A review of Dr Simarro's neurohistological legacy

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ABSTRACT

Introduction. Dr Luis Simarro (1851-1921) was a prominent figure in Spanish medicine and psychology, and also participated in numerous other social, cultural, and political activities. In his youth, philosophical and scientific influences led him to develop a keen interest in the anatomy, physiology, and histology of the central nervous system and to study neurology and psychiatry. Upon his death, Simarro left a collection of histological sections that have not previously been studied in detail.

Material and methods. The author selected and took photomicrographs of 20 histological sections of normal and pathological tissue from Simarro's collection.

Results. The histological preparations of normal tissue included in this study demonstrate Simarro's mastery of histological technique. Two preparations, one stained with the Golgi technique and the other with the reduced silver nitrate method, are particularly interesting from a historical viewpoint. The neuropathological preparations selected display a wide range of diseases, including multiple sclerosis, syringomyelia, transverse myelitis, and tabes dorsalis.

Conclusions. This review of Simarro's collection of histological sections confirms his extensive abilities as a histologist and neuropathologist; this, combined with his excellent clinical skills, could also have led him to become the first great professor of neurology, psychiatry, and neuropathology of Spain.

KEYWORDS

Simarro, Cajal, Golgi, Marchi, Weigert, histology, neuropathology

Lear: How now, what art thou?
Kent: A man, sir.
Lear: What dost thou profess? What wouldst thou with us?
Kent: I do profess to be no less than I seem, to serve him truly that will put me in trust, to love him that is honest, to converse with him that is wise and says little, to fear judgment [...]
King Lear. W. Shakespeare

Introduction

Dr Luis Simarro Lacabra (Rome, 1851-Madrid, 1921) was an extraordinarily multifaceted scientist whose career developed during the late 19th and early 20th century. However, he may well be described as a Renaissance man, due to his wide range of intellectual interests and his free spirit. Dr Simarro was a clinician with training in histology, particularly neurohistology, as well as a neurologist and psychiatrist. His insatiable curiosity led him to make incursions into comparative anatomy, embryology, the theory of evolution, philosophy, psychology, pedagogy, and even the political arena. His knowledge was not merely superficial; rather, he engaged fully in any endeavour he pursued, especially in his later years.

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Dr Simarro's personality and many interests have been the focus of numerous articles, doctoral theses, studies commemorating the centenary of his chair, and several biographies.[1-25] The information provided by these sources is summarised in the introduction with a view to contextualising the analysis of Simarro's histological and histopathological preparations.

Brief biography of Dr Luis Simarro

Luis Simarro Lacabra was born in Rome in 1851. He was orphaned at the age of four years, after his father died and his mother committed suicide, and he was raised by one of his uncles. He completed his basic studies and the first years of medical school in Valencia. His participation in the revolutionary movement of 1868 and his adhesion to positivism caused friction with some of his professors. He had to move to Madrid to complete his medical degree, in 1874, and his doctorate, in 1875. Upon his arrival at the city, Simarro came into contact with a progressive group of physicians who worked at the Free Practical School of Medicine and Surgery, operating in the Anthropology Museum, and at the Institución Libre de Enseñanza (Free Institute of Education). Simarro collaborated with the latter institution from 1876, teaching the physiology of the nervous system.[17] In 1877, he became chief physician at the psychiatric hospital of Leganés, in Madrid, where he came into conflict with the centre's management and the religious community[19] for performing autopsies. He resigned and, in 1880, left for Paris, where he stayed for five years.

Upon his return to Spain, Simarro opened a private clinic, which was highly successful. In 1892, he participated in the competitive examinations to appoint a chair of histology in Madrid; however, the chair was granted to Santiago Ramón y Cajal, whom Simarro had taught the Golgi technique in 1887. In 1893, Simarro was appointed "non-tenured physician" at Hospital de la Princesa, in Madrid, and in 1902, he became the first chair of experimental psychology at the University of Madrid. He promoted the Spanish Association for the Advancement of the Sciences and the League for the Defence of Human and Citizens' Rights. He also became an active member of several scientific and cultural societies (mainly the Ateneo de Madrid) and joined Freemasonry, becoming a Grand Master.[13] He actively collaborated with the Institución Libre de Enseñanza, publishing numerous articles in its bulletin. He taught histology at private, independent institutions, and he and Madinaveitia created a histology laboratory at their own expense, initially located on calle del Arco de Santa María and subsequently on calle del General Oráa, where the most brilliant members of the Spanish neurohistological school, namely Achúcarro and Lafora, were trained.

Simarro married twice but had no children. A well-mannered man, he dressed elegantly and had exquisite taste, as recounted by his god-daughter.[23] Upon his death, he left an important legacy, including cash, paintings and engravings, valuable objects and tools, an extensive library,[26] and a collection of histological sections; these materials were intended for the creation of a foundation. After many vicissitudes, the materials came to be held at the Foundation of the Complutense University of Madrid.

Intellectual circles and their influence on Dr Simarro

From the early 19th century, following the ideals of the Enlightenment and the French Revolution, the Western world, and particularly Europe, was seething with ideas that sought to advance humankind and to combat political, religious, or ideological tyranny: the declaration of human and citizens' rights, freedom of thought, debunking absolutism, discrediting dualism, the rise of positivism and materialism, Darwin's theory of evolution, the need for public education and secularity, etc. However, these ideas were met with great resistance from conservative forces. From a young age, Simarro was immersed in this constant ideological, political, and social confrontation, which was not always peaceful.

One implication of materialism was that the human brain, rather than the soul, became the focus of all medical and philosophical disciplines. With the precedent of phrenology, which lacked a scientific basis and was soon discredited, scientists performed the first anatomoclinical demonstrations of the cerebral localisation of higher brain functions, with Broca and other authors reporting language alterations in patients with focal brain lesions. This represented a great push to localisationism,[2] to the detriment of holism, in the study of brain function.

After this initial macroscopic approach, the natural next step was to analyse the intimate, microscopic structure of the brain. It should be noted that cell theory was still controversial in the second half of the 19th century. The methodological challenge of developing a histological technique that unravelled the mysteries of the brain

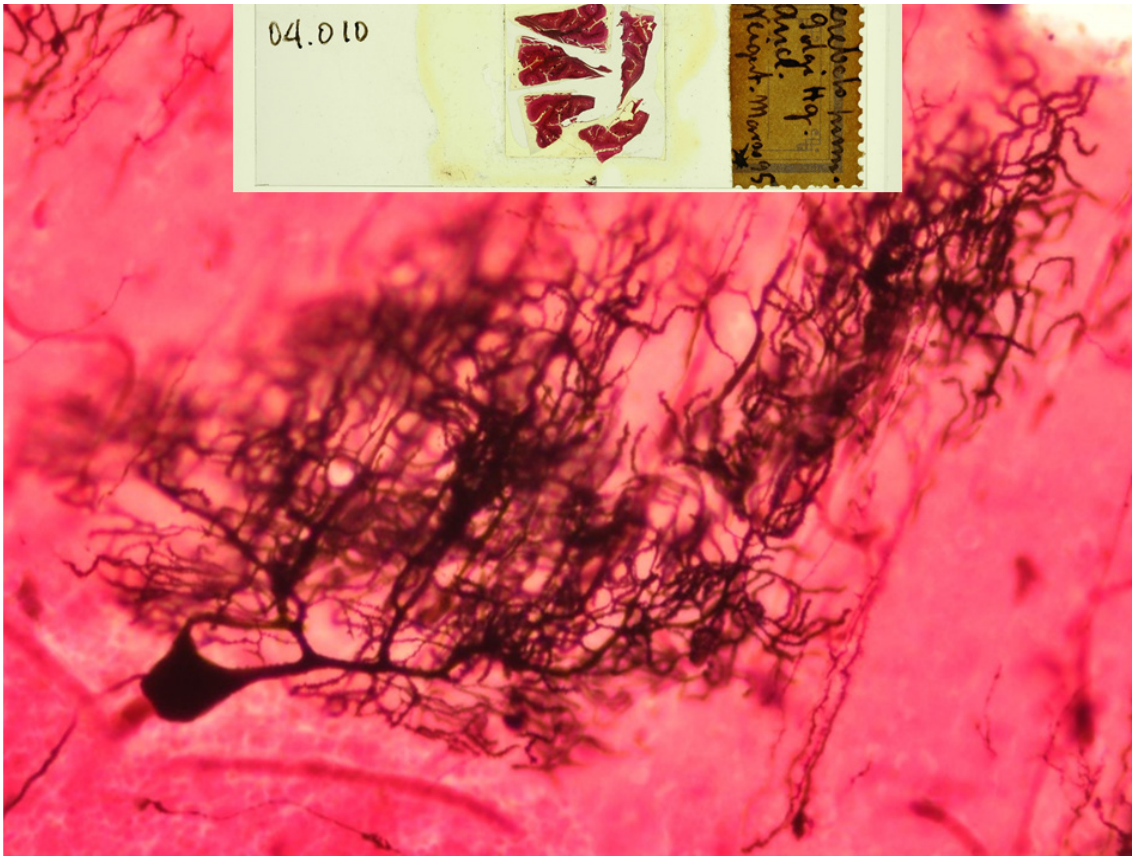

Figure 1. Preparation no. 04.010. Cerebellum (variant of the Golgi method). Purkinje cell with a long axon and a large dendritic tree.

fascinated Simarro throughout his life, and was probably one of the main driving forces in his professional career as a histologist.[1,4,8,15,18]

Simarro, a histologist and histopathologist

How and when did Dr Simarro develop an interest in histology, and particularly neurohistology?

According to his biographers,[1,12,14,15,17,18] his first main influence in the anatomical sciences was Dr Pedro González Velasco, editor of *Anfiteatro Anatómico Español* and promoter of the Society of Anatomy and the Anthropology Museum; the latter, in addition to fostering a wide range of activities in such fields as botany, the theory of evolution, and comparative anatomy, also housed a laboratory of histology. The other fundamental influence was Dr Aureliano Maestre de San Juan, who had also taught Cajal and created the Free Society of Histology in 1874, after being appointed to the chair of histology.

In 1880, Simarro admitted to his friend Dr Cortezo[8] that he needed to seek novel scientific sources and to gain a deeper knowledge, which "books and patients alone" were unable to provide, and so he left for Paris. According to Carpintero et al.,[8] Simarro went to great lengths in his search for the biological basis of the human soul. It was in Paris that he had the opportunity to visit the most important neuropsychiatric centres of the day. Above all, Simarro's visit to Paris consolidated his calling for neurohistology under Ranvier, the main authority

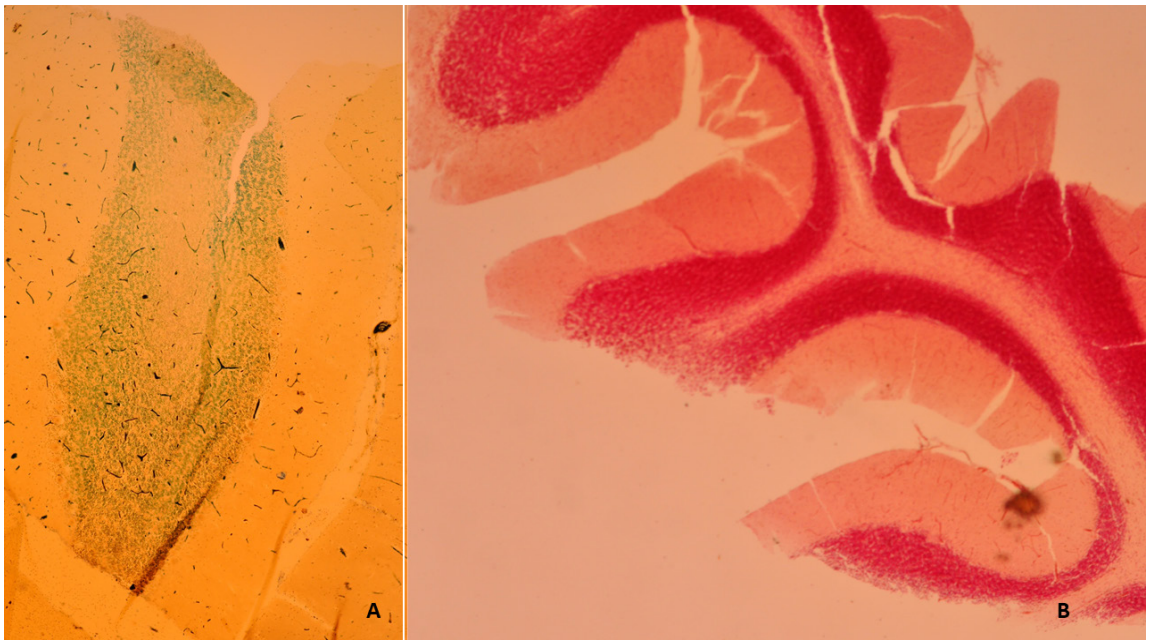

Figure 2. A) Preparation no. 04.004. Cerebellum. Labelled "verde" (green); staining technique not specified. B) Preparation no. 04.003. Cerebellum. Carmine staining. Both preparations display intense staining of the granular layer.

in the discipline and author of the reference treatise of histology of the time. It is a well-known fact that, as Simarro himself told Cajal in a letter,[4,13] Simarro did not see himself as a histologist, but rather as a neurologist; histology was simply the means of establishing clinical-pathological correlations. He returned to Spain with many histological sections[6,8]; unfortunately, this collection is not preserved in its entirety.

It is unclear whether Simarro learnt the Golgi technique with Ranvier, who apparently was not a great proponent of the technique developed by the Italian scientist,[12] or after his stay in Paris, through study of the works of Golgi, especially those published in French. In any case, Simarro came to master this fickle, uncertain technique and taught it to Cajal in 1887. He subsequently modified the technique by substituting silver chromate for silver bromide, and also experimented with other silver salts[27-29]; he also taught the technique to Cajal in 1900 and 1904, as Cajal himself acknowledged in his memoirs.

Reviewing the many scientific activities of Dr Simarro is beyond the scope of this article; rather, the study is intended to provide some novel information on his work as a neurohistologist and neuropathologist to contextualise the analysis of some histological preparations from his collection that have not previously been analysed in detail.

Material and methods

The information provided about Simarro's life and personality are taken from sources cited in the references section. The histological preparations reviewed belong to the Simarro Legacy, which is preserved at the Faculty of Psychology of the Complutense University of Madrid. The director of the Simarro Legacy, Prof J. Javier Campos, granted me access to the collection of histological preparations.[8] All preparations are numbered and archived along with the information contained in each slide. For the purposes of this study,

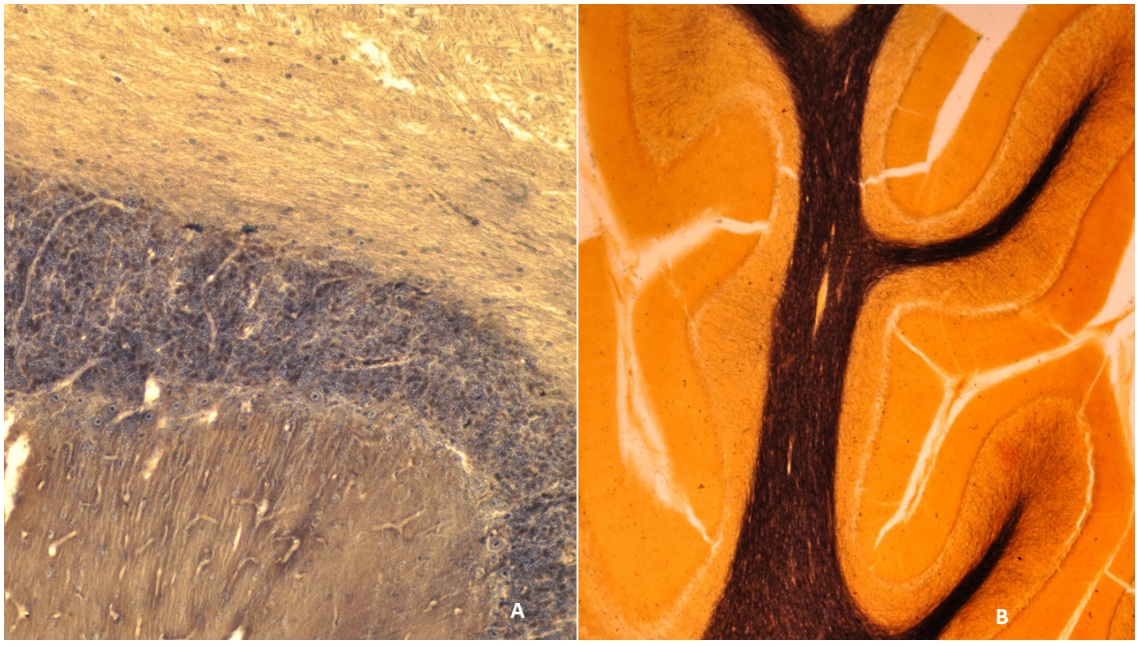

Figure 3. A) Unnumbered preparation. Monkey cerebellum. Staining technique not specified (Man?). B) Preparation no. 04.02. Human cerebellum. Weigert method for myelin staining, with excellent results.

I selected and took photomicrographs of approximately 20 preparations. The remaining preparations were not reviewed in detail, as many of them are test slides, some of which are valid but many are not. Most preparations are labelled with technical details (date, time and method of fixation, variations in temperature or staining, etc), demonstrating that Dr Simarro, like other histologists of the time, learned through trial and error. The collection also contains a number of preparations for embryology studies.

The selected preparations constitute the basis for this study. The selection criteria were as follows: *1)* preparations providing sufficient technical information for interpretation, and *2)* preparations of sufficient quality. The selected slides were preferably preparations of human tissue, either normal or pathological. The author of these pages, as was also the case with Simarro, sees himself as a neurologist with a histopathological background, which explains the bias for selecting neuropathological preparations of human tissue. I also reviewed a collection of photomicrographs accompanied by detailed technical specifications, but do not comment on these in this study.

Results

The description of the 20 preparations selected is based on the subjective judgement of the author, and does not reflect obviously the interpretations Dr Simarro would have made, nor does it necessarily coincide with the interpretation that any other observer might make.

To highlight Dr Simarro's neurohistological background, I selected some preparations where staining was successful. The first preparation (Figure 1), of particular historical significance, is a section from a human cerebellum stained with a modified Golgi technique. The slide displays several types of neurons, including well-stained Purkinje cells displaying their basal pole, dendrites, and dendritic spines. The label reads "marzo

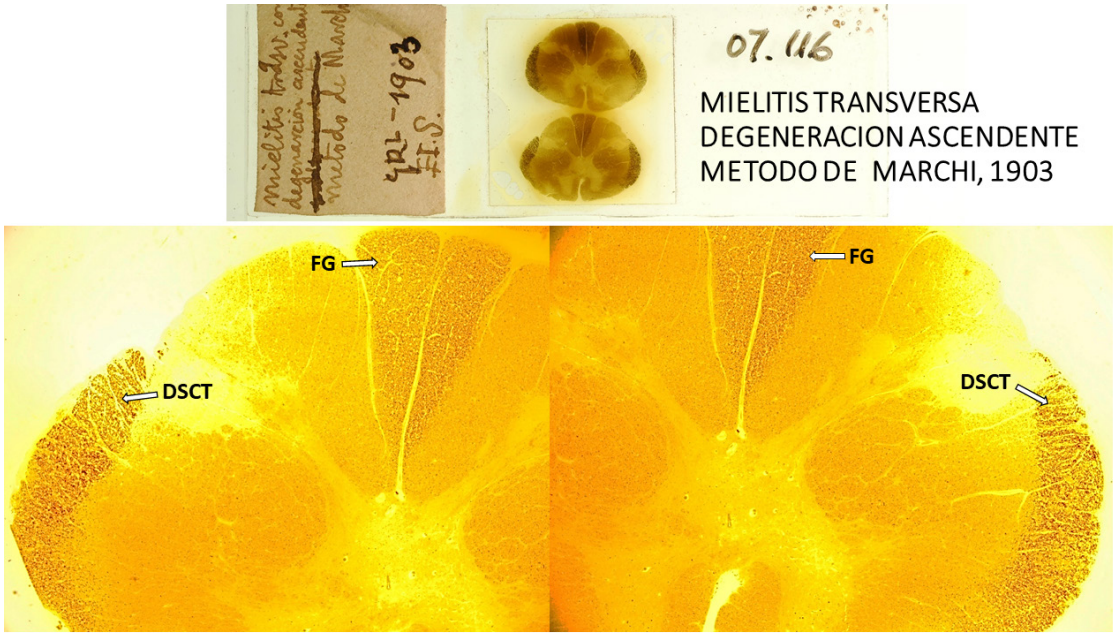

Figure 4. Preparation no. 07.116 (1903). Cervical spinal cord. Marchi staining. Case of transverse myelitis. Section taken at the level of the upper cervical spine, displaying ascending degeneration in the form of small, black spots (myelin degradation products), both in the fasciculus gracilis (FG) and in the dorsal spinocerebellar tract (DSCT).

95" (March 95); if this were the date of preparation, the specimen would have been processed after 1887, when Simarro taught Cajal the Golgi technique; therefore, this would be one of Simarro's modifications of the technique.

Figures 2 and 3 are other examples of successful staining of cerebellar tissue. The image displayed in Figure 2 uses two nuclear stains, resulting in intense staining of the granular layer. The first nuclear stain is labelled as "verde" (green), with no additional data, and "bueno" (successful), although it is weak, perhaps due to the passage of time. The second stain is the classic carmine stain, with a good result.

The staining technique used in Figure 3A is not indicated (Man?). The image displays a cerebellar section in which the astrocytes of the molecular layer are partially stained. Figure 3B displays the Weigert method for myelin staining, already a classic at the time, with very good quality, which was used in other preparations in the collection.

Figure 4 shows a preparation of pathological human tissue. The label reads "mielitis transversa con degeneración ascendente" (transverse myelitis with ascending degeneration), followed by an acronym of unknown meaning, and the year 1903, which suggests that these samples were taken from Simarro's patients, rather than preparations brought from Paris. The shape of the spinal cord indicates that the section was taken from the upper cervical spine. The preparation is stained with the Marchi method; even to the naked eye, the accumulation of myelin degeneration products (in the form of black spots) is clearly visible in the dorsal spinocerebellar tract, as well as in the gracile fasciculi, both of which ascend from the lesion focus, probably located in the dorsal region.

Figure 5 is labelled "moelle," with a French surname, which suggests that this preparation may have been brought from Paris. The label does not indicate the pathological process it presents or the staining technique, although it appears to be haematoxylin and eosin. The

dorsal columns (gracile fasciculi) and, to a lesser extent, the lateral columns (corticospinal tracts) clearly show a darker colour. This change in colouration is due to a process of active demyelination with presence of a large quantity of macrophages, or granuloadipose bodies according to the classic French denomination (Figure 6), which accumulate in dilated perivascular spaces. No foci of necrosis or perivascular or meningeal inflammatory infiltrates are observed. Such active demyelination is not compatible with chronic neurodegenerative disease; rather, it suggests an acute or subacute process. Simultaneous involvement of the dorsal and lateral columns in a demyelinating process may be compatible with subacute, combined degeneration of the spinal cord (vitamin B_{12} deficiency).

The preparations shown in Figure 7 are labelled "sclerose," which suggests that both were brought from Paris. Both used myelin staining and show extensive demyelination with well-defined edges and a reduced cell number in the centre, a typical finding in chronic multiple sclerosis plaques.

One of the preparations shown in Figure 8 is labelled "syringo" and must therefore also have been brought from Paris. The other preparation in Figure 8 is not labelled; however, the shape of the spinal cord suggests that the sample comes from the same patient. Figures 9 and 10 clearly display all the neuropathological features of chronic syringomyelia: macroscopic atrophy, anteroposterior flattening, a central cavity, and lateral cystic striations toward the grey matter. Cavity walls are lined with gliosis rather than ependymal cells, a typical finding in classic syringomyelia. The section is from the lower spinal cord, and displays signs of descending degeneration in the lateral columns as well as ascending degeneration with demyelination of the gracile fasciculi. The spinal cord presents arachnoid thickening, possibly suggesting that syringomyelia was due to spinal arachnoiditis.

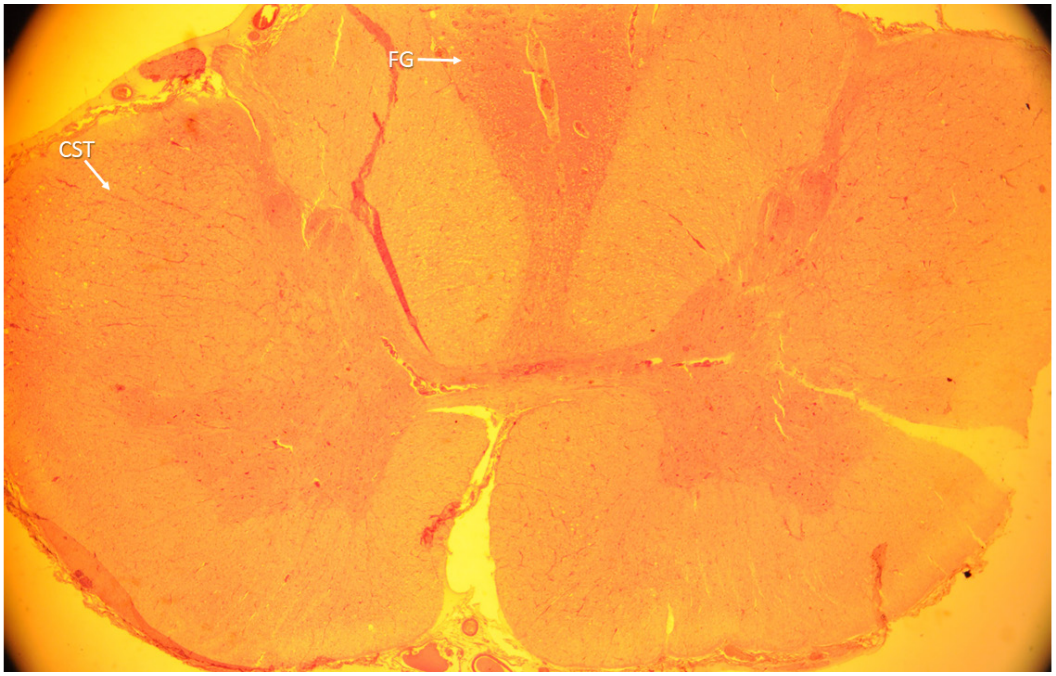

Figure 5. Preparation no. 04.078. Spinal cord, labelled "moelle." Staining technique not specified (probably haematoxylin and eosin). Magnified image (20×) displaying darker colouration of the fasciculus gracilis (FG) and, to a lesser extent, the corticospinal tract (CST), especially on the right side of the image.

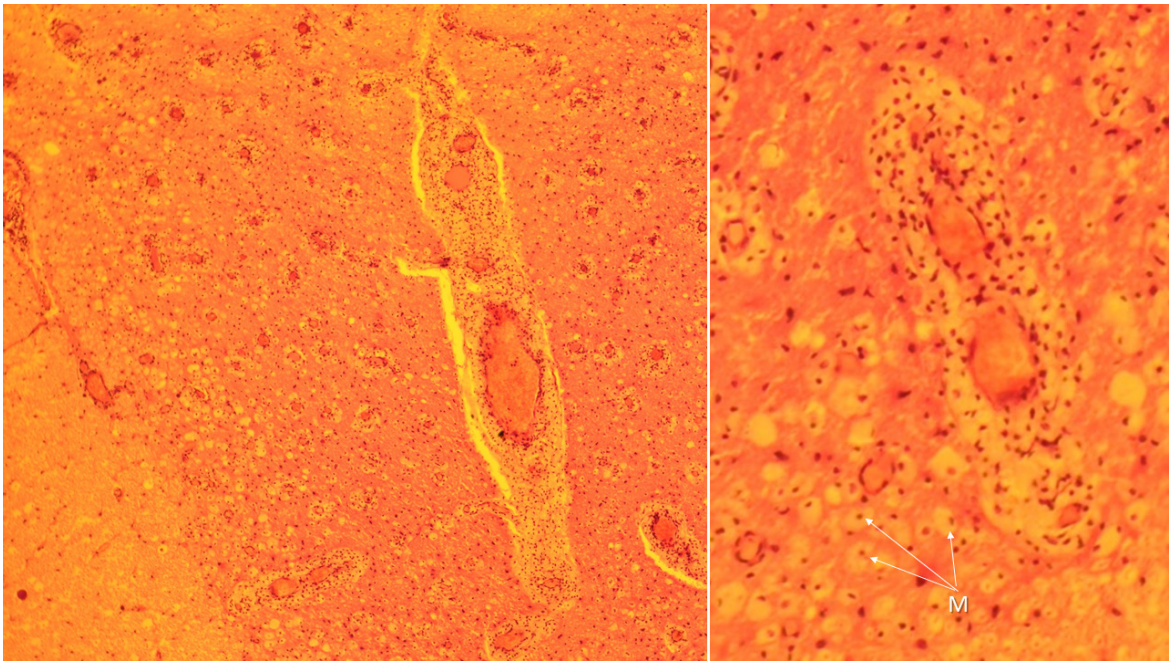

Figure 6. Preparation no. 04.078. Spinal cord, labelled "moelle." Staining technique not specified (probably haematoxylin and eosin). Image at greater magnification than Figure 5, revealing neuropil vacuolation in the fasciculus gracilis due to a process of active demyelination, with large quantities of macrophages (M), or granuloadipose bodies, accumulating around capillaries and venules for reabsorption.

Figure 11 is labelled "tabes, ganglio y raíz posterior" (tabes, ganglion, and dorsal root). The state of the dorsal columns cannot be evaluated as the section does not include the spinal cord. The small fragment of the ganglion shows some neurons; however, this section alone is insufficient to determine whether the number of neurons is preserved, as would be expected in tabes. However, in high magnification, we can clearly observe the degeneration of myelinated fibres in the dorsal root.

The preparation of Figure 12 is unequivocally one of Dr Simarro's and is labelled in his unmistakable handwriting as "arañas" (spiders), also indicating the staining technique ("plata reduc[ida]," silver reduction) and the anatomical location ("c[uerno de] Amón," horn of Ammon). From a histological perspective, neuron density is preserved in all layers and no senile plaques are observed, although the slide does display dense accumulation of silver particles, probably due to intraneuronal neurofibrillary degeneration (Figure 13A), as well as tortuous astrocytic processes (Figure 13B).

Discussion

This brief review of the Simarro Legacy confirms and provides further evidence of Simarro's interest and expertise in histology and knowledge of neuropathology.

There can be no doubt that, before leaving for Paris, he had accumulated a vast knowledge of the anatomy and physiology of the nervous system.[30,31] His first steps in neurology and psychiatry (which were yet to emerge as disciplines in their own right) between 1875 and 1880 were those of a self-taught scientist who learnt from the French and German literature. This is evident, for example, in the article dedicated to status epilepticus treated with amyl nitrite, in which he cites Charcot and Bourneville with admiration.[32] An even more illustrative example of Simarro's extraordinary knowledge of European (and particularly French) authors is the extensive list of references provided in his excellent lecture on the physiology of the nervous system,[33] a highly recommended reading for anybody interested in the history of neuroscience.

The influence of these and other great physicians of the time was surely pivotal in his choosing Paris to further his training. A detailed account of Simarro's activities in the French capital between 1880 and 1885 is not available. We do know that he visited the services directed by Charcot at La Salpêtrière and by Magnan at Asile Sainte-Anne, and attended Duval's courses on anthropology and anatomy and Ranvier's course on histology. Few details are available about Simarro's work with each of these authors, although the bulletin of the Institución Libre de Enseñanza published several articles in which Simarro praised the courses taught by Duval[34] and Ranvier.[35,36] In these articles, he made it clear that his interest in attending the courses of these great masters went beyond purely morphological anatomy and histology, as he was also interested in comparative anatomy, evolution, embryology, heredity, etc, perhaps even more so than in clinical neurology or psychiatry.

In fact, although Kaplan[15] describes how the young Simarro "devoured" Charcot's teachings and had personal contact with him, he did not leave a written account of his days at La Salpêtrière, where Charcot shined brightly. Before they met, the father of French neurology had already contributed nosological descriptions of the main neurological diseases, such as amyotrophic lateral sclerosis, Parkinson's disease, and multiple sclerosis, and published his famous lectures on nervous system diseases. In 1882, two years after Simarro's arrival in Paris, Charcot reached the peak of his career: thanks to the propaganda of his influential disciple Bourneville[37] and, more importantly, the political support of prime minister Gambetta, Charcot was appointed chair of nervous system diseases, a position that had been created expressly for him. By then, Charcot was already immersed in the study of hysteria[38] and Brouillet would soon immortalise Charcot's hypnosis sessions at La Salpêtrière in his famous painting *A clinical lesson at the Salpêtrière* (1887). It is surprising that Simarro, a scientist with extraordinary powers of observation and clinical interest in the human mind, should not leave

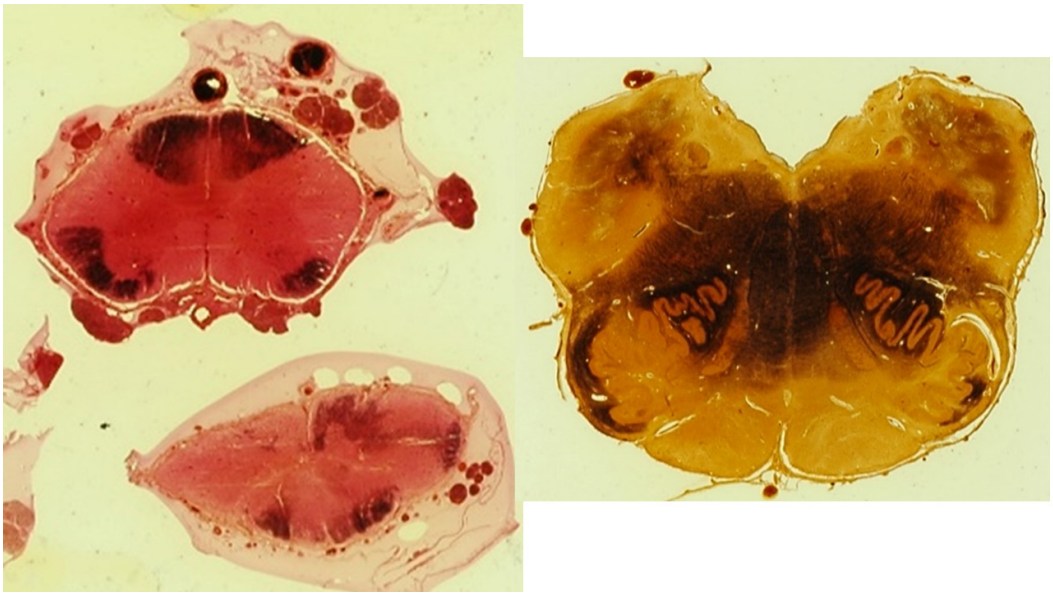

Figure 7. Preparations no. 04.071 and 04.082. Both are labelled "sclerose"; whether they come from the same patient is unknown. Myelin staining technique not specified. Both the spinal cord (left) and the medulla oblongata (right) present demyelinating plaques, compatible with multiple sclerosis.

Figure 8. Preparation no. 04.070. Labelled with what seems to be a proper noun, plus "syringo." The image displays demyelination in the corticospinal tract. Preparation no. 04.075 is unlabelled; however, the shape of the spinal cord and its cavities suggest that both tissue samples may come from the same patient.

written account of his impressions of Charcot and his sessions with hysterical patients. We would expect a young doctor (Simarro was around 30 at that time) to be fascinated, for better or worse, after attending one of those theatrical clinical sessions, as was the case with Axel Munthe and Freud shortly thereafter. We may expect that even a person with so little interest in writing as Simarro would have reported his impressions on these sessions; however, Simarro left only a short text about his view on hypnotism; this text was not published but was reproduced in a subsequent study.[5]

Did Simarro not attend one of Charcot's sessions? Was he uninterested, or did he find inconsistencies, in hypnosis and hysteria, a world so distant from the morphology of the nervous system? Was he solely focused on the histology laboratory and on neuropathology? This may have been the case, since the human neuropathological preparations that he is thought to have brought from Paris (some of which are reviewed in this article) must necessarily come from La Salpêtrière: Simarro could not perform autopsies nor did he have access to human neuropathological preparations at Asile Sainte-Anne with Magnan, at the Collège de France with Ranvier, or at Duval's School of Anthropology.

In any case, a review of Simarro's collection suggests that he had sufficient technical knowledge to perform basic histology and neuropathology studies, as he was familiar with a wide range of staining techniques, including silver staining, nuclear staining, the Cajal astrocyte stain with gold chloride, myelin staining (it was Simarro who taught Cajal the Weigert-Pal technique[17]), and stains for myelin degeneration products (Marchi method). He had a well-known interest in neuropathology and in determining the nature of disease in his patients; he had nurtured this

interest long before travelling to Paris, as he performed autopsies during his brief period at the Leganés psychiatric hospital.[19] In fact, this was the main reason that he left the centre, as he received a written order from the management to discontinue these practices; the letter is preserved today. The management cited administrative reasons, such as the patients' inability to give consent and the lack of a suitable place to perform the autopsies; however, it is believed that the true reason was the opposition of the religious community. At that time, his esteemed Bourneville[37] had already started a crusade to secularise French hospitals, winning some battles, although his enterprise was not concluded until well into the 20th century. Simarro, however, lost his first confrontation against the community of nuns; this was also the case with Achúcarro's student López-Albo at Hospital de Valdecilla several years later.[39] Simarro described his resignation at the Leganés psychiatric hospital with irony, comparing his personal failure with the days of Vesalius, when "living men suffered all manner of torture while corpses were denied the scalpel."[33] There can be no doubt that he was deeply disappointed.

After this failed attempt to gain systematic access to human corpses, Simarro never had another opportunity to perform autopsies, as he never worked at a neuropsychiatric institution that allowed such practices. His appointment as "non-tenured physician" of Hospital de la Princesa was of little help. He was occasionally sent human brains by some of his friends: his collection of photomicrographs contains at least two examples labelled as "human brain from Hospital de Asturias"; one corresponded to a woman of undetermined age and the other to an "old [!] man aged 60 years." His private clinic did not give him the opportunity to study clinical-pathological correlations. In fact, he published only one case of a patient with a brain tumour.[14,40]

Preparation no. 02.038 (Figure 12) probably corresponds to one of the brains sent to Dr Simarro (the shape and size of the hippocampus suggest that the brain was human). The section is stained with the reduced silver nitrate

Figure 9. Preparation no. 04.075. Myelin staining technique not specified, counterstained with eosin. Spinal cord section taken at the cervical level. The spinal cord presents atrophy, and is deformed (flattened) due to emptying of syringomyelic cavities, both in the central canal (CC) and in the lateral striations (S) toward the grey matter. The fasciculus gracilis (FG) present ascending degeneration, with marked arachnoid thickening (AT) around the spinal cord.

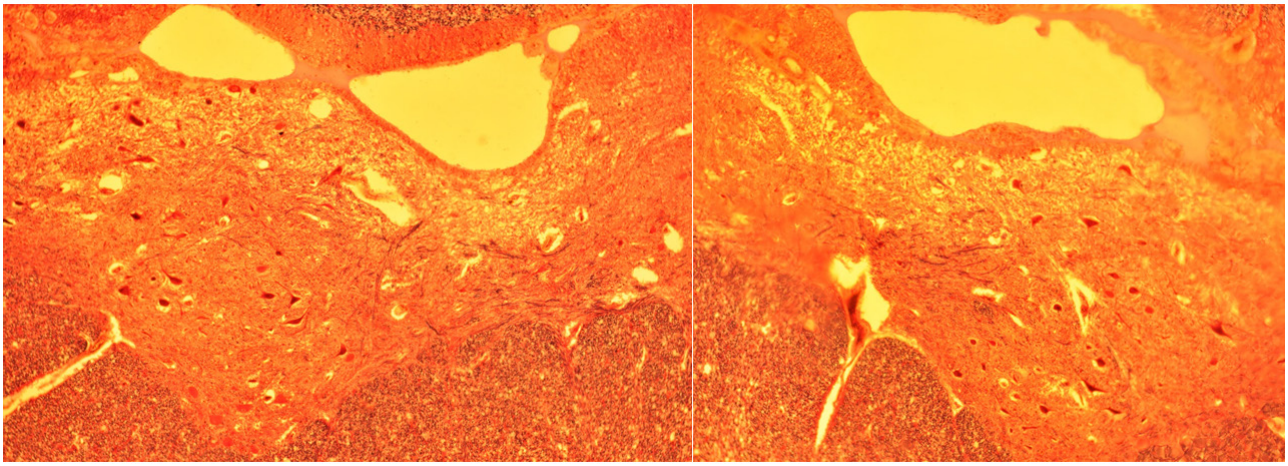

Figure 10. Preparation no. 04.075. Image at greater magnification than Figure 9. The walls of the syringomyelic striations are not lined with ependymal cells, but rather with a thick gliotic layer. Gliosis extends toward the ventral horn, which contains few neurons, many of which present signs of atrophy and degeneration.

method, as indicated in the label. This preparation is of great historical value, as it was most probably processed with Simarro's original method, which impregnated neurofibrils intensely, though irregularly; the method was published in 1900,[27-29] and continued to be used by Cajal, with some modifications.

The preparation presented in Figure 12 does not display senile plaques, although, according to Lafora,[22] Simarro observed this finding three years before Fischer, but did not publish it. This is very plausible from a chronological viewpoint, since Simarro used his reduced silver nitrate method, which displays senile plaques very clearly, before 1900, whereas Fischer used the Bielschowsky technique (described in 1902 or 1903) and published his findings on dementia and neuritic plaques in 1907.[41] The Simarro Legacy includes several drawings, one of which shows probable nerve fibres with thickened endings resembling maces, arranged around an amorphous material; these may well be the dystrophic neurites of a senile plaque. However, no legend is provided with the drawing.

In the preparation shown in Figure 12, Simarro indicated the staining technique (silver staining) and wrote "arañas" (spiders). What exactly did he mean? In his account of Ranvier's course,[36] in which he described the progress made in the understanding of cell populations in the nervous system and the considerable areas that remained to be understood, Simarro talked about "fibrils known as Deiters' spiders, which are considered elements of the conjunctive tissue." It is difficult to know what Dr Simarro was referring to as "spiders" 20 years after Deiters' description, considering that he was describing a preparation stained with a method he himself had developed, and which was unknown to Deiters and Ranvier. What fibrils or structures might he have been describing?

Although we do not know the answer, the preparation shows signs of probable neurofibrillary degeneration within many of the neurons in the pyramidal cell layer of hippocampal sector CA4, as well as fibrillary thickening and tortuosity in astrocytes (Figure 13). Unfortunately, the date of the preparation is unknown. It cannot be from earlier than 1900, as Simarro published his reduced silver nitrate method that year, using samples from animals (rabbits). However, given that Alzheimer communicated the princeps case of neurofibrillary degeneration in

1906, publishing it in 1907,[42] Simarro may have observed neurofibrillary degeneration before Alzheimer, without recognising its significance. I shall postulate another hypothesis: Simarro may have used the term "spiders" to refer to neurofibrillary degeneration (Figure 13A), or maybe to fibrillary thickening in astrocytes (Figure 13B) or "neuropil threads."

One fact undermining the hypothesis that Simarro recognised neurofibrillary degeneration is that his disciple Achúcarro did not cite him when he published a case of neuronal and glial fibrillary degeneration described during his stay in Washington.[43,44] Achúcarro mentioned that Alzheimer had observed both neurofibrillary plaques and neurofibrillary degeneration in the brain of his first patient, Auguste, and in other patients, but indicated that some brains only displayed plaques. He also cited Perusini, who had already reported the opposite observation: cases of dementia with neurofibrillary degeneration but without senile plaques. Achúcarro also described a similar case of a patient without senile plaques, and contributed the histological observation that, in addition to intraneuronal fibrillary degeneration, the patient presented fibrillary alterations in astrocytes, which he called "rings" and "basquets," and which today are known as "coils" (in oligodendrocytes). This study[43] went unnoticed for many years, even after his findings were confirmed and other authors coined the terms "tangle-only" or "tangle-predominant" dementia.[45] The histological findings of Figure 13 would be compatible with this form of tauopathy, which may be diffuse or more restricted.

It would not be surprising that Simarro should observe neurofibrillary degeneration before Alzheimer, without recognising its importance, especially considering that

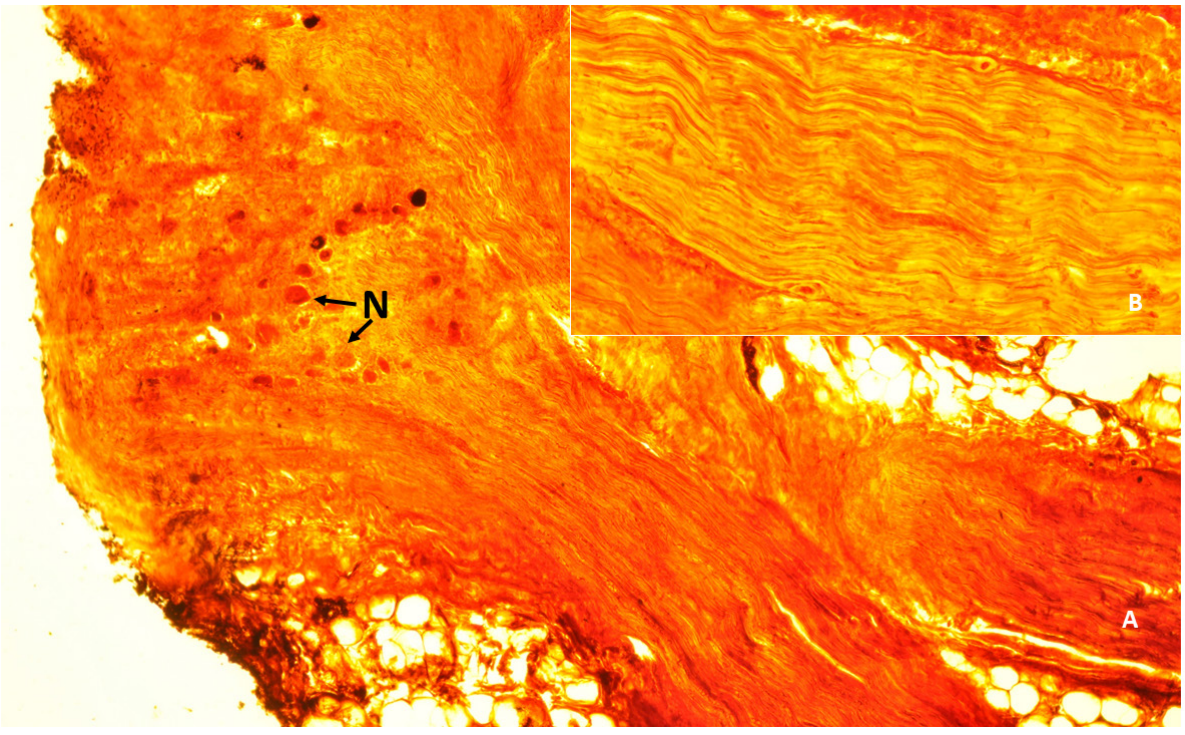

Figure 11. Preparation no. 04.068. Staining technique not specified. Image labelled "Tabes, raíz y ganglio posterior" (tabes, ganglion, and dorsal root). Some neuron cell bodies (N) are seen in the ganglion. The magnified image displays fragmentation and loss of myelinated fibres.

Figure 12. Preparation no. 02.038. Image labelled in Dr Simarro's handwriting as "arañas," "c[uerno de] Amón," and "plata reduc[ida]" (spiders, horn of Ammon, reduced silver).

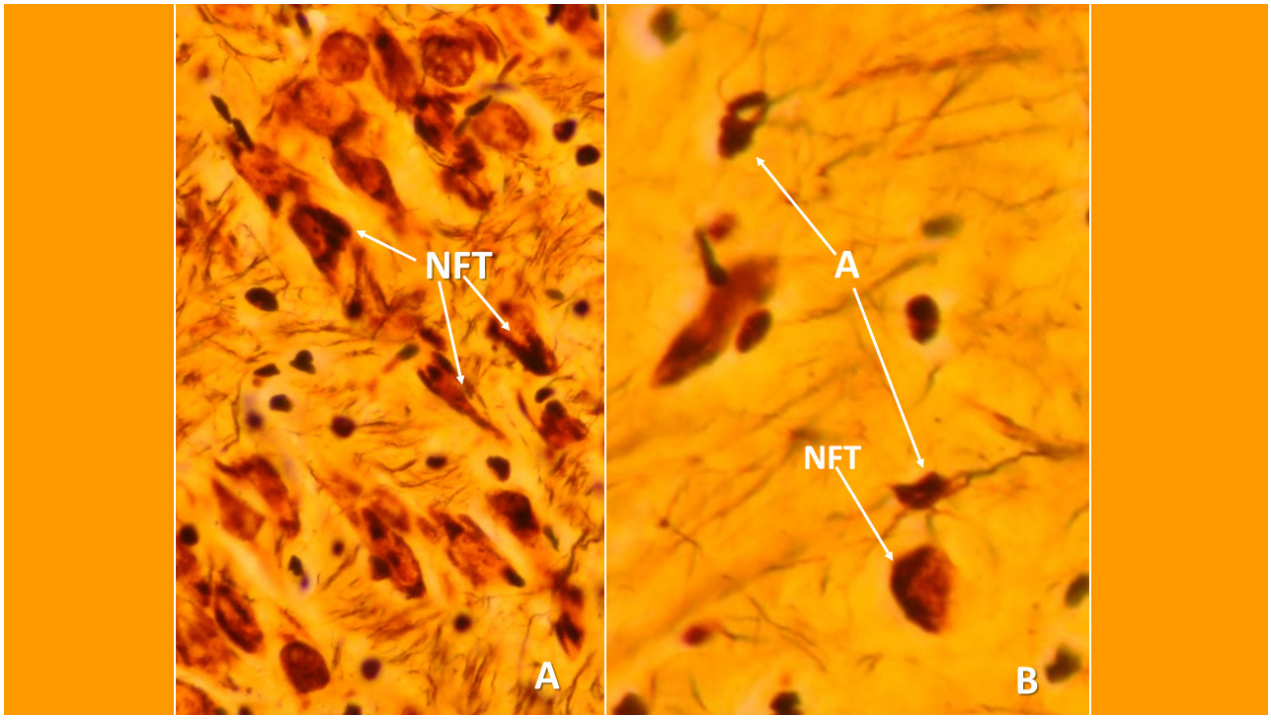

Figure 13. Preparation no. 02.038. The pyramidal cell layer of hippocampal sector CA4 shows numerous silver particles, compatible with neurofibrillary degeneration (neurofibrillary tangles, NFT). The image also reveals probable fibrillary tangles in astrocytes (A).

he had no clinical data about the brain under study. As an example of the difficulty of interpreting histological findings (and particularly novel findings), he informed in 1890 the Spanish Society of Natural History about a histological finding whose significance he could not grasp. In a session of this society,[46] Simarro reported finding fusiform bodies in the ramifications of nerve cells in fresh tissue, a novel finding of uncertain significance. This shows how bewildered the histologists of the time were by what they saw under the microscope. None other than Nissl, Alzheimer's mentor in histology, wrote about this.[44] He would spend his nights in front of the microscope, unable to interpret what he was seeing: "Any part of any preparation we studied, unintelligible and full of enigma, puzzled us. Only our purpose was clear… We sought to uncover the pathological process underlying mental illness."

Spanish universities and hospitals have never been known for their flexibility or ability to adapt to progress and talent. Upon his return from Paris, Simarro continued with his research and teaching activity,[46-48] although without institutional support. In a lecture at the Ateneo de Madrid in 1886,[9,49] he complained bitterly about the lack of support for Spanish scientists returning from other European countries. Years later, in 1902, he was appointed chair of experimental psychology, which greatly benefited Spanish psychologists and the development of Spanish scientific psychology.[6,8-10,16,17,24,25] Given his extensive clinical and neuropathological background, there can be no doubt that Simarro could also have become the first great professor of neurology, psychiatry, and neuropathology at a university hospital, nearly at the same time as Charcot.

The same could be said of his disciple Achúcarro, who was never appointed to a relevant position at a university or hospital; this is something that Kraepelin, Alzheimer, and other German and American masters and colleagues could never fathom. For Simarro, Achúcarro, and other Spanish scientists, an influential position in a university or hospital, together with institutional support for Cajal's school of neurohistology, may have changed the history of basic and clinical neuroscience in Spain. It is frequently said that Spain is a century behind other countries in many fields. This is literally the case in neurology, since the first Spanish chair of neurology[50] was established 100 years after Charcot's, and the number of neurologists serving as numerary professors in Spanish universities in recent years is alarmingly low.[51]

In summary, the historical role of Simarro in different scientific disciplines was that of a guide, promoter, and educator, although he never stood out for his ability to report his own findings.[1,6,8,16,25] He gave a decisive push to positive sciences and led the research into brain architecture to explain the wonder of the human brain, although he was well aware of his limitations in solving this riddle: "We know how consciousness occurs, but not what it is."[52]

Dr Simarro's contributions to histology, which were mainly methodological, were derived from his determination, effort, and generosity. His histological legacy awaits further analysis.

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Conflicts of interest

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References

1. Albarracín A. El Dr. Simarro y la escuela histológica española. Investigaciones Psicológicas. 1987;4:99-113.
2. Campos Bueno JJ. El estudio de las localizaciones cerebrales en los albores del siglo XX. Rev Hist Psicol. 2002;23:597-602.
3. Campos Bueno JJ. Influencia de Simarro en la obra de Cajal: la tesis de Julio Perales y García. Rev Hist Psicol. 2004;25:23-30.
4. Campos Bueno JJ. Simarro y el origen de la neurología en España. In: Martín Araguz A, coord. Historia de la neurología en España. Madrid: Saned; 2002.
5. Campos Bueno JJ. Simarro, Charcot y los orígenes de la práctica de la neuropsiquiatria y neuropsicología en España: informes médico-legales e ideas sobre la hipnosis. Rev Hist Psicol. 2002;23:85-102.
6. Yela M. Los orígenes de la psicología científica en España: el Dr. Simarro y su Fundación. Investigaciones Psicológicas. 1987;4:67-79.
7. Carpintero Capell H. Luis Simarro. Breve introducción a su figura y su obra. Madrid: Paper Plegat; 2015.
8. Carpintero H, Campos JJ, Bandrés J, eds. Luis Simarro y la psicología científica en España. Cien años de la cátedra de psicología experimental en la Universidad de Madrid.

Madrid: Universidad Complutense de Madrid; 2002.
9. Carpintero H. El Dr. Simarro y la psicología científica en España. Investigaciones Psicológicas. 1987;4:189-207.
10. Carpintero H. El doctor Simarro y la psicología española. Anales de la Real Academia de Ciencias Morales y Políticas. 2002;79:193-214.
11. De Castro F. Cajal and the Spanish neurological school: neuroscience would have been a different story without them. Front Cell Neurosci. 2019;13:187.
12. Fernández N, Breathnach CS. Luis Simarro Lacabra [1851-1921]: from Golgi to Cajal through Simarro, via Ranvier? J Hist Neurosci. 2001;10:19-26.
13. Garcia-Albea L. Luis Simarro: precursor de la neurología en España y Gran Maestre de la masonería. Rev Neurol (Barcelona). 2001;32:990-3.
14. Corral I, Corral C. Bibliografía clínica de Luis Simarro: un caso de tumor cerebral. Neurosci Hist. 2017;5:114-22.
15. Kaplan T. Luis Simarro, Spanish histologist. En: [s.n.] Actas del III Congreso Nacional de Historia de la Medicina, 10-12 abril 1969; Valencia. Vol II. Valencia (ES): Sociedad Española de Historia de la Medicina; 1969. p. 523-33.
16. Laín Entralgo P. La obra del Dr. Simarro y su entorno. Investigaciones Psicológicas. 1987;4:21-36.
17. López Piñero JM. Simarro Lacabra. In: López Piñero JM, Glick Thomas F, eds. Diccionario histórico de la ciencia en España. Barcelona: Península S.A.; 1983.
18. López Piñero JM. Luis Simarro Lacabra: las técnicas de tinción de la escuela histológica española. Mente y cerebro. 2007;25:8-11.
19. Moro A, Villasante O. La etapa de Luis Simarro en el manicomio de Leganés. Frenia. 2001;1:97-124.
20. Puig-Samper Mulero MA. Luis Simarro y las ciencias neurobiológicas (I). Rev A E N. 1987;7:649-52.
21. Rahmani R, Medrano J, Pacheco L. A modo de fichas sobre clásicos de la psiquiatría (XXXV): Luis Simarro Lacabra. Lmentala [Internet]. 2018 [accessed 15 Jul 2021];60:1-12. Available from: http://lmentala.net/admin/archivosboletin/Luis_Simarro.pdf
22. Rodríguez Lafora G. El profesor Simarro. Arch Neurobiol. 1921;2:209-11.
23. Romero M. El doctor Simarro, mi tutor y padrino. In: Campos JJ, Bandrés J, Carpintero H, eds. Luis Simarro y la psicología científica en España. Cien años de la cátedra de psicología experimental en la Universidad de Madrid. Madrid: Universidad Complutense de Madrid; 2002. p. 31-2.
24. Terol Gregori J. El doctor Simarro. Xátiva (ES): Matéu; 2006.
25. Vidal-Parellada A. Luis Simarro y su tiempo. Madrid: Consejo Superior de Investigaciones Científicas; 2007.
26. Índice topográfico de los libros del Fondo Simarro en la biblioteca de la Facultad de Psicología del UCM: colección 340y1, signaturas de FS-1 a FS-4333 [Internet]. Madrid: Universidad Complutense de Madrid; 2013 [accessed 15 Jul 2021]. Available from: https://biblioteca.ucm.es/data/cont/docs/392-2013-09-04-SimarroCat%C3%A1logoPSI2013.pdf
27. Simarro L. Nuevo método histológico de impregnación por las sales fotográficas de plata. Revista Trimestral Micrográfica. 1900;5:45-71.
28. Simarro L. Un nuevo método histológico fundado en la impregnación de los tejidos por las sales fotográficas de plata. Anal Soc Esp Hist Natural. 1900;29:255-61.
29. Simarro L. Nuevo método histológico de impregnación por las sales fotográficas de plata. Madrid: Establecimiento Tipográfico Idamor Moreno; 1900.
30. Simarro L. Fisiología general del sistema nervioso. BILE. 1878;2:167-8, 176-7.
31. Simarro L. Fisiología general del sistema nervioso. BILE. 1879;3:22-3, 31-2, 37-8, 46-7, 53-4, 61-3, 79, 126-7.
32. Simarro Lacabra L. Serie de accesos de epilepsia. Exploración de la temperatura como medio diagnóstico y guía del pronóstico y tratamiento. Nitrito de amilo. El Siglo Médico. 1877;24:361-3.
33. Simarro Lacabra L. Teorías modernas sobre la fisiología del sistema nervioso. Madrid: J.C. Conde y Compañía; 1878.
34. Simarro Lacabra L. La enseñanza superior en París. Escuela de Antropología. Curso de Mr. Matías Duval. BILE. 1880;91:173-4.
35. Simarro L. El curso de anatomía general de Mr. Ranvier. BILE. 1881;93:190-1.
36. Simarro L. El curso de anatomía general de Mr. Ranvier. BILE. 1881;94:5-7.
37. Zarranz JJ. Bourneville: un neurólogo en acción. Neurosci Hist. 2015;3:107-15.
38. Zarranz JJ. Bourneville, Charcot y la histeria: una carambola administrativa de efectos duraderos. Neurosci Hist. 2016;4:13-20.
39. Zarranz JJ. Wenceslao López Albo: precursor de la neurología en Bilbao. Neurosci Hist. 2019;7:83-96.
40. Simarro Lacabra L. Un caso de tumor cerebral. Rev Clin. 1895;2:49-56, 65-7.
41. Goedert M. Oskar Fischer and the study of dementia. Brain. 2009;132:1102-11.
42. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiat. 1907;64:146-8.
43. Achúcarro N. Some pathological findings in the neuroglia and in the ganglion cells of the cortex in senile conditions. Bull Gov Hosp Insane. 1910;2:81-90.
44. Zarranz JJ. Del empirismo a la neurociencia en la enfermedad de Alzheimer. Rev Neurol. 2004;39:576-82.
45. Jellinger KA, Bancher C. Senile dementia with tangles (tangle predominant form of senile dementia). Brain Pathol. 1998;8:367-76.
46. Simarro L. Nota sobre histología de los centros nerviosos. Anales Soc Esp Hist Nat. 1890;19:78.
47. Simarro L. Bosquejo de anatomía y fisiología del sistema nervioso. BILE. 1899;23:19-26, 82-8.
48. Simarro L. Enfermedades del sistema nervioso. En: Gayarre M, Madinaveitia J, Cisneros J, Sandoval FR, Azúa J, Simarro L, eds. Vademecum clínico-terapéutico.

Madrid: Romo y Füssel Libreros; 1898. p. 465-575.
49. Simarro L. Mata y la medicina legal. Orfila y la toxicología. La ciencia médica y las teorías modernas ante los tribunales y la ley. In: [s.n.]. Conferencias históricas del Ateneo de Madrid, 25ª Conferencia. Vol II. Madrid: Lib. A. San Martín; 1886. p. 521-60.
50. Zarranz JJ. Discurso inaugural de la cátedra de neurología de la Universidad del País Vasco. Neurologia. 1986;1:72-6.
51. Zarranz JJ. Historia de unas oposiciones y de una cátedra fugaz. Neurosci Hist. 2019;7:15-25.
52. Simarro L. La teoría del alma, según Rehmke. BILE. 1897;21:383-4.