


History of Neuroscience

I. Pío del Río-Hortega (1882–1945): The Discoverer of Microglia and Oligodendroglia

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When we think about the history of glial cells, Santiago Ramón y Cajal comes to mind, who in addition to receiving the Nobel Prize in 1906 for staining individual neurons, is also credited with being the first to be able to specifically stain astroglia (Cajal, 1913a). However, Cajal (1913b) was initially unable to stain a third set of small cells present in tissue sections which apparently did not possess any processes, and which he referred to as the “third element”. Pío del Río-Hortega (Figure 1), originally from Valladolid, Spain, where he graduated in Fine Arts and then received

a medical degree, moved to Madrid in 1912 to work with Nicolas Achúcarro from whom he learned various metal impregnation methods for staining tissues and cells (Tremblay et al., 2015). During that period, by modifying the original Golgi staining method to include silver carbonate, he was able to visualize the cells comprising the

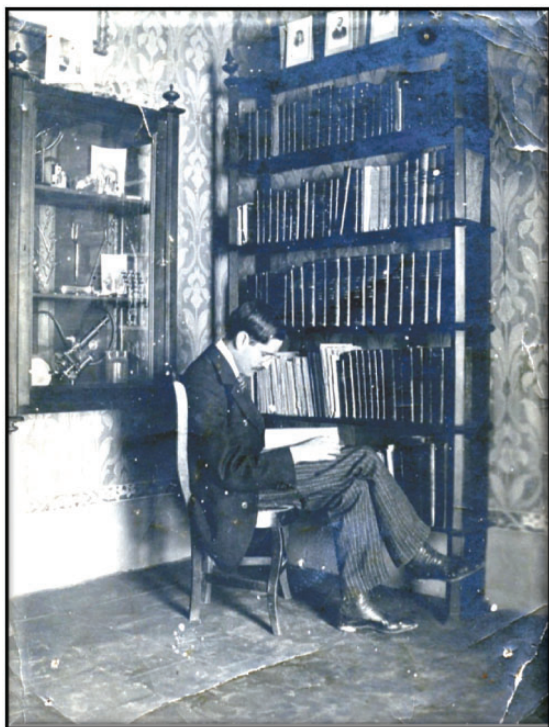


Figure 1. Pío del Río-Hortega in His Study at the Family Home at Valladolid, in 1910. Note the Microscope in the Showcase (Courtesy of Río-Hortega Bereciartu Family).



Figure 2. Early Drawing of Oligodendrocytes (“O”) Enwrapping Neurons (“N”) and Astrocytes (“A”) With End Feet Associated to Microvessels (Río-Hortega Museum in Valladolid Faculty of Medicine).

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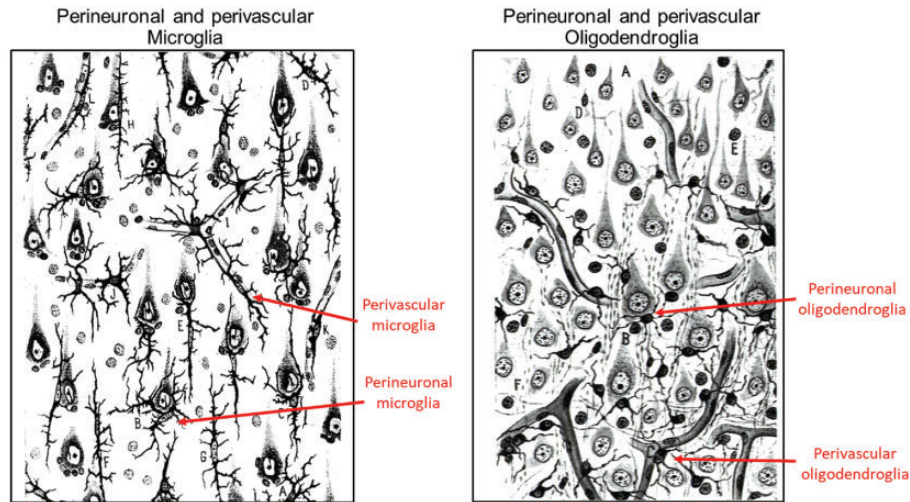



Figure 3. Images of Perineuronal and Perivascular Microglia and Oligodendroglia. Left: From Río-Hortega (1919). Right: From Río-Hortega (1921).

Table 1. Pío del Río Hortega: The discovery of microglia and oligodendroglia.

 <p>Photograph of young Pío del Río-Hortega From the Archive of Pío del Río-Hortega, Family del Río-Hortega Bereciartu</p>	•1882	Pío del Río-Hortega born in Portillo near Valladolid, Spain
	•1905	MD in Valladolid (the oldest school of medicine in Spain)
	•1909	PhD on etiopathology of brain tumors
	•1912	Moved to Madrid to work in Nicolás Achúcarro laboratory (Museum of Natural Sciences) to learn metal impregnation techniques
	•1918	Modified Golgi staining with silver carbonate, visualized Cajal's 'third element' (microglia and oligodendrocytes). Achúcarro death. Moved to Ramón y Cajal laboratory.
	•1919	Published 4 landmark papers on his studies on microglia from the Greek "micro" [small] and "glia" [glue]
	•1920	Expulsion from the Cajal laboratory (Oct 9 th). Establishment of independent lab near La Residencia de Estudiantes.
	•1921	Coined the term "oligodendroglia" to describe interfascicular glia from the Greek "oligo" [few] "dendro" [process] and "glia" [glue]
	•1928	Nominated for Nobel Prize
	•1936	Fled the civil war in Spain and found asylum in Argentina.
•1937	Again nominated for Nobel Prize	
•1945	Died from cancer in Buenos Aires.	

third element, namely, microglia and oligodendrocytes (Figure 2) for which he correctly deduced their functions of phagocytosis and myelin production, respectively (Río-Hortega, 1919, 1921).

In 1918, after Achúcarro's death, he moved to the Cajal lab where he was able to work for 2 years before being expelled due to increasing tensions between Río-Hortega and members of the Cajal laboratory. In 1920, Río-Hortega then established his own laboratory nearby at the Residencia de Estudiantes in Madrid, and as Director of the Laboratory of Normal Histology and Pathology, he started his own Histological School (Río-Hortega Bereciartu, 2020). There he became a magnet for many young scientists, continued to work on the development of further histological staining methods (Río-Hortega, 1993), and was nominated for the Nobel Prize (both for 1929 and for a second time for the 1937 prize) for his findings. Eventually, Cajal accepted the existence of microglia revealed to the world in

English by Río-Hortega in 1932 (Río-Hortega, 1932), and in 1929, Cajal finally accepted in a personal letter to Río-Hortega the identification of oligodendroglia after publication by Río-Hortega of his masterpiece book summarizing years of work on this new elusive cell type (Río-Hortega, 1928).

In 1936, the Spanish Civil War broke out, and being from a liberal family and background, he fled to work at the Pitié-Salpêtrière Hospital in Paris, then transitioned to Oxford University, England, in 1937, where he worked in neuropathology at the Nuffield Institute and was the first Spanish scientist to receive the Doctor Honoris Causa degree in 1939 (Río-Hortega Bereciartu, 2020). He permanently emigrated to Argentina in 1940 where he was recognized as an outstanding scientist and received in 1941 a Doctor Honoris Causa degree, and in 1943, he was bestowed Extraordinary Professor from Buenos Aires National Medical University of La Plata. He continued his work until his death in 1945 in Buenos

Aires. In 1942, he started the journal *Archivos de Histología Normal y Patológica* which lasted until 1966 and published papers on various aspects of glial cell biology. During his last few years, he turned his attention to the functions of glial cells in brain tumors. His legacy continued through the work of students and colleagues, including Wilder Penfield, William Gibson, Moisés Polak, Juan Manuel Ortiz Picón, and Eduardo de Robertis. A time line of the life and major accomplishments of Pío del Río-Hortega is presented in Table 1.

Although many of us are familiar with the characterization of microglia and oligodendrocytes, several of Río-Hortega's observations remain relatively unexplored to this day. In 1919 and 1921, he described perineuronal and perivascular localization of both microglia and oligodendroglia (Figure 3), sub-populations of cells infrequently studied today, and whose functions are yet to be fully characterized.

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References and Further Reading

Cajal, S. R. (1913a). Un nuevo proceder para la impregnación de la neuroglia [A new procedure for the impregnation of neuroglia]. *Boletín de la Sociedad Española de Biología*, 2, 104–108.

Cajal succeeded in being the first to stain both fibrous and protoplasmic astrocytes with unequaled selectivity while neurons remained pale, using a gold and mercury chloride-sublimate technique.

Cajal, S. R. (1913b). Contribución al conocimiento de la neuroglia del cerebro humano [Contribution to the knowledge of the neuroglia of the human brain]. *Trabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid*, 11, 255–315.

Cajal famously designated neuroglia cells he could barely visualize, despite his staining artistry and genius, as the “third element.”

Río-Hortega, P. D. (1919). El “tercer elemento” de los centros nerviosos [The “third element” of the nerve centers]. *Boletín de la Sociedad Española de Biología*, 9, 68–166.

I. La microglía en estado normal (pp. 68–82)

II. Intervención de la microglía en los procesos patológicos (pp. 91–103)

III. Naturaleza probable de la microglía (pp. 108–120)

IV. Poder fagocitario y movilidad de la microglía (pp. 154–166)

These four installments (I to IV) published back to back in the same journal issue formally introduced microglia to the world. Microglial cells had been formerly described i.e. by Alzheimer in the late 19th century, but until the 1919 Río-Hortega series, microglia were just strange amoeboid cells. Río-Hortega devised a staining which showed microglia in all their activation states from resting ramified to phagocytosing amoeboid, thereby establishing a new cell type and showing its versatility.

Río-Hortega, P. D. (1921). Estudios sobre la neurología. La glía de escasas radiaciones (oligodendroglía) [Studies on neurology. Low-radiation glia (oligodendroglia)]. *Boletín de la Real Sociedad Española de Historia Natural*, 21, 63–92.

This article introduced the oligodendrocyte as a new cell type. This report antagonized Cajal more than the newly described microglial cell, because Cajal was now famous world-wide and had already received the Nobel Prize. Despite his staining genius, Cajal failed in visualizing oligodendrocytes which he dubbed the “third element” or “apolar elements” since he could never see their processes. Cajal finally acknowledged the existence of oligodendrocytes a mere 5 years before his death in a personal letter to Pío, but never in a scientific publication.

Río-Hortega, P. D. (1928). Tercera aportación al conocimiento morfológico e interpretación funcional de la oligodendroglia [Third contribution to the morphological knowledge and functional interpretation of oligodendroglia]. *Memorias de la Real Sociedad Española de Historia Natural*, 14, 5–122.

The sum of a monumental amount of work on oligodendrocytes of which we are still rediscovering. Essentially everything Pío discovered about oligodendrocytes is contained in this book of 120 pages. The classification into four cardinal types depending upon the orientation and size of myelinated axons is still used to this day.

Río-Hortega, P. D. (1932). *Microglia in cytology and cellular pathology of the nervous system* (W. Penfield, Ed., pp. 480–534). Hoeber.

The first account of microglia in English. For a while microglia were called “Río-Hortega's cells”.

Río-Hortega, P. D. (1993). Art and artifice in the science of histology. (Originally published in Spanish in 1933, translated by W.C Gibson) *Histopathology*, 22, 515–525.

Philosophical thoughts of Río-Hortega on the relationship between histology, drawing, and art; which revealed him as a true artist. Río-Hortega could draw with both hands, and was the author of all of his drawings (like Cajal), in contrast to others who had artists draw their cells (such as Ranvier).

Río-Hortega Bereciartu, J. D. (2020). Pío del Río-Hortega: The revolution of Glia. *Anatomical Record*, 303, 1232–1241. A personal account by the grandnephew of Río-Hortega, detailing his complicated relationship with Cajal and the special WWII political upheaval in Spain that forced his exile to Argentina.

This short biography also details the unsuccessful attempt made for the discoverer of microglia to receive the Nobel Prize.

Tremblay, M. E., Lecours, C., Samson, L., Sánchez-Zafra, V., & Sierra, A. (2015). From the Cajal alumni Achúcarro and Río-Hortega to the rediscovery of never-resting microglia. *Frontiers in Neuroanatomy*, 9, 1–10.

An interesting historical account describing the context in which microglial cells were discovered, crediting Achúcarro and not Cajal, as commonly assumed. Río-Hortega never trained with Cajal, but mastered histological staining with another forgotten genius of the time: Achúcarro.