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Through neuronal avalanches to consciousness: conjectures and elaborations

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Abstract

The concept of the “conduction avalanche” as a mechanism of signal propagation in the central nervous system was introduced in 1895 by Santiago Ramón y Cajal. Through such a mechanism, stimuli received by sensory receptor cells would be augmented as they reached 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 and up to 2003, prominent neuroscientists, including 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, have referred in their writings to the principle of conduction avalanches, crediting Cajal. 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. The topic has become an issue of intensive research over the past 15 years. In this paper, we discuss the basic tenets of the Cajalian principle, followed by an exposition of ideas throughout the 20th century, and an overview, in a modern perspective, of the neuronal avalanche as a mechanism in the current study of the neural bases of consciousness.

Keywords:
Sensory perception
Neuronal avalanche
Consciousness from neurons
Cerebral cortex
Santiago Ramón y Cajal (1852–1934)

"The continued currency of Cajal's work is almost unique in modern biology—how many other observations of a hundred years ago are still fresh and useful in their original form?"

(Purves and Lichtman, 1985)

1. Introduction

The way that signals are transmitted among the cells of the nervous system to produce functional outcomes epitomizes the essence of research on the biological basis of behavior.

One of the mechanisms that integrate nervous signals, which has been intensely studied in the past two decades, is the so-called "neuronal avalanche" (Beggs and Plenz, 2003). A search in PubMed with the terms "neuronal avalanche" or "neuronal avalanches" in the title or abstract yields 131 articles published between 2003 and 2019; in 52 of them, these terms appear in the title.

The idea of a "conduction avalanche" was conceived by Santiago Ramón y Cajal (1852–1934) in 1895 in his pursuit of a psychology grounded on neurobiology and his quest to explore the inner mechanisms of mental acts in terms of cellular anatomy (Fig. 1). Cajal was convinced that cortical architecture was dynamic and that mental processes were related to histological changes (DeFelipe, 2006); he was constantly driven by a desire to sheathe his morphological discoveries with their functional implications (Marijuán, 2001; Sotelo, 2003; López-Muñoz et al., 2008).

After setting the fundamentals of the neuron theory by deciphering the morphology and connections of the nervous system in 1888, Cajal attempted to explain the histophysiological processes that may alter consciousness. Besides his two theoretical constructs—the "Conjectures on the anatomical mechanism of ideation, association and attention" (Cajal, 1895) and the "Conjectural interpretations of certain points in neurological histophysiology" (Cajal, 1896) which we have discussed previously (Antonakou and Triarhou, 2019)—Cajal reiterated the "conduction avalanche" in the original Spanish edition and the French translation of his classical *Texture of the Nervous System* (Cajal, 1899–1904, 1909/1911).

In the present study, we document Cajal's original introduction of the concept of the avalanche of conduction, followed by a brief exposition of that concept as echoed in neurological studies throughout the 20th century. We further present the current concept of neuronal avalanches, which is based on the power laws of physics. Concluding, we attempt to address certain dimensions of consciousness in relation to the Cajalian and the modern connotations of the neuronal avalanche.

2. Cajal’s postulate

The conduction avalanche as conceived by Cajal is reflected in modern definitions as a “type of conduction, in which stimulation of a single neuron may fire many secondary neurons, each of which, in turn, may fire many tertiary neurons” (Lockard, 1977) or as “the situation where one sensory neuron innervates and excites multiple cortical neurons, each of which, in turn, innervates and excites multiple motor or effector cells in a pyramid of excitation” (Swanson, 2003).

Cajal introduced this principle in the first passage of “Conjectures” (Cajal, 1895; Triarhou, 2015; Antonakou and Triarhou, 2019) and credited Golgi for having at one time envisaged this phenomenon. The passage was reused, with minor modifications, in the *Textura* (Cajal, 1899/1904, 1909/1911, 1984, 1995, 1999–2002).

The chain of cells between the sense organs and the cerebral hemispheres is one of the most interesting physiological sequels that can be induced from the morphology and connectivity of neurons. The impression gathered peripherally by a single sensory cell will spread in a ripple effect to multiple chains, such that the number of cells engaged in the conduction would increase, *in an analogy to an avalanche*. As it gathers force, the avalanche accrues a mass of more and more materials (Cajal, 1895, 1984). The cortical grey matter (tertiary sensory areas) forms the base of an influx cone and the origin of new connecting pathways (Cajal, 1937).

If each neuron were connected only to one other neuron in the chain, the nervous impulse elicited by a stimulus would be transmitted linearly. But this is not the case. Each neuron is associated with numerous other neurons through plentiful dendritic and axonal branches.

In the fovea centralis of the retina, a cone photoreceptor stimulated by light transmits its impulse to a bipolar cell, which passes it on to a subjacent cell of the ganglion layer; the profuse axonal ramification of the latter disseminates the motion over a large number of neurons in the lateral geniculate nucleus, whose axons terminate in the visual cortex over a wide radius, contacting through their remifications the dendritic tufts of, and thus activating, numerous pyramidal cells (Cajal, 1895, 1966, 1988).

The “impression unit” (i.e., the single wave received through the action of a given sensory stimulus by a sensory receptor cell) can influence hundreds or thousands of cortical neurons. Accordingly, each retinal image comprises as many impression units as the number of photoreceptor cells that are simultaneously excited. Nonetheless, the diffusion of the impression unit is not unlimited, such that it is possible to localize sensory perceptions to defined cortical fields (Cajal, 1899–1904, 1909/1911).

In the auditory system, hair cells in the organ of Corti transmit the impression they receive to the dendrite of a bipolar cell in the spiral ganglion of the cochlea, which in turn conducts it to the ventral cochlear nucleus. Through the bifurcation and emission of numerous collaterals, every acoustic root fiber propagates the impulse to multiple neurons. Axons of ventral cochlear nucleus cells course to the trapezoid body, where, through numerous collaterals, they engage into a chain of conduction a new series of adjacent neurons in the superior olive, preolivary nucleus, inferior colliculus, and so forth. Lastly, the excitation arrives, through an imposing mass of axons, at the cerebral cortex, where it will spread to an even larger group of pyramidal cells (Cajal, 1895). The flow of neuronal impulses through this series of pathways, from the hair cells to the vestibular nuclei, cerebellum, medial longitudinal fasciculus, and motor nuclei, strongly argues in favor of the theories of dynamic polarization and the conduction avalanche (Cajal, 1995).

The conduction avalanche is also evident in the olfactory apparatus and the somatosensory system. The role of mitral cell axon collaterals, which establish contact with accessory dendrites in the molecular layer of the olfactory bulb, may thus involve transmitting part of the glomerular current of the parent axon to more or less distant mitral cells, exciting more and more fibers (Cajal, 1895, 1995).

In cortical dynamics, sensory perception also results from the function of multiple neurons, and not one. From the scarce number of sensory cells stimulated, the excitation is propagated to the cortex, putting into commotion an extraordinary number of pyramidal cells. A perception is distinguishable from other senses of the same order through the number and respective position of the cortical pyramidal groups that become engaged.

Thus, cortical sensory centers represent an amplified projection of the receptive surface of sense organs (e.g. the retina or the organ of Corti) centrally. Further, the current transmission in the arc between the terminal arbors of thalamic neurons and the soma and apical dendrites of pyramidal cells contributing to the pyramidal tract involves entire groups of cells. The conduction avalanche steadily increases as impulses are transmitted along the pyramidal cell; some impulses, through axon collaterals, influence other pyramidal cells of the same layer by contacting their own accessory dendrites or the apical dendrites of adjacent neurons (Cajal, 1909/1911, 1995).

The molecular layer, because it has mostly connections and few resident neurons, is a structure of increased importance for the conduction avalanche: “Associations 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, where the Martinotti cells with the ascending axons and the multipolar cells of the first cortical layer may play an important role…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 dendritic tufts of pyramidal cells with countless terminal nerve branchlets” (Cajal, 1895).

In his memoir, Cajal (1937) noted that the Italian psychiatrists Eugenio Tanzi (1856–1934) and Ernesto Lugaro (1870–1940) of Florence profited greatly from the principle of the conduction avalanche in their explanation of the putative mechanisms of hallucination, association of ideas, and other mental processes.

Cajal mentioned conduction avalanches in the cerebellum in his sequel paper on neurological histophysiology (Cajal, 1896).

3. Twentieth-century echoes of Cajal's idea

From the turn of the 19th century through most of the 20th, influential anatomists and neurologists reiterated in their writings Cajal's concept of the conduction avalanche.

The anatomist Lewellys Franklin Barker (1867–1943) of Johns Hopkins University (Fig. 1), a foremost American advocate for the neuron theory (Harvey, 1975; Lazar, 2010), wrote: "It is much nearer the truth to think of one neuron coming by means of the terminals of its axon or axons into contact with, and thus perhaps being put into a condition to influence the processes or cell bodies of a few or of many other neurons, the conduction avalanche of Cajal" (Barker, 1899).

The comparative neurologist Charles Judson Herrick (1868–1960) of the University of Chicago devoted a couple of passages to the conduction avalanche in his textbook (Herrick, 1915). He described the avalanche as a mechanism of reinforcement, whereby a single weak afferent nervous signal received by a first-order neuron may be distributed to several second-order neurons, all of which discharge their strengthened nervous impulses into a single final common path or motor center. Such an impulse may be said to accumulate momentum as it advances like an avalanche on a mountain slope, and hence this type of reaction was termed by Cajal conduction avalanche.

The neurologist Francis Xavier Dercum (1856–1931) of Jefferson Medical College (Fig. 1), an intellectual renaissance man who described "adiposis dolorosa" and served as President of the American Philosophical Society (Sorbie, 2009; Patel and Swan, 2014), explained: "A very small stimulus may liberate a large amount of energy; each neuron is a storehouse of energy which needs but the transmitted tap of the impact to release it…Cajal has in this connection employed the expression conduction avalanche" (Dercum, 1922).

In Argentina, Christfried Jakob (1935, 1945) returned to microdynamic and macrodynamic concepts that he had been teaching since the early 1900s, in order to explain the nature of memory and conscious activity (Triarhou and del Cerro, 2006). He investigated neocortical histotopography with macrodynamic and microdynamic events, depicting the most probable trajectories of nervous currents in the cerebral cortex (Fig. 2). Donald Hebb (1949) also brought up the issue of reverberation in neuronal circuits. In his model, multiple complex pathways stand for functional units. An indefinite reverberation might be possible in irregular three-dimensional nets, constituting the anatomical basis of perceptual integration in association areas with multiple parallel units (Fig. 3).

Cajal's pupil Rafael Lorente de Nó (1902–1990) initially acknowledged that "since each internuncial axon branches out and establishes connections with a large number of other internuncial neurons, it is difficult to understand how during continued stimulation the impulses may fail to spread into neighboring channels and engage a progressively increasing number of neurons producing avalanche conduction" (Lorente de Nó, 1938). However, he pointed out (Lorente de Nó, 1933, 1934) that the conduction avalanche, predicted by Cajal strictly on the basis of anatomical divergence, does not necessarily apply to the flow of information through the hippocampal circuitry (Swanson, 1993), and expressed the concern that "the number of neurons engaged in the transmission of a peripheral stimulus should increase each time that a new central station is passed," something that was not in agreement with his own experiments (Fairén, 2007).

When Freeman (1984) inferred that olfactory mitral cells form a population with positive feedback and took that as a confirmation of Cajal's conduction avalanche, Lorente de Nó objected. Cajal had in mind a feedforward recruitment of mitral cells, whereas Lorente de Nó further suggested feedback mechanisms as a prominent feature of neuronal circuits. Lorente de Nó defined two types of circuits based on the capacity to be excited by incoming fibers, the "multiple-type" and the "closed-type" neuronal chains. Cajal's avalanche conduction, whereby a weak sensory stimulus is amplified by activating a much larger number of neurons to attain a cognitive threshold, is in accord with the open multiple-type chain, which is based on the plurality of connections, whereas the closed-type chain reflects the principle of reciprocal connections, what we currently refer to as feedback loops, and which apparently eluded Cajal's thought (Fairén, 2007; Rodríguez and Verkhratsky, 2009).

The neuroanatomist Hartwig Kuhlenbeck (1897–1984) of the University of Pennsylvania also argued that Cajal, despite many of his actual findings that clearly indicated the substantial importance of feedback, failed to realize the significance of that principle, which, apparently, he merely subsumed under the conduction avalanche concept (Kuhlenbeck, 1975).

On the other hand, Kuhlenbeck (1975, 1978) credited Cajal for recognizing the rapid dispersion of activity through nerve cell populations in the neuronal network and subsumed it under the conduction avalanche type of transmission. Kuhlenbeck subordinated the avalanche to the generalized principle of one-to-many transformations (e.g. divergence), its opposite being the many-to-one transformations (e.g. convergence). In modern terms, the conduction avalanche can obviously be kept in bounds and become suppressed by synaptic inhibition, a process not properly recognized by Cajal. An additional constraint counteracting the conduction avalanche is provided by physiological thresholds. If inhibition is experimentally suppressed, the resulting widespread convulsions could be conceived as manifestations of a conduction avalanche (Kuhlenbeck, 1975).

Kuhlenbeck (1975) was wrong in stating that "strangely enough, Cajal does not specifically refer to the cerebellar cortex, which, as manifestly shown by his own remarkable studies, displays one of the most clear-cut instances of conduction avalanche." He was right insofar as Cajal did not specifically discuss conduction avalanche in the cerebellum in the *Histologie* (Cajal, 1909/1911). Rather, Cajal expanded the idea of the conduction avalanche to the cerebellum in the "Conjectural Interpretations" (Cajal, 1896), after explaining neuronal connections and divergent systems of conduction:

> 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 (Cajal, 1896; Triarhou, 2015; Antonakou and Triarhou, 2019).

Apparently, it was Herrick (1915) who alluded to conduction avalanches in the cerebellum, implying the *Histologie* (Cajal, 1909/1911) as a source. Cornelius U. Ariëns Kappers (1877–1946) also cited the *Histologie* as the source of the cerebellar discussion. Herrick (1915) wrote:

> Since each fiber from the inferior cerebellar peduncle branches extensively and reaches many granule cells, and since the axon of each granule cell reaches the dendrites of a very large number of Purkinje cells, a single incoming nervous impulse may excite a very large number of Purkinje cells, and thus its physiological effect may be greatly enhanced. The same result is also secured by the action of basket cells and other forms of neurons with short axons within the cerebellar cortex, each of which may discharge powerful impulses directly upon several Purkinje cells…This type of reaction has been termed conduction avalanche, and its mechanism is similar to that found in the olfactory bulb, but much more complex.

Subsequently, Ariëns Kappers et al. (1936) repeated:

> The stored-up neuronic energy of many Purkinje cells may be released by the stimulation of relatively few proprioceptive terminations. This is typical of the conduction avalanche described for the cerebellum by Cajal…By such mechanisms impulses entering the cerebellum over relatively few fibers may be discharged to many Purkinje cells…The whole mechanism was conceived by Cajal as a means of increasing the response and was termed by him as an avalanche type of conduction. No account of cerebellar function can fail to take account of the fact that in its cellular organization it presents the structural basis for building up or reinforcing stimuli in the sense implied by Cajal in the term conduction avalanche as above outlined…The histological structure indicates that the impulses brought into the cerebellum are built up and strengthened along the lines of Cajal's theory of conduction avalanche…The molecular layer of the olfactory bulb is a region of reinforcement of stimuli, providing the anatomic basis for a type of conduction not dissimilar in principle to the avalanche conduction as described for the cerebellum by Cajal.

Glickstein (1987) and Glickstein and Yeo (1990) later repeated Cajal's speculation concerning the cerebellar cortex: the widespread ramification of pontocerebellar mossy fibers on granule cells and the ensuing great magnification of activated parallel fibers would produce a conduction avalanche from Purkinje cells.

As the 20th century was coming to a close, Shepherd (1991) revived Cajal's idea of a nervous excitation circulating through axonal collaterals and their connections to produce a conduction avalanche as a mechanism for bringing large neuronal populations into coordinated activity. Llinás (2003) revisited Cajal's avalanche in the functional organization of divergent neuronal networks, such that a small, well-defined stimulus may lead to the activation of numerous neurons, an important attribute for the conscious perception of a sensory stimulus of even the smallest strength.

Cajal's major discovery, dating to 1888, is considered to be the contiguity of nerve cells in their functional interaction; their contacts were termed "synapses" by Sherrington in 1897 (Purves and Lichtman, 1985). An important principle regarding the functions of neurons is that they inhibit and modulate one another, as often as they excite. Cajal considered all synaptic connections to be excitatory (Glickstein and Yeo, 1990). Although Cajal did not explicitly think of inhibitory potentials, he nonetheless had some clue on inhibition: "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 nerve fibers or the interstitial matrix…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" (Cajal, 1895).

Llinás (2003) explains that the idea of inhibition as a neuronal property was missing in Cajal's description of network function. However, Cajal felt that inhibition existed and referred e.g. to the crossed inhibitory reflex in the spinal cord and to the fact that cortical input to the spinal cord was, under certain conditions, accompanied by the inhibition of segmental reflexes (Cajal, 1899–1904). Not having defined inhibition as a specialized neuronal function, Cajal (1899–1904) proposed that such inhibition was a form of saturation that would occur with very large incoming messages. Our present understanding of inhibition had to await its demonstration in chemical synaptic neurotransmission by Eccles (1961).

4. The modern conception of the neuronal avalanche

The term “neuronal avalanche” re-emerged in the neuroscientific literature in 2003, much more specifically defined, based on the power laws of physics. Typically, the activity patterns of cortical neuron networks included oscillations, synchrony and waves. The neuronal avalanche has been added as a fourth, different mode of activity, with complex emergent properties (Beggs and Plenz, 2003). That idea was inspired by systems composed of nonlinear units that interact locally, organize into a critical state, and propagate in nature, including avalanches, earthquakes, and forest fires.

In that modern context, “neuronal avalanches” were defined as cascades of activity bursts in neuronal networks, the size distribution of which can be mathematically modelled after a power law, similar to critical sandpile models (Bak et al., 1987; Beggs, 2007). In this case, dynamic systems with spatial degrees of freedom naturally evolve into a self-organized criticality, whereby the flicker (*1/f*) noise can be identified with the dynamics of the critical state (Bak et al., 1987; Pasquale et al., 2008).

Neuronal avalanches have been described in both acute cortical slices and in slices cultured in vitro (Beggs and Plenz, 2003, 2004; Friedman et al., 2012; Hernandez-Urbina and Herrmann, 2016). Such cortical slices manifest brief bursts which last hundredths of a second and are separated by quiscent periods that last several seconds. When a multielectrode array is used to record from the slices, the number of electrodes that are driven over threshold during a burst displays the approximate distribution of a power law; that trend is reproducible and highly robust (Beggs, 2007).

Comparable cascading behavior was documented in the macaque monkey with in vivo electrophysiology (Petermann et al., 2009) and in the human brain with functional MRI and magnetoencephalography (Kitzbichler et al., 2009). Such a convergence suggests that the dynamic principles of in vitro functional networks at the microscale may operate in the intact nervous system at a macroscale level (Fornito et al., 2016).

The power law that neuronal avalanches follow is a signature of their fractal organization in time. Particularly in nervous systems, axonal and dendritic branching patterns are fractals in anatomical space. In addition to the propagation of neuronal avalanches, power laws in the brain also underpin: the distribution of periods of phase synchrony between activity time courses that are recorded by means of magnetoencephalography or functional MRI; the power spectrum of blood-oxygen-level dependent (BOLD), electroencephalography, and electrocorticography signal fluctuations; and the allometric scaling of brain size in phylogeny (Fornito et al., 2016).

As spatiotemporal patterns of neuronal activity, neuronal avalanches spontaneously occur in the upper neocortical layers; their pattern reflects a fast propagation of local synchrony and a recurring spatiotemporal diversity. The functional linking of cortical sites into avalanches occurs on all spatial, fractally organized scales (Lombardi et al., 2014). Teramae and Fukai (2007) extended the avalanche-like spiking activity specifically to the synaptic wiring of pyramidal cells and cortical interneurons, suggesting a complex topological design of local cortical circuits. Thus, network topology plays a leading role in shaping the avalanche dynamics (Yaghoubi et al., 2018). In vivo and in vitro experiments in rats, as the animals transition from the anesthetized to the awake state, demonstrate that neuronal avalanches are linked to the global physiological state of wakefulness and that the cortical resting activity organizes as avalanches from the firing of local pyramidal cell groups to global population activity (Bellay et al., 2015).

A branching parameter optimizes the transmission of information in feedforward networks and prevents runaway network excitation. Thus, in its critical state, the network can balance the competing demands of signal transmission and network stability, and avalanches may reflect the transient formation of nerve cell assemblies in the cerebral cortex (Beggs and Plenz, 2003; Plenz and Thiagarajan, 2007). The size of the avalanche and its quiet times are functionally correlated: smaller avalanches tend to be associated with faster, whereas larger avalanches tend to be associated with slower “nested” oscillations (Lombardi et al., 2014).

During the propagation of avalanches, plastic adaptation governs how the structure of the neuronal network evolves, slowly changing into a branched structure where the connectional loops are marginal (Michiels van Kessenich et al., 2016). Such an adaptation follows the principles of Hebbian plasticity, whereby synapses between correlated neurons are strengthened and those which are not used become weakened (Hebb, 1949). Hebbian-like rules also seem to govern the plasticity observed in the early stages of human vision, which has been shown to be affected by perceptual learning via a cascade of local connections (Polat and Sagi, 1994).

In the visual cortex of anesthetized cats, spontaneous activity characterizes the neuronal avalanches in local field potentials. Power law in spike clusters is accompanied by stronger temporal correlations between spiking activities of neurons that span longer time periods, compared to spike clusters that lack power law statistics (Hahn et al., 2010).

In the primary auditory cortex, where acoustic sequences are processed for the perception of meaningful sounds, neuronal avalanches maximize the dynamic range and optimize information transfer within and across networks. It has been suggested that avalanche dynamics maximize information transmission between and within the cortical layers, at the same time providing an ordered framework for diversely-tuned neuron groups for which the relative firing time could contribute to the encoding of neuronal populations (Bowen et al., 2019).

According to Delgado-García (2015), today’s science faces the challenge of providing new conceptual and fruitful insights that would open new approaches and pathways into yet unexplored domains. In contrast, neuroscientists of the “classical era” were particularly characterized by their ability to generate principles capable of supporting and assimilating the experimental data into a general theoretical perspective.

5. Discussion

Towards the end of the 19th century, Cajal pioneered the concept of the neuronal avalanche in relation to the integrative function of the central nervous system and the rising of conscious experience from sensory stimuli. His views were thoroughly discussed and extended by classical neuroanatomists of the 20th century. With the new millenium, the term neuronal avalanche has been made specific, based on the modern laws of physics, also linked to the theoretical constructs of artificial neural networks.

Cajal's theorizing was ignited both by his multifarious mind and by the general trend of the time, encompassing the entire spectrum of human enquiry and bridging philosophical ideas to the interpretation of the raw data of natural science. Thus, his propositions were largely conjectural, and not wholly grounded on experimental data or the computational models that were introduced in later years to address the problem of consciousness.

This fundamental problem has since occupied the line of thought of leading investigators, who came up with theoretical models based on diverse anatomical substrates and systems.

A century ago, placing the issue of consciousness hierarchically within the evolution of life and intelligence, Sigmund Freud contemplated: "The attributes of life were at some time evoked in inanimate matter by the action of a force of whose nature we can form no conception. It may perhaps have been a process similar in type to that which later caused the development of consciousness in a particular stratum of living matter" (Freud, 1974). On the first question, biochemistry has since elucidated the nature of forces that catalyzed the origin of life from organic cosmic products, highlighting protometabolism, the unique properties of thioesters as reversible bridges of energy transfer, and the emergence of the world of RNA, the first replicable information-bearing molecule (de Duve, 2005). On the second question, neuroscience, in one of its most challenging current endeavors, is attempting to explain how brain activity may give rise to consciousness, highlighting the role of sensory input, the prefrontal cortex, and thalamocortical interconnectedness (Reardon, 2019).

Freud (1974) further attempted to define consciousness in neural terms as follows: "What consciousness yields consists essentially of perceptions of excitations coming from the external world and of feelings of pleasure and unpleasure which can only arise from within the mental apparatus…There is nothing daringly new in these assumptions; we have merely adopted the views on localization held by cerebral anatomy, which locates the 'seat' of consciousness in the cerebral cortex."

In the late 1920s, George Campion formulated a thalamo-cortical circulation hypothesis in his attempt to explain how the various dispositions of the mind become integrated into the human personality. In particular, he wrote: "There is a continuous stream of neural impulses from the thalamus to the cortex and from the cortex to the thalamus, which keeps alive this living process of mental growth…The study of this neural machinery is essential for the understudying and interpretation of thought and behaviour…It is necessary to assume the existence of a circulation of nervous impulses from the thalamus to the cortex and to the widespread and complex mechanisms concerned with muscular activities” (Campion, 1929).

He further discussed the “central seat of consciousness” as follows: “The return paths from cortex to thalami—the cortico-thalamic paths—are means of maintaining a continuous circulation of neural impulse between the thalami and the cortex, thus keeping in an active state those ‘engrams’ or ‘schemata’ which form the neural correlates of the mental symbols or concepts which may be employed in any particular phase of consciousness through which we may at any time be passing” (Campion and Smith, 1934).

Gerald Edelman introduced his system of reentry to illustrate interconnections within the thalamocortical system (Fig. 4). Such an anatomical arrangement includes a dense meshwork of reciprocal connections between the cerebral cortex and the thalamus, as well as among different cortical areas. These reciprocal connections carry action potentials and modify synaptic strengths, integrate and synchronize the different activities of the various brain areas (Edelman, 2006).

Viewing consciousness as an integrated perception of the present, Wilder Penfield suggested that the anatomical substrate of attributes of the mind was the upper brainstem, the thalami and the cortex, constituting the source of both the stream of consciousness and the substrate of the physiology of the mind (Penfield, 1950; Leblanc, 2019). In the same spirit of the ‘unity of science’, Sperry (1969) conglomerated mentalism and materialism in his attempt to interpret conscious awareness as a dynamic emergent of higher specialized cerebral processes whose properties supervene in a molar, integrative and holistic fashion.

Contributing to our understanding of how consciousness arises from brain cells and the morphofunctional interhemispheric communication, Doty (1975) pondered that comprehending the nature of the property that couples the prosaic flux of ions into mentality is the quintessential problem of science; if consciousness arises from neural processes, then their discovery should significantly sharpen the question as to how neurons fashion the miracle of mind. Zeman (2001) investigated the neural correlates of visual consciousness, proposing that visual activity corresponds to the contents of perceptual awareness rather than the raw features of impinging stimuli.

The biological philosopher Joseph-Pierre Durand de Gros (1866, 1894) sought to establish a ‘scientific idealism’ according to which, like the organism, the soul would be composed of a number of lower entities of consciousness. Cajal corroborated this supposition, suggesting that a cerebral consciousness would dominate all the rest, since “the nervous system would consist of innumerable consciousnesses, as many as there are cells.” 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). In this context, the concept of Orpwood (1994), which engages the entire population of cortical pyramidal cells in the phenomenon of consciousness through their self-monitoring properties of pattern recognition and association in the cortex, becomes especially meaningful.

With regard to the new emerging models of the mind, Azmitia (2007) reiterated that these “would be well served by a review of the theoretical writings of Cajal that deal with higher order brain functioning, [which] have not received equal appreciation as his work on brain anatomy, [while] the longevity of Cajal’s views reflects his relation with the brain and its higher functioning.” In epitomizing his histological discoveries, Cajal (1937) established the principle of the neuronal avalanche, and thus set a foundation for what is currently called a large-size functional cortical point spread (Frostig et al., 2017).

Cajal’s principle signifies a progressive increase in the neuron numbers that propagate signals from the peripheral sense organs to the cerebral cortex. Modern wide-field imaging techniques have revived Cajal’s neuronal avalanche by imaging the entire spatial extent of the point spread, which comprises thousands of neurons engaged in coordinated activity (Frostig et al., 2017).

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Figure captions

Fig. 1. Upper: Title pages of Cajal's "Conjectures" (Cajal, 1895), left, and "Conjectural Interpretations" (Cajal, 1896), right, printed as separata. (Courtesy: Real Academia de Ciencias Exactas, Físicas y Naturales, Madrid; Bibliothèque Interuniversitaire de Santé, Paris). A portrait of Cajal in the middle, detail from the faculty roster of the University of Madrid, 1890s. (Private archive). **Lower**: Lewellys Franklin Barker (1867–1943) at the microscope, circa 1891, left, and Francis Xavier Dercum (1856–1931), circa 1919, right. (Credits: Photographs from the Lewellys Franklin Barker Papers, Item 48629, The Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions; Library of Congress Prints and Photographs Division, George Grantham Bain Collection). Title pages of their monographs (Barker, 1899; Dercum, 1922), middle. (Source: Archive.org).

Fig. 2. The cerebral cortical histotopography with its macrodynamic *(ma)* and microdynamic *(mi)* events according to Jakob (1935, 1945). (a) Cortical layers; (b) termination of a thalamocortical fiber and a large motor neuron projecting its axon such as to the pes pedunculi; (c) an incoming afferent axon *(fa)* in relation to small interconnecting cells, equivalent to the cortical 'microdynamic apparatus'; (d) probable circuits intercalated among afferent and efferent *(fe)* fibers in the cortical layers. *Z*, zonal (molecular) layer; *pe*, external pyramidal layer; *gr*, granule cell layer; *pi*, internal pyramidal layer.

Fig. 3. Arrows represent a simple "assembly" of neural pathways or open multiple chains firing according to the numbers on each assembly (the pathway "1, 4" fires first and fourth, and so on), illustrating the possibility of an "alternating" reverberation which would not extinguish as readily as that in a simple closed circuit (Hebb, 1949).

Fig. 4. Edelman's scheme of the reciprocal connectivities within the thalamo-cortico-thalamic loop. In the real brain, the numbers and the density of reciprocal connections are vaster (Edelman, 2006).