Cajal, Ramon Santiago y

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Santiago Ramón y Cajal (1852-1934)

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Santiago Ramón y Cajal (Figure 1) was born on 1 May 1852 in 'Petilla de Aragón' (Figure 2), a small village in the North of Spain, and he died on 17 October 1934 in Madrid, having become one of the most outstanding neuroscientists of all time.

Figure 1: Cajal and his histological preparations. From photographs in the Cajal Museum.

After studying medicine at the Faculty of Medicine in Zaragoza, Cajal was appointed to the chair of Descriptive and General Anatomy at the University of Valencia in 1883. In 1887 he moved to the University of Barcelona where he was elected to the chair of Histology and Pathological Anatomy. Finally, Cajal moved to the University of Madrid where he occupied the chair of Histology and Pathological Anatomy until his retirement. Cajal received numerous prizes, honorary degrees and distinctions, but undoubtedly the most important was the Nobel Prize for Physiology or Medicine he received in 1906. To describe the work of Cajal is a rather difficult task, because, unlike other great scientists, he is not known for one single discovery, but rather for his many and important contributions to our knowledge of the organization of the nervous system. Those readers interested in his life would be wise to consult his autobiography (Cajal, 1917), where there is also a brief description of his main discoveries and theoretical ideas.

Figure 2: The village of Petilla de Aragón (Navarra, Spain) and the house where Cajal was born. Photographs taken in 2001, kindly supplied by Dr Pedro Uhalte.

The detailed study of the nervous system began in the middle of the nineteenth century. Before Cajal's discoveries, very little was known about the individual elements of the nervous system, and the connections between its different parts were purely speculative. The origin of nerve fibers was a mystery, and it was speculated that they arose from the gray matter independently of the nerve cells (neurons). This lack of knowledge was mainly due to the fact that appropriate methods for visualizing neurons were not available. The early methods of staining only permitted the visualization of neuronal cell bodies, a small portion of their proximal processes, and some isolated and rather poorly stained fibers. However, in 1873 the method of Camillo Golgi (1843-1926) was developed, and for the first time it was possible to observe neurons in their entirety in histological preparations: soma, dendrites and axon. Indeed, Golgi-stained neurons displayed the most exquisite morphological details, which ultimately led to their characterization and classification, as well as to the study of their possible connections. In 1906 Golgi was awarded the Nobel Prize for Physiology or Medicine for discovering this technique, and Cajal shared this Nobel Prize for his masterful interpretations of the Golgi preparations he had prepared.

Unlike other scientists of his era, Cajal's scientific career did not commence under the direction of a more senior distinguished scientist, but rather he became a prominent neurohistologist of his own making. For practical purposes, we can divide the career of Cajal into three major phases (DeFelipe and Jones, 1991).

The first phase extended from 1877 to 1887, the point at which he was introduced to the Golgi method. During this period he published a variety of histological and microbiological studies (Figure 3), but none was of great significance.

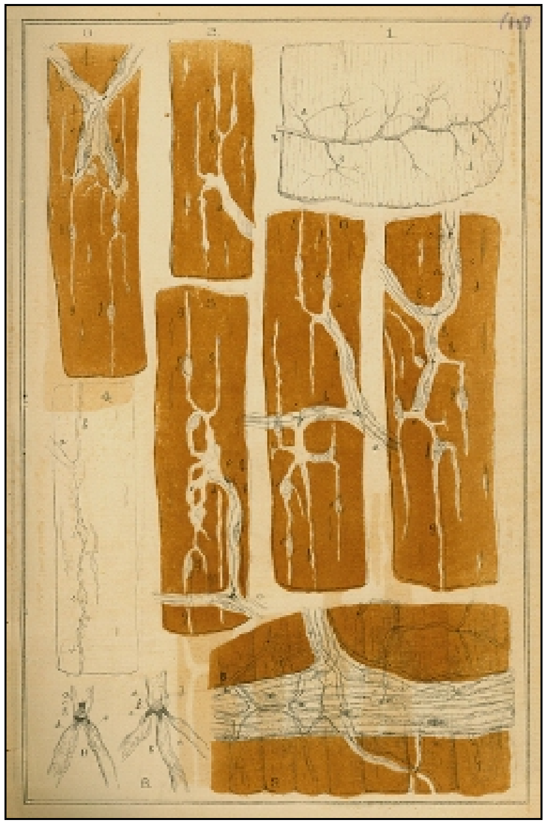

Figure 3: Drawing by Cajal showing nerve terminations in frog muscles, published in 1881 (Estudios anatómicos. Observaciones microscópicas sobre las terminaciones nerviosas en los músculos voluntarios. Zaragoza: El diario católico).

The second phase (1887-1903) was characterized by a very productive period of research activity, in which he exploited the Golgi method (Figure 4), describing almost every part of the central nervous system in great detail.

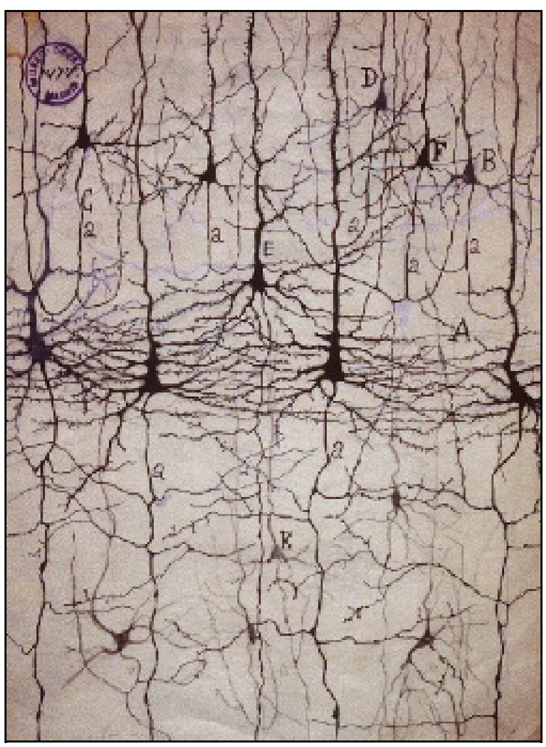

Figure 4: Drawing by Cajal showing Golgi impregnated neurons of the cat visual cortex published in 1921 (Textura de la corteza visual del gato. *Archivos de Neurobiología* 2: 338-368). From the

collection of original drawings housed in the Museo Cajal (Cajal Museum).

Cajal was introduced in 1887 to the Golgi method during a visit to the private laboratory, in Valencia, of the well-known psychiatrist and neurologist Luis Simarro. Cajal was so impressed by the beautiful and complete staining of neurons that he made a radical change in his scientific career (see Favorite Sentences, nos. 1 and 3). His descriptions of the nervous system based on his observations using the Golgi method were so accurate that his classic book Histologie (Cajal, 1909, 1911), in which these studies are summarized, is still a reference book in all neuroscience laboratories. Also, during the first few years of this phase of his life, Cajal found much evidence in favor of the 'Neuron Doctrine', which contrasted with the other more commonly accepted principle of the 'Reticular Theory'. The 'Neuron Doctrine', which now forms the fundamental organizational and functional principle of the nervous system, states that the neuron is the anatomical, physiological, genetic and metabolic unit of the nervous system. In contrast, the 'Reticular Theory' suggested that the nervous system consisted of a diffuse nerve network formed by the anastomosing branches of nerve cell processes (either both dendritic and axonal, or only axonal), with the cell somata principally playing a role in nourishment (for reviews, see Shepherd, 1991; Jones, 1994).

The third phase of Cajal's career began in 1903 with his discovery of the reduced silver nitrate method, and ended with his death in 1934. This period was also very productive and was devoted mainly to the theme of traumatic degeneration and regeneration of the nervous system (Figure 5).

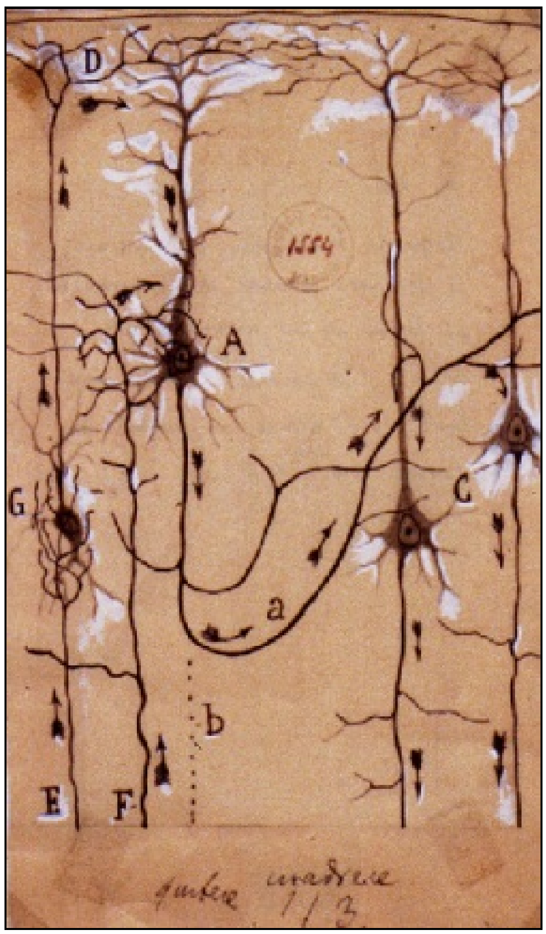

Figure 5: Schematic drawing of Cajal showing "the flow of currents in a mutilated pyramidal cell (A) furnished with hypertrophic recurrent collaterals", published in 1914 (*Estudios sobre la degeneración y regeneración del sistema nervioso*, Vol. 2. Madrid: Moya). From the collection of original drawings housed in the Museo Cajal (Cajal Museum).

He published numerous scientific papers about this subject that were of great relevance, and that were summarized in another classic book, Degeneration and Regeneration (Cajal, 1913-1914). During this phase of his life, Cajal also published some important papers on the structure of the retina and optic centers of invertebrates.

Interestingly, Golgi, as well as most neurologists, neuroanatomists and neurohistologists of that time, was a fervent believer in the 'Reticular Theory of Nerve Continuity'. However, for Cajal the 'Neuron Doctrine' was crystal clear. Nevertheless, microphotography was not well developed at that time, and virtually the only way to illustrate observations was by means of drawings, which were open to skepticism (DeFelipe and Jones, 1992). Some of Cajal's drawings were considered as artistic interpretations rather than accurate copies of his preparations. However, examination of Cajal's preparations, housed in the Cajal Museum at the Cajal Institute in Madrid (Figure 6), pays testament to the accuracy of his drawings (DeFelipe and Jones, 1988, 1992).

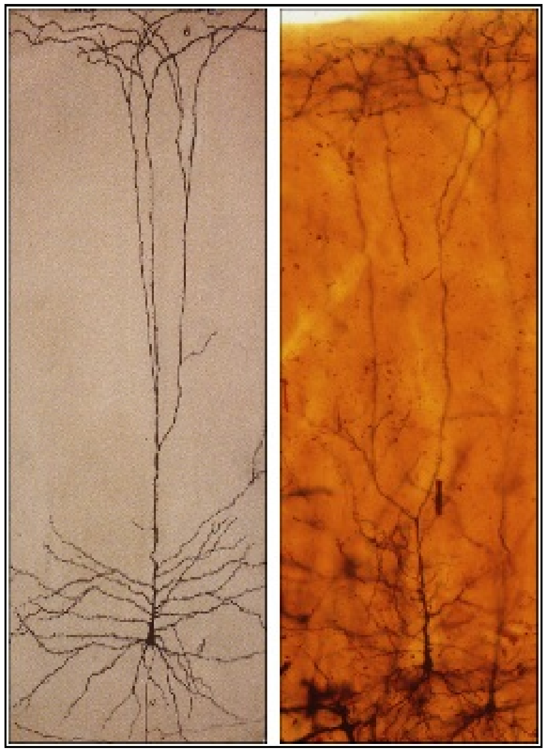

Figure 6: Left, drawing by Cajal illustrating a Golgi-impregnated pyramidal neuron of the postcentral gyrus of a child published in 1899 (Estudios sobre la corteza cerebral humana. II: Estructura de la corteza motriz del hombre y mamíferos superiores. *Revista Trimestral Micrográfica* 4: 117-200). Right, Photomicrograph from one of Cajal's Golgi preparations of the postcentral gyrus of a child showing a labeled pyramidal cell similar to the one shown in the left panel (from the collection of histological preparations housed in the Museo Cajal; published by DeFelipe and Jones, *Cajal on the Cerebral Cortex.* New York: Oxford University Press, 1988).

Another interesting example of Cajal's astuteness can be seen in his interpretation of the microscopic images that led to the discovery of dendritic spines (Figure 7).

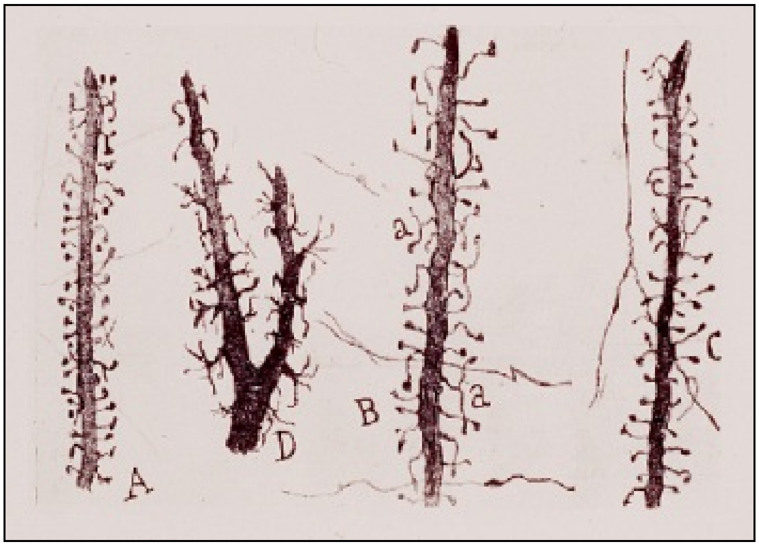

Figure 7: Drawing from Cajal illustrating types of dendritic spines published in 1933 (¿Neuronismo o reticularismo? Las pruebas objetivas de la unidad anatómica de las células nerviosas. *Archivos de Neurobiología* 13: 1-144). "Types of collateral spines of cerebral pyramids. A, rabbit; B, child of two months; C, spines of a one-month-old cat (visual region); D, portion of a dendrite of a spinal motor neuron of a cat in a phase before end feet are formed."

There were two different views at the time but for Cajal these structures represented fundamental components of spiny neurons. However, some authors (including Golgi himself) interpreted the spines as artifacts produced by the Golgi method: "a superficial precipitate, like a crystallization of needles, fortuitously deposited on the dendritic surface". As a result, the latter authors did not include spines in their drawings. Cajal explored different methods of staining to demonstrate that the dendritic spines were real morphological dispositions. Using the methylene blue method, he showed that the dendritic surfaces of pyramidal cells were covered with spines (Figure 8), thereby demonstrating that they were not artifacts of the Golgi method. Although Cajal had the same microscopes and produced similar histological preparations with comparable quality of staining as the majority of the neurohistologists of his time, he saw differently than they did.

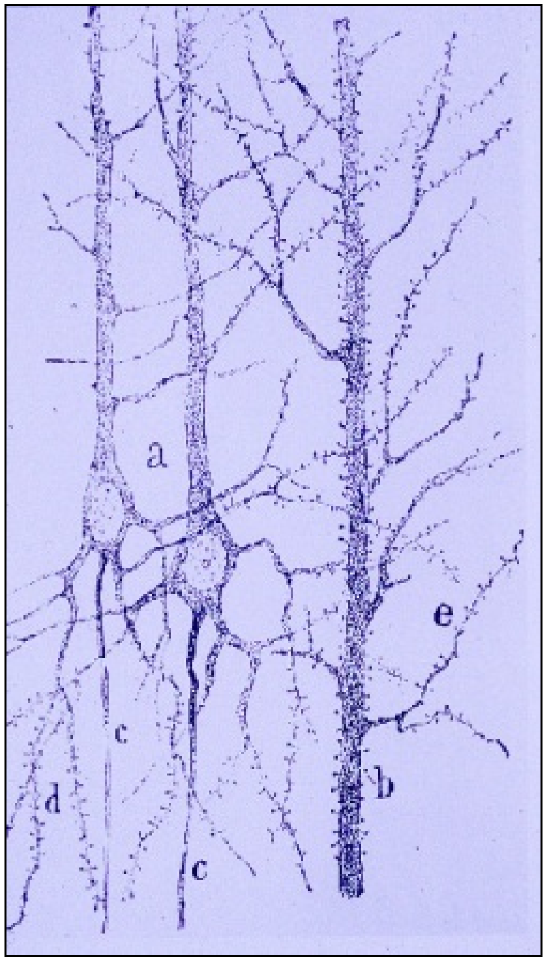

Figure 8: Drawing of Cajal published in 1896 from the collection of original drawings housed in the Museo Cajal (Las espinas colaterales de las células del cerebro teñidas con el azul de metileno. *Revista Trimestral Micrográfica* 1: 123-136). In the drawing the dendritic spines of pyramidal cells can be stained with methylene blue (method of Ehrlich modified by Cajal; this drawing has been pseudo-colored in blue).

Therein lies the genius of Cajal.

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Favorite sentences

1. Cajal said of the Golgi method:

"I expressed in former paragraphs the surprise which I experienced upon seeing with my own eyes the wonderful revelatory powers of the chrome-silver reaction and the absence of any excitement in the scientific world aroused by its discovery. How can one explain such strange indifference? Today, when I am better acquainted with the psychology of scientific men, I find it very natural … Out of respect for the master, no pupil is wont to use methods of investigation which he has not learned from him. As for the great investigators, they would consider themselves dishonoured if they worked with the methods of others."

Recuerdos de mi vida, Vol. 2, Historia de mi labor científica. Madrid: Moya, 1917, p. 76.

2. Differences between the brain of humans and nonhuman mammals:

"The opinion generally accepted at that time that the differences between the brain of [nonhuman] mammals (cat, dog, monkey, etc) and that of man are only quantitative, seemed to me unlikely and even a little offensive to the human dignity … But do not articulate language, the capability of abstraction, the ability to create concepts, and, finally, the art of inventing ingenious instrument … seem to indicate (even admitting fundamental structural correspondences with the animals) the existence of original resources, of something qualitatively new which justify the psychological nobility of *homo sapiens*? … My investigations showed that the functional superiority of the human brain is intimately bound up with the prodigious abundance and unusual wealth of forms of the so-called neurons with short axon."

Recuerdos de mi vida, Vol. 2, Historia de mi labor científica. Madrid: Moya, 1917, pp. 345-346, 350.

3. The cerebral cortex and pyramidal cells:

"the cerebral cortex is similar to a garden filled with trees, the pyramidal cells, which, thanks to intelligent culture, can multiply their branches, sending their roots deeper and producing more and more varied and exquisite flowers and fruits."

The Cronian Lecture: La fine structure des centres nerveux. *Proceedings of the Royal Society of*

London 55: 444-468, 1984. Translated by DeFelipe and Jones, *Cajal on the Cerebral Cortex*. New York: Oxford University Press, 1988, p. 87.

4. Plasticity:

"Cerebral gymnastics are not capable of improving the organization of the brain by increasing the number of cells, because it is known that the nerve cells after the embryonic period have lost the property of proliferation; but it can be admitted as very probable that mental exercise leads to a greater development of the dendritic apparatus and of the system of axonal collaterals in the most utilized cerebral regions. In this way, associations already established among certain groups of cells would be notably reinforced by means of the multiplication of the small terminal branches of the dendritic appendages and axonal collaterals; but, in addition, completely new intercellular connections could be established thanks to the new formation of [axonal] collaterals and dendrites."

The Cronian Lecture: La fine structure des centres nerveux. *Proceedings of the Royal Society of London* 55: 444-468, 1984. Translated by DeFelipe and Jones, *Cajal on the Cerebral Cortex*. New York: Oxford University Press, 1988, p. 87.