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PIONEERS IN NEUROLOGY

Rafael Lorente de Nó (1902–1990)

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Rafael Lorente de Nó (Fig. 1) stands as the ultimate alumnus of Santiago Ramón y Cajal, having played a pivotal role alongside Fernando de Castro in shifting the Cajal school of neurohistology toward neurophysiology.

Born in Zaragoza, Lorente began university studies in 1916 and quickly became interested in histology, conducting research under the guidance of Luis del Río and Pedro Ramón, Cajal's younger brother. In 1920, upon Cajal's suggestion, Lorente joined Cajal's laboratory in Madrid as a grantee while still a senior student, an exceptional occurrence. He obtained his medical degree in 1923. That year, in a course in Zaragoza, he met Robert Bárány who invited Lorente to study the vestibular system in Uppsala, where the latter stayed until 1929, occasionally visiting other research facilities in Sweden, Netherlands, and Germany.

Upon returning to Spain, Lorente could not secure a tenured position alongside Cajal, and became head of the Otorhinolaryngology Department at the newly established Casa de Salud Valdecilla in Santander. He continued to train in otorhinolaryngology in Madrid, Frankfurt am Main, and Uppsala. Lorente´s appointment at Valdecilla began in late 1929; however, the considerable volume of clinical work constrained his capacity for extensive research. Consequently, after practicing as an otorhinolaryngologist for 11 months, he accepted the position of director of the Anatomical Research Laboratory at the Central Institute for the Deaf in St. Louis, Missouri, in 1931. In 1936, Lorente relocated to the Rockefeller Institute in New York, where stayed until retiring in 1972, and next continued as emeritus professor at the University of California, Los Angeles. He died in Tucson, Arizona, in 1990.

Lorente de Nó's scientific career comprises two distinct phases. Around 1922, he began to focus on the organization of the cerebral cortex and the anatomy of the eighth cranial nerve and its central projections. He depicted the primary somatosensory cortex of the mouse [1], specifically the barrel field and glomeruli of layer IV, thus laying the groundwork for conceptualizing synaptic connectivity. Next, Lorente investigated the entorhinal cortex and introduced the concept of "physiological units" [2]; he identified four fields in the hippocampal formation, a classification that endures to date [3]. He then elucidated the organization of neuronal circuits and emphasized the role of interneurons. Lorente distinguished between chains of multiple neurons according to the "law of plurality of connections" and closed chains according to the "law of reciprocal connections" [4, 5]. Lastly, Lorente suggested a model of cortical organization into "elementary units" [6], now recognized as cortical minicolumns, which formed the basis for the columnar cortical organization hypothesis developed decades later by Mountcastle, Hubel and Wiesel.

Regarding the anatomy of the eighth cranial nerve, Lorente de Nó depicted the afferent terminations in the cristae ampullares of the semicircular ducts and maculae of the otolithic organs, as well as the projections of nerve fibers from the Scarpa ganglion to the vestibular nuclei [7–9]. He also delineated the intricate organization of the vestibular nuclei and their reciprocal connections with the reticular system. Additionally, Lorente described the connections between the vestibular nuclei and the reticulospinal tract, the medial longitudinal fasciculus, the vestibulospinal tract, and the predorsal bundle, as well as the connections between

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

the dorsal spinocerebellar tract and the interstitial nucleus of Cajal with the vestibular nuclei. He also examined the afferent terminations in the organ of Corti, the central projections of the spiral ganglion, and the organization of the cochlear nuclei, highlighting a tonotopic distribution. These studies culminated in his classic on the cochlear nuclei [10].

In his initial phase, physiological studies focused on the vestibulo-ocular reflex [5]. Lorente elucidated the mechanism of nystagmus production through the involvement of interneurons and recurrent fibers according to the principles of plurality and reciprocity of connections. Furthermore, he discovered the involvement of the reticular system in the fast phase of nystagmus. These contributions paved the way for the subsequent formulation of the velocity storage system concept.

In 1933, while examining the vestibulo-ocular reflex, Lorente presented the first biological evidence for the existence of closed neural circuits, which he termed self-reexciting or reverberating, today known as feedback loops [6]. This landmark discovery was his primary contribution to cybernetics.

The second phase of his scholarly output began in 1935, during his final years at the Central Institute for the Deaf, and continued until his retirement from Rockefeller. Interaction with the axonologists at Washington University and the availability of new electrophysiological recording techniques led him to focus exclusively on neurophysiology during the latter stage. He investigated the properties of action potentials in extraocular motoneurons, determined the refractory period and synaptic delay, and described the concepts of spatial and temporal summation. He established that action potential propagation in axons observes the all-or-none principle and is followed by a refractory period, whereas conduction in dendrites is subliminal, additive, and lacks a refractory period [3]. At Rockefeller, Lorente turned his attention to the peripheral nerve. He studied the electrotonus in intact nerves, the distribution of potential and current in volume conductors, and the influence of barium and quaternary ammonium ions on the action potential. In this context, he synthesized tetraethylammonium.

Lorente de Nó was embroiled in two scientific controversies. The first was the "War of the Soups and Sparks", a dispute concerning the nature of synaptic transmission. Lorente challenged the involvement of potassium in maintaining the resting membrane potential and of sodium in the generation of the action potential. The second controversy was the "Battle of the Sheath": by rejecting the sodium hypothesis, he incorrectly presumed that the epineurium was entirely permeable and did not serve as a barrier to ion diffusion.

The exceptional duality as morphologist and physiologist distinguished Lorente de Nó, and underpinned his nomination for the Nobel Prize four times between 1949 and 1953.

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Declarations

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