

Ramón y Cajal: a century after the publication of his masterpiece

Pedro J. Andres-Barquin

Santiago Ramón y Cajal published the first of the three volumes of his principal life's work in 1899, and published the last volume in 1904. This book remains the definitive work on the morphology of the vertebrate nervous system. In it, Ramón y Cajal describes the structure and organization of virtually all parts of the nervous system and discusses his theories, including the neuron doctrine and the law of functional polarization, which are the cornerstones of modern neurobiology. A century later, Ramón y Cajal's work is still fundamental to understanding the nervous system.

Countless modifications during evolution have provided living matter with an instrument of unparalleled complexity and remarkable function: the nervous system, the most highly organized structure in the animal kingdom. The dominant role played by the nervous system is obvious. From its inception, this system mediated ever increasing coordination between the various elements of multicellular organisms, which were essentially unstructured, disorganized, and subject to all the vagaries of the surrounding environment early on. The nervous system provided these animals with the necessary mechanisms for nutrition and defense, and the number, precision, power, and coordination of these mechanisms steadily increased. Furthermore, in the highest echelons of life, it also provided optimal means for survival: feelings, thought, and will.

Santiago Ramón y Cajal

Santiago Ramón y Cajal (1852–1934) (Figure 1) is acknowledged as the founder of neuroscience. Born on 1 May 1852 in the Spanish village of Petilla de Aragón in a very modest family¹, Santiago enjoyed a childhood in close contact with nature. Very early in his life, he showed an ability to unravel nature's secrets and a strong liking for painting and drawing, aptitudes that would later be of great importance in his scientific career. Ramón y Cajal's precocious artistic vein was repressed by his father², a man with a strong character, who persuaded him to enter medical school at Zaragoza. This was the starting point of an extraordinary scientific adventure, which led him to explore the organization and function of the nervous system and to publish the most profound body of work by a single scientist in the history of neuroscience.

Pedro J. Andres-Barquin, DVM, PhD, MPH

Is Head of Laboratory and Project Leader at the Department of CNS, F. Hoffmann–La Roche, Basel, Switzerland. He was born in Zaragoza, Spain, and received his DVM and PhD from the University of Zaragoza, and his MPH. from the Spanish National School of Public Health. He has been a fellow at INSERM Paris and at the School of Medicine of the University of California, San Francisco. e-mail: pedro_j.andres@roche.com

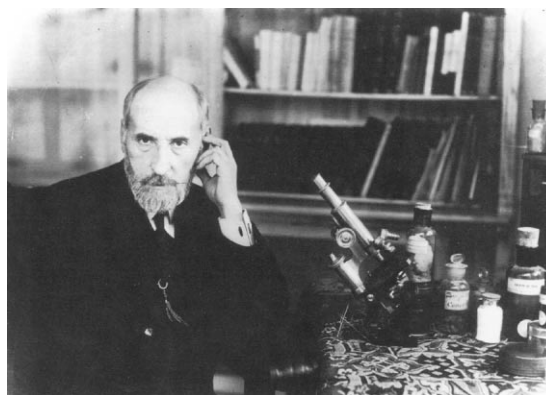


Figure 1 Self-portrait of Ramón y Cajal at the microscope, c. 1910–1912.

Scientific books

The first volume of *Textura del Sistema Nervioso del Hombre y de los Vertebrados*³ was published in 1899. This is a three-volume work that Ramón y Cajal finished in 1904 and considered the principal work of his life¹. The final version of this book, updated by Ramón y Cajal and translated to French by his friend Leon Azoulay, was published in 1909 and 1911 as *Histologie du Système Nerveux de l'Homme et des Vertébrés*⁴; this remains the definitive work on the morphology of the vertebrate nervous system. In *Textura* and *Histologie*, Ramón y Cajal summarized his work over two decades. In these books, in addition to describing the structure and organization of virtually all parts of the nervous system, Ramón y Cajal discussed his theories, among them the neuron doctrine⁵ and the law of functional or dynamic polarization⁶, which are the cornerstones of neurobiology and the natural foundation for the study of the nervous system (Figure 2).

Ramón y Cajal made countless contributions to the neurosciences, many of which can be found in his books and have been translated to English. *Textura*, *Histology*, *Les Nouvelles Idées sur la Structure du Système Nerveux chez l'Homme et chez les Vertébrés*⁷ (a work that summarizes his revolutionary view of the nervous system), *Estudios sobre la Degeneración y Regeneración del Sistema Nervioso*⁸ (a monumental study containing his works and

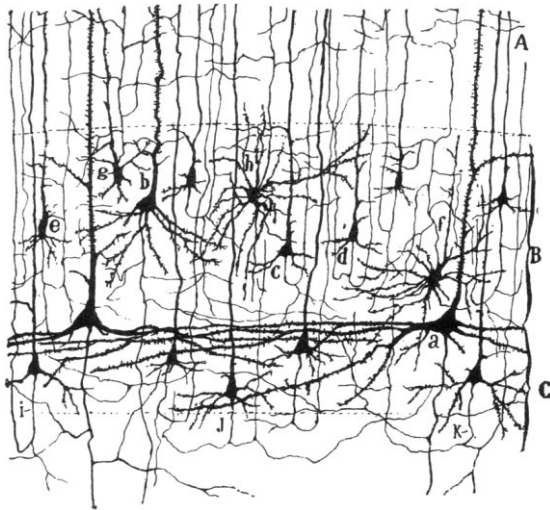


Figure 2 Ramón y Cajal's drawing of neurons in layers 5–7 of the 15-day-old human infant visual cortex, using the Golgi method. (A) Layer 5; (B) layer 6; (C) layer 7. Labels: a, giant pyramidal cell; b, medium-sized pyramidal cell with a long, descending axon; c, small pyramidal cell with an arcuate ascending axon; d, pyramidal cell with an axon that bifurcates into two arcuate branches; e, pyramidal cell with an axon that gives rise to several ascending arcuate fibres; f–h, stellate cells with an ascending axon ramifying in layers 5 and 6; i–k, pyramidal cells with an arcuate ascending axon ramifying in layers 7 and 8.

ideas relating to neurogenesis, neuronal plasticity, and nerve degeneration and regeneration), *¿Neuronismo ó Reticularismo?*⁹⁹ (his posthumous work devoted to the defence of the neuron doctrine) and his writings about the cerebral cortex¹⁰ contain seminal investigations and ideas that are as relevant today as they were when they first appeared 100 years ago.

Teaching

Ramón y Cajal was appointed Auxiliary Professor of Anatomy and Director of the Anatomical Museum at the University of Zaragoza, Professor of Anatomy at the University of Valencia, and Professor of Histology and Pathology at the Universities of Barcelona and Madrid. He also was the Director of the Instituto Nacional de Higiene Alfonso XIII (The National Institute of Hygiene), the Laboratorio de Investigaciones Biológicas (The Laboratory of Biological Research) and the Instituto Cajal (The Cajal Institute), and was President of the Junta para Ampliación de Estudios e Investigaciones Científicas (the current Consejo Superior de Investigaciones Científicas, CSIC)¹¹.

He was a dedicated teacher and mentor for more than 50 years, offering advice to students, young researchers and colleagues. In 1897, he wrote *Reglas y consejos sobre la investigación biológica*¹²; in his own words, 'Some rules and counsels designed to awaken the taste and passion for scientific investigation in our young teachers.'^{1,12} This book, recently translated into English, has been broadly acclaimed. Ramón y Cajal's scientific excellence and devoted teachings¹³ led to the establishment of the so-called Spanish school of neurohistology (a large group of outstanding pupils that continued his work) and had an enormous influence on generations of Spanish scientists.

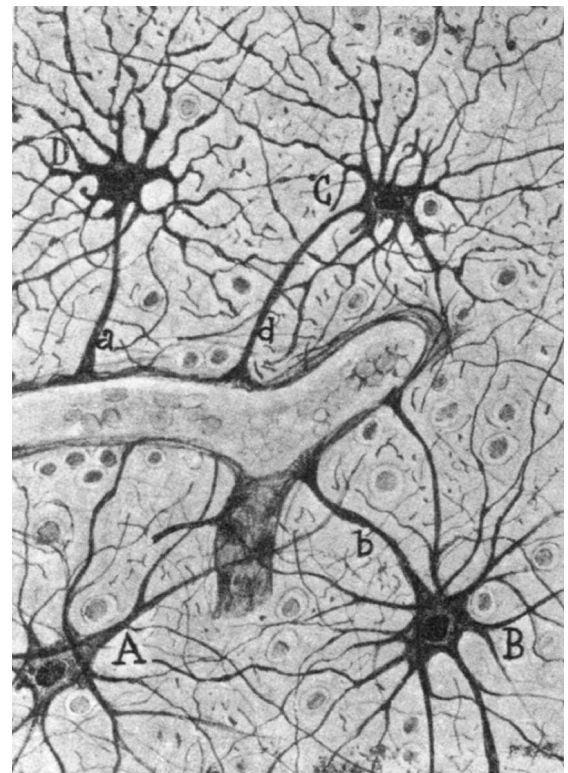


Figure 3 Ramón y Cajal's drawing of neuroglia in the white matter of the adult human brain, using the gold method³². In some cells, the fibrillary apparatus is clearly visible (A) whereas, in other cells, the strong cytoplasmic staining prevents its visualization (B, C). Labels: a, b, d, perivascular feet.

Literary works

Ramón y Cajal's literary books, and particularly his autobiography¹, have been instrumental in gaining a deep understanding of his character and the tenor of his life. In addition to being a passionate neuroscientist, he was also interested in bacteriology, psychology, philosophy, astronomy, drawing and painting, photography, literature, politics, and more^{14–19}. At the request of the provincial government of Zaragoza, in 1885, Ramón y Cajal carried out a comprehensive study of an outbreak of cholera in Valencia and described for the first time the 'experimental proof of the formation of antibodies, that is to say, of the possibility of protecting animals from the toxic effects of the most virulent bacillus by previously injecting hypodermically a certain quantity of a culture which has been killed by heat'^{1,20,21}. The prize he was awarded by the Diputación Provincial de Zaragoza for this study was a magnificent Zeiss microscope, which placed him 'on a level technically with the best equipped foreign microscopists.'

At that period of his life, he also conducted investigations into suggestion and hypnosis, and their usefulness for improving some clinical conditions and decreasing pain^{22,23}. The understanding of the human mind and the search for a link between neurobiology and consciousness are leitmotifs in the work of Ramón y Cajal. In his writings, one can find frequent thoughts about the transcendence of his discoveries for psychology and philosophy^{16–18}.

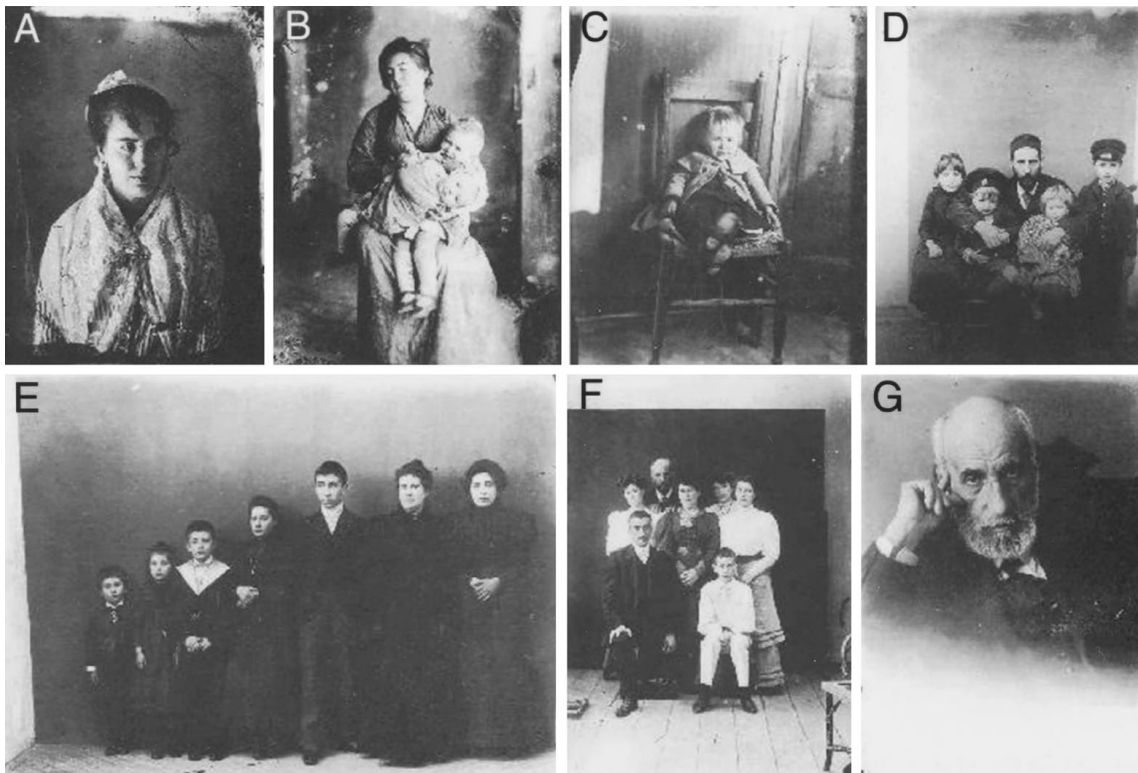


Figure 4 Ramón y Cajal's family. (A) His wife, Silveria Fañanás García³³, c. 1880. (B) Portrait of Silveria holding in her arms their two younger daughters, Enriqueeta and Paula, as an allegory of maternity, 1886. (C) Portrait of Enriqueeta³⁴, 1886. (D) Self-portrait of Ramón y Cajal with four of his children in 1888. From left to right, they are Fe, Jorge, Cajal, Paula and Santiago. (E) Family portrait in 1897. From left to right, the sitters are Luis, Pilar, Jorge, Paula, Santiago, Silveria and Fe. (F) Family portrait, c. 1906. From left to right, the sitters are Paula, Cajal, Silveria, Fe, Pilar, Santiago³⁵ and Luis. (G) Self-portrait, c. 1920. All photographs by Ramón y Cajal.

Art had an important place in Ramón y Cajal's life²⁴. Painting and drawing were two passions that led him to create some of the most beautiful scientific illustrations ever made (Figures 2,3). In collaboration with his father, he also painted a colour atlas of human anatomy that was, unfortunately, never published²⁵. Cajal was an enthusiast of the art of photography and an accomplished photographer^{1,26}. He took hundreds of photographs (portraits, landscapes and scientific photographs) (Figure 4). He had a laboratory where he used to develop, and sometimes to manufacture, the photographic films. Ramón y Cajal was one of the pioneers of colour photography in Spain. In 1912, he published *La fotografía de los colores: Fundamentos científicos y reglas prácticas*, a book entirely dedicated to this subject²⁷.

Politics and popularity

As well as being very prolific, Ramón y Cajal was a popular author. He wrote a variety of books intended for a broad public, including *Recuerdos de mi vida*¹, *Charlas de café*¹⁴, and *El mundo visto a los 80 años*¹⁵. 'I take into consideration that I am not writing exclusively for specialists, but for a cultured public of varied interests'¹. Always interested in popularizing science, he adopted the pseudonym 'Doctor Bacteria' and wrote articles about the 'marvels of histology' and science-fiction tales^{1,28}.

Ramón y Cajal was always willing to give advice to Spanish political leaders about national education and science issues. Furthermore, he regularly contributed to newspapers with editorials about a variety of issues relevant

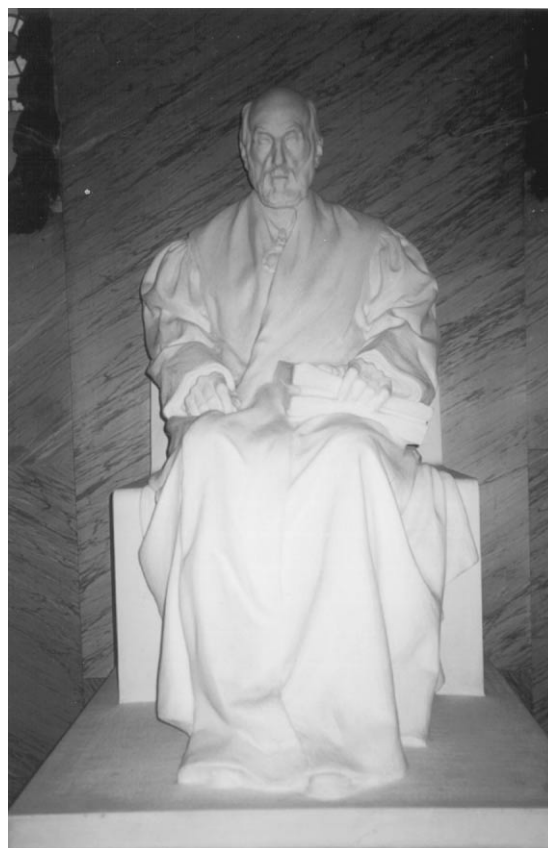


Figure 5 *Cajal* (1924). This statue in marble of Santiago Ramón y Cajal, by the sculptor Mariano Benlliure, was inaugurated in his honour at the School of Medicine of the University of Zaragoza.

to his country. He was appointed a senator for life and was offered the position of Minister at the Spanish Ministerio de Instrucción Pública (the current Ministry of Education and Culture), which he did not accept. Of the countless honours that Ramón y Cajal did receive, the one that he might have cherished most is the gratitude and affection of his fellow countrymen (Figure 5). Ramón y Cajal enjoyed enormous popularity in Spain that somehow remains today. In fact, almost every city and village in Spain has a street or square named in his honour and he is widely known among the population. The Cajal Institute of Neurobiology and many medical centres around the country have also been named in his honour. Ramón y Cajal died in Madrid on 17 October 1934, and Spanish citizens from every social class attended his funeral.

An incredible scientist, Ramón y Cajal laid firm foundations for the study of the nervous system^{29,30}. He published more than 300 major works, many of them book-length monographs. He was awarded many scientific prizes, among them the Moscow Prize by the executive committee of the International Medical Congress of Paris (1900), the Helmholtz Gold Medal by the Imperial Academy of Science of Berlin (1905) and the Nobel Prize in Physiology or Medicine (1906)³¹. Santiago Ramón y Cajal is probably the most prominent neuroscientist of all time. A century after the publication of his masterpiece, Ramón y Cajal's work is still fundamental to understanding the nervous system.

Acknowledgements

I thank Dr Ricardo Martínez-Murillo (Director of the Cajal Institute, CSIC, Madrid, Spain) and Dr Miguel A. Freire-Mallo (Scientist In Charge of the Legado Cajal at the Cajal Institute) for the permission to reproduce Ramón y Cajal's drawings and photographs. I thank Dr Maria-Clemencia Hernandez, Dr Miguel A. Freire-Mallo and Mabel Garzón for their thoughtful comments.

Notes and references

- Ramón y Cajal, S. (1901, 1917) *Recuerdos de mi vida* (Vol. 1, *Mi infancia y juventud*; Vol. 2, *Historia de mi labor científica*), Moya, Madrid, Spain. This book was first published in English in 1937 as *Recollections of My Life* (translated by E. Horne Craigie, with the assistance of J. Cano), American Philosophical Society, Philadelphia, PA, USA; a 1989 MIT Press edition is currently available (MIT Press, Cambridge, MA, USA)
- Ramón y Cajal's father, Justo Ramón Casasús, 'a pure-blooded Aragonese', was 'a modest surgeon at the time'. He was 'a man of great energy, an extraordinarily hard worker, and full of noble ambition'¹.
- Ramón y Cajal, S. (1899, 1904) *Textura del Sistema Nervioso del Hombre y de los Vertebrados*, Moya, Madrid, Spain. The first and second volumes of this book were published in English in 1999 and 2000 as *Texture of the Nervous System of Man and the Vertebrates* (translated and edited, with addition from the French version, by P. Pasik and T. Pasik), Springer-Verlag. The publication in English of the third volume is due in 2001.
- Ramón y Cajal, S. (1909, 1911) *Histologie du Système Nerveux de l'Homme et des Vertébrés* (French edition reviewed and updated by the author, translated from Spanish by L. Azoulay), Maloine, Paris, France. This book was published in English in 1995 as *Histology of the Nervous System of Man and Vertebrates* (translated by N. Swanson and L.W. Swanson), Oxford University Press
- 'A declaration of the unity and independence of the neuron and all its processes. Nerve cells always remain free, independent, and individual, and are the fundamental unit of the nervous system as a whole. Nerve impulse transmission from neuron to neuron is by contact rather than continuity'
- The law of functional, dynamic or axipetal polarization of electrical activity in neurons. 'Normally, the dendrites and cell body show axipetal conduction, that is, electrical activity is conducted toward the axon. Conversely, the axon shows somatofugal and dendrifugal conduction, that is, it transmits activity arriving from the parent cell body or dendrites, and does so from its origin to its terminals'
- Ramón y Cajal, S. (1894) *Les Nouvelles Idées sur la Structure du Système Nerveux chez l'Homme et chez les Vertébrés* (French edition reviewed and enlarged by the author, and translated from the Spanish by L. Azoulay), Reinwald, Paris, France. This book was published in English in 1990 as *New Ideas on the Structure of the Nervous System in Man and Vertebrates* (translated by N. Swanson and L.W. Swanson), MIT Press, Cambridge, MA, USA
- Ramón y Cajal, S. (1913, 1914) *Estudios sobre la Degeneración y Regeneración del Sistema Nervioso*, Moya, Madrid, Spain. This book was published in English in 1928 as *Degeneration and Regeneration of the Nervous System* (translated and edited by R.M. May), Oxford University Press. The translation was reprinted in 1991 as *Cajal's Degeneration and Regeneration of the Nervous System* (edited, with an introduction and additional translations, by J. DeFelipe and E.G. Jones), Oxford University Press
- Ramón y Cajal, S. (1933) ¿Neuronismo ó Reticularismo? Las pruebas objetivas de la unidad anatómica de las células nerviosas. *Arch. Neurobiol. Madrid* 13, 217–291 and 579–646. Published in English in 1954 as *Neuron Theory or Reticular Theory? Objective Evidence of the Anatomical Unity of the Nerve Cells* (translated by M. Ubeda-Purkiss and C.A. Fox), CSIC, Madrid, Spain.
- An English translation of Ramón y Cajal's writings about the cerebral cortex (1890–1935) can be found in *Cajal on the Cerebral Cortex* (1988) (translated and edited, with extensive annotations, by J. DeFelipe and E.G. Jones), Oxford University Press
- Sánchez-Ron, J.M. (1999) *Cinzel, martillo y piedra. Historia de la ciencia en España (Siglos XIX y XX)*, Taurus, Madrid, Spain
- Ramón y Cajal, S. (1897) *Reglas y consejos sobre la investigación biológica*, L. Aguado, Madrid, Spain. A later edition of this book was published in English in 1999 as *Advice for a Young Investigator* (translated by N. Swanson and L.W. Swanson), MIT Press, Cambridge, MA, USA
- Ramón y Cajal also wrote a number of textbooks of histology and pathology, including *Manual de Histología Normal y Técnica Micrográfica* (1889), *Manual de Anatomía Patológica General* (1890), *Elementos de Histología Normal y de Técnica Micrográfica* (1897) and *Manual Técnico de Anatomía Patológica* (1918). Several editions of these books were published in Spain between 1889 and 1953.
- Ramón y Cajal, S. (1921) *Charlas de café. Pensamientos, anécdotas y confidencias*, J. Pueyo, Madrid, Spain. Reprinted in *Santiago Ramón y Cajal: Obras Selectas* (2000), Espasa-Calpe, Madrid, Spain.
- Ramón y Cajal, S. (1934) *El mundo visto a los 80 años. Impresiones de un arteriosclerótico*, Tipografía Artística, Madrid, Spain. Reprinted in *Santiago Ramón y Cajal: Obras Selectas* (2000), Espasa-Calpe, Madrid, Spain
- Rodríguez, E.L. (1977) *Así era Cajal*, Espasa-Calpe, Madrid, Spain
- Lorenzo-Lizalde, C. (1991) *El pensamiento de Cajal*, Institución Fernando el Católico, Zaragoza, Spain
- Ibarz-Serrat, V. (1994) *La Psicología en la obra de Santiago Ramón y Cajal*, Institución Fernando el Católico, Zaragoza, Spain
- Calvo-Roy, A. (1999) *Cajal. Triunfar a toda costa*, Alianza Editorial, Madrid, Spain
- Ramón y Cajal, S. (1885) Estudios sobre el microbio vírgula del cólera y las inoculaciones profilácticas. *Tipografía del Hospicio Provincial* (Zaragoza) 1–108
- Ramón y Cajal, S. (1885) Contribución al estudio de las formas involutivas y monstruosas del comabacilo de Koch. *La Crónica Médica* (Valencia) 9, 197–204

- 22 Ramón y Cajal, S. (1889) Dolores del parto considerablemente atenuados por la sugestión hipnótica. *Gaceta Médica Catalana* 12, 484–486
- 23 ‘Turning suggestion to the therapeutic field, I succeeded in performing prodigies which would be envied by the most skilful of the miracle-workers. I may cite: the radical transformation of the emotional condition of patients (an almost instantaneous step from sadness to joy); the restoration of appetite in hysterioepileptics who would not eat and were extremely emaciated; the cure by a simple command, of diverse kinds of chronic paralysis of a hysterical nature; the sudden cessation of attacks of hysteria with loss of consciousness; the complete forgetting of painful and distressing occurrences; the total abolition of the pains of childbirth in normal women; and, finally, surgical anaesthesia, etc.’¹
- 24 Ramón y Cajal’s sensibility to art might have been encouraged by his mother, Antonia Cajal Puente, ‘a beautiful and robust highland woman’¹. As Justo Ramón Casasús, she was born in the village of Larrés in the region of Aragón.
- 25 At that time, Justo Ramón Casasús had a professorship of dissection at the School of Medicine of the University of Zaragoza. In spite of the fact that he repressed the artistic vein of his son for many years, he was on this occasion very proud of Ramón y Cajal’s anatomical watercolours. Ramón y Cajal was then at the School of Medicine and was willing to put his artistic aptitudes to the service of medicine.
- 26 A number of Ramón y Cajal’s photographs can be found in Alvarez, J. *et al.*, eds (1984) *Ramón y Cajal. Fotografía Aragonesa* (Vol. 1), Diputación Provincial de Zaragoza, Zaragoza, Spain
- 27 Ramón y Cajal, S. (1912) *La Fotografía de los colores: Fundamentos científicos y reglas prácticas*, Moya, Madrid, Spain. A 1994 edition is currently available from Libros Clan, Madrid, Spain.
- 28 Ramón y Cajal, S. (1905) *Cuentos de vacaciones. Narraciones pseudocientíficas*, Imprenta Fortanet, Madrid, Spain. This book was written in 1885–1886. A 1999 edition is currently available from Colección Austral, Espasa-Calpe, Madrid, Spain.
- 29 Swanson, L.W. *et al.* (1999) Organization of Nervous Systems. In *Fundamental Neuroscience* (Zigmond, M.J. *et al.*, eds), pp. 10, 11, 14, Academic Press
- 30 Albright, T.D. *et al.* (2000) Neural science: a century of progress and the mysteries that remain. *Cell* 100 and *Neuron* 25 (joint suppl.), S1–S55
- 31 For a list of Ramón y Cajal’s publications, prizes and honours, see Ref. 1.
- 32 Ramón y Cajal’s discovery in 1913 of the gold sublimate method for the staining of neuroglia was an important step forward to the study of glial cells and primary tumours in the central nervous system.
- 33 Ramón y Cajal married Silveria Fañanás García in 1879 and had seven children. In Cajal’s words, ‘I should be unjust if, out of mistaken discretion, I should fail to say that during my first years as a professor only the unsurpassable self-abnegation of my wife made my scientific work possible. So much so that a certain highly talented lady used to say: Half of Cajal is his wife’¹. Silveria and Santiago spent the rest of their lives together. She died in 1930, two years before him.
- 34 Enriqueta died when she was seven years old.
- 35 Santiago died when he was 29 years old.