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Rafael Lorente de Nó: the biography of a little-known neuroscientist

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ABSTRACT

Rafael Lorente de Nó (1902-1990) was a Spanish neuroscientist whose work is rarely recognised in Spain, probably because most of his activity took place in the United States. He showed his flair for research from an early age, beginning when he was still a student. He studied with Santiago Ramón y Cajal in Madrid, Robert Bárány in Uppsala, and with Oskar and Cécile Vogt in Berlin. From 1931 until his death in 1990, he worked and lived in the USA.

He described the vestibular nucleus, the nucleus acusticus, and the anatomy of the eighth cranial nerve. In his studies of the cerebral cortex, he described previously unreported arrangements of cells. Lorente de Nó studied vestibulo-ocular reflexes and their anatomical pathways, together with the nerve connections at the axonal level; he also contributed to our knowledge of the nerve impulse.

His works were not well distributed and they are mentioned in only a few studies of the history of the neurosciences.

KEYWORDS
Eighth cranial nerve, neuroanatomy, neurophysiology, nucleus acusticus, nystagmus, Rafael Lorente de Nó, vestibulo-ocular reflexes

Rafael Lorente de Nó was born in Zaragoza in 1902 (Figure 1), where he also studied at the Faculty of Medicine. During his student years, he conducted neurological experiments with guidance from Pedro Ramón y Cajal, Santiago Ramón y Cajal's brother.[1] He induced spinal lesions in tadpoles and studied eye movements in frogs.[2]

He also studied the mechanism of vestibular reflexes in laboratory animals by making an incision at the midline of the pons and medulla oblongata and then observing that horizontal nystagmus was altered. Only slow horizontal rotations of the eyes were present and the quick component of nystagmus was absent. He concluded that given the isolation of the vestibular nucleus, the quick component of nystagmus must depend on the activity of certain reticular system cells. This activity will then disappear when an incision is made at the midline of the brainstem.[3]

Lorente de Nó graduated from the University of Madrid. Short after that, he began work at the Instituto Cajal, where he remained for 8 years (1921-1929). Under Cajal's tutelage, he studied the cerebral cortex; in 1922, he published an article on that structure in the mouse.[1]

Lorente de Nó met Bárány when the Austro-Hungarian physician was presenting a series of lectures at the University of Zaragoza. Bárány, who was awarded the Nobel prize in 1914, took note of Lorente's drive and preparedness, and he invited his Spanish colleague to join him at the University of Uppsala. Once there, the two researchers studied vestibulo-ocular reflexes and identified their underlying anatomical pathways and physiological mechanisms. In 1925, Lorente de Nó journeyed on to Berlin, where he conducted research with Oskar and Cécile Vogt into the cytoarchitecture and functional organisation of the cerebral cortex.[4]

Upon returning to Spain, he set up a private otorhinolaryngology practice due to the lack of financial support for research. Lorente de Nó was later designated head of the otorhinolaryngology department at Casa de Salud in Valdecilla, Santander.[4]

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Figure 1. Rafael Lorente de Nó (1902-1990)

His relationship with Bárány led to a grant from the Rockefeller Foundation, and he moved to the USA in 1931. With the support of that Foundation, he began work at the Central Institute of the Deaf, in Saint Louis, Missouri.

The Great Depression had a detrimental effect on most research centres. Lorente de Nó then considered returning to Spain, but his prestige as a scientist was such that Herbert Gasser, the 1944 Nobel Prize laureate for his studies on the functions of nerve fibres, recommended him to the Rockefeller Institute for Medical Research, an institution which would later become a university.

Lorente de Nó was appointed professor and worked at this institution until his retirement in 1970. Upon retiring, he was designated professor emeritus of anatomy by the UCLA Brain Research Institute in California. He also became a member of the National Academy of Sciences in 1950. In recognition of his scientific contributions, he was appointed to the American Academy of Arts and Sciences and made an honorary member of the University of Uppsala, Clark University, and Rockefeller University.[5]

Scientific publications

The scientific contributions by Lorente de Nó were diverse. He studied the histological structure of the vestibular nucleus, its connections, and the eighth cranial nerve. In 1933, he published one of his most important studies, "Vestibulo-ocular reflex arc", in *Archives of Neurology and Psychiatry.* This article explores the complex mechanisms of vestibulo-ocular reflexes, the neuronal circuits at brainstem level, and the participation of the reticular system in the quick component of nystagmus.[5]

He also proposed that the nervous system is not specifically a series of chains of cells organised in a hierarchical manner, but rather a series of neurons interconnected in circuits that he classified in two types: parallel open circuits, and closed or ring circuits.[5]

Also in 1933, he published "Anatomy of the eighth nerve", an extensive description of the origin of the fibres of the eighth cranial nerve and their termination at the nucleus acusticus. The article was published in two parts in the journal *Laryngoscope*.[5]

He published his articles on the structure of the cerebral cortex between 1933 and 1934, several years after having studied it while working with Oskar and Cécile Vogt in Berlin. In these articles, he illustrates the structure of the entorhinal cortex and the hippocampus. These studies appeared in two issues of *Journal für Psychologie und Neurologie*.[5]

The section on the hippocampus was especially worthy of note. Lorente de Nó, who had studied the cytoarchitecture of this anatomical formation in detail, observed different cell types and an intricate network of connections. He divided the hippocampus into sections that he designated CA1, CA2, CA3, and CA4. CA is taken from the Latin name for Ammon's horn, cornu Ammonis.[4]

The significance of these studies led Fulton, the great neurophysiologist, to invite Lorente de Nó to author several chapters on cerebral cortex that would then be included in his neurophysiology textbook. Below are some excerpts written by Lorente de Nó.

> This study can be carried out in any cortical area of any mammal, but it is facilitated by investigating the same region in various types of mammals and deter-

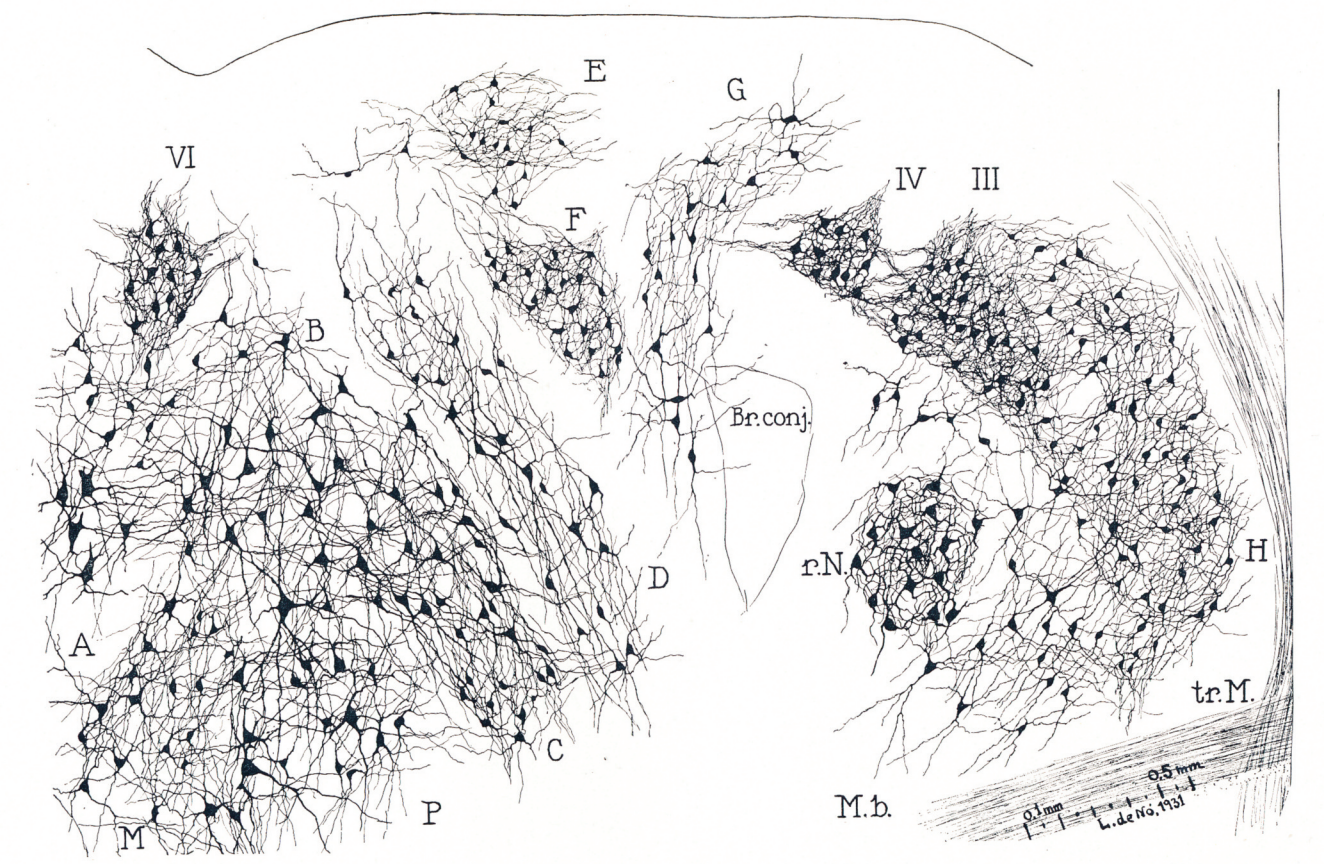

Figure 2. Rafael Lorente de Nó. Activity of internuncial neurons[8]

mining the structural traits that are common to all.

A number of cortical areas, although not many, can easily be recognised in all the mammals studied, i.e., in mouse, rat, cat, monkey, and man.[...] When any of these areas is studied intensively in different mammals, it is found that some of the structural details remain constant despite the variations in cell number, cell form and size, and the disappearance in the lower mammals of any type of cells found in the brains of the monkey and above all of man. What remains constant is the arrangement of the plexuses of dendritic and axonal branches, i.e., of the synaptic articulations though which nerve impulses are transmitted. This constancy is fortunate, because if it were otherwise studies made of the comparative anatomy and physiology of the cortex would have but a limited value.

Studies on the fine structure of the cortex have revealed that, although in architectonic pictures the horizontal stratification seems to be the most important factor in cortical organisation, the intracortical connections are established chiefly in vertical directions so that the whole vertical section of the cortex must be considered as a unitary system. The cortical cells are arranged in vertical chains and the architectonic layers indicate only where the bodies of cells, which are similar links in the chain, are located. But those cells, by means of long dendrites, establish connections in other layers (...) The main projections of the cerebral cortex are divided into two groups: pyramidal or corticospinal, and extrapyramidal. The corticospinal tract mainly originates from Betz cells in the fifth layer of the cortex, of areas 4 and 5 of Brodmann; some fibres may originate from the giant pyramidal cells in the areas 5 and 6.

The extrapyramidal projections comprise the cortico-pontine, cortico-nigral, cortico-tegmental, cortico-rubral, cortico-midbrain, and cortico-striatal projections, plus the different motor projections from the parietal, occipital, and temporal lobes.[6(p290-326)]

This study specifies that cerebral cortex is arranged vertically in functional units. Unlike the type of cell organi-

sation that creates horizontal layers, vertical organisation requires the presence of interneurons that interconnect while also following reentrant pathways into the vertical columns. Lorente de Nó's hypothesis was confirmed in 1957 by Mountcastle, who acknowledged him as the first author to describe this finding.[4]

Another of Lorente de Nó's fields of research was neurophysiology (Figure 2). He also conducted several studies on axon conduction velocities, as well as studies of temporal and spatial summation of conduction in the synapses. He observed that the sum of subliminal changes induced by different impulses reaches a certain threshold value which originates a discharge through the axon; thus, the axon enters into a refractory period immediately or else undergoes subliminal changes.[4]

In the course of his research into nervous transmission, he studied neurotransmitters, especially acetylcholine. However, he did not publish any studies on that topic, which was just beginning to attract interest at that time. He used tetramethylammonium (TMA) to study how nerve impulses are transmitted; this quaternary ammonium inhibits impulse transmission by selectively blocking potassium channels. He also investigated the electrical activation of postsynaptic cells.[7]

Lorente's last book, which he published in 1981 in partnership with Victor Goodhill (head of the otorhinolaryngology division of the UCLA Ear Institute) was *The primary acoustic nuclei*. Most of the text had been drafted some 50 years before, but due to financial hardships, he had been unable to publish it, and the abundance of illustrations made printing even more expensive. This book provides a detailed description of the anatomy and physiology of the nucleus acusticus. The text is accompanied by a series of illustrations prepared by Lorente himself.[5]

Now afflicted by emphysema and other respiratory problems, he moved to Tucson, Arizona in the hope that a dry climate would make it easier to breathe. Lorente de Nó died of cancer on 2 April 1990.[5]

His contributions to neuroanatomy were extremely valuable; his studies on vestibular and auditory nuclei, as well as the nucleus acusticus and the cerebral cortex were also groundbreaking, especially his new conception of cellular architecture in the cortex, in which vertical columns were added to the previously recognised horizontal layers.

Conflicts of interest

The author has no conflicts of interest to declare.

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