed, thick, and have typical rigid expansions which are sleek with rigorous contours. Their mission seems to be, as suggested by my brother, to interpose a poor conductive substance between the nerve fibers and the currents that circulate in them and to concomitantly maintain the space or the gaps through which the lymph is widely diffused.

(b) *Perivascular neuroglial cells* reside only in the proximity of the capillaries of the grey matter, to which they send one or more thick appendages inserted into the external layer of the endothelium. Each such capillary insertion provides thousands of pseudopodia ["end-feet" or "sucker processes"], which diverge in all directions. The objective of these elements is to spark, through the contraction of the appendages, the local dilation of the vessels and thus, physiologically congest and link to a greater or lesser degree the mental processes.

(c) *Neuroglial cells of the grey matter* exhibit, as Andriezen (1893a, 1893b), Retzius (1894) and I have shown, a particular and highly typical physiognomy. Their shape can vary from star-shaped to elongated in the manner of a comet (the caudal cells of Retzius). Their expansions, which are extremely numerous, bristle with numerous short lateral appendages which branch out; this provides an overall aspect of a star with feathers. I previously mentioned that in these cells one can observe two states: a state of "relaxation," which is the one just indicated, and a state of "contraction," during which the cell body increases its cytoplasm while its expansions decrease in length, become swollen, and lose the secondary appendages. Under such a concept, these cells would be compared to the pigment cells or chromatophores in the skin of certain animals, which are contractile cells that stretch their expansions in the resting state and retract them in the contraction state. It is worth noting that neuroglial cells are clearly abundant in places where connections with currents exist, e.g., in the molecular layer of the cerebral cortex, where they contact the peripheral tufts of the pyramidal cells with countless terminal nerve branchlets.

During the state of relaxation, the neuroglial appendages, which in fact represent a current-insulating material, would penetrate between the axons and the soma or their dendrites. As a consequence, the passage of currents would be suspended or severely hampered. This explains the mental rest and sleep, regardless of whether it is natural or induced (by narcotics or hypnotism).

During the state of contraction, the pseudopodia would shrink, absorbing, so to speak, the protoplasm of the secondary appendages, and making it possible for cells and nervous arborizations that were previously separated to come into contact. Through such a mechanism, the cerebrum would switch from the resting to the active state. These contractions can occur automatically, but are more often caused by volitional stimulation, which, by working upon a particular group of neuroglial cells, can convey the process of association in specific directions. The unusual turn of events that sometimes happens by association, the flight of ideas and words, the transient clumsiness of language, the obsession with a memory, the suspension from memory of an idea or a specific expression, the same exaltation of thought and all

sorts of conscious motor reactions, and many other phenomena of mental order can be understood well in the framework of the aforementioned hypothesis, by only imagining neuroglial cells at rest at certain points and in a state of energetic contraction in others. In sum, the neuroglia of the grey matter represents an isolating device and a switch of the nervous currents; a releasing switch in the active or contraction state, and an insulator in the resting state.

Note that the contraction of these cells does not coincide, as in Duval's hypothesis, with mental rest, but with the activity of the cerebral cortex.

2.3. Theory of attention

Under ordinary conditions, the motor apparatus of the grey matter would suffice to explain the turn of events of association and volitional motor reactions. In fact, from the moment that the attention is concentrated on an idea or a small number of associated ideas, a new factor comes into play in addition to the violent neuroglial retraction of the corresponding cortical area: the active congestion of the capillaries of the hyperexcited territory, through which the energy of the nervous wave reaches a maximum, thereby sequentially increasing the heat and the nutritive metabolism of the local hyperemia. Lehman (1890) and Nordau (1894) sought to explain such a congestion, demonstrated by the experiences of physiologists (Mosso, 1892), by assuming an action of volition over the vasodilator nerves of different cortical localities. However, in the intimate process of attending, in which the mental activity is concentrated within a very limited field of representations, an exclusive and ineffective sympathetic activity is observed. In fact, cerebral capillaries lack nerves and smooth muscle fibers, and the relatively thick arteries of the pia mater have a muscular layer (tunica media) that is only provoked under the influence of sympathetic activity to extensive and ill-limited congestions. The difficulty increases if we remember that every vasomotor action is involuntary, whereas, on the contrary, the process of attention is eminently conscious and volitional.

In my hypothesis, such difficulties fade to a great extent. Under the influence of volition, the fixed pseudopodia in the capillaries of a more or less considerable group of perivascular neuroglial cells would contract; the capillary that stretches in all directions toward the immediate grey matter would in turn increase its diameter and occupy almost the entire surrounding lymphatic cavity. This would lead to congestions of the grey matter as precise and specific as would be required by the "monoideism" of attention (for more details on the mental process of attention, cf. Ribot, 1894). Even the perivascular lymphatic spaces appear to serve the purpose of facilitating such congestions by preventing the pressures or commotions that an extremely abrupt vascular turgescence would cause in the neighboring nerve cells.

2.4. Comment

And here I comment on my conjectures. It is useless to note that I do not consider the hypotheses just stated as theories exempt from reproach. To the contrary, I think that everything I said about the deeper mechanism of mental acts is premature, given the immense difficulty of the problem and our limited anatomical and physiological knowledge of the nervous cytoplasm. However, not all rational hypotheses that have their point of departure in some known facts cease to be legitimate or fruitful. A scientific hypothesis represents a new direction, a path that is traced by observation and experimentation, which, even if not immediately leading to the truth, always generates research studies and critiques that will bring us closer to the truth. If our subsequent experiences do not confirm our assumptions, the result would not be any less positive; a negative fact simplifies the domain of possible hypotheses and consequently reduces the chances of error in future inquiry.

5 May 1895

3. Conjectural interpretations of certain points in neurological histophysiology [1896], by S. Ramón y Cajal (English translation)

Of all the domains of anatomy, none has gained more momentum in the last decade than the one related to the structure of the nervous centers. This explains the great current bibliographic trend, and the excellent welcome given by the public to the books of van Gehuchten, von Kölliker, Edinger, Déjerine, Obersteiner, and von Lenhossék, which detail the recent and momentous progress surrounding the microscopic anatomy of the nervous system.

As is the case for any science that relies on observation, anatomy owes its latest progress to the application of new methods of study. The method of Flechsig for embryonic tissues combined with the myelin stain of Weigert, the degeneration method conceived by Waller and Türck, the secondary atrophy method conceived by Gudden, and the procedures of selective staining of nerve cells discovered by Ehrlich and Golgi allowed the in-depth study of the pathways and special conduction of white matter bundles, as well as the clarification of the origin and termination of nerve fibers, and the mode of connection of nerve cells.

The reticular theory of Gerlach and Golgi, which was not based on exact observations but rather on physiological bias, was succeeded by the theory of the contacts and morphological independence of cells, i.e., the *neurons*, to use the pertinent expression of Waldeyer (1891). Owing to the clarity brought about by these new facts, the arborization of the soma, i.e., the dendrites, whose mission was previously thought to be accessory and unrelated to transmission, has gained capital importance, because it was demonstrated to represent a necessary link in the chain of conduction, in which it intervenes by directing the nervous signal to the cell body, from which it is carried, by way of the axon or functional expansion, to other neurons or peripheral cells.

The success of the new ideas has been great and surprised those who were unaware of the rigor and the caution with which the underlying facts were observed and interpreted. Many people did not know about the extraordinary clarity of the staining of nervous centers achieved with the metallic impregnations of Golgi. The images obtained were so conclusive, that they cannot be compared to the results of any other method. Moreover, the images produced by the Golgi method had no precedent in the technique of photomicrography.

The road travelled since 1888 has been long. Mistrust was followed by confidence, and doubt was followed by enthusiasm. The new concept of the structure of nervous centers was acknowledged by eminent histologists, including von Kölliker, His, Waldeyer, Retzius, Duval, von Lenhossék, van Gehuchten, and Obersteiner. Physiologists began to use the new facts to explain the reflexes and the diverse questions of association. Pathologists used the new findings to contribute to the interpretation of the symptoms and lesions of atrophies and degenerations. Even psychologists took note of the recent findings to the aim of clarifying the mechanisms of mental functions.

The work carried out has been great, but the accomplishments yet to be realized are even greater. Each problem solved leads to new deeper problems; discovered facts expand the scientific horizon in all directions, rather than closing it.

Even when the focus is merely restricted to physiology (i.e., the functional significance of the recently elucidated structures), so many questions remain to be answered!

What meaning should we attribute to the short-axon or Golgi cells? Since the Nissl method defines a structural difference between the soma and the initial part of the expansions of the perikaryon on one hand, and the fine dendritic appendages on the other, should we not imply a contrast or differentiation of their physiological properties? Are the connections of the collaterals in the grey matter the same as those maintained by collaterals in the white matter? Is the current that travels through the axon disseminated, when it is weak, by the primary collaterals or is it channeled by the main conductor to the terminal arborization? Looking back at the oldest problems, why do the cells of the spinal cord, which have essentially the same chemical and morphological composition as the cells of the cerebral cortex, produce

reflexes, whereas cortical cells produce ideas and volitions? Do ideas, i.e. the transformed sensory images, rely on one or on a subordinate group of cells? Does the supreme phenomenon of consciousness have as its "substrate" all the cerebral cells or exclusively those of association?

Let me expound somewhat upon these imperative and interesting problems. However, since we still lack satisfactory methods, I can only make interpretations by means of mere conjectures. Leveraging the forbearance of the author of this book and the freedom typically granted any preface writer, I shall expand on certain points concerning the questions raised.

(1) It seems to me highly likely, based on some facts recently discovered in the retina, that the so-called Golgi cells or short-axon cells serve to disseminate the nervous impulse, received by a single fiber, over a considerable number of cells located within a short distance. These short-axon cells are comparable to a system of divergent conductors that amplify the final arbors of the axon from which they receive the current. Such an interpretation suggests that, among the amacrine cells of the retina, certain cellular elements can be observed, which I have designated as "horizontal" or "association spongioblasts." Their main morphological characteristic is a large horizontal axon that elaborates extensive and dense flattened branches, which establish contact with the shafts of a large number of regular spongioblasts. Nevertheless, precisely around the soma of the mentioned horizontal or nervous spongioblasts terminate, in a pericellular nest, the free arbors of those centrifugal nerve fibers that were discovered by myself and confirmed by Dogiel (1895). Thanks to these cells (which can overall be compared to short-axon cells), the nervous current arriving from the centers through centrifugal fibers may propagate to a large number of adjacent amacrine cells over a long distance.

It appears that the Golgi cells located in the granular layer of the cerebellum have a similar role; from them emanate the branches of the functional [axonal] elongation. The so-called mossy fibers enter into contact with the soma of the Golgi cells as rosettes *(eflorescencias)* or terminal branchlets *(ramúsculos terminales)*, while the collaterals of the mossy fibers establish relations with the granule cells. Consequently, the impulse that arrives at the cerebellum through the mossy fibers is broken into two currents: one that directly pervades the granule cells, and another, which, through the mediation of Golgi cells, propagates to that special group of granule cells dynamically intermingled with them. At the same time, the granule cells would take the nervous impulse through their ascending axon to a large number of Purkinje cells. Such an impulse would grow like an avalanche and affect a greater number of neurons in succession, and thus accumulate the energy of the current as a result of the abundance of the cells involved in the conduction.

(2) Because the soma of the nerve cells possesses a positive quality, i.e. the existence of some chromatic granules, and a negative quality, i.e. the absence of spines, the opposite of what occurs in the fine branches of the perikaryon that exhibit spines and no granules, simple common sense dictates that some difference in activity must separate the two portions of the cellular perikaryon. If we pay attention to their connections and review the diverse cells of the cerebral hemispheres, the cerebellum, the spinal cord, and so on, we shall notice that the soma and the initial segment of the thick [dendritic] branches usually receive pericellular nervous arborizations, i.e., a thick nervous plexus, disposed in a terminal nest. On the other hand, the spiny branchlets solely establish contact with fibers en passage that in most cases are perpendicularly oriented. In other words, the relations established by the fine or spiny dendritic appendages are multiple and occur by crossing without extensive contacts. The relations established by the soma, on the other hand, are more individualized (each cell may receive one or two, rarely three terminal arbors), and follows the principle of multiplication of the surface of influence. The closeness between the soma and the pericellular arborization is really great, and is often accentuated by the presence of a special conducting material, a type of granulous plate that fills the gaps of the ramification. Such a circumstance, together with the consideration that neuroglial filaments are never interposed between the elements of the somatic-nervous articulation, seems to indicate that the connection through cellular somata has an invariable and fixed character and is always at hand for the transmission of currents. The connection between the fine

branches of the perikaryon, on the other hand, may be of a variable nature, because of the retraction of the numerous neuroglial appendages that touch those branches at multiple loci or, as Duval and Lugaro suggest, owing to an alternating shrinking and swelling of the two elements of the articulation.

(3) With regard to the meaning of the two forms of collaterals, those in the grey and those in the white matter, my views are fairly conclusive. Observations made in almost all the areas of the nervous system, and specifically in the root cells of the spinal cord, the motor nucleus of the trigeminal nerve, the Purkinje cells, the cortical pyramidal cells, the mitral cells of the olfactory bulb, and so forth, allow me to establish that the "initial collaterals," or those of the grey matter, always branch around congener cells of a similar physiological nature. Thus, the collaterals of Purkinje cells carry their excitation to other neighboring Purkinje cells, those emanating from the mitral cells of the olfactory bulb are connected to other mitral cells, and so on.

This is not the case with collaterals in the white matter or "terminal collaterals," for these establish relations with elements of diverse significance and usually at a long distance. To just cite one example: recall the fibers of the pyramidal tract, which contact the striatum, the pons and the spinal cord via their extracortical trajectory collaterals. To my mind, the terminal collaterals, or those of the white matter, are none other than the anticipated branches of the arborization of the terminal nerve, which exhibit in many sensory nerves the same direction, having the same fineness and morphological and connectional properties as the genuine collaterals of the white matter.

In sum, the initial collaterals have the objective of making other cells of the same nature participate in the conduction; whereas the terminal collaterals and arbors serve for delivering the impulse to a series of cells of different nature that are usually located in other foci of the grey matter.

I shall dispense with other problems that are equally important; but let me touch upon one of the deepest aspects of nervous physiology. Reduced to its bare terms, this question can be stated as follows: why does the spinal cell produce movements while the cerebral cell elaborates ideas? This cardinal difference cannot be attributed to morphology, because that cannot explain the quality of function, but rather to the complexity of the cerebral cell or, better said, tp the multiplicity of dynamic relations. Such a difference cannot be attributed to the structure and the chemical composition because, until today, the same reactions and the same direct principles have been found in the perikaryon of a spinal motor cell as in a cerebral association cell.

To tell the truth, the problem is vastly simplified by adopting the ingenious hypothesis of polyzoism, conceived by Durand de Gros and warmly welcomed by Forel. In harmony with that hypothesis, each nerve cell, spinal or cerebral, is susceptible to reflect, under the form of conscious activity, a part of the excitation received from the external world. Thus, the nervous system consists of a countless number of consciousnesses, as many as there are cells or ganglia or organized foci in view of a special reflex act. Therefore, there are one or multiple spinal consciousnesses, other bulbar and pontine, and one cerebral consciousness, superior and autocrat to all the rest. What we call the *ego*, or subject, would be nothing other than the cerebral consciousness which ignores, as it is external, the conscious self of all the subordinate ganglionic individualities. Likewise, these other consciousnesses ignore the content of the superior individuality represented by the central cerebral matter. However, the fundamental problem still stands. Giving a spark of consciousness to every nucleus fills in part the abyss between conscious cerebral function and automatic spinal function, but that may still not explain why the cerebral cells elaborate ideas while the spinal cells reflect motor incitations.

The way I see it, it is necessary to seek the reason for this dynamic contrast in the distinct sensory relations of each nuclear focus. The cerebral matter, by means of the senses of hearing and vision that it receives from the outside world, does not report motor solicitations, but true images or copies of reality. The extremely delicate filter of the organ of Corti, as well as that of the rods and cones of the retina, operate, in the complexity of stimuli received from the environment, by

effecting a true selection of undulations, organized according to spatiotemporal relationships and projected to the cerebral cortex as a bundle. Therefore, the brain does not need to create images: these are provided completely formed and organized by the sensory organs, thanks to their marvelous architecture. Hence, the role of the "psychic cell" is to elaborate, to combine and to reproduce the representations arriving from the olfactory apparatus, the eye, and the ear. Therefore, the more distinct the sensory impression is (compare e.g. olfactory to visual impressions), the more correct is the resulting conscious representation.

As far as the sympathetic and the spinal cells are concerned, the conditions of their dynamics are very distinct. In favor of sensory nets, most likely tactile and thermal, these cells gain from the external world vague, uncertain impressions without precise relationships of extent or form. Therefore, the conscious elaborations or representations of the spinal cord will be obscure, indeterminate, and good only for provoking motor reactions. Consequently, the spinal cell must reflect and conserve gross impressions of contacts and codes of motor reactions disguised as memories, rather than true ideas.

In brief, the morphology and chemical composition of a cell are so important for the form and complexity of mental work, but they do not determine its hierarchy, which mainly depends on the nature of the excitation received from the outside world. It seems plausible to me that, if the cerebral ganglion of invertebrates can successively dominate and control all the remaining ganglia, as well as organize an ever increasing complexity, this is due to the privilege of representing the terminal station of the optic nerve and, thus, to the reception of a "primary sensory material" that is vastly superior in quality and quantity to that collected by the esophageal and the abdominal ganglia. If, through a capricious anomaly, it were possible in a vertebrate for the optic nerve to terminate in the spinal cord, then the spinal neurons would elaborate visual images instead of motor associations. Further, if adaptation and selection were apprehended in such an organism, then spinal cells would gradually acquire the form and abundance of expansions and the luxury of associations characteristic of cortical pyramidal cells.

Such is in essence the conjecture that I venture on, in the attempt to answer the question formulated earlier. However, God forbid we take this conjecture as a conclusive and satisfactory explication of a question of such difficulty and scope!

In the penury of my analytical resources, I can do little to verify or to contrast this conjecture. Therefore, it is impossible to say how far it conforms to reality. It is also possible to encounter other conditions that are currently inaccessible and are even more deeply related to the singular and extraordinarily dynamic evolution reached by the cerebrum.

Meanwhile, while resolving these and other momentous issues of general biology, it is good not to relent the analytical work nor to quench the sacred fire of investigation. Let us not be impatient in contemplating the realization of the grand edifice. The ultimate synthesis will only come much later, when all of the materials have been gathered, and when neither the chemistry nor the structure of nerve cells hold secrets from us.

However, the researcher, contemplating the capstone that he must sculpt for the construction and the erection of a great work that he will not see completed in his days, runs the risk of ignoring, locked in his particularity, the general state of the work, and not fully appreciating the scope of the contribution effected by his analytical work. Therefore, one is forced, from time to time, to look at the whole and to take note of the overall height of the edifice by consulting a book that thoroughly summarizes the state-of-the-art of science. More urgently still, professionals and students need those textbooks in which newly conquered facts of nature are found next to the gaps that future inquiry should fill in.

The monograph under the title "Anatomy of the Spinal Cord" written by doctor López-Peláez (1897) belongs to this class of important books. He certainly does not need my introduction to the medical community, given the renown of his qualifications. This distinguished anatomist methodically introduces us to the mysteries of the form and detailed structure

of the spinal cord with copious and first-hand erudition; with a critical caution not expected from a new author; with a style both plain and eminently didactic; and with a preoccupation for meticulousness in the extensive and exact descriptions. This text plants flowers, and eases and smooths a lane where the beginner would otherwise have met with obstacles.

Hopefully such a meritorious work will not take long to accrue imitators, and the public will welcome it with the applause it deserves! I am delighted to pay tribute to the talent and industriousness of the author, the illustrious professor of the University of Granada, and his first didactic fruit!

25 November 1896

4. Discussion

Cajal often used the term “nervous centers” to denote what we today call cortical and nuclear assemblies in the structural organization of the grey matter.

In the first essay (Cajal, 1895a, 1895b) he attempted to interpret the mental acts of the elaboration and spatiotemporal association of ideas, repetitive attention and memory retrieval on anatomical and physiological grounds. He introduced the concepts of the “impression unit” and the “conduction avalanche”, and applied them to the cerebral cortex, especially the afferent or sensory systems of vision, hearing, taste, and olfaction. Next, he rebutted the neuronal amoeboidism hypothesis and instead proposed the amoeboid movement of glial processes to account for the states of sleep and wakefulness.

In the second essay (Cajal, 1896, 1897) he presented arguments for the neuron theory and its implications, with special emphasis on histological methods. He differentiated the functions of dendrites from those of the axon, the functions of axosomatic from axodendritic contacts, and detailed the role of axon collaterals and their connectivity patterns in the grey and white matter.

4.1. Impression units: from stimulus to cognitive modules

At the time, Cajal’s novel perspective was close to the psychological trend of associationism. Cajal’s concept of impression units provided a bridge between the psychological trend of associationism and localizationism, particularly when he asserted that the “impression unit” is stored in the nerve cell (López-Muñoz et al., 2008). He exemplified it in the sentence, “I also consider it likely that each group of pyramidal cells, which is anatomically connected to a sensory cell, maintains the various images, or impression units, which the cell communicated at different times, in a latent state.”

The neurologist Francis Xavier Dercum (1856–1931) of Jefferson Medical College noted that Cajal’s discoveries demonstrated that, “everywhere, and no matter in what light we view the nervous system, the signal of the nerve-cell as an individual entity is strikingly apparent” (Dercum, 1896). Dercum’s analysis on the physiology of memory presented an example on the “purely mechanical lines of thought, in which a sequence of sound-vibrations impinging upon the peripheral auditory neurons, produces in them a change, which in turn affects the relations that their neuraxons bear to the auditory nuclei, and secondary to the auditory cortical neurons.” He suggested that the latter are not only affected by the impressions received from afferent axons, but they in turn react in such a way as to change their relations to each other; the new positions assumed by them will largely depend on whether a similar sequence of impressions has passed through them before.

In contrast to the narrower reductionist postulates, Cajal (1895) proposed his principle of

“avalanche conduction” or “nervous avalanche”, whereby sensory impressions, for example, would constitute basic units or “impression units” registered upon individual cortical cells.

Cajal defined the impression unit as “the simple movement gathered during the sensory impression by a single retinal cone or rod, or by a hair cell of the cochlea.” It formed a clear sequence: one unit, one neuron, and each neuron connected to others in order to generate ideas by means of “association fibers” (Køppe, 1983).

The Cajalian relationship between neuron theory and the associationist postulates influenced the thought of numerous scientists, including Freud, who, in his “Project” (Freud, 1966) suggested similar ideas, in an attempt to explain the mechanisms of memory, in accord with the concept of nervous energy (the Cajalian “impression unit”) and the Freudian “contact barrier” (a kind of early, speculative approximation to the concept of the synapse).

In the “Conjectural Interpretations” Cajal (1896) supported the polyzoism hypothesis of the biological philosopher, Joseph-Pierre Durand de Gros (1826–1900), according to which, each neuron, regardless of location, would partially reflect the stimulation incoming from the outside world (López-Muñoz et al., 2008). Thus, “the nervous system would consist of innumerable consciousnesses, as many as there are cells”, while there would be a cerebral consciousness that dominated all the rest. Accordingly, the self, or the person, *is* the cerebral consciousness, which, at the same time, “ignores, and is external to, the conscious self of all the subordinate neuronal individualities” (Cajal, 1896).

Cajal’s passion for those topics is reflected in the original Spanish edition of his major work, the *Textura del Sistema Nervioso del Hombre y de los Vertebrados* (Cajal, 1899–1904), where a brief chapter of a physiological nature on reflections about the mechanisms of thought, consciousness and sleep is included. However, almost 30 years later and, through incipient morphological discoveries, he was led to retract his bold claims and affirm definitively that the participation of astrocytes in the mental acts of attention and association of ideas was:

“A frankly inadmissible conjecture … Moreover, the processes of attention, association of ideas, emotion, intellectual phenomena, and so forth, are so enormously complex and so enigmatic today, from the histological, histochemical and energetic perspectives, that all research carried out in this direction would appear quite audacious … Centuries, perhaps millenia, will pass before man is able to catch a glimpse of the unfathomable mystery of the mechanism, not just of our own psychology, but even of that of the simplest insect” (Cajal, 1923).

In that context, what comes to mind is “The Modularity of Mind” of Jerry Fodor (1983), who expressed the view that the mind cannot consist of only one, “general use” program. Instead, he introduced the theory of multiple programs of “specific use,” each one with its own rules, the so-called “modules.” His “modular theory,” whereby such programs receive the incoming information

from the sensory or “input systems” and eventually lead to action (“output systems”), was widely accepted in cognitive and evolutionary psychology. Subsequently, John Tooby and Leda Kosmides took the idea further, and introduced the theory of “massive modularity,” which holds that there are hundreds or even thousands of such modules in the human mind, each subserving a specific task; they argued against the existence of a “central processor”, as problems are specific, not general (Tooby and Kosmides, 1992).

4.2. Synaptic transmission and neuronal avalanches

One of Cajal’s major discoveries, dating to 1888, was the contact between contiguous nerve cells as a potential mechanism for their functional interaction; that contact was termed “synapsis” by Sir Charles S. Sherrington (1857–1952) in 1897 (Purves and Lichtman, 1985).

“Cajal’s speculations were limited by the fact that he thought that all synaptic connections are excitatory. The widespread nature of the pontine terminals on the cerebellar cortex, he suggested, would produce an *avalanche* of *conduction* that could be used to overcome resistance to movement” (Glickstein and Yeo, 1990).

In modern terms, one of the most important concepts in thinking about the functions of neurons is that they inhibit, and also modulate, one another, as often as they excite. Because that was purportedly not one of Cajal’s underlying premises, he saw only excitation, hence his occasional reference to the “avalanche of conduction.” However, judging researchers of the past by the present state of knowledge is an anachronistic enterprise. Cajal may not have discovered the inhibitory postsynaptic potentials, but his contributions to neuroscience were both momentous and revolutionary, especially if one considers that in his era the holding view of the central nervous system was a continuous network (“reticulum”) or a system of fused cells, through which impulses would travel in all directions.

In reviewing the idea of inhibition as a neuronal property, Llinás (2003) underlined that such a concept was missing in Cajal’s description of network function. Nonetheless, Cajal was aware that inhibition existed, and referred to it in the *Textura* (Cajal, 1899–1904). More specifically, he had described the crossed inhibitory reflex in the spinal cord and the inhibition of segmental reflexes that under certain conditions accompanied the corticospinal transmission. Because he did not have knowledge of the inhibitory synapse as a specific element of the neuron, he theorized that such inhibition was the end product of the saturation that would result from very large incoming excitations (Cajal, 1899–1904; Llinás, 2003). Our present understanding of inhibitory neurotransmission had to await its unequivocal demonstration through the work of the late Nobel laureate, Sir John C. Eccles (1903–1997) (Eccles, 1961).

The fact is that, in the "Conjectures", Cajal (1895a) explicitly mentions: "… Variations may be related, to a certain extent, to the inhibition of certain cerebral areas, to interference of the currents, to increases in the resistance of the conductors on the occasion of changes in the chemical composition of the nerve fibers or the interstitial matrix." And also, "… The neuroglial appendages, which in fact represent a current-insulating material, would penetrate between the axons and the soma or their dendrites. As a consequence, the passage of currents would be suspended or severely hampered." Therefore, a seed of the concept of inhibition indeed existed in his mind.

On the other hand, Freud, in the early stages of his career as a neuroanatomist, had a clearer insight into inhibition. In the "Project for a Scientific Psychology," drafted in 1895 (Freud, 1966), he hinted "the existence of resistances between neurons that opposed discharge at locations called *Contactschranke* ('contact barriers'), some of which allowed the passage of excitation easily, while others might do so partially or with difficulty" (Triarhou and del Cerro, 1985).

Cajal was aware of Freud's early histological studies on lampreys and crayfish, which he cited in the *Textura* (Cajal, 1899–1904). In a remarkable convergence, Cajal and Freud postulated that learning might produce prolonged changes in the effectiveness of neuronal connections, and that such changes could serve as the mechanism of memory (Kandel, 1981). Moreover, the general idea of Cajal (1895a) that learning is predicated by the selective strengthening of synapses has since been accepted and elaborated in various forms (Jacobson, 1991).

The concept of the conduction avalanche as a mechanism of signal propagation in the central nervous system was introduced in 1895 by Cajal. Through such a mechanism, stimuli received by sensory receptor cells would be augmented as they reach the cerebral cortex through the corresponding anatomical pathways, leading to conscious perception. Cajal applied the concept to the visual, auditory, olfactory, and somatosensory systems, and in 1896 extended it to the cerebellar cortex. Beginning in 1899, through 2003, prominent neuroscientists referred in their writings to the principle of conduction avalanches, crediting Cajal. Among such authors, one finds Lewellys F. Barker, C. Judson Herrick, Francis X. Dercum, Rafael Lorente de Nó, Cornelius U. Ariëns Kappers, Hartwig Kuhlenbeck, Gordon M. Shepherd, and Rodolfo Llinás.

In 2003, John Beggs and Dietmar Plenz introduced the concept of the "neuronal avalanche," modelled after the power law of physics, as a property of neocortical networks and a new mode of spontaneous activity, distinct from the oscillatory, synchronized and wave states previously conceived to underpin the integrative function of the cerebral cortex (Beggs and Plenz, 2003; Plenz and Thiagarajan, 2007; Lombardi et al., 2014). The topic has since become an issue of intensive research, with over 100 articles appearing in PubMed from 2003 onwards with the terms "neuronal avalanche" or "neuronal avalanches" in the title or abstract.

Owing to the continuing interest of physiologists in the phenomenon of neuronal avalanches,

the basic tenets of the Cajalian principle will be discussed in a historic and a modern perspective in a separate study, with a detailed overview of the neuronal avalanche as a mechanism underlying the neural basis of consciousness.

4.3. Amoeboidism, neuronal versus neuroglial

Cajal (1895a, 1895b, 1896) suggested that mental repose and sleep, natural or evoked, may be attributed to the isolating properties of neuroglia in the grey matter. At the times of "relaxation," he hypothesized, astrocytes grew appendages that would penetrate between the neuronal connections and thus block the conduction of the "nervous current."

There is a certain merit in Cajal's insight, as it favors the dynamic, rather than fixed, nature of cortical histophysiology and the underpinning of all mental and conscious activity; the "neuroglial amoeboidism hypothesis" might in some way even relate to modern findings that favor an involvement of astroglial processes in the elaboration and modification of synapses (DeFelipe, 2006; Sotelo and Dusart, 2014).

In describing the role of glial cells, Cajal made a functional distinction between those located in the white matter and those located in the grey matter, respectively known as *fibrous* and *protoplasmic* astrocytes, an old histological classification that still holds today (Andriezen, 1893b; Weigert, 1895; Peters et al., 1991). On the other hand, oligodendroglia was only discovered and named so in 1921 by Cajal's pupil, Pío del Río Hortega (1882–1945), as a distinct second cell class of the macroglia (del Río Hortega, 1921; Iglesias-Rozas and Garrosa, 2012; Pérez-Cerdá et al., 2015). Thus, Cajal's discussion, especially when he talks about the insulating properties of glial cells around axons, could be confounded with the role of oligodendrocytes, which are classified as *interfascicular* in the white matter and *perineuronal* in the grey matter (Peters et al., 1991).

A heated debate broke out in the 1890s as to whether neurons and their connections remained fixed throughout the lifetime of the individual or whether they changed in a dynamic manner. Some of the most important studies that attempted to resolve this issue were those carried out by two comparative anatomists, Robert Wiedersheim (1848–1923) in Freiburg im Breisgau, and Hermann Rabl-Rückhard (1839–1905) in Berlin (Fig. 4).

The anatomist Lewellys Franklin Barker (1867–1943) of Johns Hopkins University briefly referred to the hypothesis of Rabl-Rückhard (1890), as well as its modifications by Tanzi (1893), Duval (1895), and other authors (Barker, 1899). The principle that underlies sleep, anesthesia, hysteric conversion reactions, dual personality, among others, was explained by presumed amoeboid movements of dendrites, in the so-called "retraction theory." That theory was based on Wiedersheim's observations, firstly, of amoeboid movements by neuronal processes in the water flea, *Leptodora*

hyalina (commonly referred to as *Leptodora kindtii* today), and, secondly, of undulatory movements by the distal processes of olfactory peripheral neurons.

Changes in connectivity causing changes in function were proposed early on by Rabl-Rückhard, who, by studying the crustacean cerebral ganglion, suggested that changes were brought about by the amoeboid movement of axon terminals approaching or withdrawing from cells and dendrites. Rabl-Rückhard held this to be the basis of remembering, forgetting, dreaming, hypnotic trances, alertness, and so on — the concept of *amoeboidism* (Ochs, 2004). That concept and allied theories were discussed at length by Soury (1898, 1899), who had actually exchanged correspondence with Cajal regarding amoeboidism (English translations of these letter can be found in Triarhou, 2016), and by Bawden (1900).

In August 1894, without any knowledge of Rabl-Rückhard's theory, in a paper titled "A case of hysteria of peculiar form," the physiologist Raphaël Lépine (1840–1919) in Lyon (Fig. 5) advanced the same idea (Lépine, 1894). Lépine proposed that the inactivity induced by anesthesia, hysterical paralysis, as well as somnambulism and normal sleep, could be mechanistically explained by a retraction of nerve processes. On the contrary, during active states, there would be a re-establishment of contacts by *éréthisme* (an increase in local stimulation or irritation) of the neuronal processes. In tackling the substrate of the various shifting phenomena observed in his clinical case, he advanced the idea that neurons were capable of movements that allowed a varied degree of interneuronal relationships.

About half a year later, the histologist Mathias-Marie Duval (1844–1907) in Paris (Hervé, 1907) proposed that the gap between the neuronal terminations might vary depending on specific functions, such as imagination, memory, and idea association (Fig. 5). Certain chemical agents, such as those found in tea or coffee, could facilitate those functions by stimulating the amoeboid movements of freely terminating neuronal processes, whereby they would come closer and consequently enhance the passage of the nervous currents. Duval, without prior knowledge of either the views of Rabl-Rückhard or those of Lépine, in a communication made to the *Société de Biologie*, advanced the same theory, and compared the movements of neurons to those of blood leukocytes. By combining data of his own, as well as of other investigators — for example, the shrinking of cones in the fish retina after exposure to light, a presumed dendritic retraction under the influence of anesthetics, dendritic changes upon fatigue in rodents, and the movements of olfactory cilia — he used the theory of amoeboidism to explain sleep, learning, and memory (DeFelipe 2006).

Duval (1895), recalling that Wiedersheim had observed amoeboid movements in the nerve cells of *Leptodera*, extended his idea in a general way and applied it to all nervous systems (Sotelo and Dusart, 2014). The neuron and its processes would be comparable to the amoeba and its pseudopodia, lengthening or retracting under various influences, and resulting in a greater or lesser

degree of *contiguity* among cerebral neurons. Although observations of a similar nature to those of Wiederheim, and equally conclusive, were also published by Freud (1882), who described rods and angular-shaped shreds in the nucleus, that changed form and moved rapidly in the ganglia of the river crayfish (Freud, 1882; Triarhou and del Cerro, 1985), for some reason they were not referred to by Duval (Bawden, 1900).

The idea of the contractility of nerve cells had also been propounded by other investigators, including Robert Odier (1898a, 1898b), who was working under the supervision of Professor Auguste Éternod in the Laboratory of Histology and Embryology in Geneva (Fig. 6A,B) and Duval's pupils in Paris, the physician Charles Pupin (1896) in his theoretical thesis, and the histologist and poet Yervante Manouélian (1898). Moreover, the theme of amoeboidism in the nervous system (Fig. 6C,D) attracted several expositions, critiques, and reviews by renowned authors (Binet, 1897).

A week after Duval, Lépine (1895) repeated his former arguments before the same body in support of neural amoeboidism. He recalled that a year earlier (Lépine, 1894), he had already formulated the hypothesis that central and peripheral sensory anesthesia and motor paralysis in hysteria resulted from a disrupted contiguity between nerve terminals. He further pointed out that different varieties of somnambulism could be explained with the same hypothesis (Beaunis, 1895).

Those basic ideas had already been embraced in 1893 by the psychiatrist Eugenio Tanzi (1856–1934) in Cagliari, who theorized that the passage of a nervous impulse could cause a neuron to increase in length, through the elongation of its protoplasmic filaments, and postulated that with additional activating stimuli, the filaments could grow even closer to the postsynaptic cells, making conduction across the synapse, and an associative bond even more likely (Tanzi, 1893; Finger, 1994). The psychiatrist Ernesto Lugaro (1870–1940) in Florence accepted the amoeboid movement of dendrites with some reservations (Lugaro, 1895; Cajal, 1999).

Bawden (1900) supported the theory of Duval (1895), arguing that it was strengthened by data from histological specimens prepared with the Golgi and Cajal impregnation methods, which showed that cortical neurons did not form a continuous pathway for the nervous impulse, but that these were related by the simple contiguity of their terminal arborizations. In sleep and wakefulness, the neuronal terminals would respectively retract or elongate; weak stimulation might perhaps call forth certain reflexes, but not suffice to establish full connection of lower centers with the cerebral cortex.

The histologist Jean DeMoor (1867–1941) in Brussels (Fig. 7) reported, using the Golgi method, that neuronal processes assume a "moniliform" (or *beaded*) shape in the canine brain after high doses of morphine and chloral hydrate (DeMoor, 1895). He compared the phenomenon to the pseudopodia induced in amoebas by narcotics or other types of excitation, and attributed the changes to the properties of the dendritic cytoplasm, which would conceivably modify its form (Fig. 8). DeMoor (1896a, 1896b) employed the term "morphological plasticity" in place of Duval's

"amoeboid movement"; in that context, he was one of the first authors after William James (1842–1910) to use the term "plasticity of neurons," albeit virtually equating neuronal plasticity with neuronal amoeboidism (Berlucchi and Buchtel, 2009). DeMoor considered the beaded state of neurons important for the theory of amoeboid movement, as it would indicate the retraction of dendritic cytoplasm, and the ensuing contact between afferent and efferent nerve processes. Neurons were thus "plastic," and such a property became meaningful in view of their function and interconnections (Bawden, 1900). The changes in the form of the dendrites were invoked to account for a modulation of function. Whereas apical dendrites are generally seen to be smoothly tapering from their origin in the cell body, varicosities (beading) were reported in dendrites after the administration of a wide variety of chemical agents or by electrical stimulation. DeMoor (1898) hypothesized that, as a result of such a change of form, the closeness of contact was altered to produce functional changes. Such beading cannot be ascribed to an artifact brought about by differences in the early use of the Golgi method (Ochs, 2004), since the beading of dendrites was reported from the 1960s onwards with the Golgi technique in focal epilepsy (Ward, 1969; Scheibel and Scheibel, 1973) and other pathological conditions in children (Purpura, 1974). Regarding neuronism versus reticularism, DeMoor was one of the supporters of the concept of the morphofunctional independence of the nerve cells, which simply come into contact through their processes, and the question is whether, in the mental act, such processes are rigid or mobile (Droz-Mendelzweig, 2010).

Cajal did not accept the idea of *neuronal* amoeboidism, because he had never observed any separation of synaptic elements by astrocytes. In the cerebral cortex, Cajal observed forms of glial cells with short and thick prolongations ("retracted" state), forms with numerous, long and branched prolongations ("resting" state), as well as intermediate forms. Based on those observations, he reckoned that glial cells would change their form during mental labor, and accordingly formulated a *glial* amoeboidism hypothesis (DeFelipe, 2006).

In arguing for neuroglial, rather than neuronal, amoeboidism, Cajal emphasized the insulating properties of glia. However, the admission that glial processes entered between neuronal processes and blocked the passage of the nervous currents was obviously against his own contention that neuronal elements cannot be separated, based on his extensive studies on the cerebellum, olfactory bulb, acoustic ganglia, optic lobes, and cerebral cortex, among other areas. Moreover, neurons maintained their shape regardless of the mode of death of the animal.

The hypotheses of neural and glial amoeboidism had their share of criticism. One of the most fervent critics of that theory was the anatomist and histophysiologist Albert von Kölliker (1817–1905) in Würzburg, who argued that axons simply did not contract to any kind of excitation. Instead, they were solid, and amoeboid movements were typically related to thermal and nutritive stimuli, as

opposed to mental functions. For Kölliker (1895, 1896), the glial variation of this theme was no better (Finger, 1994). Further, Barker (1899) wondered, how could a theory, feebly supported by facts, not only be widely accepted, but also lead to massive clinical generalizations.

On the other hand, Dercum (1922) considered the observations of Wiedersheim (1890) weak as well, since movements of neurons had not been observed in vertebrates. However, Dercum commented that the esophageal ganglion of *Leptodora* might in a sense be regarded as the brain of that particular arthropod, also receiving optic nerve axons. Thus, Wiedersheim's observation of protoneuronal movement in an invertebrate, although a far cry from the nerve cells of vertebrates, might illustrate an elemental fact, compatible with the concept that the connections of primordial neurons are not fixed, as opposed to the adult spinal and brainstem neurons in the vertebrate nervous system (Dercum, 1922).

Barker (1899) wrote that "Cajal's hypothesis, according to which the penetration of glial fibrils between the processes of neighboring neurons played a part in the make and break of conduction paths, had little basis directly dependent on anatomical observation." Dercum (1922) concluded: "Curiously enough, this view, so suggestive, so pregnant with possibilities, did not meet with the endorsement either of that veteran histologist, von Kölliker, or that other high authority, Cajal."

The theory that dendrites change shape and retract or extend in response to functional demands was widely held at the end of the nineteenth century (Jacobson, 1991). Cajal specified it to the glia. Later, Cajal (1909/1911) argued that the theory was unsupported by any evidence showing the required anatomical changes at synapses. However, the lack of evidence is not a sufficient reason for abandoning a theory. Sherrington (1906) obtained some counterevidence, pointing out that the reflex delay ("latent period"), when a reflex is produced in two stages, is longer on the second occasion: "This argues against an amoeboid movement of the protoplasm of the cell being the step which determines its conductive communications with the next." That might have been a meaningful argument at the time, but subsequent studies revealed stimulation-induced changes of synaptic size and shape (Sotelo and Palay, 1971; Jacobson, 1991).

The movement of thin astrocytic lamellae, entering, or retracting from, the gap between presynaptic and postsynaptic elements, somewhat relates to a kind of plasticity observed in the supraoptic nucleus of the hypothalamus, whereby astrocytes may withdraw their covering of oxytocin and vasopressin neurons (Hatton, 1997). Nonetheless, the exact mechanism conceived by Cajal has not been confirmed (Sotelo and Dusart, 2014).

In all, some of Cajal's early experiments and reflections on the relation between neuronal plasticity and behavior, and those concerning the effect of the environment on cerebral ontogeny and function have a modern pertinence.

Specifically, the glial amoeboid hypothesis may be in line with the findings of modern studies in

certain brain areas, where astrocytic processes are involved in the formation and plasticity of synapses. One such example is the suggestion that sex steroids influence synaptic connectivity in the hypothalamic arcuate nucleus by regulating astrocytes (DeFelipe, 2006).

In the first edition of his *Textura*, Cajal (1999) called Duval's hypothesis "ingenious", as it attempted to explain sleep and various functional states of neurons with the amoeboid movements of nerve cell processes. He also credited Lépine's idea that in motor and sensory paralysis in hysteria, articulations established among neurons could become looser, such that the passage of impulses would be impeded or arrested.

Cajal (1999) reviewed the experimental studies of other supporters of amoeboidism, including DeMoor (1896b), who reported a shortening and deformation of pyramidal cell dendrites and disappearance of spines in rabbits anesthetized with chloral hydrate or chloroform (Fig. 8), and Micheline Stefanowska (1855–1942) and her adviser Paul Héger (1846–1925) in Brussels (Fig. 9), who arrived at similar results in guinea pigs (Fig. 10) after electrical stimulation of the cerebral cortex under ether anesthesia (Stefanowska, 1897, 1898, 1899, 1900a, 1900b, 1901; Héger, 1898, 1899). The beaded dendrites in those classic Golgi drawings are much reminiscent of the varicose dendrites in the midbrain of the laboratory mouse (Fig. 11) in contemporary studies (Triarhou, 2002).

However, Cajal (1999) cautioned that, to accept those facts unreservedly, one would have to prove, firstly, that the lesions were not technical artifacts, and, secondly, that such changes also occur under normal conditions at rest. Regarding the methodological reservations, one should take into account that a delay in the fixation of tissues can cause dendritic varicosities and the transformation or disappearance of spines, especially deep inside the tissue blocks, whereas in small specimens impregnated with the Golgi method, dendritic spines are seen in all the cerebral regions.

4.4. Regional blood flow and mental activity

In *Conjectures*, Cajal (1895a) theorized that astroglia are core regulators of functional hyperemia, whereby the contraction and the relaxation of perivascular glial end-feet may increase or decrease the diameter of brain capillaries and thus regulate local blood flow (Cajal, 1895a, 1895b; Verkhratsky and Butt, 2013). He wrote: "From the moment that the attention is concentrated on an idea or a small number of associated ideas, a new factor comes into play in addition to the violent neuroglial retraction of the corresponding cortical area: the active congestion of the capillaries of the hyperexcited territory, through which the energy of the nervous wave reaches a maximum, thereby sequentially increasing the heat and the nutritive metabolism of the local hyperemia (…) The perivascular lymphatic spaces appear to serve the purpose of facilitating such congestions by preventing the pressures or commotions that an extremely abrupt vascular turgescence would cause

in the neighboring nerve cells."

According to Cajal, during periods of increased metabolic demand, astrocytes cause vessels to dilate by mechanical movements. Such a dilation is reversible. When attention is not necessary, astrocytes could cause vasoconstriction. Cajal further suggested astrocyte-induced vasodilation as a mechanism to explain attention. In particular, by retracting their end-feet, astroglia would cause an arterial dilation and an increase in the supply of nutrients to a specific region of the brain. In the relaxation phase, when attention is not needed, astrocytic processes would elongate, causing local cerebral vasoconstriction (García-Marín et al., 2007).

Modern studies showed that, during high synaptic activity, glutamate provokes a response in astrocytes, which release vasoactive agents, presumably from their end-feet; that response is mediated by an increase in intracellular calcium concentration (García-Marín et al., 2007).

The phenomenon of functional hyperemia in the brain was observed by Mosso (1892) right after astrocytic morphology was described (Virchow, 1860). Astroglia were additionally found both to contact cerebral capillaries with their end-feet and to envelope neurons; the physical association of astrocytes with blood vessels was the element that led Cajal to suggest that astrocytes might regulate blood flow in the nervous system.

The interplay between astrocytic end-feet and cerebral vasculature is currently an area of intense study. Astrocytes are ideally positioned to mediate neurovascular coupling by relaying signals from neurons to blood vessels (MacVicar and Newman, 2015). They can regulate cerebral blood flow in several ways, as e.g. by the calcium-dependent synthesis of metabolites of arachidonic acid. Blood vessels are dilated by prostaglandin E2 and epoxyeicosatrienoic acids, whereas they are constricted by 20-hydroxyeicosatetraenoic acid. The release of potassium may also contribute to vasodilation (MacVicar and Newman, 2015).

It is today understood that synaptic activation triggers a local signal that leads to functional hyperemia, or regional increase of blood flow. Such a process is effected through a synchronous drop of calcium in the smooth muscle cells and in the pericytes that enwrap the small vessels which supply blood to the activated synapses. Both arterioles and capillaries respond to neuronal activity by actively dilating and thus bringing about the functional hyperemia (Rungta et al., 2018).

The coupling between regional blood flow and neuronal activity in the human brain is the basis of many of the modern imagin methods used to study functional localization (Nippert et al., 2018). When neurons become highly activated in a particular brain field, blood flow and glucose uptake in that particular area increase in a spatiotemporally coordinated manner. Brain imaging methods are used to depict neuroanatomical networks associated with mental acts, such as attention and language perception, and to record signals related to intracranial events subserving cognitive and affective acts. Thus, fMRI (functional magnetic resonance) records fluctuations of local blood flow

across the brain; PET (positron emission tomography) further records the rate of oxygen and glucose metabolism in neurons; and MEG (magnetoencephalography) records the electrochemical signaling of cortical neurons (Billingsley-Marshall et al., 2004; Crosson et al., 2010; Papanicolaou, 2017).

4.5. Astroglial regulation of neurotransmission, learning and memory

Cajal was convinced that astrocytes modulate or influnce neuronal activity. The idea that glia may be involved in information processing, learning and memory, and other higher brain functions has been considered between the 1880s and the 1960s by other neurobiologists as well, including Fridtjof Nansen (1861–1930), Fernando de Castro (1896–1967), and Robert C. Galambos (1914–2010) (Verkhratsky and Butt, 2013).

With current methods, the motility of astroglial process endings, which is mediated by lamellipodia and filopodia, can be observed with two-photon microscopy. The astrocyte-neuron interaction is dynamic and essential for the modulation of synaptic transmission (García-Marín et al., 2007). In particular, learning and memory in the hippocampus is subserved by acetylcholine release from neurons located in the medial septal nucleus and the diagonal band of Broca. The release of acetylcholine from the septohippocampal cholinergic pathway leads to a slow and long-lasting GABAergic inhibition of dentate granule cells via astroglial intermediaries, both in vivo and in vitro. Septohippocampal acetylcholine activates hilar astrocytes, which in turn provide a glutamate-mediated excitation of inhibitory hilar interneurons, thus inhibiting granule cells (Pabst et al., 2016).

4.6. Sleep and wakefulness

By the end of the nineteenth century, several theories of sleep had been put forth, such as the circulation, the vasomotor, the chemical, the combustion, the autointoxication, the evolutionary, and so forth; these were reviewed in detail by Henry Hubbard Foster (1876–1947), at the time a recent graduate with a B.A. from Cornell University, and eventually Professor and Dean of Law at the University of Nebraska (Foster, 1901). In that context, the neuronal and glial amoeboidism theories of the 1890s provided grounds for new, histological theories of sleep.

Cajal viewed the glia as being continuously in a state of flux and modification (Verkhratsky and Butt, 2013). He suggested that protoplasmic (perineuronal) astrocytes may actively regulate the transmission of signals between neurons, and that such a mechanism may underpin the sleep-wakefulness cycle (Fig. 12). Acting like a switch or circuit-breaker between the active and the passive state, astroglia would presumably retract their processes to permit the flow of currents between neurons in the waking state. To induce sleep, astrocytes would extend their processes among neurons, halting the flow of currents (Cajal, 1895a, 1895b; García-Marín et al., 2007; Verkhratsky and

Butt, 2013).

The mechanism theorized by Cajal on the role of astrocytes in natural or induced sleep via their interposition between synapses is echoed in modern studies across various anatomical areas, such as the hypothalamic arcuate nucleus and the magnocellular nuclei (for a complete discussion, see García-Marín et al., 2007).

Cellular rebalancing mechanisms operate in sleep. Electron microscopic and biochemical studies in mice showed that the structure of synapses changes during sleep and thus confirm the concept of synaptic downscaling during sleep and synaptic upscaling during wakefulness (Acsády and Harris, 2017). Measurements of the area of contact between an axon terminal and a dendritic spine, or axon-spine interface, showed a decrease by about 18% during sleep (de Vivo et al., 2017). Hence, a core function of sleep may be to renormalize overall synaptic strength, which is increased by wakefulness (de Vivo et al., 2017).

During sleep, the spine size is also decreased. A truncated form (*Homer1a*) of a gene encoding the scaffold protein Homer moves to the synapse and the content of Gria1 (an ionotropic AMPA-type glutamate receptor) is decreased via an alternative pathway of dephosphorylation. Such a homeostatic downscaling by the weakening and remodeling of synapses may participate in the consolidation of contextual memory (Diering et al., 2017).

In wake periods, synapses are often strengthened, and thus need to be homeostatically readjusted. During slow-wave sleep, synaptic depression dominates via sharp wave and ripple events, i.e., transient high-frequency field oscillations that spontaneously occur in the brain (Draguhn, 2018). Such events induce long-term depression of hippocampal synapses and may help to refine recently acquired memories. In practical terms, neuronal activity during sleep allows us to remember a vast number of items, considering the finite cellular structure of the hippocampus. Clearing neuronal networks from transient memory engrams during sleep consolidates memories. Slow-wave sleep helps to consolidate spatial and declarative memories (Norimoto et al., 2018).

4.7. The dénouement of "el neuronismo"

Cajal rebutted the view of the "reticulum" and, based on his observations, solidified the neuron theory, the cornerstone of our current understanding of the cellular basis of nervous function. Cajal's discovery that nerve cells were independent required a new model for how the nervous system functioned; his proposition that electrical impulses were conducted through chains of nerve cells in a fixed direction (the principle of "dynamic polarization") disproved the reticular theory and led to a whole new understanding of how information is transmitted around the nervous system (Story, 2013). In recognition of the work on the structure of the nervous system, Cajal shared the 1906 Nobel Prize in Physiology or Medicine with his rival, Camillo Golgi (1843–1926), whom he

nevertheless addressed as “the savant of Pavia” (Cajal, 1988). Cajal commented about the joint award: “What a cruel irony of fate to pair, like Siamese twins united by the shoulders, scientific adversaries of such contrasting character!” (Cajal, 1988).

In his “Memoir of Dr. Cajal”, Sherrington, the 1932 Nobel laureate, reckoned: “Is it too much to say of him that he is the greatest anatomist the nervous system has ever known? Cajal made it possible even for a tyro to recognize at a glance the direction taken by the nervous current in the living cell, and in a whole chain of nerve cells. He solved at a stroke the great question of the direction of the nervous currents in their travel through brain and spinal cord” (Cannon, 1949).

Cajal followed up on his “Conjectures” (Cajal, 1895a) with the preface (Cajal, 1896, 1897) to a book authored by Pedro López-Peláez y Villegas (1863–1903). The title of that book was “Normal Anatomy of the Human Spinal Cord with Some Clues on Comparative Anatomy” (López-Peláez, 1897). A few years earlier, in 1892, López-Peláez had occupied the Chair of Anatomy at the University of Granada, and, in 1893, he was admitted as a member to the Royal Granada Academy of Medicine (Medina Doménech et al., 1994; Gutiérrez Galdó, 2003).

In this sequel (Fig. 3) Cajal revisited some of the hypotheses set forth earlier and presented crucial arguments to support the neuron theory. He placed special emphasis on the differentiation of function between spinal motor neurons and cortical pyramidal cells, which subserve movement and consciousness, respectively, despite their common morphological characteristics.

For Cajal, the final stage where everything was made clear in the development of the neuron theory, in other words, its dénouement, was a lifelong endeavor, from his early neurohistological works to the last manuscript in his deathbed (Cajal, 1952). Along that path, “like a Renaissance anatomist,” he sought to explain physiology by anatomy, venturing into hypothetical speculations, with uneven success (Pi-Suñer and Pi-Suñer, 1936). Contrasting with his exact neuroanatomical papers, in which “speculative development follows the observed facts very closely” and “general conceptions are legitimate deductions of plausible hypotheses, susceptible to confirmation a posteriori” (Cajal, 1988), Cajal later viewed his “Conjectures” as a venturesome lucubration, where unfounded imagination had run riot, lagging in correspondence with empirical data, save a few concepts that hit the mark, such as the “impression unit” and the principle of the “conduction avalanche” (Cajal, 1988). Cajal felt that the rest of the enunciated conceptions would rapidly fall “into deserved oblivion, for science is interested only in ideas open to experimental verification and stimulative to further work” and did not cite that paper much in his subsequent anatomical works.

Nonetheless, as Efrain C. Azmitia put it, “The emerging models of the mind would be well served by a review of the theoretical writings of Cajal … dealing with higher order brain functioning [which] have not received equal appreciation as his work on brain anatomy, [while] the longevity of Cajal’s views reflect his relation with the brain and its higher functioning” (Azmitia, 2007).

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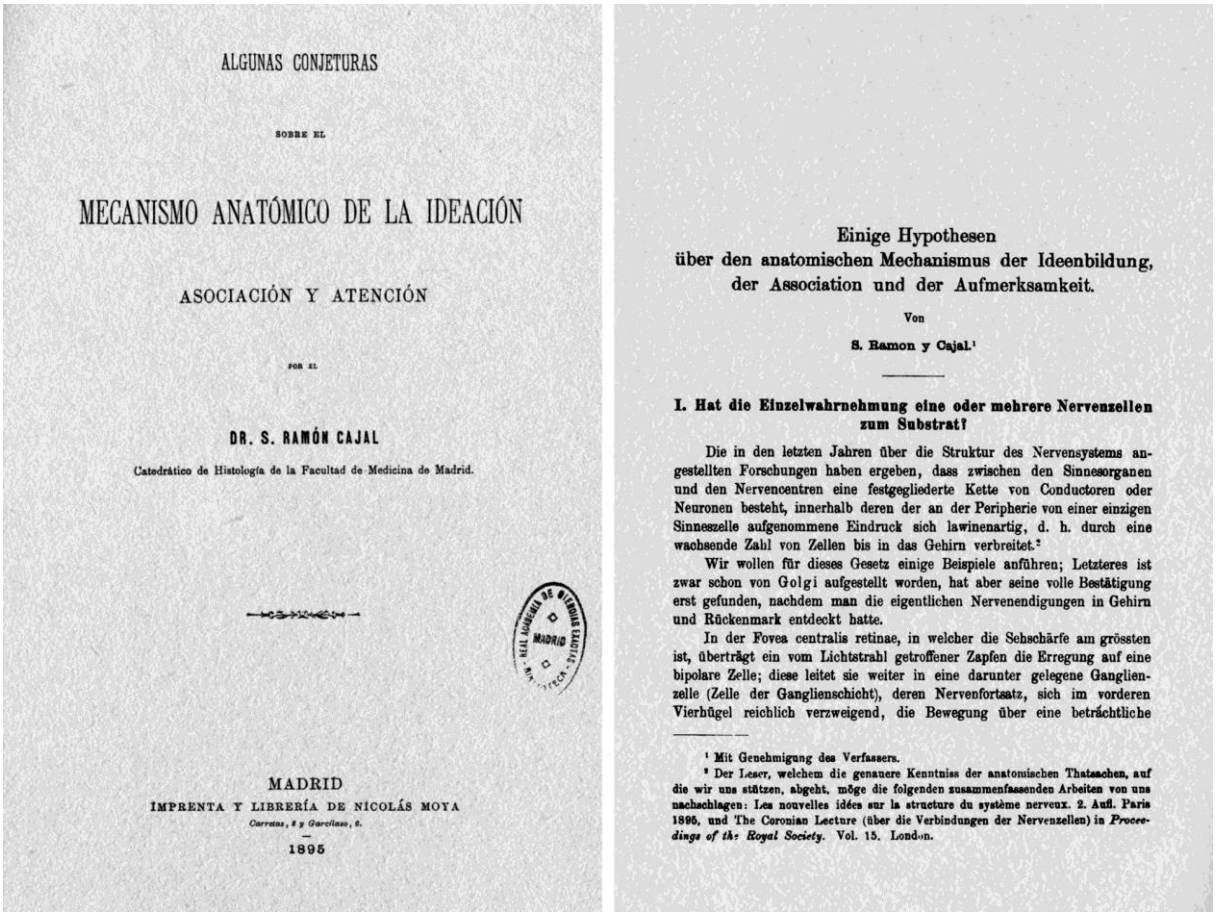
Figure captions

Fig. 1. The 42-year-old Cajal, bearing his academic medal. Engraving based on a portrait photograph taken by Julio Derrey ("First Royal photographer of Valencia") in 1894, the year that Cajal received a doctorate *honoris causa* from the University of Cambridge and gave the Croonian Lecture. Frontispiece of *La Ilustración Española y Americana*, Madrid, issue of 8 March 1894, volume 38, number 9, page 141, with an article by José Rodríguez Mourelo (1857–1932) under the title "El doctor Cajal" on pages 146–147. Author's archive.



ALGUNAS CONJETURAS

SOBRE EL

MECANISMO ANATÓMICO DE LA IDEACIÓN

ASOCIACIÓN Y ATENCIÓN

POR EL

DR. S. RAMÓN CAJAL

Catedrático de Histología de la Facultad de Medicina de Madrid.

MADRID
IMPRENTA Y LIBRERÍA DE NICOLÁS MOYA
Carretas, 8 y Garcilaso, 6.
1895

Einige Hypothesen
über den anatomischen Mechanismus der Ideenbildung,
der Association und der Aufmerksamkeit.

Von

S. Ramon y Cajal.[1]

I. Hat die Einzelwahrnehmung eine oder mehrere Nervenzellen zum Substrat?

Die in den letzten Jahren über die Struktur des Nervensystems angestellten Forschungen haben ergeben, dass zwischen den Sinnesorganen und den Nervencentren eine festgegliederte Kette von Conductoren oder Neuronen besteht, innerhalb deren der an der Peripherie von einer einzigen Sinneszelle aufgenommene Eindruck sich lawinenartig, d. h. durch eine wachsende Zahl von Zellen bis in das Gehirn verbreitet.[2]

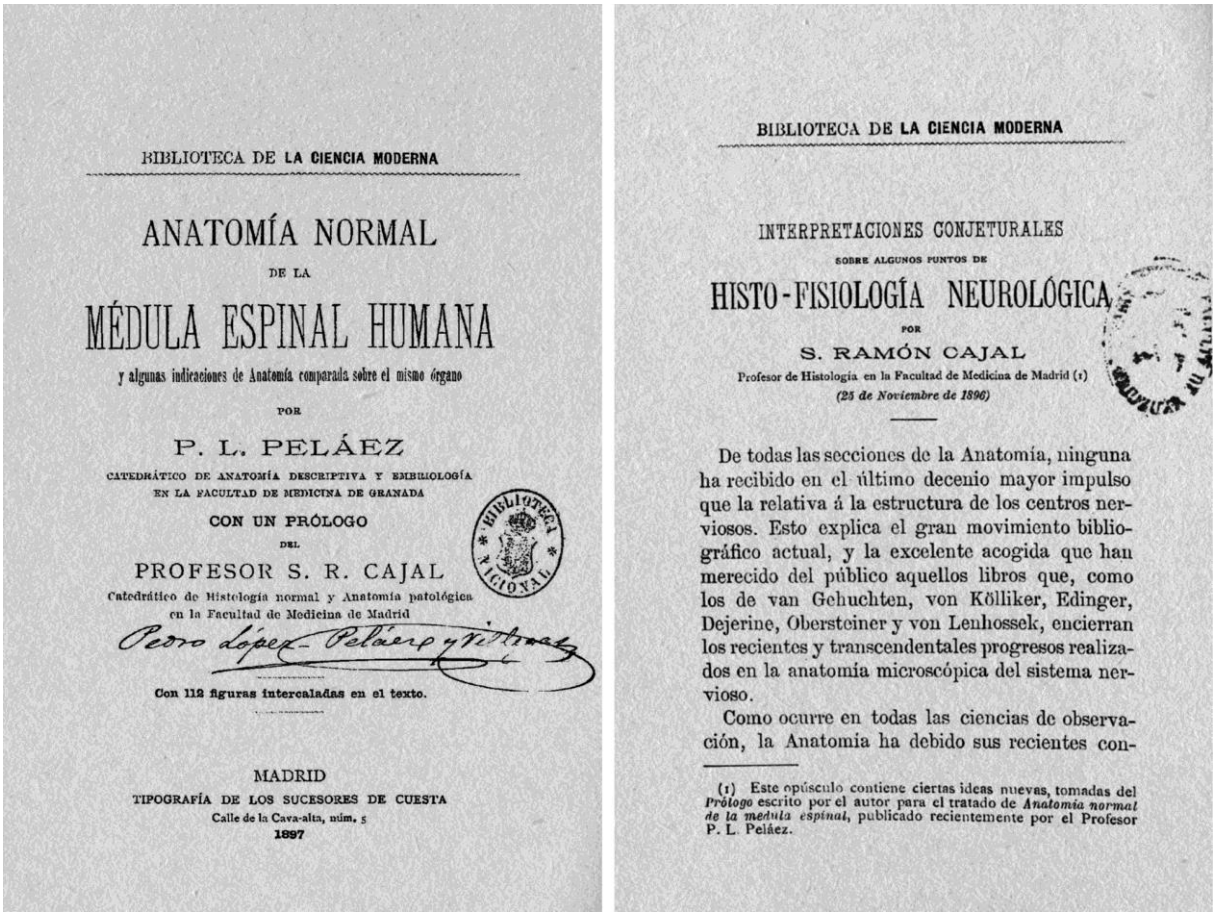
Wir wollen für dieses Gesetz einige Beispiele anführen; Letzteres ist zwar schon von Golgi aufgestellt worden, hat aber seine volle Bestätigung erst gefunden, nachdem man die eigentlichen Nervenendigungen in Gehirn und Rückenmark entdeckt hatte.

In der Fovea centralis retinae, in welcher die Sehschärfe am grössten ist, überträgt ein vom Lichtstrahl getroffener Zapfen die Erregung auf eine bipolare Zelle; diese leitet sie weiter in eine darunter gelegene Ganglienzelle (Zelle der Ganglienschicht), deren Nervenfortsatz, sich im vorderen Vierhügel reichlich verzweigend, die Bewegung über eine beträchtliche

[1] Mit Genehmigung des Verfassers.

[2] Der Leser, welchem die genauere Kenntniss der anatomischen Thatsachen, auf die wir uns stützen, abgeht, möge die folgenden zusammenfassenden Arbeiten von uns nachschlagen: Les nouvelles idées sur la structure du système nerveux. 2. Aufl. Paris 1895, und The Croonian Lecture (über die Verbindungen der Nervenzellen) in *Proceedings of the Royal Society*. Vol. 15. London.

Fig. 2. Title page of the Spanish edition of Cajal's "Conjectures" printed as a separatum (Cajal, 1895a), left. Courtesy of Real Academia de Ciencias Exactas, Físicas y Naturales, Madrid. Title page of the same article published in German (Cajal, 1895b), right. Credit: Archive.org.



BIBLIOTECA DE LA CIENCIA MODERNA

ANATOMÍA NORMAL

DE LA

MÉDULA ESPINAL HUMANA

y algunas indicaciones de Anatomía comparada sobre el mismo órgano

POR

P. L. PELÁEZ

CATEDRÁTICO DE ANATOMÍA DESCRIPTIVA Y EMBRIOLOGÍA EN LA FACULTAD DE MEDICINA DE GRANADA

CON UN PRÓLOGO

DEL

PROFESOR S. R. CAJAL

Catedrático de Histología normal y Anatomía patológica en la Facultad de Medicina de Madrid

Con 112 figuras intercaladas en el texto.

MADRID

TIPOGRAFÍA DE LOS SUCESORES DE CUESTA

Calle de la Cava-alta, núm. 5

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BIBLIOTECA DE LA CIENCIA MODERNA

INTERPRETACIONES CONJETURALES

SOBRE ALGUNOS PUNTOS DE

HISTO-FISIOLOGÍA NEUROLÓGICA

POR

S. RAMÓN CAJAL

Profesor de Histología en la Facultad de Medicina de Madrid (1)

(25 de Noviembre de 1896)

De todas las secciones de la Anatomía, ninguna ha recibido en el último decenio mayor impulso que la relativa á la estructura de los centros nerviosos. Esto explica el gran movimiento bibliográfico actual, y la excelente acogida que han merecido del público aquellos libros que, como los de van Gehuchten, von Kölliker, Edinger, Dejerine, Obersteiner y von Lenhossek, encierran los recientes y transcendentales progresos realizados en la anatomía microscópica del sistema nervioso.

Como ocurre en todas las ciencias de observación, la Anatomía ha debido sus recientes con-

(1) Este opúsculo contiene ciertas ideas nuevas, tomadas del *Prólogo* escrito por el autor para el tratado de *Anatomía normal de la medula espinal*, publicado recientemente por el Profesor P. L. Peláez.

Fig. 3. Title page of the monograph of López-Peláez (1897) on the anatomy of the human spinal cord, with a preface by Cajal (1897), left. Credit: Biblioteca Digital Hispánica, Biblioteca Nacional de España, (http://www.bne.es/es/Catalogos/BibliotecaDigital). Title page of Cajal's text printed as a separatum (Cajal, 1896), right. Courtesy of Bibliothèque Interuniversitaire de Santé, Paris.

Bewegungserscheinungen im Gehirn von Leptodora hyalina.

Von R. WIEDERSHEIM.

Mit 5 Abbildungen.

Schon seit einer Reihe von Jahren war mir aufgefallen, daß in den feineren Strukturverhältnissen des oberen Schlundganglions, d. h. des Gehirnes, von Leptodora hyalina bei verschiedenen Individuen derselben Größe und desselben Geschlechtes mehr oder weniger bedeutende Verschiedenheiten existieren. Im Oktober dieses Jahres konnte ich sogar konstatieren, daß bei einem und demselben Individuum, welches ich mehrere Tage hindurch lebendig in der Gefangenschaft hielt, die betreffenden Strukturverhältnisse einem fortwährenden Wechsel unterworfen waren, ja, daß gewisse Elementarorgane des Gehirnes zu verschiedenen Stunden des Tages eine wechselnde Beschaffenheit und Gruppierung zeigten.

R. Wiedersheim

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3. Sind die Ganglienzellen amöboid?

Eine Hypothese zur Mechanik psychischer Vorgänge.

Von Prof. Dr. **Rabl-Rückhard** in Berlin.

Bekanntlich sind eine Anzahl Ganglienzellen durch den Besitz von zweierlei Arten von Fortsätzen ausgezeichnet: einerseits der Axencylinder- oder Deiter'sche Fortsatz, der ungetheilt als markhaltige Faser das Centralorgan verlässt, und andererseits die mehrfach vorhandenen sogenannten Protoplasmafortsätze, die sich, unter Abgabe von zahlreichen Verästelungen, in ein feines nervöses Netzwerk auflösen. — Wir finden diese Art von Ganglienzellen ausschliesslich in den nervösen Centralorganen, sowie in den Schichten der Retina, als multipolare Ganglien der grauen Substanz des Rückenmarks, als Pyramidenzellen der Grosshirnrinde, als Purkinje'sche Zellen des Kleinhirns, als Ganglion nervi optici. Vergleichen wir sie mit den uni- und bipolaren Ganglienzellen, so stellen sie offenbar höher differenzirte Gebilde mit entsprechenden höheren Aufgaben dar.

Professor Dr. Rabl-Rückhard

Fig. 4. Cabinet photo of Robert Wiedersheim, left, taken at Freiburg im Breisgau in 1895. Credit: New York Academy of Medicine, Carte-de-Visite Collection (http://dcmny.org/islandora/object/nyam%3A673). The original paper by Wiedersheim (1890) in the *Anatomischer Anzeiger*, upper right, titled "Movement phenomena in the brain of *Leptodora hyalina*"; the original paper by Rabl-Rückhard (1890) in *Neurologisches Centralblatt*, lower right, titled "Are nerve cells amoeboid?—A hypothesis on the mechanism of mental processes."

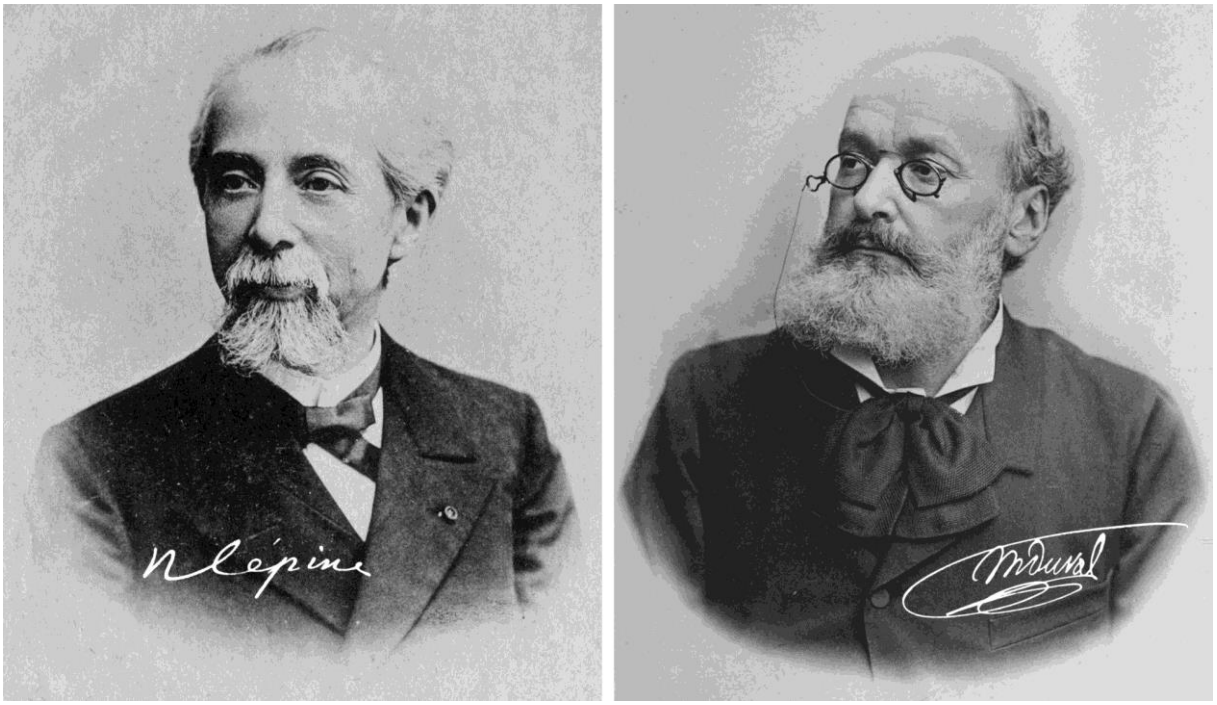


Fig. 5. Raphaël Lépine, left; collotype photo (author's archive). Mathias Duval, right (Hervé, 1907); credit: Archive.org.

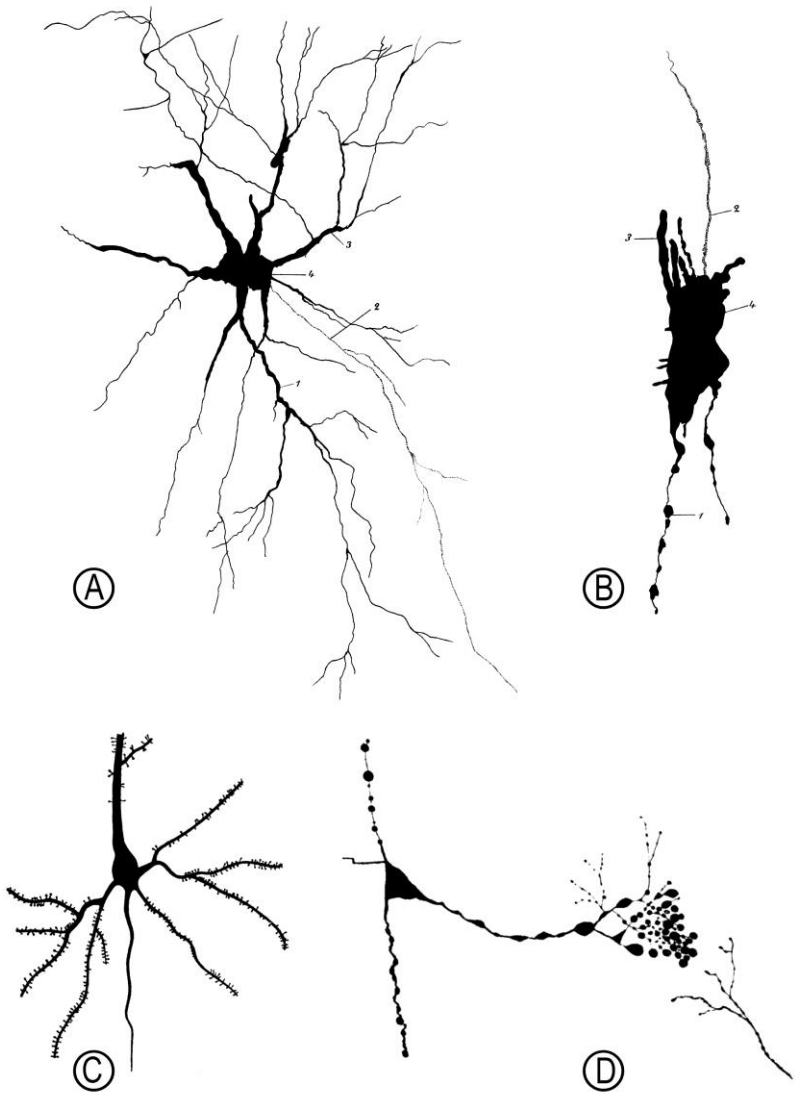
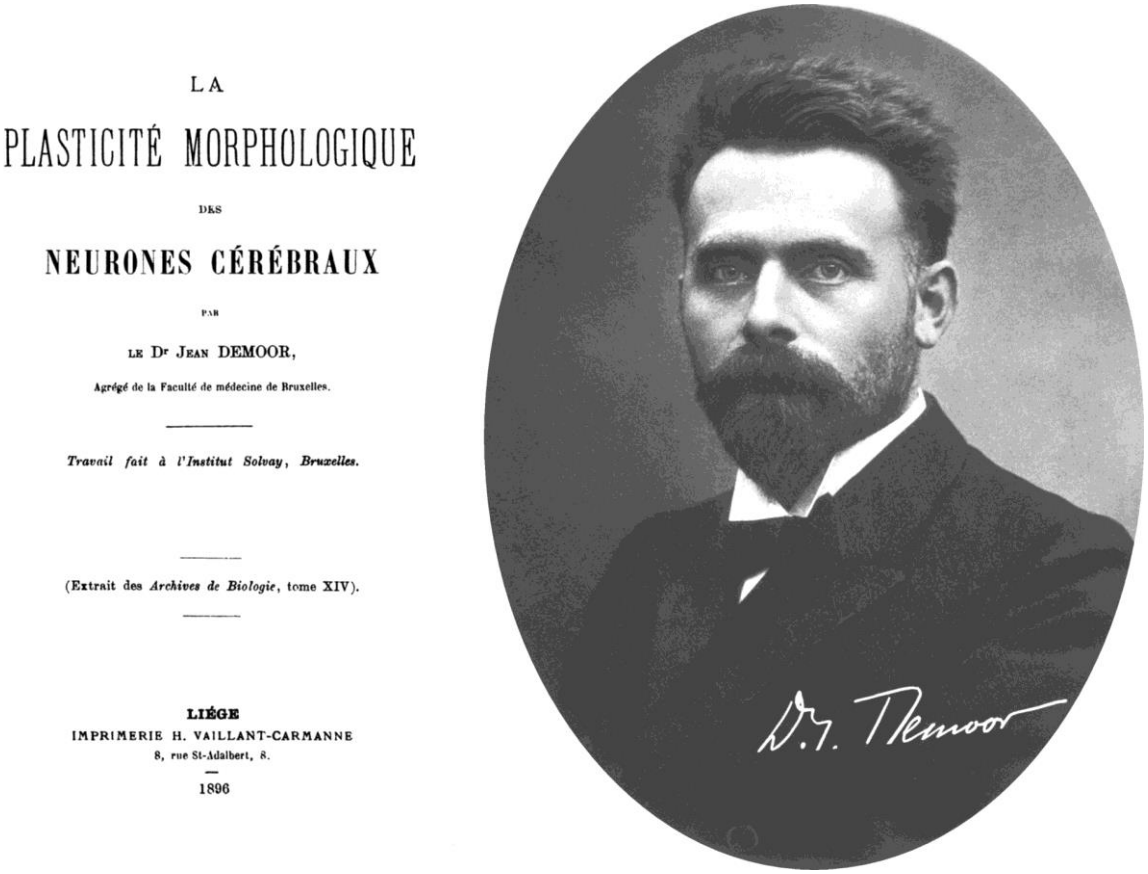


Fig. 6. (A) A neuron from the spinal cord of a rabbit anesthetized for 2¼ h; 1 and 3, dendritic processes fully relaxed; 2, axon; 4, cell soma (Odier, 1898). **(B)** A neuron from the spinal cord of a rabbit subjected for 5 h to an induced current. Notable retraction of the dendritic processes; 1, accumulated masses along one dendritic process; 2, axon with thickening at places; 3, dendritic process strongly retracted and thickened; 4, cell soma. Prepared according to the Cajal modification of the Golgi method; drawings made with the camera lucida at a magnification of 1800 diameters and slightly enlarged at the pantograph (1898). **(C)** A nerve cell equipped with piriform processes, after Stefanowska (Binet, 1897). **(D)** A mitral cell from the olfactory bulb of an adult mouse exhausted by fatique. Magnification 350 diameters. The dendrites have a pearled state. As a result of the formation of bulges in a ball, the dendritic bouquet is retracted, it is no longer in contact with the arborisation of the neighboring olfactory process, which has become slightly varicose itself. Unpublished figure communicated by Manouélian to Binet (1897).



LA

PLASTICITÉ MORPHOLOGIQUE

DES

NEURONES CÉRÉBRAUX

PAR

LE Dr JEAN DEMOOR,

Agrégé de la Faculté de médecine de Bruxelles.

Travail fait à l'Institut Solvay, Bruxelles.

(Extrait des *Archives de Biologie*, tome XIV).

LIÉGE
IMPRIMERIE H. VAILLANT-CARMANNE
8, rue St-Adalbert, 8.
1896

Fig. 7. Title page of the article by DeMoor (1896b), left, titled "The morphological plasticity of cerebral neurons". Credit: Archive.org. Portrait of Jean DeMoor, right. Credit: Images from the History of Medicine, U.S. National Library of Medicine, Bethesda, MD.

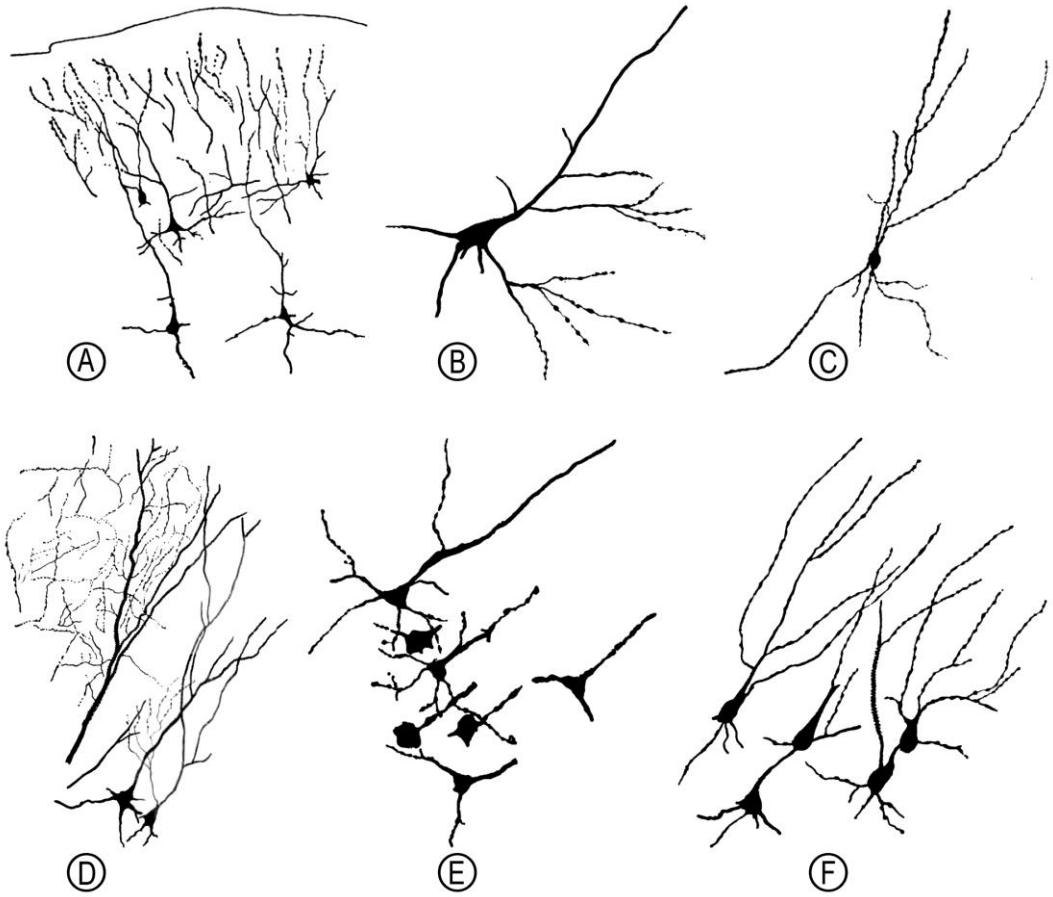


Fig. 8. Golgi preparations drawn by DeMoor (1896b). **(A)** Cortical neurons of a morphinized dog; the dendritic processes are moniliform. **(B)** Cortical neuron from a morphinized dog; detail of the beaded structure. **(C)** A cortical neuron of a morphinized dog; beaded state of Martinotti cells dendrites. **(D)** Cortical neurons in a dog put to deep sleep with chloral hydrate; beaded state of the fine neuronal ramifications. **(E)** Neurons of a dog whose brain was subjected to electrical current; the cell soma is deformed and dendrites are moniliform. **(F)** Neurons in the fascia dentata of a dog whose brain was subjected to electrical current; moniliform dendrites.

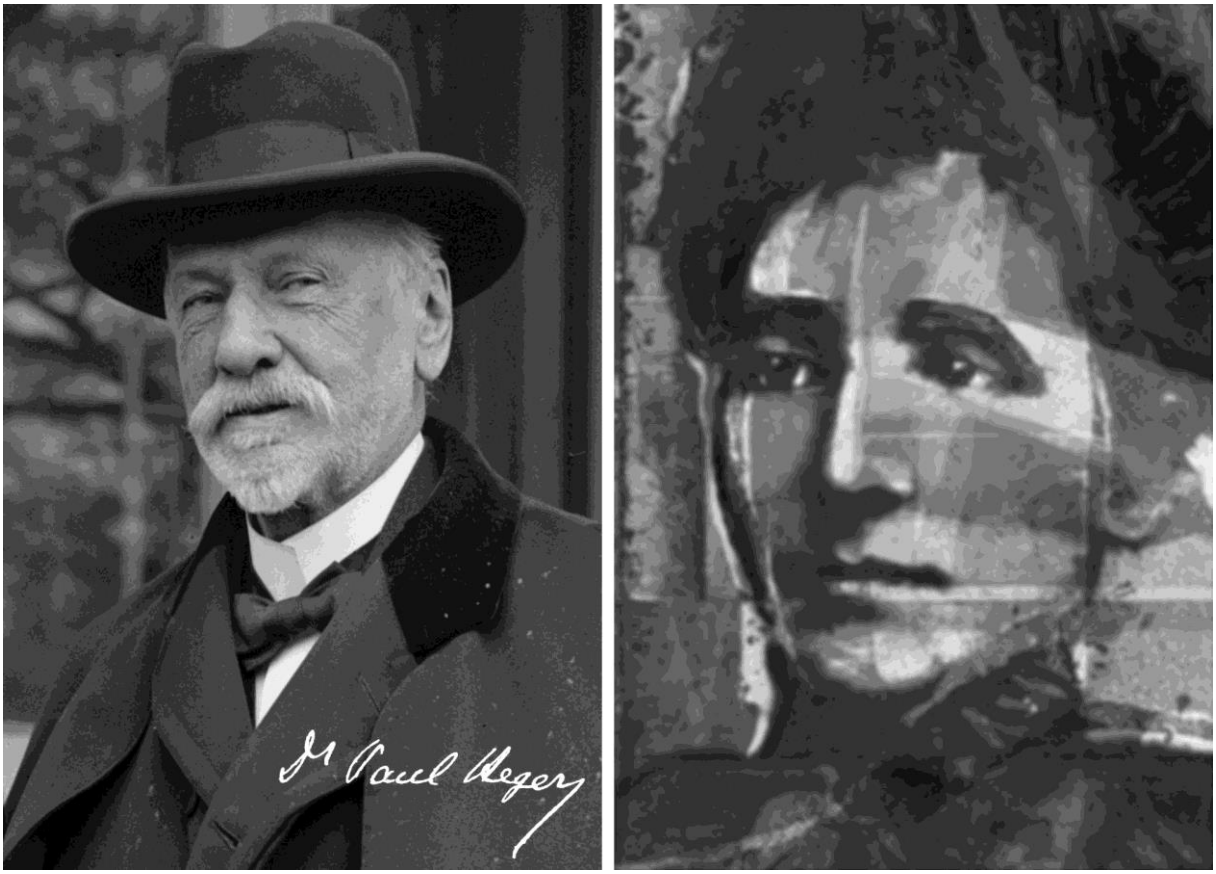


Fig. 9. Paul Héger, left. Credit: Library of Congress, Washington, DC (http://www.loc.gov/pictures/item/2016848260). Micheline Stefanowska, right. Credit: Section of Biology Hall of Fame, University of Geneva Faculty of Science, Switzerland (http://biologie.unige.ch/fr/la-section/le-hall-dhonneur).

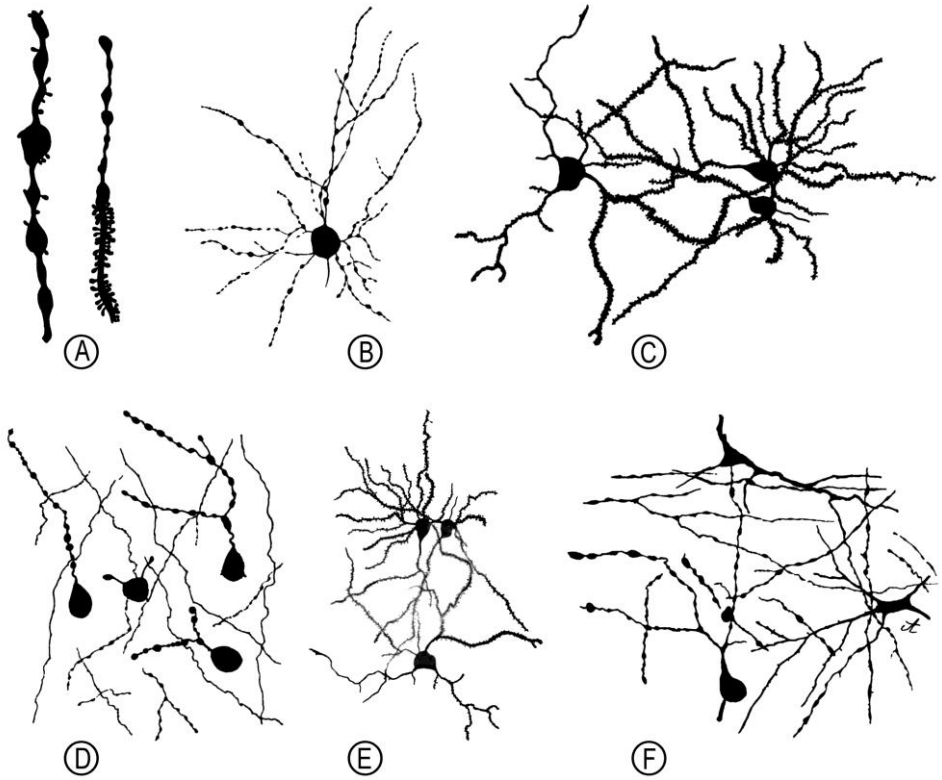


Fig. 10. Nerve cell drawings from the experiments of Stefanowska (1897, 1900a, 1900b). **(A)** On the left, an apical dendrite in a varicose state with some piriform appendages; on the right, a dendritic process whose upper varicose segment is completely devoid of piriform appendages, whereas the lower part is normal. Guinea pig, Zeiss objective C, ocular 4 (Stefanowska, 1897). **(B)** A cortical neuron of the occipital region from a mouse that was etherized for 20 min and was left to live for 5 days afterwards. **(C)** Neurons in the caudate nucleus of a mouse etherized slowly until death; the cells do not present any alteration, and are laden with numerous piriform appendages. **(D)** Neurons of the superior colliculus from a mouse killed by ether. The cell bodies are swollen, and the dendrites are beaded. Magnification 289 diameters (Stefanowska, 1900a). **(E)** Normal neurons in the caudate nucleus; all dendrites have a regular course and are lined with numerous piriform appendages. Magnification 280 diameters. **(F)** Normal neurons in the spinal cord of a decapitated mouse; the dendrites are covered with swellings variable in form and volume, but generally less regular than those induced by the action of ether (Stefanowska, 1900b).

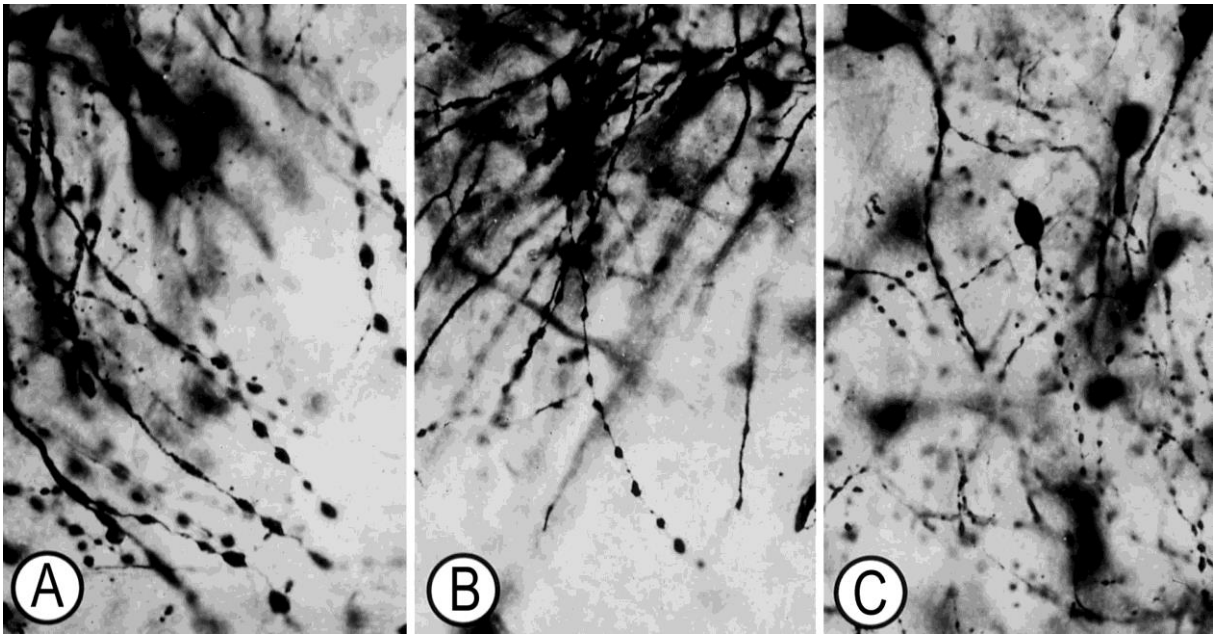


Fig. 11. A modern histological Golgi-Cox preparation showing varicose dendrites in the substantia nigra pars reticulata of a normal, a heterozyous, and a homozygous weaver mutant mouse. Varicosity diameter is reduced in the mutants, and the intervaricose segments are elongated. Heterozygous mice manifest epileptic discharges, associated with a severe atrophy and loss of dopaminergic dendrites and therefore a disruption of striatonigral transmission; homozygous mice manifest a movement disorder, resulting from neuron loss in the substantia nigra pars compacta and the cerebellar cortex, owing to a missense mutation of the potassium channel gene *Kcnj6* (or *Girk2*) in mouse chromosome 16. The G→A substitution in nucleotide 953 of *Girk2* leads to a Gly→Ser replacement at residue 156 of the encoded protein in the pore-forming H5 region that disturbs the homomeric channel properties and producess a lethal depolarized state in weaver neurons. Magnification 150 diameters (Triarhou, 2002).

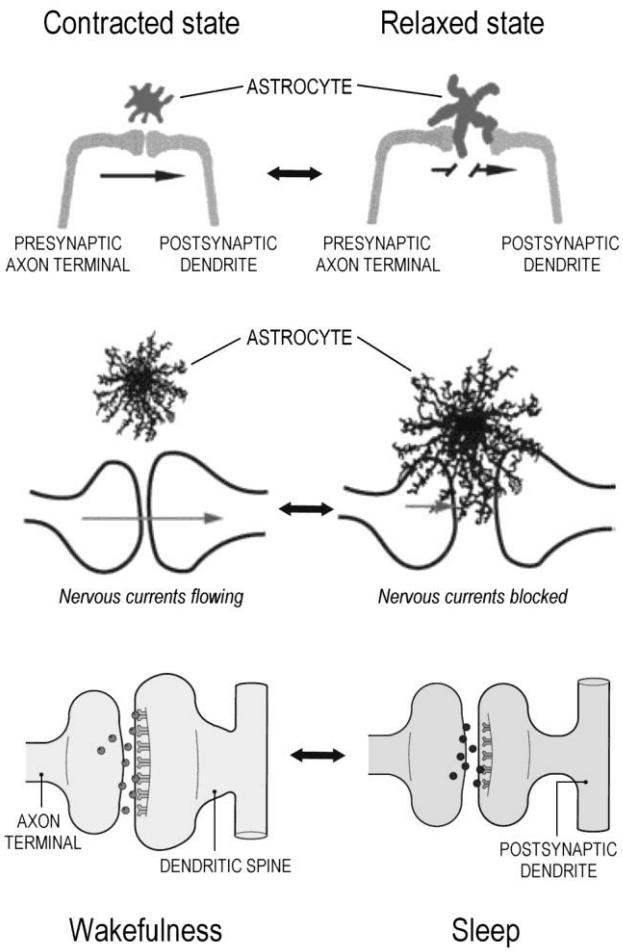


Fig. 12. The upper drawing illustrates Cajal's proposition regarding the awake and sleep states, whereby astroglia contract or extend their processes, like amoeboid pseudopodia, to allow or prevent the flow of the nervous current at the synapse, thus acting as circuit-breakers. The drawing in the middle shows the same concept: astrocytes regulate wakefulness and sleep phenomena by contracting or relaxing their processes, respectively permitting or interrupting the flow of information from one neuronal element to the next. The lower scheme depicts a modern concept of the dynamic interchanges at an axospinous synapse between the awake and sleep states; in sleep, the contact area between the presynaptic terminal and the postsynaptic dendritic spine decreases, accompanied by a decrease in the content of neurotransmitter receptor molecules at the postsynaptic density, such as the ionotropic AMPA 1 receptor, Gria1. Based on the work of García-Marín et al. (2007), Verkhratsky and Butt (2013), and Acsády and Harris (2017), respectively, with slight modifications.