The meeting of Cajal and Simarro at calle del Arco de Santa María

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ABSTRACT

Luis Simarro is inevitably linked to the figure of his friend Cajal due to their fruitful relationship since they met during their doctoral studies under Maestre de San Juan. Simarro generously taught his friend different techniques; some of these were later perfected by Cajal. The best known were the Golgi method to stain neurons, and the Simarro staining method to observe neurofibrils. Both contributed strong arguments to the neuron doctrine and against Golgi's reticular theory. The theory established that the brain network was made up by a network of tubes, similarly to the vascular system or the striated muscular fibre. Both were candidates to the chair that was left vacant after the death of Maestre de San Juan. Cajal won the chair with more than enough merits, with Simarro in second place. Simarro became chair of experimental psychology 10 years later.

The public recognition that both received years after their death was very different from the appreciation they received during life. The Simarro Foundation was seized by the winners of the Spanish Civil War, at the same time that the Cajal Museum was created. Throughout their lives, both showed social and political concerns, although these were more intense in the case of Simarro, even interfering with his scientific activity towards the end of his life. Both legacies have been unfairly treated in material terms, but both personalities are well-recognised in academic settings. We still lack appropriate museums to display the great achievements in Spanish neurohistology made by Cajal and Simarro.

KEYWORDS

Luis Simarro, Ramón y Cajal, Spanish Histological School, Simarro Legacy, 14th International Congress of Medicine

Introduction

Santiago Ramón y Cajal and Luis Simarro were unique references for the new generations in Spain at the turn of the 20th century, who were waking from their lethargy after the crisis of 1898. It is not surprising that José Ortega y Gasset, Gonzalo Rodríguez-Lafora, and José Manuel Sacristán should acknowledge their significant contribution to the development of neurobiology, psychology, neurological histology, and psychiatry in the editorial of the first issue of the journal that the three edited together.[1] This praise for Simarro is not exaggerated: with his intellectual efforts, he had contributed to the modernisation of Spain and, with his word, he vindicated Spaniards, staying away from what would have been the complicity of remaining silent with respect to many of the injustices of the time. In this article, we will review the personal and scientific paths that crossed at different times. Undoubtedly, Simarro would be less recognised and less well known today without

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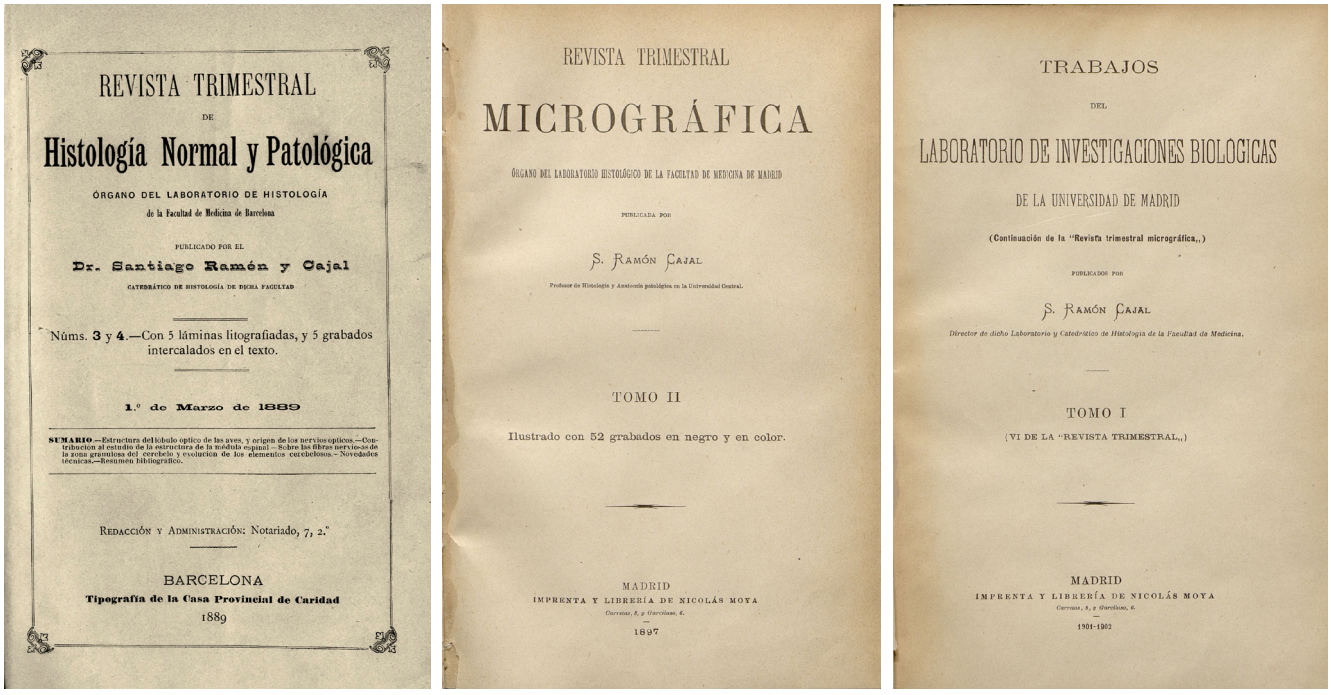
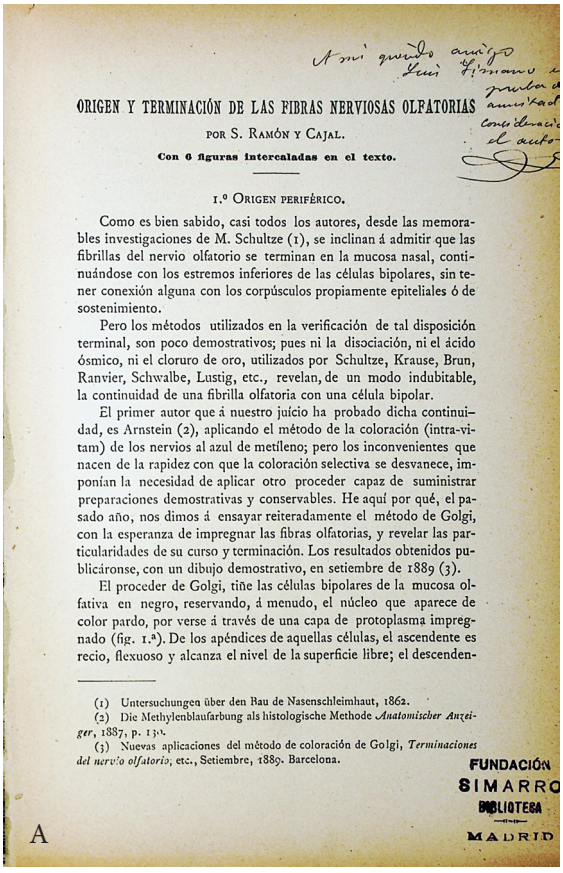


Figure 1. Ramón y Cajal edited three journals that mainly helped to disseminate the works of his laboratory among his European colleagues. The *Revista Trimestral de Histología Normal y Patológica* (1888-1892) was published in Barcelona; around 60 copies were printed, including works from the Biological Research Laboratory at the School of Medicine in Barcelona. The other two journals were published in Madrid by the Nicolás Moya press: *Revista Trimestral Micrográfica* (1892-1901) and T*rabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid* (1901-1937). In 1940, after the end of the Spanish Civil War, the latter was renamed *Trabajos del Instituto Cajal de Investigaciones Biológicas* (1940-1979).

the generous recognition expressed by his friend Cajal. Ramón y Cajal recalled him as a talented and educated rival and one of the few persons who contributed to "jolt the drowsiness of our young people for a constellation of worthy investigators to rise among us," undermining the concept of Spaniards' supposed inability to conduct science.[2(p245,406)]

To understand this mutual esteem, we will review the occasions in which their work and common interests coincided. In particular, we will describe the deliberate meeting of Cajal with Simarro, aiming to learn about the novelties of European science. They first met during their doctoral studies, when both already showed an interest in microscopy. They met again 10 years later, in the depth of winter, and Simarro invited Cajal to his laboratory on calle del Arco de Santa María. This reunion was decisive for Cajal's career and represented a turning point in the study of the nervous system.

From this providential vision, Cajal started working frenetically, conducting research with the Golgi method, first in Valencia with Bartual, and later in Barcelona. Despite the prevailing theories at that time, his studies led him to suspect that the basic principle of the Darwinist biology, the autonomous cellular unit, also applied to the nervous system. To disseminate his vast scientific production, he launched the journal *Revista Trimestral de Histología Normal y Patológica* (Figure 1), published two textbooks, travelled to Berlin, showed his preparations to Kölliker, and obtained the international recognition he yearned for by distributing his studies among colleagues. One of these studies is dedicated to his friend Simarro (Figure 2A).



ORIGEN Y TERMINACIÓN DE LAS FIBRAS NERVIOSAS OLFATORIAS

POR S. RAMÓN Y CAJAL.

Con 6 figuras intercaladas en el texto.

1.º ORIGEN PERIFÉRICO.

Como es bien sabido, casi todos los autores, desde las memorables investigaciones de M. Schultze (1), se inclinan á admitir que las fibrillas del nervio olfatorio se terminan en la mucosa nasal, continuándose con los estremos inferiores de las células bipolares, sin tener conexión alguna con los corpúsculos propiamente epiteliales ó de sostenimiento.

Pero los métodos utilizados en la verificación de tal disposición terminal, son poco demostrativos; pues ni la disociación, ni el ácido ósmico, ni el cloruro de oro, utilizados por Schultze, Krause, Brun, Ranvier, Schwalbe, Lustig, etc., revelan, de un modo indubitable, la continuidad de una fibrilla olfatoria con una célula bipolar.

El primer autor que á nuestro juicio ha probado dicha continuidad, es Arnstein (2), aplicando el método de la coloración (intra-vitam) de los nervios al azul de metileno; pero los inconvenientes que nacen de la rapidez con que la coloración selectiva se desvanece, imponían la necesidad de aplicar otro proceder capaz de suministrar preparaciones demostrativas y conservables. He aquí por qué, el pasado año, nos dimos á ensayar reiteradamente el método de Golgi, con la esperanza de impregnar las fibras olfatorias, y revelar las particularidades de su curso y terminación. Los resultados obtenidos publicáronse, con un dibujo demostrativo, en setiembre de 1889 (3).

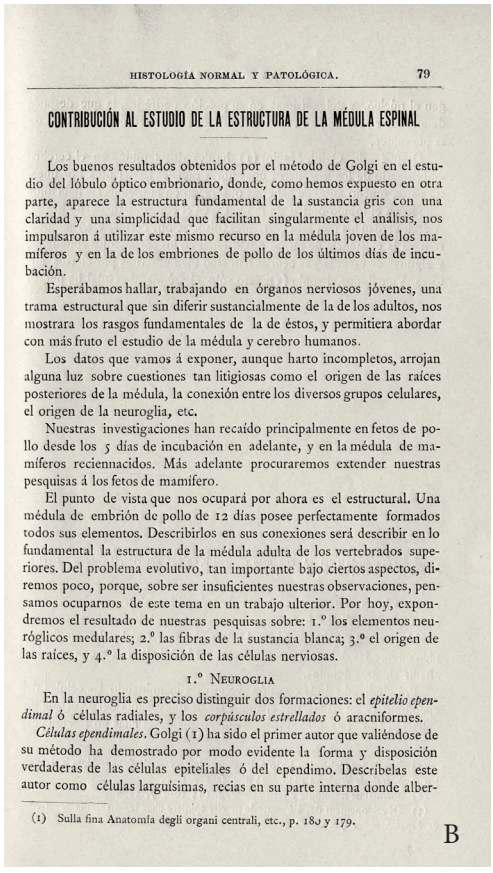
El proceder de Golgi, tiñe las células bipolares de la mucosa olfativa en negro, reservando, á menudo, el núcleo que aparece de color pardo, por verse á través de una capa de protoplasma impregnado (fig. 1.ª). De los apéndices de aquellas células, el ascendente es recio, flexuoso y alcanza el nivel de la superficie libre; el descenden-

(1) Untersuchungen über den Bau de Nasenschleimhaut, 1862.

(2) Die Methylenblaufarbung als histologische Methode *Anatomischer Anzeiger*, 1887, p. 131.

(3) Nuevas aplicaciones del método de coloración de Golgi, *Terminaciones del nervio olfatorio*, etc., Setiembre, 1889. Barcelona.

A



CONTRIBUCIÓN AL ESTUDIO DE LA ESTRUCTURA DE LA MÉDULA ESPINAL

Los buenos resultados obtenidos por el método de Golgi en el estudio del lóbulo óptico embrionario, donde, como hemos expuesto en otra parte, aparece la estructura fundamental de la sustancia gris con una claridad y una simplicidad que facilitan singularmente el análisis, nos impulsaron á utilizar este mismo recurso en la médula joven de los mamíferos y en la de los embriones de pollo de los últimos días de incubación.

Esperábamos hallar, trabajando en órganos nerviosos jóvenes, una trama estructural que sin diferir sustancialmente de la de los adultos, nos mostrara los rasgos fundamentales de la de éstos, y permitiera abordar con más fruto el estudio de la médula y cerebro humanos.

Los datos que vamos á exponer, aunque harto incompletos, arrojan alguna luz sobre cuestiones tan litigiosas como el origen de las raíces posteriores de la médula, la conexión entre los diversos grupos celulares, el origen de la neuroglia, etc.

Nuestras investigaciones han recaído principalmente en fetos de pollo desde los 5 días de incubación en adelante, y en la médula de mamíferos reciennacidos. Más adelante procuraremos extender nuestras pesquisas á los fetos de mamífero.

El punto de vista que nos ocupará por ahora es el estructural. Una médula de embrión de pollo de 12 días posee perfectamente formados todos sus elementos. Describirlos en sus conexiones será describir en lo fundamental la estructura de la médula adulta de los vertebrados superiores. Del problema evolutivo, tan importante bajo ciertos aspectos, diremos poco, porque, sobre ser insuficientes nuestras observaciones, pensamos ocuparnos de este tema en un trabajo ulterior. Por hoy, expondremos el resultado de nuestras pesquisas sobre: 1.º los elementos neuróglicos medulares; 2.º las fibras de la sustancia blanca; 3.º el origen de las raíces, y 4.º la disposición de las células nerviosas.

1.º NEUROGLIA

En la neuroglia es preciso distinguir dos formaciones: el *epitelio ependimal* ó células radiales, y los *corpúsculos estrellados* ó aracniformes.

Células ependimales. Golgi (1) ha sido el primer autor que valiéndose de su método ha demostrado por modo evidente la forma y disposición verdaderas de las células epiteliales ó del ependimo. Descríbelas este autor como células larguísimas, recias en su parte interna donde alber-

(1) Sulla fina Anatomía degli organi centrali, etc., p. 180 y 179.

B

Figure 2. Two of the first works that Cajal sent to Simarro after their meeting at calle del Arco de Santa María. Both were written in Spanish and published in Barcelona. A) First page of the article "Origen y terminación de las fibras nerviosas olfatorias" (Origin and endpoint of the olfactory nerve fibers) by Cajal, published in *Gaceta Sanitaria Municipal* on 11 October 1890. We can read the dedication "to my beloved friend Luis Simarro, as a proof of our friendship and consideration. Simarro Legacy, Universidad Complutense de Madrid. B) The second article, "La contribución al estudio de la estructura de la medula espinal" (Contribution to the study of the structure of the spinal cord), was published on 1 March 1889 in *Revista Trimestral de Histología Normal y Patológica*, founded by Cajal to distribute his work among the scientific community.

The instruction he received at Simarro's laboratory had a crucial effect on Cajal, who from that time definitively focused on systematic anatomical and functional study of the brain, establishing a foundation for the development of neurosciences in the next century.

Two personalities with the same scientific, social, and reforming objective

Simarro is often said to have published very few works, to have made no effort in organising his work, and to have left no written work.[3] This statement should be analysed in context: Simarro was a clinical neurologist who had a private laboratory where he trained a few selected students, and obtained a chair of experimental psychology, an emerging and promising area, towards the end of his life. He was not lazy, but he probably observed the world around him with sceptical eyes. Furthermore, he was convinced that written work was less valuable than direct instruction between master and student. In a sense, Cajal also contributed to promote this stereotype, which was only partially justified. It seems undeniable that Simarro was a restless master. He enjoyed multiple subject areas and interests, which

probably led to "distraction." When he lost interest in any activity, he needed to focus his attention on other tasks that he found more attractive at that time. This impatience was probably explained by the accurate judgement that Cajal mentioned in *Recollections of my life*: "it was due, no doubt, to these inconstancies of chrome-silver impregnation that Simarro, introducer of the methods and discoveries of Golgi into Spain, abandoned his efforts in discouragement."[2]

In a letter sent to Cortezo before the publication of *Recollections of my life*, he confesses, somewhat bitterly, that the student sent by Ranvier generously shared his histological knowledge in Spain for the general benefit but "has not received the due praise as he was caught in the net of the Institución Libre de Enseñanza, one of whose sacred principles is to study and not to write."[4] While it is true that at that time, scientific work could not be understood without publication of the results in journals or books, we have also seen how Cajal sometimes considered more important what he saw than what he read, as was the case when he first saw preparations stained with the Golgi method.[2(p190)] Even without publishing, Simarro was a great master.

The brief written works of Simarro offer a deeper perspective of his thinking, impregnated by "scientific regenerationism": conducting science to serve civilisation. Therefore, it is not surprising that in 1903, soon after he got the chair of Experimental Psychology, and at the invitation of his friend Vicente Blasco Ibáñez, he visited the Universidad Popular in Valencia to give a presentation entitled "The mission of science in civilisation." In the presentation, he explained several interesting ideas on his understanding of scientific practice. One is particularly relevant to understanding the paucity of his written work:

> Science, he says, is simply created as follows: studying things and not studying books. Books are helpful for *studying things* but not for *teaching them* [original emphasis]… It also has an intrinsic subjective function, the function of knowledge, even if this is worthless.[5]

Neither Cajal nor Araquistain (nor the many others who have also done so) was mistaken when they lamented the limited body of written work by such a talented man. This scarce written work may not be attributed to laziness. On the contrary, it is important to highlight that both men were tireless workers.

Both addressed the problems of neurohistology of their time, with brilliance, intelligence, rigour, and the most recent knowledge. However, with respect to their scientific output, they may seem to belong to different times. We can compare both work styles to understand this statement.

In 1887, Simarro, before the age of 40, had a good command of French, Italian, and German; he travelled abroad to gain first-hand knowledge of European science. Due to his sceptical and self-demanding personality, he seemed not to aspire to glory, although he was a well-known personality in society, brilliant and popular. He resigned from a promising position as director of the Santa Isabel asylum in Leganés to continue his training in Paris. At the same age, Cajal had not yet left Spain. He had travelled to the Americas, but when he visited Cuba, the island was still a Spanish province. Cajal was also self-demanding, read as much as he could, and worked hard. Furthermore, he was already chair in Valencia and aimed to stand out professionally, but did not know how to achieve this. He did not become complacent with his privileged position, and continued to search for an area of study that better fit this purpose. Although he had not left Spain, from his position as chair he became familiar with the modern scientific methods of European and American researchers. He studied the nervous tissue, seeking to understand the functionality of the anatomical structures he observed. Furthermore, he knew that results should be published to enable faster dissemination of scientific knowledge.

Material and methods

Among many other reference books, we have used two chapters published in *Santiago Ramón y Cajal, 100 años después* (*Santiago Ramón y Cajal: 100 years later*), edited by Ferrús and Gamundi in 2006: "One day at calle del Arco de Santa María"[6] and "Career and circumstances of Cajal and Simarro."[7] These chapters describe the meeting at calle del Arco de Santa María as well as other vicissitudes in both men's lives. Two other key sources were *1)* the monographic issue of *Investigaciones Psicológicas*, which includes the contributions presented at the first congress held in Spain to study Simarro's work[8] at the initiative of Javier Campos Bueno and Rafael Llavona; and *2)* the catalogue of an exhibition commissioned by Carpintero, Campos Bueno, and Bandrés to commemorate the centenary of the chair of Experimental Psychology.[9] Due to their unquestionable

interest, the books by Carpintero[10] and Vidal Perellada[11] were also consulted. The first doctoral thesis dedicated to Simarro was written by Temma Kaplan in 1969, under the direction of López Piñero.[12] Information about Cajal is much more abundant and better known; in this work, we can highlight his book *Recollections of my life*[2,13] and the books by Fernando de Castro[14] and López Piñero.[15,16]

Results

A trip through time

In Madrid 1887, Santiago Ramón y Cajal met his host and friend Luis Simarro at his laboratory on calle del Arco de Santa María. This was not their first meeting. In fact, they had met 10 years before, when Cajal had just obtained his modest position as director of the Anatomical Museums in Zaragoza. He worked as assistant lecturer of anatomy after failing in the competitive examinations for the chairs of Anatomy in Granada and Zaragoza. In July 1877, he travelled to Madrid to defend his doctoral thesis. Cajal met Simarro during his visit to the laboratory of Maestre de San Juan. There, they shared a master, a laboratory, and an interest in microscopy studies, and thanks to their good master Aureliano Maestre de San Juan, they discovered the countless possibilities of microscopy to study anatomy.

Simarro had also just taken a position at Hospital de La Princesa. However, he managed to be appointed director of the Santa Isabel asylum in Leganés as he was interested in the study of mental disorders. At this centre, autopsy studies were performed sporadically, but Simarro, as soon as he took position, showed a great interest in performing them systematically. He wanted to identify the possible causes of mental disorder and also tried to implement humanitarian reforms for the insane. In a short period of time, his positivist mentality and opposition to vitalism led him to confront the ecclesiastical authorities and his colleagues who opposed Darwinism. Simarro was a popular physician and was already famous for his speeches at the Institución Libre de Enseñanza, for his publications in the bulletin of the Institución, and the brilliant debates held at the Ateneo de Madrid. Even the journal *Nature* mentions the young professor Simarro in a review of science in Spain published by Ginez (sic) de los Ríos.[17]

However, neither his prestige nor his popularity would protect him. By late 1879, Simarro lost his position as director and was transferred back to Hospital de La Princesa. Furthermore, an inquiry was opened into him. In response, on 11 March 1880, he resigned to his position as a public employee at the hospital,[18] and soon travelled to Paris, following Maestre de San Juan's advice. He followed in the footsteps of his master, who in 1860, after obtaining the chair of Anatomy in Granada, had travelled around France, Germany, Great Britain, and the Netherlands to continue his training.[19] With the same motivation, Simarro decided to exile himself to Paris to continue his training at institutions where the most prestigious professors of the time were researching and teaching.

We can imagine how disappointed Simarro would have been with the new political situation. In little more than a decade, Simarro had seen great historical changes that had led to a new system of government in Spain, the Republic. But in just six very agitated years, the Bourbon monarchy had regained the throne. This culminated in the failure of the Glorious Revolution and represented the end of the Sexenio Democrático (six-year period of democracy in Spain). In 1868, at the age of 17, Simarro had actively participated in the September revolution. The following year, he became the treasurer of the revolutionary junta in Valencia. Later, once in Madrid, he also lived in the midst of an agitated political situation. A young, liberal republican, Simarro surely would have felt disillusioned with the political events of that decade, which ultimately led to the return of the Bourbon monarchy. Furthermore, he also experienced a professional disenchantment. His expectations were seriously affected after being obliged to renounce his position at the asylum in Leganés and having a professional inquiry opened against him. On top of that, his financial situation was precarious due to his eagerness to buy books and conduct research. By that time, he had already met Mercedes, his future wife, but he could not consider starting a family with her.

All these circumstances surely influenced his decision to leave Spain and renounce his position as physician, to continue his training in Paris, where he sympathised with many Spanish Republicans in exile there. Professional and political disenchantment were the motivation for his journey to Paris, but Simarro did not intend to flee. His intention was to return to Madrid with a prestige that would enable him to earn enough to pay off his debts and satisfy his cultural and scientific interests.

Before going to Paris, he made a significant donation of books (approximately 800) to the emerging library of

the Institución Libre de Enseñanza. He was completely determined to start a new life, although his friend and fellow student Cortezo showed him the difficulty of the project he was about to start. Its execution required financial means that Simarro did not have. Furthermore, he had to renounce to his official position at the hospital.[20]

Years later, after the shock caused by the loss of the last of Spain's overseas territories, this tragic and defeatist spirit can be clearly observed in the written works of many intellectuals of the Generation of 1898. Cajal himself is very critical of the defeatist spirit so present among the Spaniards of that time, which did not occur in other countries. Cajal was a patriot. After the loss of Cuba, he accepted an invitation from Clark University when the organisers ensured him that the Spanish flag would preside over the conference together with the American flag. Spain's tragedy lies in the disregard promoted by the extremism of many Spanish intellectuals. This situation caused pain to him and to the whole Generation of 1898.

Simarro was hurt by Spain and so was Cajal. Like Cajal, Simarro was also a patriot. Both shared the idea, popular among the great European and American scientists, that science should have a fatherland.

Simarro seems to show some traces of melancholy and scepticism from his childhood at boarding school. In Valencia, he identified himself as a declassed and talented young man. This vital disenchantment would accompany him throughout his life, although unlike the "corrected pessimist," he will always maintain, with reason, a high degree of "self-confidence."

Cajal, unlike the sceptical and melancholic Simarro, stayed as far away as possible from defeatism, although he was not always successful. With the loss of Cuba and the Philippines, Cajal experienced discouragement, as did most of the Spaniards of that generation. He felt dejected and acknowledged that his "productive capacity is diminished, though it is also livened up by the vibrant and passionate literature of regeneration" led by Costa with his slogan "school and larder." Cajal, like many other Spanish intellectuals of the time, could not avoid this moment of weakness, a rare occurrence in his life.

Time in Paris

In late 1880, Simarro arrived in Paris, where he stayed until mid-1885, studying under several masters. He reinforced his adhesion to Darwinism under Duval and consolidated his interest in neurohistology under Ranvier, whereas Charcot and Magnan would be responsible for his orientation towards neuropsychiatry.[16(p17)] These influences would enable him to learn about the discoveries that were leading to the creation of new specialties: clinical neurology and experimental psychology.

During this self-exile, he maintained contact with the Institución Libre de Enseñanza, sending news on the scientific activity of the masters he was working with to be published on the bulletin.[21,22] We can also find a column signed by him in *El Imperial*, in which he described how dangerous it would be for train operators to present colour blindness, a disease that was more frequent in the population than assumed.[23] This collaboration, probably paid, would be one of the sources he used to pay his expenses.[24]

Furthermore, he would be in contact with exiled Spanish politicians with similar ideas. Among these, we can highlight his friendship with Nicolás Salmerón, whom he accompanied to the clinic of Charcot, Guyau, and Bruchard in 1881. A mutual esteem developed between the politician and the young physician, and Simarro would become a frequent guest to lunch on Saturdays. Through this friendship with Salmerón, who had been president of the government cabinet, opportunities arose for him to meet other noteworthy Spanish visitors, both exiles and tourists in the great metropolis.[25(p53)] A detail that would have a decisive influence over Simarro's professional future as clinical neurologist, reported for the first time in this study, is that it was in Paris that he met the Brazilian noblewoman María Buschental, wife of José Buschental, a banker with links to the Marquess of Salamanca. The lady had settled in Madrid during the First Carlist War. During the 1940s, barely 25 years old, she tried to stimulate cultural life in Madrid, organising political gatherings in her house until her death in 1891. These soirées, inspired by those that became popular in France during the times of Madame de Pompadour, Madame de Staël, and Madame de Récamier,[26] were attended by aristocrats, politicians, businessmen, and artists. Her friends included Espronceda, Larra, Serrano, Castelar, Echegaray, and Galdós.[27] Art patrons in Madrid regularly organised meetings that may include balls or theatre performances. The aim of these meetings was to establish relationships through which to influence politics and conduct businesses. María Buschental's salon was the most relaxed, and was known for proudly

being "a neutral dwelling for opinions." The hostess, while sympathising with Republicans, also had good relationships with Queen Isabella II. Spain was living troubled times and the Buschentals had to leave Madrid several times to take exile in Latin America, London, and Paris.[28] This is why María Buschental was in Paris during the 1880s, and her salon and some of her friends also travelled with her. During one of these soirées she met the young doctor. Simarro made a great impression on her, and solid bonds of appreciation and respect were established between them. In addition to these Parisian contacts made between Simarro and Spanish Republicans and other intellectuals, it is also very likely that he also attended some Masonic lodge.[29]

Sagasta proclaimed an amnesty in 1881, a few months after Simarro arrived in Paris. This encouraged many exiles to return to Spain in a constant trickle. Salmerón returned in 1885, and so did Simarro. The alternation between political parties was a fact, and the death of king Alfonso XII in November did not affect the political stability he achieved during his reign. Miracles take time, and the Republican ideals of many intellectuals became less radical. During the first half of the 1880s, Cajal, unlike Simarro, had achieved the financial stability of occupying the chair in Valencia, as well as personal stability thanks to the family he created after marrying Silveria. The world changes rapidly and, as opposed to the elitism of salons, gatherings began to be held in cafés, which were accessible to all. It became fashionable for friends to routinely meet at a café to converse on all manner of subjects. These gatherings were an intimate show and guests needed an invitation. Friends rotated between the different gatherings in Madrid, and preferences were established. Cajal was a regular at Café Suizo[30] or Café del Levante, and Simarro at Café Regina.[31(p74-5)]

Return to Spain as a famous, prestigious physician

In July 1885, Simarro was back in Madrid, participating in debates at the Ateneo on the efficacy of inoculation to treat cholera, described by Dr Ferrán.[32] He had permanently been in contact with his friends and was determined to practice medicine privately so that he could have his own laboratory. He would soon see his efforts rewarded. Within a few months, the press would report on Simarro, the doctor who had returned from Paris and conducted significant studies on nervous and brain diseases. One detail that had been completely forgotten is how he gained this fame and prestige as clinical neurologist and psychiatrist. In a short period of time, after his return from Paris, he would have the best private clinical neurology consultation in Spain. As fate would have it, General Serrano, who had been president of the government, presented severe senile dementia that no doctor had been able to treat satisfactorily. One day, General López Domínguez, who was in charge of the illustrious patient, met his friend María Buschental. She recommended doctor Simarro, who had just returned from Paris. The new treatment indicated by the young specialist managed to relax the patient, who was finally able to sleep after several months of insomnia. The press picked up the story, highlighting the relief experienced by the patient[33] and referring to Simarro as "the man of the hour in Madrid." Simarro treated the general for 10 days, until his services were no longer needed because the patient was considered terminally ill.[34]

Newspaper reports had brought the young doctor Simarro national recognition as a "specialist in mental disorders." Several days later, he was called by the eminent singer Antonio Vico. When it seemed that all was lost, Dr Simarro took charge of the patient and hoped to save him with a treatment plan that yielded good outcomes. The press published the story and eagerly followed the patient's progression. The patient started to recover and was healed. Several years later, he was considered the best tenor in Spain.[35] Simarro, a specialist in the diagnosis and advanced treatment of mental disorders and neurological diseases, became a well-regarded doctor among the aristocrats and high society of Madrid and Spain, although he never stopped attending the working classes at much lower prices.

He diversified his activities, working in academia, his laboratory, and his private consultation, and participating in debates at the Ateneo. His fame as an alienist led him to work as expert witness in cases of great public interest, as they involved aristocrats or famous criminals (Galeote, the Marquess of Larios, and Antonio de Orleans y Borbón). A few months after the death of General Serrano, in April 1886, the first bishop of Madrid, Martínez Izquierdo, was murdered. The event had a great impact on the Spanish public, who eagerly followed the news of the trial of the priest Galeote. He was sentenced to death at first instance, but after the reopening of the case he escaped the garotte. The judge took into consideration the report by Escuder, Vera, and Simarro, which found that the defendant presented "persecutory delusions."[36] The reopening of the case

had great repercussions across the Spanish press[37] and even abroad, thanks to Galdós' chronicles published in *La Prensa* in Buenos Aires.[38] Simarro and his two other colleagues also participated in 1888 in the trial of the Marquess of Larios, another somewhat morbid case with a significant social impact. The widowed Marquess had secretly married his cousin. This marriage was considered inappropriate by the mother and mother-in-law of the Marquess, who started legal proceedings for a judge to declare the patient mentally incompetent and to manage his assets. For the incapacity report, the family of the bride employed Simarro's former Parisian master Charcot, whose prestige and fame crossed borders. The Marquess turned to Simarro, and a forensic report by the three expert witnesses successfully refuted Charcot's diagnosis.[36] Soon before his death, Simarro drafted another forensic report, in this case together with Rodríguez Lafora, to assess the mental capacity of a patient in a case that the press described as the fanciful adventures of a Spanish royal: the escape of Antonio de Orleans y Borbón.[9,39]

Simarro had achieved the objective he had set himself when he moved to Paris. He had become a clinical neurologist with a private consultation, renowned for his intelligence, and enjoyed financial stability and social recognition. Simarro achieved this shortly after Cajal, who was already married when Simarro moved to Paris and was chair in Valencia by 1884. Simarro married in 1887, two years after returning from Paris, enjoying fame and freedom from debt. Soon after, he left his flat on calle del Arco de Santa María to move to another, very close by, on the other side of Paseo de Recoletos. He moved to Madrid's elegant Salamanca area with Mercedes, a short distance from the laboratory he preserved for 15 years, where Sorolla would paint his portrait years later. The building on calle del Conde de Aranda, built in the Parisian style, was also the home of illustrious neighbours such as Pi y Margall. The Simarro couple, as was typical in the high society, asked two significant painters to paint a portrait of them: Simarro's godfather Luis de Madrazo (Figure 3), and his friend Joaquín Sorolla.

Cajal and Simarro built two magnificent houses in Madrid that included a laboratory, enabling them to work from home: Cajal in the city centre, on the elegant calle Alfonso XII, close to the School of Medicine; and Simarro on calle General Oráa, in a new area in the outskirts of Madrid, next to the Museum of Natural Sciences, close to the house of Sorolla and the Institución Libre de Enseñanza. Both had comfortable homes, Simarro's more decadent and luxurious than Cajal's, which was more in line with the more austere spirit that would enable him to maintain "a balanced budget, [which] is an irrevocable condition for peace at home and the necessary peace of mind for scientific activity."[13(p40)]

A winter day at calle del Arco de Santa María

On 8 December 1886, the Directorate General of Education, through the *Gazeta de Madrid*, published a call for candidates to competitive examinations for the chair of General and Descriptive Anatomy at the School of Medicine in Zaragoza. Santiago Ramón y Cajal[2] writes in *Recollections of my life* that in 1887 he was appointed as a member of the examining board. The examinations would be held at the beginning of January when Cajal arrived in the Spanish capital. He was going to sit on the examining board of a competitive examination with many candidates, and knew that he would have to stay for several days. His only duties were to participate in the examinations and to visit his friends and acquaintances during his free time. Thanks to his testimony, we know that he was "anxious to take advantage of my stay in Madrid to inform myself of the latest advances in science, I got into communication with those in the capital who cultivated microscopic studies."[2] He recalled that he arrived full of doubts that he anxiously wanted to solve as when systematically studying the domains of microscopic anatomy, when the turn of the nervous system came, "that masterpiece of life… It is important to remember that the technical resources of those times were quite inadequate for attacking the great and alluring problem effectively."

In addition to this technical difficulty, histologists faced a "reticular theory… simplistic and seductively unifying" that was supported by talented scholars and helped to explain the "constitution of the striated substance of muscles."[2] Starting from this theory, Cajal stated:

> What captivated us specially was that this speculation identified the complex structural substratum of the striated fibre with the simple reticulum or fibrillary framework of all protoplasm. Whatever the cell might be, amoeba or contractile corpuscle, the physiological basis or rather the active factor, was always represented by the network or elementary skeleton.[2]

And he concluded that "ruled by the theory, we who were active in histology then saw networks everywhere."

Figure 3. The Simarros, painted by Luis de Madrazo. Portrait of Mercedes Roca, Simarro Legacy, Universidad Complutense de Madrid. Portrait of Luis Simarro, donated by Marina Romero to Universidad Complutense de Madrid.

It was not easy to develop a theory to explain the findings observed from the existing staining techniques. In fact, although some staining techniques were successfully performed, they revealed little about the origins and pathways of the nerve fibres, and were indeed useless for application to the "analysis of ganglia, of the retina, of the spinal cord, or of the brain" to disentangle and understand all these branches.

With his technique, Golgi could study crucial aspects of the morphology of nerve cells, but the "admirable method of Golgi was then (1887-1888) unknown to the immense majority of neurologists or was undervalued by those who had the requisite information about it."[2]

Until that time, it was obvious that for Cajal and for many histologists, the Golgi method described in the book of Ranvier was just one among many other existing methods. However, Golgi's "reazione nera" method had not been overlooked by Simarro, who patiently and systematically had been testing in Paris many of the staining methods described by Ranvier; he had been writing some results on his notebooks, to practise the methods back in his laboratory.

Microscopy laboratories in Madrid

Ramón y Cajal knew well four of the six existing microscopy laboratories in Madrid. The oldest two were already operational in 1875, when he travelled to Madrid for his doctoral studies.

— Laboratory at Hospital Clínico

Aureliano Maestre, founder of the Spanish Histological Society, who taught Cajal and Simarro microscopy techniques, directed the histology laboratory at Hospital Clínico San Carlos, linked to the School of Medicine. This laboratory became a reference centre in Spain for modern studies in bacteriology and histology. Leopoldo

López García also completed his doctoral thesis there and, like Simarro, studied under Ranvier. During the three years he spent in Paris, at the same time as Simarro, they surely would have met again. When he returned to Spain in 1883, Aureliano designated him assistant to the chair and made him responsible for microscopy analysis at the hospital. Leopoldo López García was the first Spanish researcher to observe *Mycobacterium tuberculosis*; shortly after, in 1885, he was sent by the Spanish Ministry of Development to study the recently discovered rabies vaccine with Pasteur.

— Laboratory at the Anthropological Museum

This laboratory was directed by Pedro González de Velasco, founder of the Free School of Medicine and Surgery. In his last will, he stipulated that the Museum should be transferred to the State after his death, which occurred in 1882. Years later, in 1901, at the premises of the Museum on calle Atocha, Cajal would establish the Laboratory of Biological Research Alfonso XII. In 1903, in this same place, Cajal and Simarro showed several foreign scholars attending the 14th International Congress of Medicine wonderful preparations of the neurofibrillary network, obtained with the silver nitrate method developed by Simarro.[13(p413)]

— Laboratory at Hospital de San Juan de Dios

The third laboratory had recently been created, in 1885, at the former Hospital de San Juan de Dios. In Spain, a cholera epidemic had been declared, and Olavide had authorised the creation of a laboratory to study the condition. The new micrography techniques will help to identify the comma or virgule bacillus recently discovered by Koch, which was thought to be the cause of cholera. After his return from Paris, Simarro attended all types of patients, including aristocrats, politicians, and artists. But he was still a restless doctor. Therefore, without neglecting the consultation that provided him with professional prestige and considerable incomes, he remained interested in microscopy studies, to which he dedicated several hours a day. Workers at the laboratory included Federico Rubio, Alejandro San Martín, Carlos de Vicente, and occasionally Leopoldo López García and Luis Simarro.

— Laboratory at the Biological Institute

Cortezo writes that all the workers at the laboratory of Hospital de San Juan de Dios, promoted by San Martín and Simarro, decided to create the Biological Institute on calle de la Gorguera to continue their microscopy studies.[6(p69)] Simarro, in addition to continuing with his private laboratory, dedicated part of his time to working in the recently created Biological Institute.

— Laboratory at the Museum of Natural History

Located in Madrid, the laboratory was operational in 1887 under the direction of Ignacio Bolívar, also director of the museum.

— Simarro's laboratory on calle del Arco de Santa María

In 1887, Simarro had a laboratory at no. 41, calle del Arco de Santa María, just below the flat he shared with Mercedes. The flat and the laboratory were connected by a telephonic device he installed that attracted the attention of all visitors. In 1902, the laboratory was transferred to his new home at no. 5, calle General Oráa, where it was integrated into the basement of the house. The laboratory was connected by a door with the laboratory of Juan Madinaveitia, who lived at no. 3.

Cajal recalled how he took advantage of his visit to gain first-hand knowledge of the activity that was being developed in both laboratories. The meeting with Simarro was far from being coincidental or random, as he had the intention to make "training visits," as he wrote in his autobiography. Cajal needed to connect with someone whose interests complemented his own; he was interested in understanding how the mind works, and tried to study, with precarious techniques, the structure of the nervous system. Simarro, on the other hand, studied the same structure from a clinical mindset, to explain neurological and psychological phenomena. As Cajal writes, Simarro, "devoted to the professional specialty of mental diseases, was engaged in analysing the changes in the nervous system."[2(p75)] Cajal went to the Biological Institute to find Simarro; there he told him of the problems he was facing with the techniques for staining nervous tissue. Albarracín highlighted that Cajal's problems were similar to those of Simarro. Simarro, "with his usual selflessness with no restrictions," then told Cajal about the methods he had used in Paris and invited him to the laboratory on calle del Arco de Santa María to show his results as well as the histological preparations.[40]

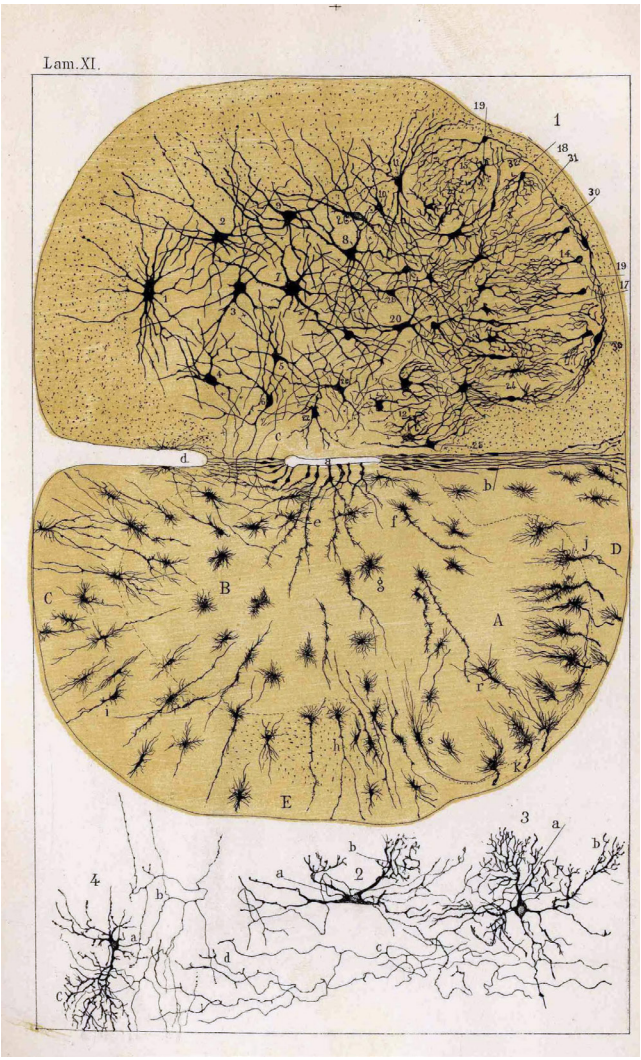


Figure 4. *Revista Trimestral de Histología Normal y Patológica*, published by Cajal to rapidly distribute his research. The published articles were accompanied by beautiful coloured lithography prints and exquisite black and white graphics.

From calle del Arco de Santa María to the chair of Madrid

After this meeting, Cajal would focus all his efforts on testing the Golgi method in his studies of the nervous system and publishing his results. Cajal's visit with Simarro took place in January 1887; in November of the same year, Cajal would become chair in Barcelona after applying for a transfer from Valencia. In April 1892, four years after their meeting, Cajal obtained the chair in Madrid after winning a competitive examination. The competition had lasted more than 20 months, during which he had to interrupt his research activity for trips to Madrid.

This was an extraordinarily productive period for Cajal, despite the time invested in the competitive examination. From late 1888, he became editor of the journal *Revista Trimestral de Histología Normal y Patológica* (Figure 1). He personally financed the journal, not sparing any expense, therefore including beautiful, coloured lithography prints and exquisite black and white graphics (Figure 4). The journal enabled him to disseminate the numerous results he had been obtaining. It was worth the effort, because he was certain that the Golgi method showed "the fundamental structure of the grey matter with a clarity and simplicity that especially facilitate analysis."[41] His main aim was to disseminate his research among his colleagues, mainly those from abroad.

Simarro was one of the researchers receiving his studies. Cajal sent one of these works, *Origen y terminación de las fibras nerviosas olfatorias*[42] (Origin and endpoint of the olfactory nerve fibres) (Figure 2A),[43] with a dedication; the article is preserved as part of the Simarro Legacy. Cajal was certainly anxious to share the promising new findings obtained with the Golgi method that Simarro had shown him. He also sent him an offprint on the structure of the spinal cord (Figure 2B).[41] In this work, Cajal categorically states that: "The method of Golgi is the only one that has clearly shown the generalised presence of the mentioned layout in the epithelial cells of the embryonic nerve centres."

Simarro's answer to Cajal was so surprising that Cajal recalled it in *Recollections of my life*:

> In a letter to me in 1889 he said: "I received your last publication on the structure of the spinal cord, which seems to me an important work but not convincing, because of the method of Golgi, which, even in your hands, who have perfected it so much, is a method which suggests rather than demonstrates."[2(p191)]

And Cajal sadly concluded: "Unfortunately, Simarro, who was endowed with great talent, lacked perseverance [sic], the virtue of the less brilliant."[2(p191)]

To elucidate some key aspects in their personal and academic relationships throughout their lives, we should also address the details surrounding the competitive examination, how they experienced it, and the image that may have been recorded for posterity. One of the

three final candidates for the position was Simarro, a prestigious neurologist and psychiatrist from Madrid, who had already won a position of physician at Hospital de La Princesa, from which he had resigned. The other two candidates were already chairs of the universities of Barcelona and Santiago, and both had vast experience in competitive examinations.[44]

The documents concerning these examinations are preserved in files held at the general archive of the Spanish central government. The circumstances surrounding these examinations can be consulted, revealing that they were not suspended on several occasions. Cajal spoke about interruptions. Seven appeals had to be resolved before the first examination. Five were filed by Varela, and Simarro, citing similar arguments, joined two of them. There were also delays due to withdrawals and sickness. So many interruptions delayed the start of the examinations by almost a year and a half. When all these events were finally resolved, the examination process began, specifically, on 17 December 1891, and it was not suspended at any time, until on 14 January 1892 the board unanimously proposed Cajal for first place. On 16 January, as no appeal was presented against this decision, the proposal was declared definitive. Simarro, and also Varela, unquestionably acknowledged the superior merits of Cajal. On 10 February, Cajal was appointed as chair at the School of Medicine at Universidad Central de Madrid.[44] The four examinations were held within less than a month, including the Christmas holidays.

The minutes do mention some minor event totally unrelated with the supposed frictions between Cajal and Simarro. For example, on 15 June 1891, in the first call for the examination, only Cajal and Simarro arrived on time. The board and examinees agreed to wait a while longer for doctor Varela to appear. The board could have eliminated him to start the proceedings but they decided to wait for him. Neither of the candidates affected by the delay protested, and courtesy prevailed. Finally, Varela arrived altered half an hour later, claiming that the board had been illegally constituted and was biased. The process was interrupted once more, and the draw for interventions could not be held. The first exercise consisted of the notorious *trinca* or "ganging up," in which candidates boasted about their curriculum vitae while discrediting their competitors. This favoured shenanigans and complaints, all of which were encouraged in accordance with law, and were present in all examination procedures. Furthermore, appeals, as vexatious as they may be, could be used by candidates to delay the examinations.

The three candidates who finally sat the examination had to do so in a strained atmosphere. Not even two good friends, as Cajal and Simarro were, were able to stay away from these controversies. Cajal and Simarro faced one another in the *trinca*, and it is easy to imagine how uncomfortable it would have been for each to criticise the works of the other to highlight their own. Both shared the same model, openly opposed to that of Golgi, and had studied the nervous system; however, the work that Cajal was performing on the structure and function of neurons was far better than that of Simarro. Nonetheless, Cajal knew that, unlike Simarro, he had barely no practical experience in performing autopsy studies. Furthermore, Simarro was a better orator. It surely would have come easier to both to oppose the reticular vision of Varela.

It is not surprising that, as Cajal wrote in his *Recollections of my life*, regrettable tensions and resentments emerged that dampened their friendship. We also may not forget, as mentioned above, the serious indiscretion committed by Cajal. At this point of the examination process, he would have already regretted having committed the conceited imprudence of commenting in public that the president of the board, Julián Calleja, had sent him a letter where he said he "was clearly supporting him, acknowledging his extraordinary achievements." Cajal, against the elementary sense of caution, instead of remaining silent, proudly mentioned the letter in the café; word inevitably reached the ears of Simarro, increasing the tension between them.[45(p228)] However, beyond the insinuations of Durán Muñoz and Alonso Burón, written at the height of the Franco dictatorship in 1960, no further reliable information has been found that supports the existence of rows or physical confrontations between the supporters of Simarro and Cajal. They also ignored Dr Varela, who was unfairly considered the most conflictive candidate, as an inquiry was opened into him in 1874 by the University of Barcelona. Simarro knew well the academic environment in which he moved and did not delude himself into expecting a good final result. But he knew it would give him a head start for a future chair. Simarro had acknowledged this to Cajal in a letter.

In spite of everything, these frictions, which certainly existed, did not prevent them from keeping a somewhat normal relationship during those days, the type of

relationship between two friends who value one another's work. To understand the context of these competitive examinations we should consider that while Simarro was very well-known in Madrid, Cajal was famous abroad. Simarro knew this, and so did the members of the board, especially Cajal's students.

This fame abroad was a very strong argument used by Cajal in the examinations. By that time, Cajal, as determined as he was to share his findings with his European colleagues, had already come forward in an 1889 meeting of anatomists, captivating Kölliker. He returned from Berlin as part of a selected community of European histologists. This would enable him to maintain correspondence with the most representative and influential scientists in Europe. And, of course, he showed these letters in the Madrid circles that were following the competitive examination.

It is surprising that Cajal, 30 years later, made the mistake of mentioning the seven members of the selection board for the chair in Madrid. He mentioned as members of the board the two professors of the subject. It should be noted that Calleja had included them because this was a requirement of the examination proceedings. They were friends and students of Cajal, Cerrada and Saltor. However, Saltor, possibly weary of so many delays caused by the appeals filed by Varela, had voluntarily resigned on 16 June 1891. In fact, the seventh member of the board, whom Cajal had omitted and who actually acted as secretary, was another good friend and student, Dr Bartual. Cajal describes Bartual elsewhere, saying that when he was in Valencia, the latter had been "one of the most frequent attendees to my lectures […] Dr Bartual, with a solid and harmonious talent […] had exceptional skills in diligently making appropriate preparations for scientific research."[13(p41)]

He surely knew Bartual well, and the praises that Cajal dedicated to his friend are not surprising. It was precisely with the help of Bartual that Cajal fine-tuned the Golgi method, after his fortuitous meeting with Simarro.

A friendship put to the test

The competitive examination process was complicated, and plagued by events that personally affected the candidates. Both friends drifted apart and their relationship may have become colder, but there is no doubt that they always supported one another. In fact, their scientific exchange never ceased. Simarro, with his usual selflessness, continued teaching Cajal the new microscopy techniques he had been working on, which may have been useful for Cajal's research. Cajal expressed his gratitude in his publications and lectures. If we exclude the students who worked with Cajal at his laboratory, Simarro is the Spanish researcher most frequently cited by Cajal in his studies; thanks to Cajal, Simarro's techniques and findings were known abroad. Simarro was cited in the large book *Texture of the nervous system of man and the vertebrates* (1899-1904)[46] due to his interesting staining method for neurofibrils. Simarro's technique for staining neurofibrils showed that the start of the axon does not display chromatic spindles, as Simarro used to call them. Another important finding of Simarro's is mentioned in *Degeneration and regeneration of the nervous system* (Figure 5).

Cajal's words during the Nobel Prize acceptance speech in 1906 supporting the neuron doctrine are even more interesting. Among the studies used as references in his work, in addition to foreign scholars, Cajal mentions four Spaniards: three from his own school (Tello, Sala, and his brother Pedro Ramón y Cajal), and Simarro. Thanks to his staining method to observe neurofibrils, perfected by Cajal, the existence of the supposed intercellular continuity described by Golgi was refuted.

Cajal's recognition of his friend Simarro is present throughout his life. Several years after the competitive examination, in a letter sent to Retzius, he praised the novelty of the osmic acid method created by "my friend Dr Simarro" to stain axon fibres.[3] They were together at important moments, interested in one another's success; for example, Simarro congratulated Cajal from San Sebastián for winning, in competition with Pavlov, the Moscow Prize at the International Congress of Medicine in Paris in 1900. Cajal had the same appreciation for Simarro, as shown by his invitation in 1903 for him to participate in the 14th International Medical Congress, held in Madrid.[47] His aim was for Simarro to explain the findings obtained with his method to stain neurofibrils, as it was superior to that of Bethe.

Family life

The attitudes of Simarro and Cajal towards their scientific works are better understood if we pay attention to the personal circumstances surrounding each of them. Both are good examples of the social change that took place in Spain during the 19th century. Coming from

modest families, Cajal and Simarro climbed socially thanks to an education acquired with perseverance and intelligence. This social step up is a phenomenon we can observe in other great figures of that time who also had an extraordinary talent and perseverance that led them to stand out in their fields. These two lives ran in parallel, but there were significant differences in their family environment. Cajal had a happy family and home life, whereas Simarro, who enjoyed staying at home, had experienced a family tragedy that left him orphaned at the age of 3 years; disenchantment accompanied him throughout his life.

A very different family situation surrounded Cajal when he planned to marry Silveria Fañanás. Cajal's health was fragile due to the fevers he had contracted in Cuba as a military physician. In 1875, sick with malaria, he returned home after his discharge from service, and had to find new employment. After obtaining his doctorate degree in 1877, two years after Simarro, Cajal got sick again. His convalescence lasted months, and he failed in the competitive examinations for the chair of anatomy in Zaragoza and Granada. Finally, in 1879, he accepted a very poorly paid position as director of the anatomical museums at the school of medicine in Zaragoza. He declined to work as a rural doctor in one of the two positions that his father procured him. On top of that, he decided to marry that same year. These decisions greatly displeased his father. However, marrying was a decisive event in Cajal's career, and Silveria would become his great companion and permanent support for 50 years, until her death in 1930.

On the other end, we find the orphaned Simarro, whose personal life was more tormented and tragic. He never had parental support, as his mother committed suicide the day after his father's death due to tuberculosis. Instead, he had the support of his aunt and uncle during his childhood. Later, his godfather Luis de Madrazo secured him a scholarship to study in Valencia. He met Vicente Boix, a remarkable liberal and director of the boarding school, who would treat him as a son. However, during the 1868 revolution, the provisional government seized the San Pablo school and closed it, and Simarro lost his scholarship. Jaime Banús welcomed him into his home. He scheduled private lessons for him and provided him with translations of French texts, which did not remedy the extreme poverty in which Simarro lived. Beatriz Tortosa, a cultured lady with advanced ideas, also showed great appreciation for the young Luis

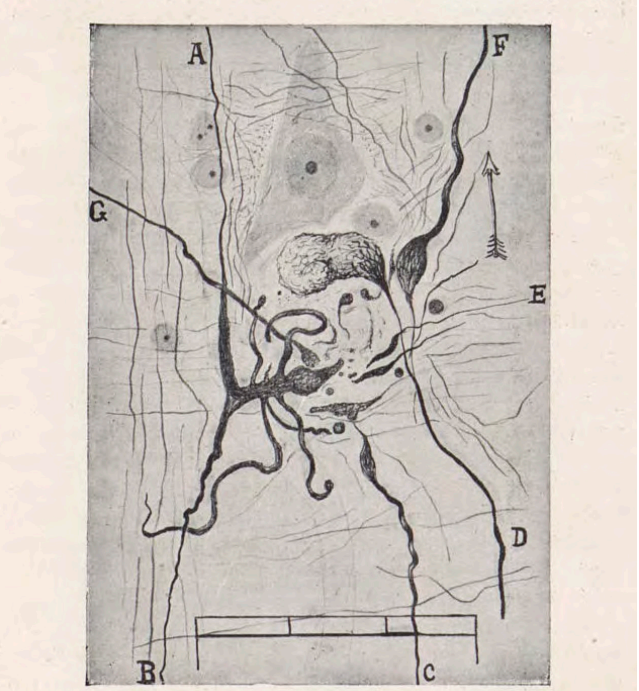


Fig. 310.—Detalles de una placa de Fischer en vías de formación.—A, axon de proyección hipertrofiado junto á la placa, á la que envía recia colateral acabada en bulbo y numerosas ramas terminales; D, G, F, fibras terminadas en la región de la placa mediante botones ó bolas. (De un dibujo de Simarro).

Figure 5. Details of a developing Fischer plaque. Drawing by Simarro, published by Cajal in *Degeneration and regeneration of the nervous system*, vol. 2, p. 375. (The original is preserved in the Fernando de Castro Collection).

Simarro. Years later, after Simarro returned from Paris, while he was drafting the Galeote report at her home, she organised a meeting with Mercedes Roca, the love of his life. He went to Valencia to find her, as Simarro had fallen in love with her in his youth. Since departing for Paris, overcome by his professional situation and debts, he had not seen her or written to her.[25(p69)] Mercedes had waited for him all that time, and their wedding took place a few months after that meeting.

They married in 1887, after Cajal, and had no children. They were married for only 15 years, as Mercedes Roca died in 1903. Once more, a tremendous sadness impregnated his life. In 1908, joy returned to his home on calle General Oraá with the birth of Marina Romero, to whom he was godfather and whom he treated as a daughter.

Several months before his death, and already very sick, he married again, this time with his housekeeper Amparo Nieto, and they had no children.

The influence of Simarro in Cajal's work

The two scholars met one day in January 1887 in Madrid. Cajal wanted to meet Simarro because he knew his friend had patiently and carefully tried numerous novel techniques that were emerging abroad; Simarro became his accidental master. Cajal was no longer in Zaragoza, where he had established a microscopy laboratory only to "satisfy my curiosity without method, examining things superficially." By then, he was chair in Valencia and was interested in the study of brain tissue. However, he did not achieve the desired results and may have been on the verge of abandoning the project.

Cajal acknowledged that seeing Simarro's microscopy preparations was a decisive moment in his career. Their meeting changed the history of neuroscience, accelerating its development. That day marked the beginning of the research project that earned him the Nobel Prize in 1906. The goal he set himself in 1887 was brilliantly achieved with the publication of the final volume of *Texture of the nervous system of man and the vertebrates* in 1904. The three volumes brought together the effort of more than 15 years of frantic work. Throughout this journey, Simarro accompanied Cajal in several decisive steps.

— The study of the structure of neurons: the Golgi method

At Simarro's laboratory, Cajal could observe for the first time the soma, dendrites, and axons of neurons in a tissue stained with chrome-silver impregnation.

Simarro explained how to stain neurons with this procedure. First, the fragile brain tissue had to be submerged in a potassium dichromate and osmic acid solution. Next, the tissue was submerged a further two days in a silver nitrate solution to obtain a "reazione nera." Finally, slices were made, dehydrated in alcohol, washed with clove oil, rinsed well, and mounted on a plate. Then, when observing the preparation under the microscope, neurons appeared in black against an amber-yellow background.[48(p515)] The significance of the method resided in its ability to clearly and selectively stain neurons and their projections. Impregnation of the nervous tissue with heavy metals (gold or silver) enabled researchers to study the morphology of the cell body, together with axons and dendrites of neurons. Thick histological slices greatly increased the probability of observing a large section of the cell or even the entire cell. This technique was able to display the branching pattern of axons and dendrites together with their connections with other neurons.

— The study of myelin: the Weigert-Pal method

The Weigert-Pal method used haematoxylin to stain the myelin (white matter) of the nerve fibres; however, the grey matter remained unstained. With this method, it was possible to visualise the distribution and organisation of fibres, and Cajal could observe spiral masses, an unpublished finding discovered by Simarro.[49(p294)] After returning to Valencia and visiting Simarro's laboratory, Cajal became determined to systematically study nervous structures using the Golgi method. For 15 years, he explored the olfactory bulb and retina, spinal cord, cerebellum, brainstem, and brain.

His great project would primarily consist of demonstrating the individuality of neurons and explaining their genesis. He would also offer a structural model of the functioning of the nervous system. Finally, his research would elucidate the internal structure of the neurons. Simarro did not influence the development of the circuit network model, but did contribute to solving the remaining problems, showing Cajal new techniques that enabled him to better study the external and internal structures of the nervous tissue.[6,50,51]

The Golgi method enabled random measurement of a small percentage of neurons, which facilitated disentangling the neuronal forest; however, the direct exploration of the full-grown forest (in Cajal's own words), of the trees of the grey matter, was not appropriate. He opted to study the "young wood," choosing embryos of birds and mammals.

Simarro had good knowledge of photographic techniques. His time with Ranvier enabled him to expand his knowledge, testing numerous procedures. He returned from Paris with the "good news of histology," which he shouted from the rooftops. However, both the Golgi method and techniques using silver nitrate salts or those using osmic acid and pyrogallic acid yielded inconsistent results. Cajal realised that the importance of the method was that regardless of the unpredictable results, when it did work, it helped to obtain excellent preparations. These preparations clearly showed the

structure of neurons and the entire network, with findings unquestionably favouring the neuron doctrine. As the results were excellent, he only needed to improve the technique in order to increase the productivity of the research by using stable staining methods. This was another of Cajal's great achievements: improving the staining techniques that he learned from Simarro. With double or triple impregnation, the Golgi method was faster and more stable. By using younger tissue, Cajal needed only one day to obtain adequate results, instead of the five days required by the Golgi method.[13(p100)]

As previously mentioned, when Simarro received Cajal's offprints, he was not initially able to fully assimilate the advances achieved by his friend by modifying the method to obtain more stable results. Simarro commented that he considered it a method "which suggests rather than demonstrates." Cajal regretted that Simarro could not directly examine his preparations, as if he had done so, he would have been equally convinced as his colleagues at the International Medical Congress in Berlin in 1889. Their meeting at the laboratory on calle del Arco de Santa María was not the only occasion on which Simarro generously shared his knowledge. He did it again in 1890.

— The study of the structure of the nervous protoplasm: Ehrlich's methylene blue staining method as modified by Simarro

The complexity of the nervous tissue made it essential to combine different staining methods. Ehrlich discovered that the methylene blue staining method obtained similar results to those yielded by the Golgi method. Although only silhouettes could be observed, images were displayed with much higher definition.

In 1890, Simarro's doctoral student Julio Perales y García presented a doctoral thesis analysing chromatic spindles.[52,53] Simarro had modified Ehrlich's methylene blue technique for use in fresh tissue to describe a new stage in the structure of protoplasm. This reveals that Simarro discovered three years before Schaffer that the intimate nature of the start of the axon is clearly different from dendritic thickening.

— The study of axon fibres: osmic acid and pyrogallic acid

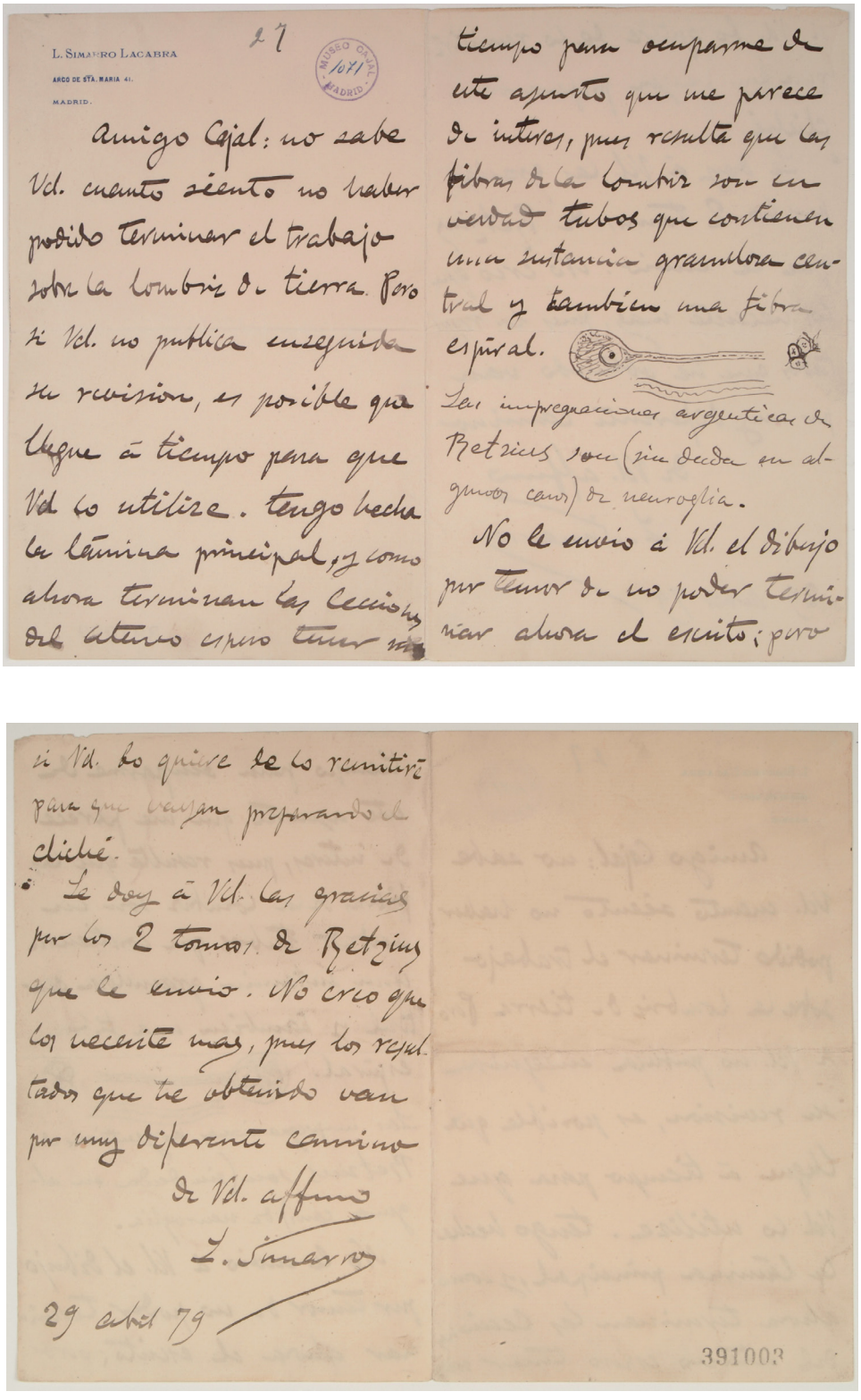
By the late 19th century, Simarro was still studying the internal structure of the nervous cells and axon fibres by testing new procedures. This is shown by the letter he wrote to Cajal in 1879 (Figure 6), in which he expresses his desire to study the intraprotoplasmic filaments of axons in earthworms. He explained that he was using a technique with osmic acid and pyrogallic acid. He planned to publish his study in Cajal's journal, but never did and, as occurred with most of his work, it was only distributed among his students and colleagues.

Simarro also sent his findings to Cajal, correctly assuming that he would appreciate them. And he was right: Cajal communicated his interesting results in a letter to Retzius:

> More than a year ago, I observed the spinal fibre of the axon in preparations of earthworms by my friend Dr Simarro, with the help of a special method (staining with osmic acid and pyrogallic acid).[54]

— The study of neurofibrils: Simarro's method using silver nitrate salts

At the turn of the century, Simarro again influenced the path of Cajal when he attempted to clearly observe the internal structure of the neuron protoplasm. A new technique was needed. Once again, Simarro would conceive a solution to the problem using silver nitrate salts.[55] Cajal was not satisfied with the new technique as the results were unstable; therefore, he performed a meticulous study with the famous reduced silver nitrate method. In his biography, he detailed how he was able to improve Simarro's photographic method with silver salts. This ingenious method, he noted, was far from being consistent, but on the few occasions that it was successful, the results were excellent. Before abandoning the method, he decided to carefully analyse it by recording and changing procedures (doses and type of poisoning, heating times, proportion of silver nitrate, etc) "to determine, if possible, the causes of this discouraging inconsistency." He thus discovered that two reactions were interfering with each other in Simarro's preparations. He believed that he had decisively perfected Simarro's method, but soon realised that the staining process was very complicated and involved indeterminable actions. This continued disturbing his sleep for a long time, until he finally found the solution after several experiments. Unquestionably, and following the example of Cajal, we can conclude that perseverance is a requirement for researchers.



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Amigo Cajal: no sabe Vd. cuanto siento no haber podido terminar el trabajo sobre la lombriz de tierra. Pero si Vd. no publica enseguida su revision, es posible que llegue á tiempo para que Vd lo utilize. tengo hecha la lámina principal, y como ahora terminan las Cecilias del Caturro espero tener mas tiempo para ocuparme de este asunto que me parece de interes, pues resulta que las fibras de la lombriz son en verdad tubos que contienen una sustancia granulosa central y tambien una fibra espiral.

Las impregnaciones argenticas de Retzius son (sin duda en algunos casos) de neuroglia.

No le envio á Vd. el dibujo por temor de no poder terminar ahora el escrito; pero si Vd. lo quiere se lo remitiré para que vayan preparando el clichè.

Le doy á Vd. las gracias por los 2 tomos de Retzius que le envio. No creo que los necesite mas, pues los resultados que he obtenido van por muy diferente camino

De Vd. affmo
L. Simarro

29 abril 79

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Figure 6. Hand-written letter sent by Luis Simarro in 1897 to to Santiago Ramón y Cajal. The letter is addressed "To my friend Cajal" and in it, Simarro laments not having completed his study on earthworms and thanks Cajal for lending him the two volumes by Retzius. Dated in Madrid, on 29 April '79. The letter is erroneously dated in 1879 as it was written in 1897. Cajal Museum, CSIC (courtesy of Juan de Carlos).

The culmination of a work

The use of Simarro's method at Cajal's laboratory for more than a decade "revealed the neurofibrillary structure in the nervous protoplasm and pericellular arborisations, and discredited critics of the neuron doctrine."[51]

Fifteen years before, Simarro had taught Cajal the Golgi method, unknowingly becoming a master of masters. Since then, he had closely followed his friend's research, and on several occasions provided technical solutions that Cajal incorporated to solve practical problems. The latest was the silver salt method. As on previous occasions, Cajal modified and perfected the method.

The year 1903 represented a great occasion to disseminate his work internationally. In April, the 14th International Medical Congress took place, where scientific advances were presented. Cajal was famous as he had been awarded the City of Moscow prize, competing with Pavlov. The organisers of the Congress aimed to achieve the recognition of scientific activity in a country located at the edge of Europe. Due to national and foreign prejudices, Spain was far from the focus of international research.

However, at the Congress in Madrid, the international novelties were the discoveries by Pavlov and Ramón y Cajal. These works presented in Madrid decisively influenced the subsequent development of their respective disciplines during the 20th century. Pavlov, dedicated to the study of reflexes as basic behavioural units, presented his theory on conditioned reflexes (metaphorically called psychic reflexes). Cajal, who was studying nerve cells (metaphorically called psychic cells) as a basic unit or "physiologically autonomous canton," presented his neuron doctrine. Within three years, both had received the Nobel Prize for their work.[47,56]

The congress represented a significant stimulus for Spanish scientists who aspired to distribute their works among the international community. Cajal participated in the Congress with a controversial communication on the structure and connections of neurons, strongly criticising the implausible reticular theories. He had invited Simarro, who also actively participated, presenting his data and observations on the neuron doctrine. Simarro showed images obtained with his own technique, enabling staining of the neurofibrillary network with silver salts. This technique would be perfected by Cajal in the following months. This method was completely different to that developed by Bethe, and was also highly superior. It displayed the structure of the neuron protoplasm in such a way that neurofibrils in its interior were shown not to be part of a continuous interneuronal network. Cells were studied in vivo, as part of an active and individualised whole.

The Nobel Prize

In Cajal's work, the Golgi method was just as important as Simarro's method to his winning the Nobel Prize. At this point, it should also be noted that both procedures were improved thanks to the determination of the great Aragonese neuroscientist. Gunnar Grant has studied the details of the awarding of the Nobel Prize in Physiology and Medicine in 1906. The decision was intensely debated as it was the first time that the prize would be awarded jointly. Golgi had enjoyed strong support since the first edition of the Prize, including from Emil Holmgren, professor of Histology at the Karolinska Institute. However, Holmgren had changed his mind in the following years due to Cajal's important and valuable findings and his correct interpretation of these. Simarro's method was decisive in this decision, as the impregnation of neurofibrils led to a better understanding of the internal functioning of axons, together with the studies on the regeneration of peripheral nerves and growth cones. Simarro's method led to the replacement of the reticular theory with the neuron doctrine, which was increasingly accepted. In a few words, Holmgren concluded that Cajal's results would falsify Golgi's theory. With these new findings, the hypothesis that dendrites were nutritional elements of neurons and were not involved in the conduction of nervous impulses was no longer applicable. The majority of the committee's members decided to make an exception for the first time, and award the Nobel Prize in Physiology and Medicine jointly. Two members voted against this decision; although no names are mentioned, one of them would very likely have been Holmgren. According to the data provided by Grant, the other was probably Theodor Ziehen, whose *Introduction to physiological psychology* had been translated by Rodríguez Lafora and used by Simarro in his classes.[6(p83),57]

Discussion

Simarro was an exceptional clinician and his talent would have enabled him to achieve higher scientific goals, as

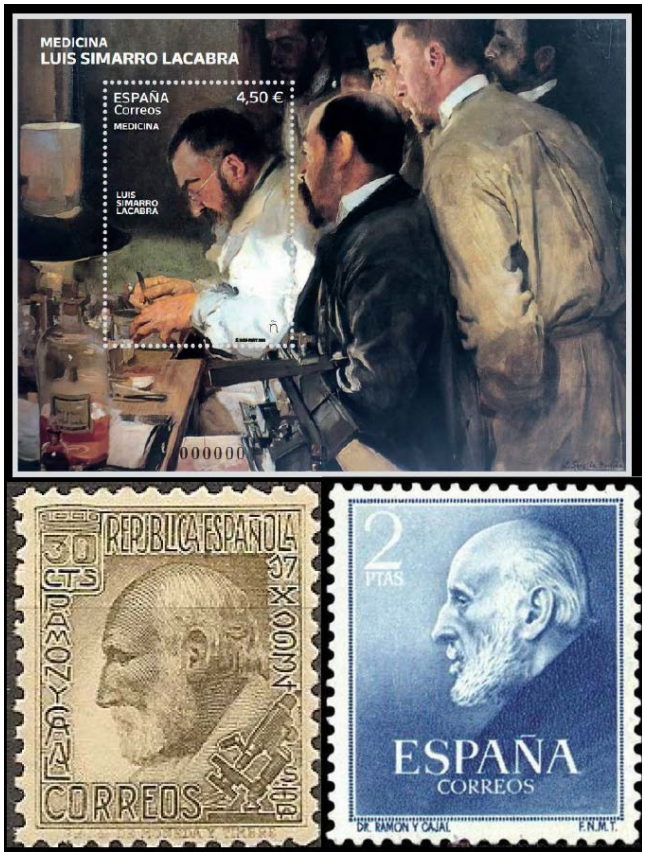

Figure 7. Stamps from the Royal Spanish Mint showing the profile of Santiago Ramón y Cajal issued in 1934 (the year of his death) and 1952 (the centenary of his birth). The stamp of Luis Simarro was issued in 2022 at the initiative of Dr Belén Yuste. It shows the Sorolla painting *A research* and commemorates the centenary of his death in 1921 (personal collection).

acknowledged by Cajal. He enjoyed social recognition and sought to right social injustices through politics. It is true that he published very little, and although he had more than enough skills to do so, only a few of his articles fully met the standards of the scientific journals in which Cajal published.[55] However, the best testimony of his work is the memory of a life full of dedication.

Nevertheless, the figure of Simarro has been distorted by some. Unjustified allegations have been made without demur regarding his clashes with Cajal or his inability to publish, despite his friendship with Cajal and his being a rigorous, strict worker and selfless master. Furthermore, he ticked all the boxes to be scorned by the dictatorship. As politician, he was a freemason and a liberal, enabling allegations of a conflict with the figure of Cajal. This was also convenient for the Franco dictatorship, which started to disseminate this image of a man of science ruined by politics. At the same time that a museum was being built to honour Cajal, the Simarro Foundation was seized and its trustees were prevented from sitting on the board. This led to the silencing of the influence of Simarro's work on the development of neurology, psychiatry, and psychology in Spain.

Once democracy was restored, society focused once more on all those figures overshadowed by the Franco dictatorship, and an article in the newspaper *El País* recovered the memory of Dr Simarro.[58] Campos and Llavona considered it the perfect moment to organise a series of monographic sessions, under the title *Dr Simarro and the origins of scientific psychology in Spain*.[8] Participants included, among others, Laín Entralgo, Albarracín, Peset, Yela, and Carpintero, who discussed the legacy of the Simarro Foundation and the author's work for three days. However, despite greater study and recognition of Simarro from that time, shadows remained over his figure, which is still recovering from the ostracism imposed by the Franco dictatorship. Examples of this recovery include the exhibitions held to celebrate his contribution to science in Spain. In 2002, coinciding with the centenary of the creation of the chair of Experimental Psychology occupied by Luis Simarro, the Complutense University of Madrid's Historical Library, the Simarro Legacy, and the School of Psychology organised an exhibition to mark one hundred years of the institutionalisation of scientific psychology in Spain.[9] The same year, the Spanish Society of Neurology invited me, as director of the Simarro Legacy, to give a lecture on Simarro to raise interest in his work among young neurologists who were barely aware of him. In 2018, the Spanish Society of Neurology's Museo Archivo Histórico presented an exhibition commissioned by Díez Tejedor, Campos Bueno, and Balcells: *Luis Simarro: neurología e histología del sistema nervioso* (*Luis Simarro: neurology and histology of the nervous system)*.[59] To commemorate the centenary of Simarro's death, the Simarro Legacy, with the collaboration of the School of Philosophy and the Spanish Society of Neurology, organised the exhibition *Luis Simarro. Centenario (1851-1921)* (*Luis Simarro. Centenary [1851-1921]*).[60] The interest in

Table 1. Comparison of the characteristics of the works by Simarro and Cajal.

Luis Simarro Lacabra	Santiago Ramón y Cajal
— **Importer of science** to Spain.	— **Exporter of Spanish science**
— **A disperse and restless man** who cultivated many fields of the European culture of the time.	— **A focused and restless man**, he exported his knowledge to the European scientists of the time.
— **Neuropsychiatrist** with broad intellectual and artistic horizons. He inherited the redemptionist vision of such psychiatrists as Jaime Vera and Esquerdo. He is interested in psychology.	— **Neurohistologist** focused on his work, with broad intellectual, artistic, and literary horizons, but without the dispersion of Simarro.
— **He helped others to advance**, but did not cultivate his own work, which as a result did not reach the stature it deserved according to his talent and knowledge.	— **He directly advanced science** thanks to his extraordinary personal work and created a school.
— **He trained excellent students**, some shared with Cajal. He undertook several related projects (neurology, psychiatry, psychology, histology) and promoted the social role of science and its distribution.	— **He created the Spanish Histological School**. He pursued a single project focused on the structure of the nervous system and the social role of science and its distribution.
— **His popularity rapidly dissipated** after his death. He was actively discredited by the Franco dictatorship and his foundation disappeared in 1945; the heritage administered by Rodrigo Lavín, who was exiled to Paris, was dissolved. His legacy was seized and divided between the Universidad Complutense and the CSIC's Luis Vives Institute. In 1982, the whole Simarro Legacy was transferred to the Universidad Complutense. A very advanced project, which was started long time ago, to create a great museum of healthcare science at the Universidad Complutense was abandoned in 2019.	— **His popularity persisted over time**, and his fame and prestige grew after his death. During the Franco dictatorship, his figure was praised, and in 1945, the Cajal Museum was inaugurated as part of the Cajal Institute. His material legacy has still not reached the recognition it deserves. Spanish society has no museum reflecting the great achievements of Spanish neurohistology that began by Cajal. He is the most universal Spanish scholar and one of the greatest scientists worldwide.

Simarro has transcended academia to reach other fields. One of these is philately, with a stamp commemorating the centenary of his death (Figure 7). The arts have also paid attention to his figure, as shown by the portraits painted by Sorolla and Luis de Madrazo (Figures 7 and 3). On the centenary of Simarro's death, the digital artist David Bokeh presented a video showing him working alone at his laboratory on calle del Arco de Santa María, the same visited by Cajal in January 1887.[61]

Cajal's work, like that of Simarro and his contemporaries:

> Represented the perfect culmination of two centuries of Spanish tradition in the field of microscopic anatomy, which developed during a period in which scientific activity recovered a significant level in Spain, overcoming the great collapse it suffered during the first third of the 19th century. This recovery involved significant help from Aureliano Maestre de San Juan and Luis Simarro Lacabra, two great figures whose teachings were enthusiastically and generously praised by Cajal.[50]

The influence of Cajal on the development of neurosciences is comparable to that of Einstein, Darwin, Galileo, Newton, Humboldt, or Champollion, who also created initial models that permitted the future development of their respective disciplines. Cajal did the same, and his model of the structure of the nervous system and its basic working mechanisms remain applicable today.

Sometimes students surpass their masters, and when this occurs there is no embarrassment for either. There is no reason to think that Simarro ever considered himself to be Cajal's master, or boasted of having been a helpful master. Both were students of Aureliano Maestre de San Juan, who in turn had been a student of Marcos Viñals in Madrid and Carlos Ordóñez in Paris.

Cajal's intended meeting with Simarro led to an invitation to visit Simarro's laboratory on calle del Arco de Santa María. There, Cajal was able to observe tissues that Simarro had stained using the Golgi method and other techniques. This visit was decisive in accelerating his discoveries on the structure and function of the nervous tissue. In 1906, Cajal was awarded the Nobel Prize. Simarro's teaching to Cajal and influence on his work are those of a colleague. Simarro was definitively a colleague for Cajal, an exceptional collaborator in the scientific field, brilliant, hard-working, and well-informed; he was also a generous friend who enthusiastically and openly shared useful information that would help Cajal on his own path. The dedication to science and the personal honesty of these two great men rose above the academic meanness and envy that, born of mediocrity, so often accompany scientific work. This was not the case of these two friends.

Today, as we commemorate the centenary of Simarro's death (1921) and Cajal's retirement (1922), we observe that time has shown the true stature of both of these great men (Table 1).

Acknowledgements

Forty years ago, Dr Mariano Yela entrusted me with continuing his work in the Simarro Legacy and dedicating part of my time to keep that flame alive. Over the years, I have shared the same interests with many people, including the librarians at CSIC, and the Sorolla Museum and its Foundation, and the librarians and curators of the museums and heritage of the Universidad Complutense, who have enthusiastically helped to preserve the Simarro Legacy for more than 30 years, whether directly or providing information. I would also like to thank Vanessa Cisteré of the Spanish Society of Neurology and its Museo Archivo Histórico, who has supported and embraced the project of recovering the figure of Simarro. There is not enough space to show my gratitude to all the people who have helped me.

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