

The vestibular system: Contributions of Lorente de Nó

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Abstract.

BACKGROUND: Rafael Lorente de Nó was a neuroscientist that worked alongside two of the giants of Medicine, the Nobel Prize winners Cajal and Bárány.

OBJECTIVE: To describe the contributions of Lorente de Nó to vestibular neuroscience.

METHODS: Detailed review of the publications of Lorente de Nó and analysis of the archives from Junta para Ampliación de Estudios e Investigaciones Científicas at Residencia de Estudiantes (Madrid, Spain), Casa de Salud Valdecilla at Hospital Universitario Marqués de Valdecilla (Santander, Spain), Becker Medical Library at Washington University (St. Louis, MO, USA), Rockefeller Archive Center (Sleepy Hollow, New York, NY, USA), Archivo Fernando de Castro (Madrid, Spain), Biblioteca Nacional de España (Madrid, Spain) and Legado Cajal at Instituto Cajal (Madrid, Spain). Most of this material is unpublished and includes over a hundred letters to or from Lorente.

RESULTS: Lorente de Nó made a substantial contribution to our understanding of the vestibular system. Amongst these, he meticulously detailed the course of the vestibular nerve and its central projections. He described the vestibulo-ocular reflex as the consequence of an integration of the various nuclei and connections across the vestibular system, rather than a simple three-neuron arc. He also highlighted the role of the reticular formation in the generation of the fast phase of the nystagmus.

CONCLUSIONS: Lorente de Nó was a pioneer of modern neuro-otology, having made outstanding contributions to vestibular neuroscience, forging novel discoveries that still burn true today.

Keywords: Lorente de Nó, vestibular, vestibulo-ocular reflex, history of neuro-otology, physiology, anatomy

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1. Introduction

1.1. A roadmap of Lorente de Nó's working life

Rafael Lorente de Nó (Fig. 1) was born in Zaragoza, Spain in 1902 and died in Tucson, AZ, USA in 1990. His life and work were greatly determined by the influence of his two masters: (i) Santiago Ramón y Cajal (1852–1934), father of Neurosciences, awarded the Nobel Prize in Physiology or Medicine in 1906 for his work on the structure of the nervous system; (ii) Robert Bárány (1876–1936), father of Neuro-otology, awarded the same prize in 1914 for his work on physiology and pathology of the vestibular system, and himself a disciple of Adam Politzer (1835–1920), the grandfather perhaps of Otology. In fact, Lorente de Nó was himself nominated for the Nobel Prize on at least four occasions, although the prize ultimately eluded him [1].

Lorente began to study Medicine in Zaragoza (Spain) and whilst still a medical student published two neuro-histological works. His then professor of histology stated, prophetically:

“He has a true vocation, few will be equal to him in quickly learning the techniques that are taught to him, and he experiences flashes of originality, perhaps a little compressed. I firmly believe that if he persists in the laboratory he will mature and become a good teacher” [55].

After completing his third- and fourth-year examinations, he went to Madrid to work as a fellow at the Cajal Institute in 1920, aged 18 years old. During his time with Cajal, he learned to master a range

of central nervous system staining methods, especially those using silver salts. According to Charles S. Sherrington (1857–1952), the neurophysiologist who introduced the term ‘synapse’: “if ever a man had a school, it was Cajal; a school of colleagues and pupils” [56]. Amongst these disciples were Francisco Tello, Pío del Río-Hortega, and Fernando de Castro, and whom, with Lorente, constituted the so-called Spanish Neurohistological School [3].

In 1923, as a doctoral student, Lorente published a paper on the rodent brain [14], culminating in a seminal work on the cytoarchitecture of the cerebral cortex in 1938 [47]. His descriptions formed the basis for the hypothesis on the columnar organization of the somatic sensory cortex developed by Vernon Mountcastle [53] and later, the organization of the visual cortex by David Hubel and Torsten Wiesel [12].

Toward the end of 1923 he attended a course on physiology and vestibular exploration in Zaragoza taught by Bárány. There, Lorente impressed Bárány with the results of his own investigations and was invited to Uppsala (Sweden) to continue these studies [50]. Lorente remained with Bárány until 1929, working mainly on the anatomy and physiology of the vestibulo-ocular reflex (VOR). During these years, he also made several stays in Berlin with Cecile and Oskar Vogt investigating the cytoarchitecture of the hippocampus.

Upon his return to Spain, he did not find a stable position at the Cajal Institute, so he trained as an otolaryngologist in Madrid, Berlin, Königsberg, Frankfurt and, once again, in Uppsala with Bárány. He then worked for eleven months as head of the Otorhinolaryngology service in a newly created modern hospital (Casa de Salud Valdecilla, today Hospital Universitario Marqués de Valdecilla), in Santander, Spain. Despite an excellently equipped laboratory of histology and of auditory and vestibular physiology, his clinical workload prevented him from dedicating himself to research. So, in 1931, he accepted a position as director of research at The Central Institute for the Deaf (CID) (St. Louis, MO, USA) [9].

Lorente continued his work on the auditory and vestibular systems and on the cytoarchitecture of the hippocampus at the CID until in 1936 Herbert Gasser –a renowned electrophysiologist and then director of the Rockefeller Institute for Medical Research – invited him to move to New York. At the Rockefeller Institute, Lorente devoted himself fully to the neurophysiology of nerve impulse transmission. There, he worked with his student Vicente Honrubia, later a prominent clinical neurophysiologist of the vestibulo-



Fig. 1. Rafael Lorente de Nó 1902–1990) (Courtesy of the Rockefeller Archive Center).

lar system, in the flow of action currents in isolated myelinated nerve fibers. After his retirement in 1972, Lorente then moved to the University of California in Los Angeles (UCLA) as Professor emeritus, where he resumed his research on cochlear nuclei, an interest he had first developed in Santander [49].

Although the Google scholar profile of Rafael Lorente de Nó accumulates currently more than 13,000 citations, nowadays his role in the history of neuro-otology often lies forgotten in works on vestibular-ocular reflex and in textbooks. The aim of our study is to highlight his contributions to the anatomy and physiology of the vestibular system, drawing upon many unpublished works and documents.

2. Lorente de Nó and the study of the vestibular system

When at the beginning of the 20th century Lorente de Nó began to investigate the vestibular system, the scientific panorama was dominated by the Dutch school. Rudolf Magnus (1873–1927) and his disciples Adriaan de Kleijn (1883–1943) and G.G.H. Rademaker (1887–1957) had been doing extensive experimental work on postural control at the Utrecht Institute of Pharmacology. Magnus and his collaborators studied the vestibulo-spinal reflex and the function of otolithic organs in decerebrated and labyrinthectomized cats and rabbits, which allowed them to describe the straightening reflexes, published as *Korperstellung* (Posture) in 1924 [51]. We owe Magnus our current understanding of the balance system based on the visual, proprioceptive, and vestibular afferences. Within the positional reflexes Magnus distinguished labyrinthine tonic reflexes from cervical tonic reflexes; however, it is noteworthy that Magnus did not devote himself too much to the study of the physiology of the vestibular-ocular reflex itself.

The study of the vestibular system was one of the fundamental axes of Lorente de Nó's research work, steered by Cajal. While he was working in the Cajal Institute, he was already engrossed in research related to the vestibular system, even before joining Bárány in April, 1924. Using Marchi, Golgi and Cajal staining methods, Lorente had studied the cerebello-vestibular pathways in adult guinea pig, highlighting that two-fifths of the afferent fibers of the vestibular nuclei comes from Purkinje cells of the vermis, paramedian lobe and flocculus [15, 16]. Similarly, he

showed that interruption of these fibers is responsible for the limb hypotonia that appears after sectioning the cerebellum through the midline [17].

When in 1924 Lorente applied for a grant from the *Junta para Ampliación de Estudios e Investigaciones Científicas* (Council for the Extension of Studies and Scientific Research) to continue his research on the vestibular system in Uppsala, he reported in the text of his application a series of findings he had previously made in Cajal's lab and that he had discussed with Bárány during the vestibular course he taught in Zaragoza in December 1923. According to Lorente himself these included: (i) the discovery of five independent axonal systems contained within the vestibular nerve that arrive independently at the vestibular nucleus. Lorente proposed that each of these axon systems corresponds to each of the sensory organs of the posterior labyrinth. (ii) the description of direct connections between the cerebellum and the nuclei of the floor of the fourth ventricle, including fibres from Purkinje cells to the lateral vestibular nucleus (Deiters nucleus), which were known, but had not been so precisely described. Lorente explained to Bárány that he had been able to demonstrate that each cerebellar region is connected to different areas of the vestibular nuclei, attributing new functions to the cerebellum; (iii) identification of connections between the cervical ganglia and the vestibular system, thus being able to explain the anatomical substrate of the cervico-ocular reflexes; (iv) describing connections between the restiform body and the vestibular nucleus, hitherto unknown; (v) identifying connections between the secondary vestibular pathways and the reticular substance of the medulla and midbrain, the origin of a large part of the vestibular reflexes [18].

Lorente also performed dissections with Bárány in Zaragoza where, by inducing lesions within the medulla oblongata, they were able to eradicate the fast phase of a vestibular nystagmus, with preservation of its slow phase [50]. Such lesions induced tonic labyrinthine reactions in the limbs despite these no longer being apparent in the eye. Recognising the talent of this young student, Bárány invited Lorente to carry out a research stay in Uppsala. Thus, Lorente was able to continue his research on the vestibular system in Uppsala from April 1924 (Fig. 2).

Before leaving for Uppsala, Lorente published a preliminary work in which he collected his research on the VOR carried out in Madrid [20]. Based on the experimental work carried out by Kubo, van der Hoeve, Fleisch, and Magnus and De Kleijn, Lorente

A tu Excmo., don Presidente de la
 Junta para Ampliación de Estudios
 e Investigaciones Científicas.
 Don Jesús de Dr. R. Lorente de Nó.
 me he permitido decirle, que yo soy
 en interés de una adecuada formación
 de Dr. Lorente de un buen profesor
 de anatomía y fisiología del aparato
 vestibular y de otros problemas de fisiología
 y de otros problemas de fisiología
 para un adecuado desarrollo de la
 vida, cuando la Universidad de
 Suecia en colaboración con
 Dr. Lorente de Nó y mi clínica en Uppsala
 es posible.
 Madrid, 2. Januar 1924 Prof. Dr. R. Bárány

Fig. 2. Letter of acceptance of Lorente's stay in Uppsala, signed in Madrid by Prof. Dr. R. Bárány. (Archivo de la Junta para Ampliación de Estudios e Investigaciones Científicas, Residencia de Estudiantes, Madrid, Spain).

studied the effect of the section of each extra-ocular muscle on the ocular movements of the rabbit according to head position. For this purpose, he applied two methods: a) removing the eyeball and then isolating the six muscles at the bottom of the orbit, b) sectioning four muscles while retaining two antagonist muscles. Lorente learned the first method from Bárány in Zaragoza. The contralateral eye was preserved to compare the effects of each section. Lorente evidenced the precise role of each extraocular muscle; he also observed that the six muscles participate in the VOR, with contraction of three of them and relaxation of the others, thereby supporting the Sherrington's law of reciprocal innervation demonstrated by De Kleijn when studying the cervical reflexes. Nevertheless, Lorente disagreed with Magnus and De Kleijn conceiving that each muscle had secondary actions and thus the neural circuitry was more complex than the model presented by the Dutch researchers [26]. Conspicuously, on his way to Uppsala Lorente visited Rudolf Magnus (1873–1927) and De Kleijn in Utrecht, and Jan van der Hoeve in Leyden.

Lorente reflected on how his anatomical techniques allowed him to explore physiology in greater depth:

“... thus making possible a more abundant fruit; the knowledge of the selective methods of preparation of the nervous system, and therefore, of the fine anatomy of the same, had to then be united, (...) with the enormous clinical and physiological experience of R. Bárány” [18].

The monthly reports required to maintain the scholarship and addressed to the Council for the Expansion of Studies lay claim to the volume and depth of his studies, ranging from an understanding of the pathways involved in the proprioceptive sensitivity of the ocular muscles, brainstem, thalamic, and cortical vestibular pathways, and the sensory innervation of the ocular muscles. In these reports he questioned the theories of Mach-Breuer, Magnus, and Maxwell on the tonic oculomotor responses to head turns, identifying brainstem structures receiving simultaneous inputs from the vestibular nerve, the trigeminal nerve, the tractus of Gowers, a bundle of collaterals from the superior cerebellar peduncle, the tractus of Russel, and superior cervical nerves [21].

His first publications related to his investigations in Uppsala appeared in 1925; one on the VOR and its changes in the course of development [22], the other about the anatomy of the posterior labyrinth and the mechanisms of the VOR [23]. This latter paper was considered by Lorente as the first part of his studies on the vestibular system. The second part would appear the following year [25].

During his years in Uppsala, Lorente wrote to Cajal frequently telling him about the progress of his investigations. These letters mainly focused on the anatomy of the medulla, including the auditory and vestibular pathways, and the VOR. The anatomical studies were performed in mice, mainly using the Golgi method, while the physiological experiments were performed in rabbits [27]. Lorente did not abandon his critical spirit to question previous physiological discoveries, be they by Magnus, the great Sherrington or any other researcher [28, 29].

Lorente studied analytic geometry and infinitesimal calculus to apply them to the study of the mechanics of eye movements. In a letter dated 1925 he says: “During the current month of November, I have begun to develop a mathematical theory of how the labyrinth works” [24]. That theory was indeed developed and later published [30].

Upon his return to Uppsala, from Berlin, where he was with Cécile and Oskar Vogt between October 1926 and February 1927, he continued his work on the vestibular system and finished what he called the “third part of my monograph on the vestibular system” that appeared as a series of four articles published in *Monatschrift für Ohrheilkunde* throughout 1927 [31]. These articles, in which he studied the direct effects on the VOR of lesions in the medulla oblongata, would serve as a fundamental basis for later influential articles, in which Lorente collected

all his knowledge about the vestibular system. These papers were gathered later as a book that was published in 1928 [32]. At that time, Cajal wrote a report stating that this “work accredits him as an exceptional specialist in this field of studies and proves the reputation he enjoys abroad” [54]. Lorente’s findings were unique for they involved direct recordings from the ocular muscles, thus not relying (like others before him) on subjective reports of eye movements.

In these works, Lorente denied the existence of reciprocal innervation of the antagonistic extraocular muscles in the tonic labyrinthine reflexes. These findings were used by Dusser de Barenne and De Kleyn to criticize his working methods with the technique of Bartels [8]. Specifically, they pointed out the lack of controls in his records of muscle contractions with the kymograph and the problems with keeping a steady baseline in the tracings in a living animal. Lorente’s rebuttal was long in coming [45].

Lorente attended the first International Oto-Rhino-Laryngological Congress held in Copenhagen in July 1928, where he presented an oral communication on the VOR that would appear published later [33]. Finally, the fourth part of his vestibular monograph, as he referred to it, appeared in *Travaux*, with a short version published in *Archiv für Ohren, Nasen- und Kehlkopfheilkunde* [34, 35]. Here he used caloric stimulation to assess the VOR via direct recording from the horizontal semicircular canal afferents.

Despite the frenzied activity in Uppsala, Lorente received other researchers, who came to carry out work under his direction. Prof. Artur Blohmke, from Königsberg, for example, had approached Lorente at the conference in Copenhagen expressing his desire to work alongside him to investigate the pathophysiology of nystagmus. Following Barany’s suggestion, they studied the central nystagmus induced by faradic currents on the quadrigeminal tubercles and the thalamus, being able to demonstrate that focal thalamic lesions caused nystagmus in the opposite direction to the nystagmus induced with stimulation of the quadrigeminal tubercles. Subsequently, Lorente travelled to Königsberg at the end of 1928 to complete these studies.

Lorente’s stay in Uppsala ended in September 1929, returning then to Spain. Despite broad research activities (e.g., cytoarchitecture of the cerebral cortex) Lorente had already become an international reference in the anatomy and physiology of the vestibular system [37]. In November 1929 he defended in Madrid his doctoral thesis, entitled “Some data on the Physiology and Anatomy of the

vestibular system”. After working as an otolaryngologist in Spain, in 1931 he then travelled to the USA to take up his position as the director of the anatomical research laboratory of the CID.

At the end of his first year in America, Lorente published a very extensive work in German, in which he collected his vestibular works performed in Uppsala [38]. Later in “The regulation of the eye positions and movements induced by the labyrinth” [39], Lorente reviewed his own research on ocular reflexes, and perhaps because these were now in the English language, they gained even greater visibility and importance than the many discoveries that he had been making over previous years under the auspices of Bárány in Uppsala. This work occupied the full 96 pages of the corresponding issue of *The Laryngoscope*. This long paper complemented the findings described in the previous article. He again stated that the law of reciprocal innervation is not valid in the case of postural reflexes.

Finally, Lorente de Nó was able to debut in public before the American scientific community at the 65th annual meeting of the *American Otological Society*. This congress was held in May 1932 in Atlantic City (New Jersey, USA), where he gave a presentation on *Researches on Labyrinth Reflexes* making a masterful demonstration on experimental nystagmus [40].

The volume of knowledge about the vestibular system accumulated by Lorente de Nó over the years reached its zenith in 1933 with the publication of a series of pioneering works for vestibular science. The first one was a classical contribution on the anatomy of the eighth nerve in which he described accurately five groups of fibers in the vestibular nerve [41] (see below). In 1933 Lorente also published the famous article “Vestibulo-ocular reflex arc” [42], of paramount importance for our current understanding of the physiology of the vestibular system. Lorente summarizes the work of his last 12 years on the vestibular system. He states the “law of plurality of connections between nuclei” by specifying that each nucleus in the nervous system receives connections from more than one neuron, and the “law of reciprocity of connections”, where he confirms that the connections between nuclei are always reciprocal; that is, when a nerve cell sends fibres to another, the latter does the same with the first. And this, of course, happens with the fibres of the vestibular nucleus. Lorente draws the connections between the vestibular nucleus and the reticular formation, the posterior longitudinal fasciculus and the *tractus predorsalis*, marking the origin of its journey to the external mus-

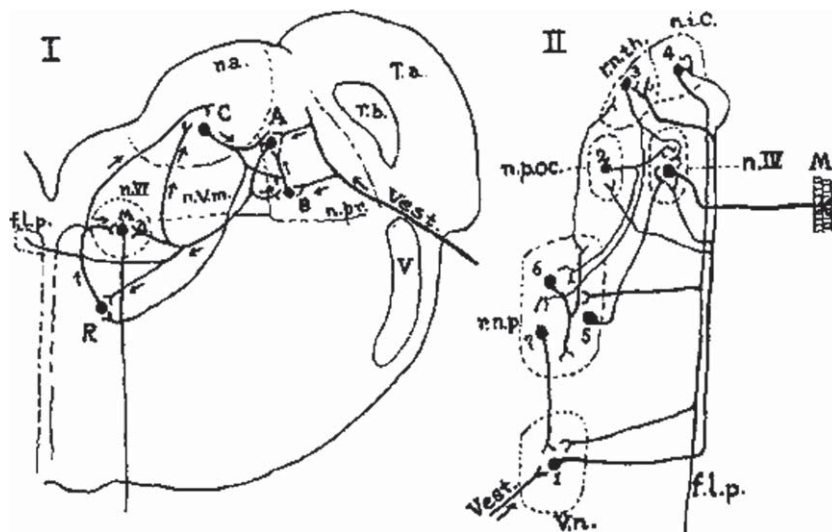


Fig. 3. Diagram I shows the connections of the neurons in the smallest part of the medulla oblongata, which still is sufficient to set up the slow phase of the nystagmus in the external rectus muscle. Diagram II illustrates the main connections of the posterior longitudinal bundle representing the law of plurality of connections and the law of reciprocity of connections (From Lorente de N6, 1933 [42]).

cle of the eye (Fig. 3). Current theories of the time had instead stated that vestibular nystagmus was due to direct connection between the vestibular nuclei and the ocular motor nuclei. Lorente was able to section this direct path and verify that nystagmus was not abated, explaining then that the connections between the vestibular nuclei and the reticular formation were part of the VOR. Lorente challenges the concept of the VOR as a reflex arc formed by two or three neurons and proposes the participation of numerous interneurons composing a complex polysynaptic reflex in a model close to current conceptions [6].

This body of work details some of the most fundamental principles of the vestibular system. Here, Lorente describes the different neuronal sub-types within the vestibular nucleus; the direction of the transmitted reflex; the differences in the VOR produced by a rotating stimulus versus a caloric stimulus; the need for asymmetric involvement in the cerebellar vermis for nystagmus to be triggered, which can overlap with vestibular nystagmus but from which it is also differentiable; the presence of spontaneous neuronal activity within the vestibular nuclei; the different types of nystagmus and of reactions of the ocular muscles consequent to the selective damage of the various parts of the central nervous system; the relationship between the vestibular system on one side and the right and left ocular muscles of both eyes; the importance of the posterior longitudinal fasciculus in the VOR; the collateral and secondary role of the cerebellum in the VOR; and most importantly: he explains

that the principle of neuronal feedback ensures that, despite the multiple connections between the vestibular nuclei and related nuclei, neurons involved in the VOR are unequivocally directed to the appropriate muscle group. Finally, Lorente challenges – perhaps for the first time – the notion that the fast phase of vestibular nystagmus is purely “central” in origin, questioning whether this may in fact be related to the reciprocal inhibition of the antagonist ocular muscles. He establishes the presence of two different types of cells or systems (which he calls ‘VN’ and ‘Q’) involved in the VOR within the vestibular nucleus. But above all, this is a seminal article because his demonstration of closed self re-exciting or reverberating chains of neurons in the brainstem is considered to be the first biological evidence of a feedback loop. This was a key concept in the later development of Cybernetics, a field in which Lorente was a pioneer as well [10].

In 1933 he was also working on the relationship between the corneal and vestibular reflexes [43]. Lorente studied the corneal reflex produced by faradic stimulation of the trigeminal branch that innervates the upper eyelid and confronted it with a pre-existing vestibular nystagmus. The results that he obtained could not be explained by the simple assumption of an algebraic sum of the impulses that reach the motor neurons. He gave as the only possible explanation that the trigeminal arch is made up of at least two different neural chains, one of which includes internuclear neurons that are shared with the vestibular arch. He

found no evidence of an active inhibition of motor neurons in the case of vestibular reflexes. Around this time, he was also working on the interaction of the various vestibular reflexes [44].

Lorente continued working on the study of nystagmus, collecting his data and theories in another influential work [46]. Here, measuring ocular muscle responses using myography and recording action potentials, he simultaneously studies responses from two antagonistic muscles, the lateral rectus and medial rectus. He postulates that innervation of the ocular muscles does not differ from that of other striatal muscles, and that the response of antagonist muscles during nystagmus also has asynchronous inflection points.

Lorente's ultimate leap from neuroanatomy to neurophysiology took place at the end of his stay at the CID [9]. Contact with axonologists of Washington University and the availability of novel electrophysiological techniques likely migrated his interest toward the study of neural activity, such as the action potential, refractory period, and synaptic delay, following which he developed the concept of temporal and spatial impulse summation, using the oculomotor neurons with which he was most familiar. In this context he made his last vestibular contribution in the article entitled "Analysis of the activity of the chains of internuncial neurons" [48]. In this paper, Lorente explains again the law of plurality of connections and the law of reciprocity of connections, and the two types of chains formed by internuncial cells (interneurons): multiple (M) and closed (C) chain. He studied the transmission of nerve impulse and stated that "the mechanism of the stimulation of neurons is the delivery of impulses at their synapses. The effect of the individual impulses is brief, but the continuous arrival of impulses ensures constant stimulation. The neuron responds whenever the stimulating effect of the impulses that arrive within a period of effective summation reaches its threshold." In contrast to Sherrington's concept of central excitatory state, he considered that "continuous stimulation by internuncial bombardment places the excitatory and facilitatory mechanisms outside of the cell." Lorente contemplated the multiple chains of internuncial cells as "elementary units of transmission" and, again, stated that "the reflex arc with a fixed number of internuncials (interneurons), lose their physiological meaning as the internuncials are not intercalated between afferent fibers and effector cells. They form collateral chains superimposed upon the shortest path which, if a sufficient background of

facilitation exists, is undoubtedly passable". According to Lorente, "the rate at which a multiple chain may transmit impulses depends upon the number of neurons it contains; the greater the number of links, the lower the minimal rate." [48].

In those years, Lorente, like other neurophysiologists such as Eccles, Gasser, and Erlanger, claimed synaptic transmission to be electrical in nature. Therefore, specific inhibitory impulses were considered to be non-existent, and reciprocal inhibition was a difficult issue to explain. Lorente proposed that "the closed chain of neurons may play different roles according to the number of links that it contains. If the number is small, activation of the chain may result in inhibition, but if the number of links is large enough it may result in sustained facilitation or discharge." [48]. This hypothesis was used by Lorente in this paper to explain the vestibular nystagmus as a rhythmic reflex, characterized by a succession of contractions and relaxations of the eye muscles (Fig. 4). The classical theory sustained by authors like Spiegel accounted for simultaneously reciprocal innervation and rhythm based on a succession of states of activity and rest [57]. For Lorente, "the stream of impulses created in the vestibular nuclei is constant. The interrupted discharge of the motoneurons is attributable to the activity of neurons located in the reticular formation" and "... the relaxation of the agonist is not attributable to an active inhibitory process but only to a lack of excitatory impulses" [48].

From that moment on, he focused on other neurophysiological questions, in particular the mechanisms underlying synaptic transmission, to which he would devote the rest of his professional life, although at the end of his days he returned to research in the auditory pathways [49].

3. Lorente's contributions to vestibular science

3.1. Anatomy of the vestibular system

Between 1922 and 1933 Lorente conscientiously studied the trajectory of the vestibular fibers from the cristae ampullaris and the otolithic maculae to Scarpa's ganglion and from there to the vestibular nuclei. He described in detail the innervation of the sensory cells of the cristae ampullaris and maculae in the mouse. He pointed out how the vestibular ganglion is separated into a superior and inferior portion. He detailed that the fibers of the superior vestibular

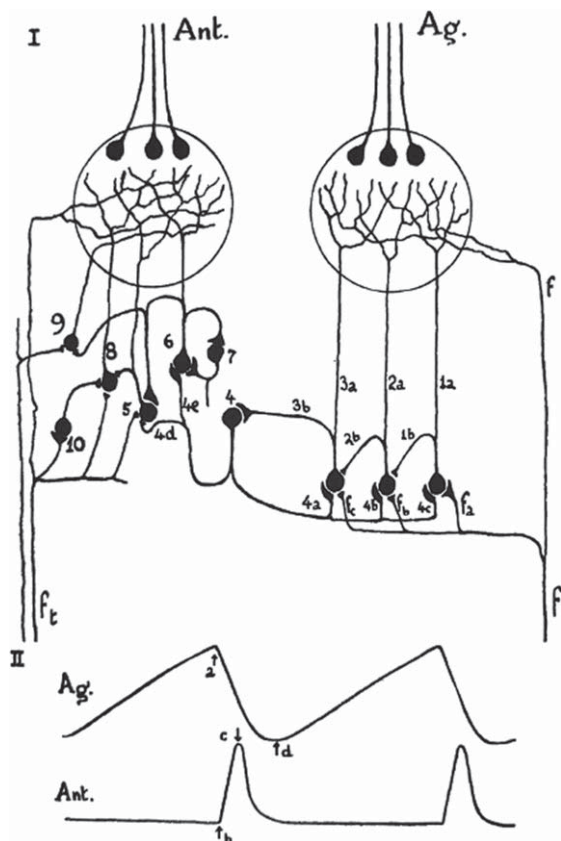


Fig. 4. I. Diagram I explains the production of rhythm during vestibular nystagmus. Fiber *f* is supposed to carry the continuous series of impulses started at the cristae of the semicircular canals which set up the nystagmus. Fibers *ft* are supposed to be maintaining the tonus of the antagonistic muscle. Diagram II shows the rhythmic succession of contractions and relaxations of the antagonistic muscles during the nystagmus explained by diagram I (From Lorente, 1938 [48]).

nerve innervate the cristae ampullaris of the anterior and horizontal canals, as well as the macula of the utricle, while the inferior branches innervate the crest of the posterior canal and the macula of the saccule [25, 38].

Winkler had unsuccessfully used Marchi's technique in an attempt to follow the trajectory of the vestibular fibers [60]. Lorente, however, used the Golgi method, the Cajal silver method and the Weigert-Kulschitzky method in mouse and cat embryos allowing him to study the distribution of the central projections of the vestibular nerve, easily differentiating them from other fibers that were not yet myelinated. He thus distinguished five groups of fibers in the vestibular nerve [41]:

The fibers of Group I were finer, and those of Group II, thicker, both innervating the semicircular

canals and terminating in the superior, medial, and inferior vestibular nuclei. He identified that the sensory cells of the cristae ampullaris of the anterior and horizontal canals were innervated by fibers whose soma is located in the anterior and dorsal portion of the vestibular ganglion, while the cells of the cristae ampullaris of the horizontal canal are located in the dorsocaudal portion of the vestibular (Scarpa's) ganglion. Contrary to descriptions by Jones [13], Lorente identified that the fibers of the three semicircular canals run in parallel as they project towards the medulla oblongata. On the other hand, the fibers of the anterior utricular and saccular nerve are arranged more caudally and form group IV that project in the lateral and inferior vestibular nuclei. The fibers of the posterior saccular nerve constitute Group V. Lorente stressed that the fibers that innervate the saccule have no connection with the cochlear nerve and that the macula saccularis has no auditory function [41]. He was unable to determine whether Group III fibers originated from the cristae ampullaris or from the maculae. In addition, he confirmed Cajal's finding that upon reaching the brainstem the primary vestibular fibers divide into ascending and descending branches [41]. Lorente described how the fibers of the cristae ampullaris end in the superior vestibular nucleus, the most lateral aspect of the descending and medial nuclei, whilst the fibers of the utricle macula are directed toward the lateral nucleus of Deiters that also receive fibers from the saccular macula [41]. He also reported that the fibers from the saccule project to the vestibulocerebellar nucleus [41].

Regarding the Oort anastomosis between the cochlear and vestibular nerves, he stated that it was not a real anastomosis, but that it is formed by cochlear fibers that follow a somewhat abnormal path in such a way that they seem to join the vestibular nerve [25, 38, 41].

Lorente carried out a complex classification of the vestibular nuclei that renders correlation with later descriptions by Brodal, Pompeiano and Walberg somewhat challenging. For the upper portion of the vestibular nucleus, he maintained the established name of "Betchterew's core". However, he designated the lateral nucleus (of Deiters) as the vestibulocerebellar nucleus, distinguishing the ventral part of the Deiters nucleus from its dorsal part. On the other hand, he divided the medial nucleus (of Schwalbe) into a dorsal part that he termed nucleus angularis and a ventral part, nucleus triangularis. This distinction corresponds to the rostral and caudal portion, respectively, of the classic triangular nucleus.

Likewise, Lorente called nucleus ventromedialis a cell group located between the inferior nucleus and the medial nucleus. Finally, he correctly identified the nucleus of the descending root, equivalent to the inferior nucleus [41]. Lorente did not recognize any primary vestibular afferents ending in the region of the dorsocaudal lateral nucleus that contain Deiters cells [41].

Lorente described the existence of fibers from the medial vestibular nucleus that crossed the midline [44], although he could not demonstrate that they reached the contralateral nuclei [42]. He found that most of the neurons in the vestibular nuclei have long axons (Golgi type I) with hardly any interneurons (Golgi type II) [42].

Lorente, unlike Cajal, did not find primary (direct) vestibulocerebellar fibers using the same Golgi method that his teacher had used [19, 41]. However, he did confirm the existence of the colossal fibers described by Cajal in 1909 [27].

Lorente described the reciprocal relationship between the vestibular nuclei and the reticular formation [32, 38, 41]. Using the Golgi method, he found projections of the vestibular nuclei to the brain-stem reticular formation [41], demonstrating that the VOR was more complex than a three-neuron arc. He also identified collaterals from the primary vestibular fibers to the reticular formation [41]. And conversely, he found afferents to the vestibular nuclei, especially the medial vestibular nucleus, originating from the bulbopontine reticular formation [42]. Lorente discovered that each semicircular canal is related to each and every one of the extraocular muscles through the reticular formation and that the fibers that ascend through the medial longitudinal fasciculus can indirectly influence the extraocular muscles through the interstitial nucleus of Cajal [38, 42].

He described collaterals to the vestibular nuclei from the reticulospinal tract, the medial longitudinal fasciculus, the vestibulospinal bundle, and the predorsal bundle [42]. Also in a mouse and using the Golgi method, he found that most of the fibers of the dorsal (posterior) spinocerebellar tract give collaterals to the vestibular nuclei, concretely to the ventrocaudal portion of the descending nucleus and the ventrolateral portion of the medial nucleus [19]. He also considered that the existence of collaterals from olivocerebellar fibers to the Deiters nucleus was likely [19]. Again, using the Golgi method in mice, he described fibers from the interstitial nucleus of Cajal entering the vestibular nuclei [42].

3.2. *Physiology of the vestibular system*

Following De Kleyn, Lorente summarized the labyrinthine reflexes in the rabbit, distinguishing within the ocular reflexes of labyrinthine origin what he described as positional or 'tonic' reflexes (e.g., ocular counterroll), and dynamic reflexes in relation to head movement (e.g., nystagmus) [32]. Nevertheless, Lorente considered that this classification, although didactic, was erroneous [36].

The description of the VOR arc as an elementary three-neuron arc was first stated by Lorente in 1933 [42], and later by Szentágothai in 1950 [59]. Lorente considered the nystagmus as an alternating reflex similar to other rhythmic reflexes and emphasized that it is impossible to localize each labyrinthine reflex in a determined anatomic structure since the whole system is a functional unit. For Lorente, the reflex reactions are the consequence of the interaction of all the nuclei and the paths of the whole vestibular system. Therefore, "the whole vestibular system has revealed itself as constituted by numerous chains of neurons, reciprocally connected in many ways and having their links in various anatomic nuclei. All the chains work in intimate collaboration, and all are necessary for the production of the normal reflex reaction." [42]. Lorente explained the mechanism of the production of the rhythm of the nystagmus taking into consideration the participation of the interneurons and the recurrent fibers (collaterals of the axons and centrifugal fibers), attending to the law of plurality of connections and the law of reciprocity of connections.

But more importantly, Lorente highlighted the importance of an intact reticular formation for the generation of the quick phase of nystagmus after unilateral labyrinthectomy. Indeed, he described how the fast phase of a horizontal nystagmus was abolished through destructive lesions of the paramedian pontine reticular formation, whilst lesions of the vestibular nuclei, be they ascending tracts to the higher brain-stem and thalamus, or through the medial longitudinal fasciculus, did not completely abolish the fast phase of nystagmus [32, 38, 42], leading him to conclude that the reticular formation was critical to the generation of nystagmus fast phases. Doubt was cast over these findings when Spiegel and Price failed to find abolition of the nystagmus fast phases with lesions of the reticular formation [58]. Eventually, however, Lorente's findings were indeed corroborated decades after by Duensing and Schaefer [7], Bender and Shanzer [2], McCabe [52], Cohen et al.

[4, 5], and Fuchs and Luschei [11]. This would be also the substrate to elaborate the concept of the velocity-storage mechanism.

Lorente furthermore studied the vestibular compensation process after labyrinthectomy in rabbits, appreciating that the static and the dynamic components are carried by different pathways [27].

4. Conclusions

Rafael Lorente de Nó was a true pioneer in the study of the anatomy and physiology of the vestibular system. He worked tirelessly in this quest alongside some of the greatest minds in this field, leaving us with an extraordinary number of relevant contributions, many of which continue to shape our understanding of the vestibular system. Most importantly however, his greatest legacy is the desire for scientific truth, a relentless need to question, validate, or refute even the most fundamental beliefs of the time.

Note

The translations of the original primary sources from Spanish into English have been made by the authors.

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