CAJAL'S BUTTERFLIES OF THE SOUL

SCIENCE AND ART

Javier DeFelipe

OXFORD

Cajal's Butterflies of the Soul

There can be no doubt, only artists are attracted to science [. . .]. I owe what I am today to my boyhood artistic hobbies, which my father opposed fiercely. To date, I must have done over 12,000 drawings. For a profane man they are strange drawings, the details of which are measured in thousandths of a millimetre although they reveal mysterious worlds emanating from the architecture of the brain. . .

Santiago Ramón y Cajal, 1900[*]

* Cajal at the age of 42 years. This paragraph was taken from an interview given by Cajal to a journalist in 1900 (María de los Ángeles Ramón y Cajal Junquera; *Cajal, Artista*, in *Paisajes Neuronales. Homenaje a Santiago Ramón y Cajal*. Madrid: CSIC, 2007).

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For my wife Alicia and my daughter Alicia

To know the brain—we said to ourselves in our idealistic enthusiasm—is equivalent to discover the material course of thought and will. [. . .] Like the entomologist hunting for brightly coloured butterflies, my attention was drawn to the flower garden of the grey matter, which contained cells with delicate and elegant forms, the mysterious *butterflies of the soul*, the beating of whose wings may some day (who knows?) clarify the secret of mental life. [. . .] Even from the aesthetic point of view, the nervous tissue contains the most charming attractions. In our parks are there any trees more elegant and luxurious than the Purkinje cells from the cerebellum or the *psychic cell*, that is the famous cerebral pyramid?

Santiago Ramón y Cajal,
Recuerdos de Mi Vida

FOREWORD: CSIC

On January 11, 1907, Amalio Gimeno (Minister for Public Instruction and Fine Arts) created the Council for Extension of Studies and Scientific Research by ministerial decree ("Junta para Ampliación de Estudios e Investigaciones Científicas," or JAE). This institution was created to end Spain's cultural and educational isolation and in an attempt to bring Spain up to the level of the most advanced European countries at the time. For this ambitious project to succeed, it was felt that the JAE must be presided over by the most relevant scientists. Hence, it was evident that Santiago Ramón y Cajal should be appointed as the first president of the JAE, with the collaboration of José Castillejo as its Secretary. The scientific and cultural program implemented by the JAE represented the most innovative project in Spain between 1907 and 1939, involving the creation of laboratories and research centers, awarding scholarships to study abroad, etc. In addition, it also brought leading Spanish thinkers and scientists into contact with those in other countries and continents, thereby opening up a new way of bringing people together through science and culture. The JAE pursued various goals, such as enabling students to undertake their higher studies in Spain and abroad, sending delegations to scientific conferences, establishing an overseas information and international relations service on issues concerning teaching, promoting scientific research, and protecting educational establishments involved in secondary and higher education. However, in the midst of the Spanish Civil War, on May 19, 1938, the JAE was shut down, its laboratories and centers were closed, and many of its scientists fled to exile. In 1939, Franco's newly installed regime created the Spanish National Research Council ("Consejo Superior de Investigaciones Científicas," or CSIC) in the JAE's laboratories, premises, and centers. The CSIC was presided over by the Minister for Education, José Ibáñez Martín, with the close collaboration of José María Albareda, who was appointed Secretary General of the CSIC. The law passed on November 24, 1939 to create the CSIC established that "all the centres belonging to the dissolved Council for the Extension of Studies and Scientific Research (JAE), the Foundation for Scientific Research and Reform Trials, and those created by the Spanish Institute, would become part of the Spanish National Research Council."

We are very proud that Cajal, whom we truly consider to be our first President, is now considered the father of modern neuroscience and that he serves as an example for young scientists through his many teachings and scholarly approach to the study of the most enigmatic and attractive organ in the human being, the brain. Thus, it is with great pleasure that we participate in the production of this marvellous book, not only because it represents an excellent opportunity to commemorate the figure of Cajal but also because this book contains a fantastic collection of old illustrations. We are confident that these amazing drawings will serve as both an inexhaustible source for artistic inspiration in general and as a way to divulge and increase the interest in research into the nervous system.

Rafael Rodrigo
President of the CSIC
Madrid, May 2009

FOREWORD: UPM

The Universidad Politécnica de Madrid (UPM; Technical University of Madrid) is the oldest and largest of the Spanish technical universities, covering most of engineering and architecture disciplines. Most of its schools are over 100 years old, dating back to the eighteenth and nineteenth centuries, and they existed independently until they were grouped together as the UPM in 1971. Hence, it is no exaggeration that much of the history of Spanish technology for over 150 years has been written by the Schools of Architecture and Engineering of this university, as for many years some of them were the only technical schools in existence in their fields in Spain. Indeed, many of the leading Spanish educators and researchers have been involved with the UPM either as students, teachers, or both.

Recently, the UPM has opened new avenues for research, which include expanding our particular interest in neuroscience, since unravelling the complexity of the brain from all possible scientific angles (morphological, genetic, molecular, physiological, and computational) represents the most ambitious and major challenge in science for many years. We think that an important starting point has been the implication of the UPM in the Blue Brain Project, which represents the first comprehensive, worldwide effort to reverse engineer the structure and function of the brain's components. The main aim of this project is to better understand the normal function and dysfunction of the brain through detailed simulations. The participation of Spain in this project constitutes the so-called Cajal Blue Brain, which involves several research groups belonging to various public research institutions.

The Cajal Blue Brain project was born with the idea of combining our expertise, long tradition, and resources in informatics and computational sciences with the excellent Spanish tradition in the field of the neuroanatomy that dates from Santiago Ramón y Cajal. Indeed, thanks to the school and the pioneering work of Cajal, renowned scientists and professionals have travelled worldwide and contributed to the remarkable advances in neurobiology. Thus, we would not only like to promote this research but to go a step further, embarking on the first large-scale attempt to unravel the complexity of the cerebral cortex at nanometer resolution through a multidisciplinary approach and employing new techniques. The development of these methods will open up new horizons and opportunities to examine the nervous system in general, both in health and disease, at a level of detail never reached before. Therefore, we are very pleased to participate in the production of this gorgeous book, not only as a tribute to Cajal but also as a further expression of our interest in developing new perspectives and tools to bridge neurobiology and computational neuroscience.

Javier Uceda
President of the Universidad Politécnica of Madrid
Madrid, May 2009

FOREWORD: FUNDACIÓN CIEN

The *Fundación Centro de Investigación de Enfermedades Neurológicas* (*Fundación CIEN*; "Neurological Diseases Research Center Foundation") is a public institution in Spain supervised and coordinated by the *Instituto de Salud Carlos III*, a public research institution that pertains to the Ministry of Science and Innovation. The *Fundación CIEN* was created to endorse and organize a research network that supports, promotes, and coordinates research in all fields of neuroscience, including basic, clinical, and epidemiological issues, paying special attention to problems related to diseases of the nervous system. It is organized in such a way that research teams distributed across Spain are coordinated into scientific groups working on different areas of the neurosciences in order to not only share ideas and techniques but also the facilities provided by the *Fundación CIEN*. The foundation also manages the Center for Neurodegenerative Diseases within the Biomedical Research Network, which includes 63 research groups in Spain and around 800 investigators. In addition, it manages the Alzheimer's Project Research Unit, which is part of a new hospital dedicated primarily to the care of patients with Alzheimer disease.

Diseases of the brain affect the whole spectrum of society, with potentially devastating psychiatric and neurological consequences. The increase in age of our society is accompanied by an increase in the risk of developing brain diseases such as Alzheimer disease. Indeed, this disease is close to being considered a true worldwide pandemic problem. Vast resources have been invested around the world to fight this condition, such as the creation of the *Fundación CIEN*, although this still appears to be insufficient given the magnitude of the problem. Unfortunately, our society is not fully aware of the importance of studying the brain, perhaps due to the small amount of scientific information that reaches the general public in an effective manner. Thus, another important objective of the foundation is related to teaching and informing the public on issues related to neurological sciences. This wonderful book, where neuroscience and art are fused, represents a magnificent opportunity to bring the mysterious world of the brain to the general public. The work not only contains a beautiful collection of old drawings, but it also includes introductory information that will give readers unfamiliar with the nervous system a better understanding of the importance of the scientific illustrations produced in the early days of research into the nervous system. As a consequence, we decided to collaborate and to help make this project a reality from the very moment we became aware of the book. Furthermore, the book represents another good excuse to pay tribute to the father of modern neuroscience, Santiago Ramón y Cajal. Indeed, one of Cajal's masterpieces, his book *Estudios Sobre la Degeneración y Regeneración del sistema nervioso* (1913–1914), represented a major starting point in the battle against brain diseases. Thus, the *Fundacion CIEN* enthusiastically supports this book, since it represents an excellent tool to draw society's attention to the problems of the nervous system. We are confident that readers will be captivated by the beautiful illustrations in the book

and that this will aid their introduction to the brain's complex neuronal jungle. No doubt, our society, and the scientific community in particular, must make an effort to better understand the brain in health and disease. Such efforts are not only motivated by the fact that the brain represents the essence of our humanity but also because it is the root of many frightful diseases for which we presently do not have a satisfactory solution. We hope that this book may serve to strengthen our resolve in the fight against brain diseases.

Julián Pérez
Managing Director of the Fundación CIEN
(Instituto Salud Carlos III)
Madrid, May 2009

PREFACE

Once upon a time, the scientists who studied the microscopic world of the nervous system had to be true artists in order to communicate their observations. Indeed, if we go back to the nineteenth century, when the detailed analysis of the nervous system began, microphotography was not a well-developed technique. As a consequence, most scientific figures presented by the early neuroanatomists were their own drawings, providing a valuable "pretext" for those scientists to express and develop their artistic talent. Of course, the scientists did not reproduce the entire field of the histological preparations they observed through the microscope, but rather, they only illustrated those elements they thought were important for what they wanted to describe. As such, these illustrations were not necessarily free of technical errors and they may have been subject to the scientists' own interpretations, at times hindering their acceptance by their fellow scientists. Nevertheless, this interpretation of the image also represented an interesting source of artistic creativity. During this period the exchange of information between scientists was difficult, not least because some of these drawings were considered to be essentially artistic interpretations rather than accurate copies of the histological preparations. Indeed, this issue also makes it difficult for us to interpret some of these figures today. As a result, this period of scientific "art" and skepticism constitutes a fascinating page in the history of neuroscience. In the present book, we have included a total of 339 figures, most of which date from 1859 to 1932 and represent some characteristic examples of this golden era for artistic creativity in neuroscience.

It should be noted that the illustrations included in this book represent only a small sample of the thousands of figures that were produced during this period. Indeed, each time I discovered a beautiful figure, as if unearthing a hidden treasure, the feeling of joy that came over me was mixed with a sense of frustration . . . how many beautiful pictures had I still yet to see! Of course, I have not been able to go through all the articles and books of the time, yet perhaps this book will encourage other scientists to continue this quest for the hidden beauty in the neural forests once created by our old masters, many of which have been lost in our memory with the passing of time. In addition, only selected figures have been included due to space limitations and this selection reflects my own interests, which may not be fully shared by other readers. Nevertheless, I think this book will be of general interest, not only due to the captivating aesthetic appeal of the illustrations but also because they represent the bases of our current understanding of the nervous system. Indeed, in the words of Santiago Ramón y Cajal (1852–1934, **Fig. P-1**), in most cases they are "pieces of reality":

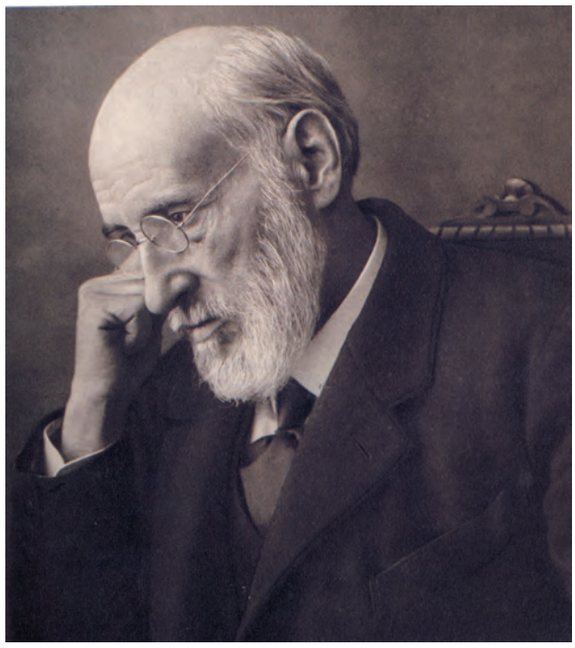

FIGURE P-1. Santiago Ramón y Cajal (1852–1934), 1920. Taken from Santarén JF (2006) Cronología 1852–1934. In *Santiago Ramón y Cajal. Premio Nobel 1906,* ed. J. F. Santarén. Madrid: Sociedad Estatal de Conmemoraciones Culturales.

> A good drawing, like a good microscope preparation, is a fragment of reality, scientific documents that indefinitely maintain their value and whose study will always be useful, whatever interpretation they might inspire.
>
> *Santiago Ramón y Cajal, 1899*

Fernando de Castro (1896–1967) (**Fig. P-2**), one of the most prominent disciples of Cajal, commented: "Science becomes art through the drawings of Cajal." Looking at the illustrations in this book, the readers will not only marvel at Cajal's drawings but will also find that many of the other early researchers that studied the nervous system were also true artists, of considerable talent and aesthetic sensibility.

These artistic skills were also shared by de Castro and Pío del Río-Hortega (1882–1945, **Fig. P-2**), as well as by other famous disciples of Cajal and many other important pioneers in neuroscience, including Deiters, Kölliker, Meynert, Ranvier, Golgi, Retzius, Dogiel, and Alzheimer (**Fig. P-3**). Indeed, I was impressed by the wonderful, mostly unknown drawings of de Castro and del Río-Hortega. It is for this reason that I have included numerous drawings by these two great scientists and artists. The reader will find that many of the illustrations can be considered to belong to different artistic movements, such as modernism, surrealism, cubism, abstraction, or impressionism. Indeed, these illustrations may also provide artists with a source of inspiration since they reveal a fantastic and virtually unknown world of forms, a microuniverse with an aura of mystery. The coming together of the fields of art and science was beautifully explained by Cajal in an interview given by him to a journalist in 1900 (María de los Ángeles Ramón y Cajal Junquera; *Cajal, Artista*, in *Paisajes Neuronales. Homenaje a Santiago Ramón y Cajal*, Madrid: CSIC, 2007):

> There can be no doubt, only artists are attracted to science [. . .]. For a profane man they are strange drawings, the details of which are measured in thousandths of a millimetre although they reveal mysterious worlds emanating from the architecture of the brain . . .

Another interesting aspect of the book is that many of the illustrations are virtually unknown to both young neuroscientists and to the general public alike. Indeed, the books and journals where these figures were originally published are frequently very hard to find or of limited access, making the present book all the more attractive. I would like to caution the reader that I have restrained from attempting to explain these figures in detail (with a few exceptions), as they cover many diverse fields of neuroscience. Instead, each image is accompanied with a title based on the description given by the original author, and I have identified its source to enable the readers interested in a particular figure to satisfy their curiosity regarding the significance of these early figures. The original labeling used to describe the illustrations has been preserved and, where possible, so have the original descriptions. Many of these figures have been retouched and restored in order to remove stains, wrinkles, or

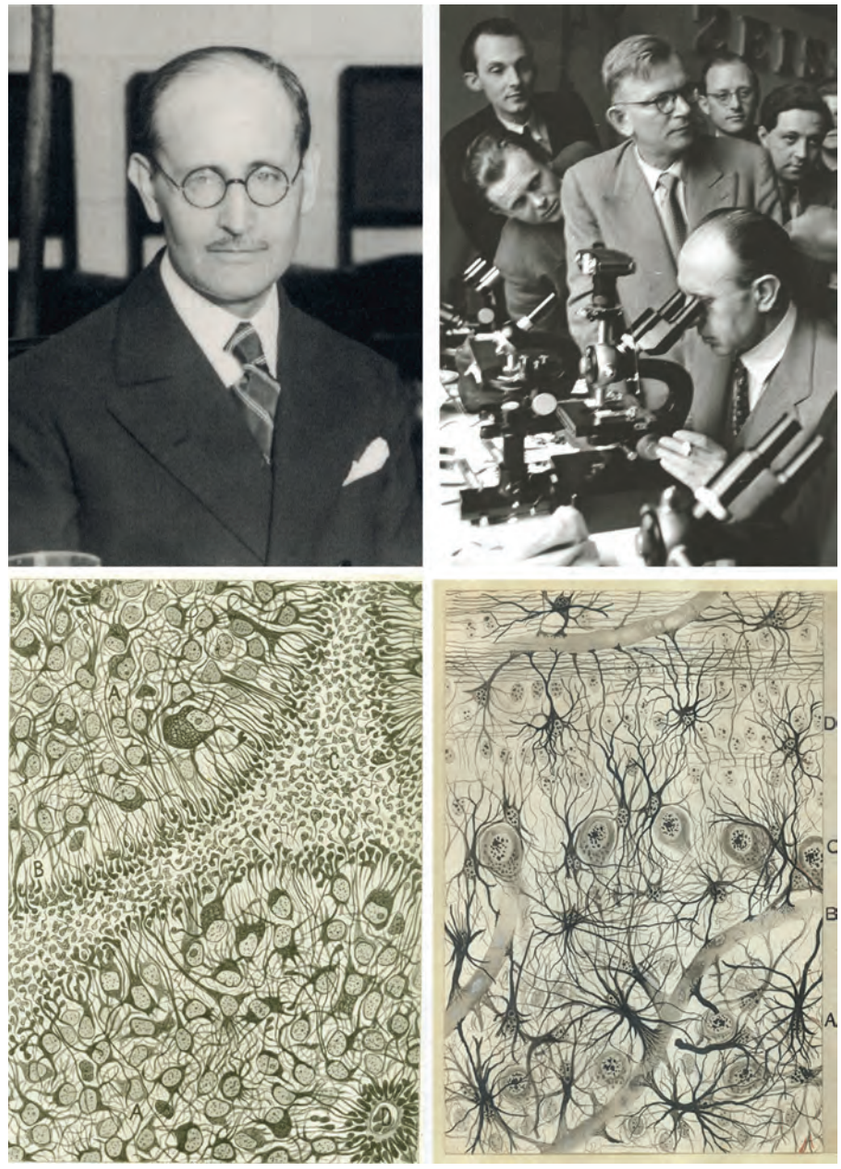

FIGURE P-2. (*Left*) Pío del Río-Hortega (1882–1945). (*Right*) Fernando de Castro (1896–1967), looking through the microscope at the Congress of Wiesbaden held in 1950 (Archivo Fernando de Castro). *Drawings*: *(left)* Del Río-Hortega (1922), (*right*) de Castro (1920). Del Río-Hortega P (1922) Constitución histológica de la glándula pineal. I. Células Parenquimatosas. In *Libro en honor de D. Santiago Ramón y Cajal,* Vol 1. Madrid: Jiménez y Molina, pp 315–359; de Castro F (1920) Estudios sobre la neuroglia de la corteza cerebral del hombre y de los animales. I. La arquitectonia neuróglica y vascular del bulbo olfativo. *Trab. Lab. Invest. Biol. Univ. Madrid* 18, 1–35.

FIGURE P-3. (*Top left*) From left to right, first row: Giulio Bizzozero (1846–1901) and Camillo Golgi (1843–1926); second row, Edoardo Perroncito (1847–1936), Rudolf Albert von Kölliker (1817–1905), and Romeo Fusari (1857–1919). Courtesy of Paolo Mazzarello, University Pavia. (*Top right*) Magnus Gustaf Retzius (1842–1919) (Legado Cajal). *Drawings* (from left to right and up to down): Taken from Retzius G (1891) Zur Kenntniss des centralen Nervensystems der Crustaceen. *Biol. Untersuch. Neue Folge* 1, 1–50; Golgi C (1882–1883) Sulla fina anatomia degli organi centrali del sistema nervoso. *Riv. Sper. Freniat. Med. Leg.* Reprinted in *Opera Omnia,* Vol I. *Istologia Normale*, Chapter 16. Milano: Ulrico Hoepli, 1903; Fusari R (1887) Untersuchungen über die feinere Anatomie des Gehimes des Teleostier. *Internat. Mschr. Anat. Physiol*. 4, 275–300; Kölliker A von (1893) *Handbuch der Gewebelehre des Menschen,* Vol II. *Nervensystem des Menschen und der Thiere*. Leipzig: Engelmann; Retzius G (1894) Die Neuroglia des Gehirns beim Menschen und bei Säugethieren. *Biol. Untersuch. Neue Folge* 6, 1–28; Retzius G (1891) Zur Kenntniss des centralen Nervensystems der Würmer. *Biol. Untersuch. Neue Folge* 2, 1–28.

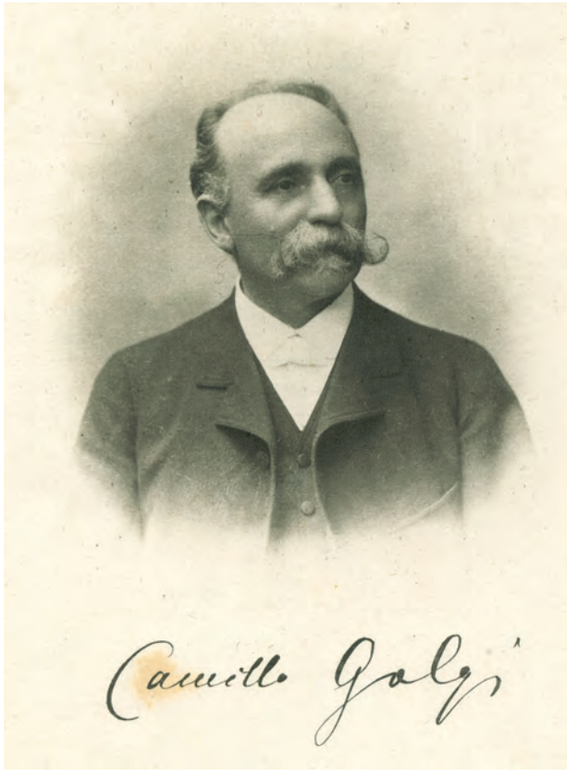

FIGURE P-4. Camillo Golgi (1843–1926). Taken from Golgi, C. *Opera Omnia*. Milano: Ulrico Hoepli, 1903.

other artifacts, and some of them are reproduced from original drawings.

The book has been divided into two Parts, Part I and II, the latter containing the main body of the work. Part I contains introductory information, including a general description of neurons and glia that will give readers unfamiliar with the nervous system a better understanding of the importance of the scientific illustrations produced in those days. This part also contains a section that refers to the methods used and the issues surrounding the interpretation of microscopic images through drawings in that period. However, the main section in Part I is titled "A Sketch History of the Microscopic Anatomy of the Nervous System," and this chapter has been divided into three sections that serve as an introduction to the three subdivisions established in Part II.

The second part of the book, Part II, contains the collection of 288 figures with the intention of transforming the reader into an observer. These illustrations have been divided into three main categories: Section 1, The Benedictine Period: The Early Days; Section 2, The Black Period: Neurons, Glia, and the Organization of the Nervous System; and Section 3, The Colorful Period: Internal Structure and Chemistry of the Cells. These titles are explained in Part I. Section 1 includes early figures of the nervous system before the discovery of the "*reazione nera*" (black reaction) by Camillo Golgi (1843–1926, **Fig. P-4**). In the hands of Cajal, this technique represented the principal tool that was to change the course of the history of neuroscience, signifying the birth of modern neuroscience. Section 2 is related to the Golgi method and other techniques used to analyze the morphology of neurons and glia, as well as the microanatomy, organization, and meaning of different regions of the nervous system (e.g., the pattern of connections between neurons, and the relationship between neurons and glia). The techniques to visualize the peripheral terminals of afferent and efferent nerve fibers are also included here. Indeed, some of these images show the structure and micro-organization of the nervous system as true maps, identifying the routes followed by nerve impulses through the intricate neural forest of the brain. Section 3 is mainly concerned with the internal structure of the cell body of neurons and glia revealed by a variety of staining procedures to visualize the nucleus and nucleolus, as well as the organelles present in the perikaryon. The first set of illustrations are not necessarily the oldest figures because, despite the years that passed since Golgi published this method in 1873, it was still not a commonly used technique when Cajal initiated his studies of Golgi-stained material in 1888. The second and the third sets of illustrations mostly coincide in time. Moreover, these illustrations not only deal with the normal nervous system but also with the alterations observed in the naturally diseased nervous system (e.g., Alzheimer disease), or after infection, trauma, and exposure to other external factors.

Many figures and particularly those dealing with the internal structure of the neuron also illustrate the response of neurons when experimental animals are manipulated in some way (e.g., their response to injury, electrical stimulation, or the toxic effects of chemical substances). The text included in Sections 1 and 2 of Part I are mainly based on articles on the history of the neuron, and they refer to the scientific atmosphere in Cajal's times. These articles were either published by myself (some of them in Spanish), or they were prepared in collaboration with Edward G. Jones. In addition, Section 3 not only deals with the early methods to selectively label the internal structure of the neurons or different histological aspects of the nervous system (in different colors), but it also contains a summary of how "multicolor microscopy" has evolved to date.

In producing this book, I am very grateful to the members of my laboratory: Lidia Alonso-Nanclares, Lidia Blázquez-Llorca, Ruth Benavides-Piccione, Isabel Fernaud, Ana García, Virginia García-Marín, Juncal González, Asta Kastanauskaite, Shira Knafo, Ángel Merchán, Paula Merino, Miguel Miguens, Alberto Muñoz, and José Rodrigo-Rodríguez, for their comments on the structure of the book and the figures, for their support, and for maintaining the laboratory at work while I was occupied in the preparation of the book. I would like to especially thank Ruth Benavides-Piccione and Alberto Muñoz for their criticisms on the text, and Ana Garcia for helping me with the scanning of the original drawings and in preparing the figure legends. The retouching of the images was largely done by myself, with much assistance from Roberto Rives.

I am deeply indebted to the publishers and the other organizations that have offered their support in producing this book: Oxford University Press, CSIC, Universidad Politécnica of Madrid, and Fundación CIEN /Instituto de Salud Carlos III. I would also like to express my gratitude to Mark Sefton for his editorial assistance and to María de los Ángeles Langa, librarian at the Instituto Cajal, for her help in obtaining some of the very inaccessible books and articles from which I obtained many of the figures presented here. I am also grateful to the granddaughters of Cajal, María de los Ángeles Ramón y Cajal Junquera and Silvia Cañadas, and to the son and grandson of Fernando de Castro, Fernando-Guillermo de Castro Fernández and Fernando de Castro Soubriet, respectively, for allowing us to use some of Cajal's and de Castro's original drawings and pictures. I also wish to thank Inigo Azcoitia, Ruth Benavides-Piccione, Marina Bentivoglio, Miguel Freire, Pablo García, Virginia García-Marín, Laurence Garey, Asta Kastanauskaite, Antonio Martín-Araguz, Paolo Mazzarello, Alberto Muñoz, Jorge Larriva-Sahd, Jeff Lichtman, Constantino Sotelo, and Tamily Weissman for kindly supplying or preparing some of the figures included in the book. I would like to extend my gratitutde to Craig Allen Panner (Executive Editor, Neuroscience and Neurology of Oxford University Press), Rafael Rodrigo, Miguel Ángel Puig-Samper, and Jose Manuel Prieto (President, Chief Editor, and Director of the Department of Publications of the CSIC, respectively), Javier Uceda and Gonzalo León (President and Vice President for Research, of the Universidad Politécnica of Madrid, respectively), and Julián Pérez (Managing Director of the Fundación CIEN/Instituto Salud Carlos III) for their enthusiastic support and help of this project.

Javier DeFelipe
Madrid, April 2009

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PART I: INTRODUCTION

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BRAIN
A JOURNAL OF NEUROLOGY

BOOK REVIEW

Beautiful pictures

There is a rich history, now often overlooked, in the study of the microscopic appearance of cells in the brain and spinal cord. Before photo-microscopy was common, the appearance of tissue in dissection or under the microscope was usually drawn or painted. 'Cajal's Butterflies of the Soul', collated and edited by Javier DeFelipe, is a rich treasury of some of that work. The title derives from a quote from Santiago Ramon y Cajal describing nerve cells as having 'delicate and elegant forms, the butterflies of the soul'.

Some years ago on a visit to the medical school in Torino, I met and talked to Professor Mario Dianzani. He gave me a book published by Enrico Gravela (1989) on the life and work of Giulio Bizzozero, a contemporary of Camillo Golgi. The book contains 76 full colour plates showing the appearance of tissues under the microscope. The figures are copied from a series of much larger plates that were produced to help teach histology to the medical students. Most of the plates had long been forgotten. Professor Dianzani rescued some of them from the bottom of a stack of animal cages and helped to produce an elegant volume. The pictures in 'Cajal's Butterflies of the Soul' have not suffered such a degrading history. Javier DeFelipe has produced a beautiful book containing full colour reproductions of figures published over a period of about 80 years from the mid-19th century to 1932.

There are three sections: Benedictine, Black and Colourful periods. In his description of the early histological studies in which individual elements were isolated by dissection, Cajal (1989) wrote:

> The isolation of the elements was usually accomplished by means of needles upon slides, following maceration of the nervous feltwork in weak solutions of bichromate of potash. In the case of nerves, such a method produced very clear images, if, following the example of Ranvier, Schiefferdecker, Segall etc. it was combined with the impregnating action of silver nitrate or osmic acid – either before or afterwards, according to the circumstances. Applied, however to the analysis of ganglia, of the retina, of the spinal cord or of the brain, the delicate operation of freeing the cells from their matrix of cement substance and of disentangling and spreading out their branching processes with needles was an undertaking for a Benedictine.

Not all of the 12 figures from the Benedictine period were based on such laborious dissection. The first of these is a sepia figure of the rabbit hippocampus, from an inaugural dissertation of Kupffer's, dating from 1859. The final figure in the section shows one of Ranvier's 1878 drawings of nerve fibres. The language of the captions reflects the times in which they were written. The caption for Kupffer's figure is in Latin. The final figure in the group, by Ranvier, has a French caption. The captions for the other 10 figures in this section are in German. Figure 6 is a drawing by Deiters of a motor neuron dissected from the grey matter of the spinal cord. It is beautiful. All of the parts are there: a nucleus with a nucleolus within it, a rich spread of dendrites and a single axon emerging from the cell body. Figure 12 is Ranvier's drawing of degenerating axons from several birds and mammals, most having been dissected along their length. Figure 11 shows a section of the cerebellar cortex by Denissenko, published in 1877. The cellular elements are present, but the true organization is not revealed. Comparing this figure with Figure 37, which Cajal published in 1904, shows the magnificent improvement in clarity and detail offered by the Golgi stain. Cajal's figure informed many of the later physiological studies of the cerebellum by Eccles and his collaborators.

Biology in general, and neuroscience in particular, recognizes many heroes of the past for their great contributions to knowledge. Perhaps there should be alternative recognition of those who, either by example or bad advice, dispatched people into a different field from the career path that they had initially planned. Alexander Monro III, whose grandfather and father had previously held the chair of Anatomy at the University of Edinburgh was, by all accounts, of a lesser stature than his forebears. We are, however, deeply indebted to Monro tertius since Charles Darwin left medical school, driven out in good part by the dreariness of Monro's anatomy lectures. Cajal's career was similarly influenced by another person. From his autobiography, it is clear that Cajal must have been a gifted artist as a child. He tells us that as a

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young boy he planned to pursue a career in art. His father was obviously sceptical, but he took young Santiago's work for an opinion from the best he could find as a local expert. Cajal wrote (1989):

> As there was no one in the town sufficiently qualified as critic of drawing, the author of my days turned to a certain plasterer and decorator from somewhere else who arrived at the time in Ayerbe, where the chapter had engaged him to whitewash and paint the walls of the church. Cajal's father asked: ''but does the boy really show no aptitude for art?'' . . . ''None my friend replied the wall scraper . . .''.

Two great scientists were directed away from alternative careers by a bad lecturer and a superficial wall painter. DeFelipe's book is valuable in that it details a much more positive influence on Cajal; that of Don Luis Simmaro, a psychiatrist who was experimenting with the then new staining technique of Camillo Golgi. Cajal wrote:

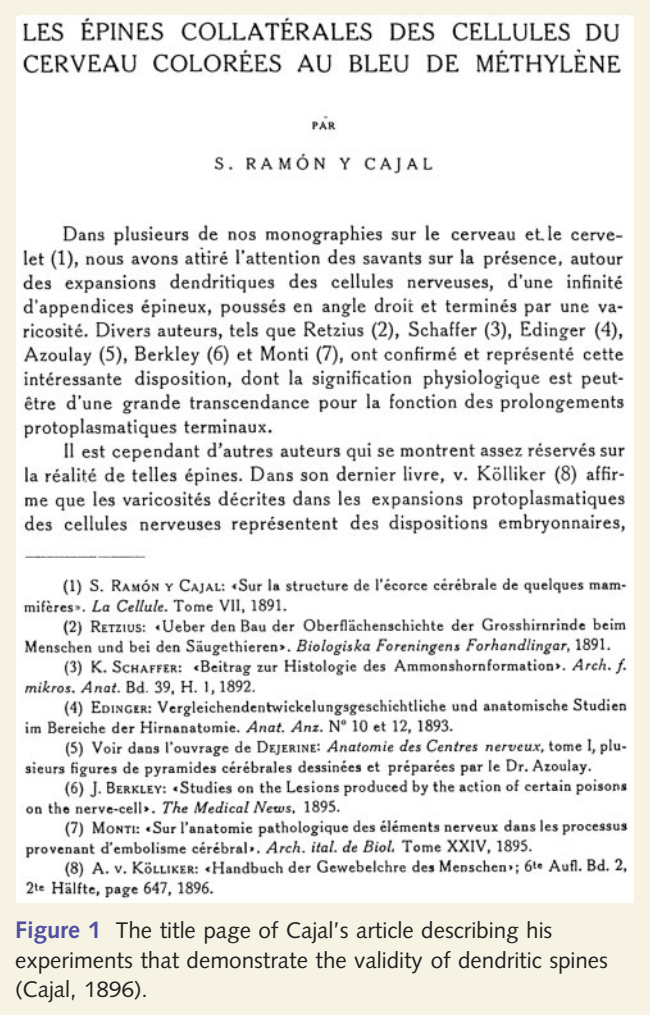
> I owe to Luis Simarro, the famous psychiatrist and neurologist of Valencia, the unforgettable favour of having been shown the first good preparations made by the method of chromate of silver which I ever saw, and of his having called my attention to the exceptional importance of the book of the Italian scientist devoted to the examination of the finer structure of the grey matter. In the year 1887 I was appointed judge for the examination for professorships in descriptive anatomy. 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. . . . I spent some time in the private library of the distinguished Valencian neurologist who, being devoted to the professional specialty of mental diseases, was engaged in analysing the changes in the nervous system . . . It was there in the house of Dr. Simarrro, situated at number 41 Calle el Arco de Santa Maria that for the first time I had an opportunity to admire excellent preparations by the method of Weigert-Pal, and particularly, as already mentioned those famous sections of the brain impregnated by the silver method of the savant of Pavia.

The contrast with the tedious and demanding method of isolating individual elements by dissection was clear. Golgi had developed a technique for labelling a small percentage of cells in a block of tissue. The cell body and all of its processes could now be seen clearly. It was the Golgi method that Cajal used for the great majority of his studies into the histological structure of the brain and spinal cord.

Cajal's contribution to Neuroscience is so important that others studying the histological structure of the brain and spinal cord have often been ignored. This book goes some way towards setting that right. Twenty-one of Cajal's figures are represented, but there are twice as many by two other Spanish histologists: del Rio-Hortega and de Castro. Both had been students of Cajal. It was del Rio-Hortega who identified microglial cells and described their role in responses of the nervous system to injury.

Viewed as a beautiful picture book, this volume excels. There is also a history embedded within it, although that is not its primary mission. One question that can be detected is the controversy over the existence of dendritic spines. Golgi, and many of his contemporaries thought that the spines, which are so clearly present in a Golgi-stained preparation, were merely an artefact of the method—a random distribution of silver grains on the cell surface. Kölliker, who published the major handbook of histology in his day, thought that they might be real, but were present only in the juvenile or developing brain. Golgi and his followers simply drew them out. Figure 14 of this book is of a cerebellar preparation published by Golgi in 1882. Figure 18 is of a Golgi-stained preparation of the cerebral cortex in a publication by Martinotti. The dendritic tree of the cortical pyramidal and stellate cells are clearly drawn in both papers, but neither Golgi nor Martinotti show cells as having dendritic spines. Figure 23 is an elegant picture of the cell types in the human cerebral cortex, reproduced from Kölliker's textbook. In this figure as well, all of the cells have perfectly smooth dendrites.

It was Cajal (1896) who argued most forcefully that spines must be a true element of the neuron (Fig. 1). He reasoned: 'if they are an artefact of the Golgi method, why do I see spines only on dendrites, not on axons? Why do I see the spines when I use a non silver-based Golgi–type stain?' But Cajal agreed that to prove the validity of spines they should be seen to be present using a totally different method. Ehrlich had used methylene blue to stain nerve cells. The stain has the advantage of coating the cell from inside, thus avoiding the criticism that spines merely reflect the



LES ÉPINES COLLATÉRALES DES CELLULES DU CERVEAU COLORÉES AU BLEU DE MÉTHYLÈNE

PAR

S. RAMÓN Y CAJAL

Dans plusieurs de nos monographies sur le cerveau et le cervelet (1), nous avons attiré l'attention des savants sur la présence, autour des expansions dendritiques des cellules nerveuses, d'une infinité d'appendices épineux, poussés en angle droit et terminés par une varicosité. Divers auteurs, tels que Retzius (2), Schaffer (3), Edinger (4), Azoulay (5), Berkley (6) et Monti (7), ont confirmé et représenté cette intéressante disposition, dont la signification physiologique est peut-être d'une grande transcendance pour la fonction des prolongements protoplasmatiques terminaux.

Il est cependant d'autres auteurs qui se montrent assez réservés sur la réalité de telles épines. Dans son dernier livre, v. Kölliker (8) affirme que les varicosités décrites dans les expansions protoplasmatiques des cellules nerveuses représentent des dispositions embryonnaires,

(1) S. Ramón y Cajal: «Sur la structure de l'écorce cérébrale de quelques mammifères». *La Cellule*. Tome VII, 1891.

(2) Retzius: «Ueber den Bau der Oberflächenschichte der Grosshirnrinde beim Menschen und bei den Säugethieren». *Biologiska Foreningens Forhandlingar*, 1891.

(3) K. Schaffer: «Beitrag zur Histologie des Ammonshornformation». *Arch. f. mikros. Anat.* Bd. 39, H. 1, 1892.

(4) Edinger: Vergleichendentwickelungsgeschichtliche und anatomische Studien im Bereiche der Hirnanatomie. *Anat. Anz.* N° 10 et 12, 1893.

(5) Voir dans l'ouvrage de Dejerine: *Anatomie des Centres nerveux*, tome I, plusieurs figures de pyramides cérébrales dessinées et préparées par le Dr. Azoulay.

(6) J. Berkley: «Studies on the Lesions produced by the action of certain poisons on the nerve-cell». *The Medical News*, 1895.

(7) Monti: «Sur l'anatomie pathologique des éléments nerveux dans les processus provenant d'embolisme cérébral». *Arch. ital. de Biol.* Tome XXIV, 1895.

(8) A. v. Kölliker: «Handbuch der Gewebelchre des Menschen»; 6te Aufl. Bd. 2, 2te Hälfte, page 647, 1896.

Figure 1 The title page of Cajal's article describing his experiments that demonstrate the validity of dendritic spines (Cajal, 1896).

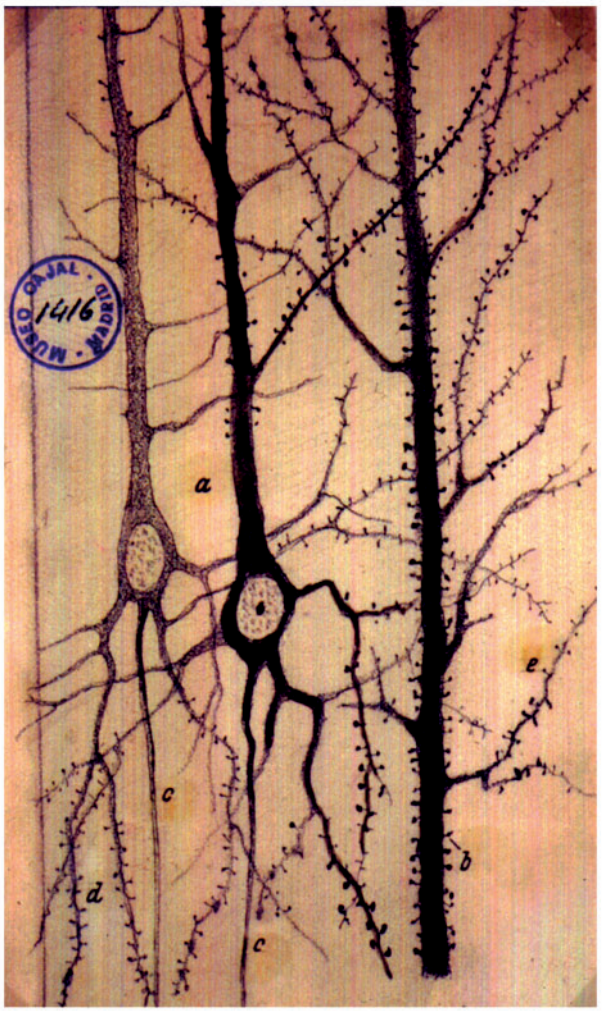


Figure 2 A drawing by Cajal showing the dendrites of a cortical pyramidal cell stained with methylene blue (courtesy of the Cajal Institute, Madrid).

presence of metal deposits on the cell surface, since methylene blue colours the cell from within. After two unsuccessful attempts, Cajal produced beautiful pictures of cortical pyramidal cells stained with methylene blue (Fig. 2). He wrote that the matter was now over and that he would not consider it further. Within a few years, textbooks began to show spines on dendrites in their portrayal of cortical cells.

Although his stain made a major contribution, there are only three figures from Golgi's publications in this volume. In the late 19th century, there was a sharp disagreement of views on how the brain and spinal cord are organized: the neuronal versus reticular theories. For Golgi, axons joined to form a net or *reticulum*. He thought that axons fuse in a plexus and that this plexus constitutes the basic functional element of brain. The nerve-cell body and its dendrites are relegated to a nutritive role. Conversely, Cajal and others insisted that the nervous system is made up of single elements, which his contemporary Waldeyer labelled 'neurons'. The cornerstone of the neuron doctrine is that neurons may touch one another but they do not fuse. Given the limitation in resolution of the light microscope, there was no way to rule definitely on either view. But Cajal's instincts were correct. Gaps between neurons exist, but since they are below the resolution limit of light microscopy, no final resolution of these divergent views was possible prior to the advent of studies using the electron microscope in the 20th century.

There was no love lost between Cajal and Golgi. The former gave Golgi rather grudging credit for his discovery of the stain, *la reazione nera*. In his autobiography Cajal (1937) wrote:

> It was discovered by C. Golgi, the famous histologist of Pavia, through the favour of chance, the muse who inspires great discoveries. In his staining experiments, this savant noticed that the protoplasm of the nerve cells, which is so refractory to artificial staining, possesses the valuable attribute of attracting strongly a precipitate of silver chromate when this precipitate is produced right within the thickness of the piece of tissue'. Cajal goes on '...thanks to such a valuable reaction, Golgi succeeded during several years of labour in clarifying not a few points of importance in the morphology of nerve cells and processes.

The fact that there are only three figures from Golgi's in the book fails to convey the full importance of the man and his work. Golgi and Cajal shared the Nobel Prize for Physiology or Medicine in 1906. The deliberations of the committee (Grant 2007) make it clear that it was Golgi's method and Cajal's insights that provided the modern view of cellular organization in the brain.

The book is filled with elegant images; here I list some of my favourites. I have already mentioned Cajal's drawing of the cells and fibres of the cerebellar cortex. Figure 15 is from the work of Tartuferi on the retina (1887). The cellular elements and laminar structures are clear, but the links from photoreceptors through to ganglion cells are vaguely drawn. There are several excellent figures of studies on the invertebrate nervous system. Figure 34 of the squid retina by Kopfsch shows that although the cephalopod eye forms an inverted image as it does in the mammalian eye, axons of the photoreceptor point toward the light, and they connect directly to an optic lobe behind the eye. Our common ancestor was an eyeless worm. Some of the macro sections are fully as beautiful as those at higher magnification. Figure 168 from Sobotta (1906) is a splendid cross-section of the human spinal cord. The motor neurons and cells of the dorsal horn are beautifully represented as are the massive number of fibres in the white columns. The book contains not only images of normal histology of the brain and spinal cord, but also the pathological changes associated with neurological and psychiatric disease. Striking among its figures is a composite by Rezza (Figure 237) of chromatolysis revealed in Nissl-stained cells; and one by Creutzfeld (Figure 271) showing degenerative changes in neurons, and the incrustation of glial cells in a dying neuron.

I recommend this book unreservedly; and I thank Javier DeFelipe and Oxford University Press for giving us so much beauty.

Acknowledgements

I thank my friend and colleague Miguel Marin-Padilla who first called my attention to the 1896 paper of Cajal, and clarified details

of the careers of de Castro and del Rio-Hortega. I also thank the Cajal Institute in Madrid for providing me with a slide of Cajal's drawing of the dendritic spines that had been labelled with the methylene blue stain.

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Gravela E. Giulio Bizzozero. Torino: Allemandi; 1989.

Fusion of neuroscience and art

Cajal's Butterflies of the Soul: Science and Art
Javier DeFelipe.
Oxford University Press, 2009
Pp 384. £50
ISBN:978-0-19-539270-8

Javier DeFelipe should be congratulated on assembling such a beautiful book about the earliest microscopic investigations of the nervous system conducted at the end of the 19th century and early 20th century. DeFelipe is an accomplished neurobiologist at the Cajal Institute, Madrid, Spain, where his research has focused on the micro-organisation of the cerebral cortex and the alterations of cortical circuits in epilepsy and Alzheimer's disease. His professional background, research accomplishments, and affiliation with the Cajal Institute place him in a situation of unique expertise to analyse the early history of research into the cellular organisation of the nervous system.

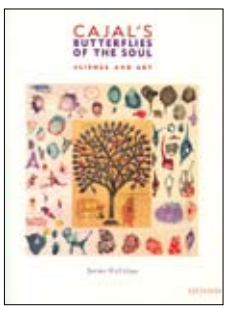
The book is organised into two parts. In the first part DeFelipe succinctly and thoroughly reviews the history of neurobiological investigations from 1859 to 1932. Of central importance was the widely accepted reticular theory of nerve continuity in which the cells of the nervous system were all thought to be cytoplasmically interconnected. Camillo Golgi published his results using a silver staining method in 1873, which Santiago Ramon y Cajal started using in 1887. Cajal's

results gave credence to the alternative neuron doctrine in which nerve cells are entirely separate entities. For their accomplishments, Golgi and Cajal received the Nobel Prize for Physiology or Medicine in 1906.

However, at this time adequate microphotographic technology had not yet been developed. Therefore, scientists had to hand draw illustrations from the microscopic slides to demonstrate their findings. Most often, camera lucida drawing techniques were used. As a result, extremely beautiful and artistic images of the nervous system were created. A fusion of neuroscience and art occurred. "There can be no doubt, only artists are attracted to science", said Cajal.

The second part of the book contains 288 hand-drawn figures by 95 authors. Drawings by Cajal and Golgi are included, along with the artistic accomplishments of Alzheimer, de Castro, Meynert, Nissl, Ranvier, Retzius, del Rio-Hortega, and many others. The first section of illustrations covers "The Benedictine Period: The Early Days." The drawings are of globules, granules, and corpuscles, all indistinct forms of what we call neurons. Most of these illustrations were thought to substantiate the reticular theory. Of note are the neuronal cell body drawings by Butzke and Deiters for their elegance and simplicity. The second section of drawings covers "The Black Period: Neurons, Glia and the Organization of the Nervous System." With the use of the Golgi staining technique, individual neuronal cell bodies could be defined, showing their incredible complexity. Of interest are the drawings of microglia by del Rio-Hortega and de Castro's images of ganglion cells for their intricate complexity, visual movement, and aesthetic appeal. The final section covers "The Colorful Period: Internal Structure and Chemistry of the Cells." Using various stains, coloured drawings were generated. Righetti's and Holmgren's drawings of individual neuronal cell bodies are extremely elegant works of art.

As Cajal wrote, "...my attention was drawn to the flower garden of the grey matter, which contained cells with delicate and elegant forms, the mysterious butterflies of the soul, the beating of whose wings may someday...clarify the secret of mental life." This book is a wonderful addition to the library of any neuroscientist or neurologist. It is worthy of attention of artists who enjoy the beauty of the natural world.



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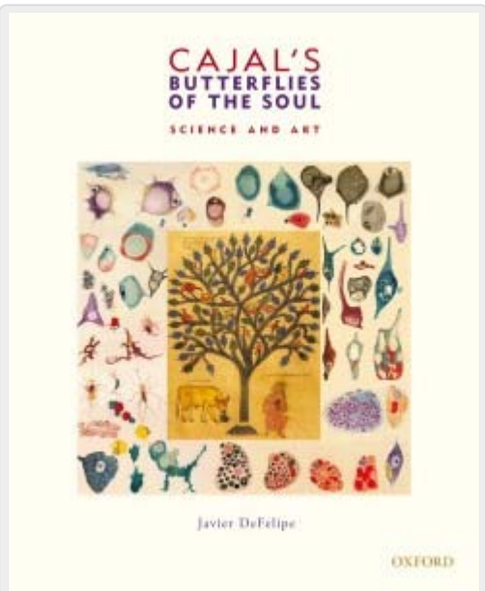
Exquisite Data: a Review of Cajal's Butterflies of the Soul

By Ben Ehrlich

Filed under Reviews February 8th, 2010 no comments

Long before fMRI and EEG, the light microscope was the only way to illuminate the world of the infinitely small that exists inside the brain. In the nineteenth-century, pioneering investigators of the central nervous system had to compensate for primitive technology with extraordinary artistic talent. These men produced drawings of their experimental slides in order to preserve the revelations therein. Strange, complex, and utterly gorgeous, these figures are the inspiration for *Cajal's Butterflies of the Soul* (2010) by Javier DeFelipe. The book, published by Oxford University Press, contains two-hundred and eighty-two one-of-a-kind images, truly exquisite neuroscientific data.



"Cajal's Butterflies of the Soul" by Javier DeFelipe. Oxford University Press, 2010.

But this is not merely a picture book; there is an abundance of valuable text. The first part contains a detailed, well-told background and history of neuroscience and technology. Like an art historian, DeFelipe separates the material into three periods: Benedictine, Black, and Colorful. ("Black," for example, refers to the revolutionary *reazione nera*, the chemical stain invented by Camilo Golgi that earned him a share, with Cajal, of the Nobel Prize in 1906). I cannot imagine that a traditional textbook could do a better job of presenting this information. The writing is approachable and engaging, and surely enhances the visual experience that follows in the second part. After their introduction, the images become more than aesthetic stimulation; they acquire special meaning because they represent the seeds of early anatomical discovery that grew into the field of modern neuroscience.

Although the book includes the work of ninety-one scientists, *Cajal's Butterflies of the Soul* is named for only one: Santiago Ramón y Cajal, the Nobel Prize-winning "father of modern neuroscience" who

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compared himself to an entomologist and described pyramidal cells (neurons that he himself discovered) as "butterflies of the soul." Cajal, who said that "only artists are attracted to science," originally wanted to be an artist. He spent countless hours during his youth drawing natural scenes. In the end he found aesthetic fulfillment in science, and his iconic figures are still used in textbooks. Cajal is one of the greatest examples of a jointly artistic and scientific mind, one that could only have flourished in harmony. (The book's author, Javier DeFelipe, is a research professor at the Cajal Institute in Madrid).

Cajal's Butterflies of the Soul, with big, glossy pages and a fancy silver place-holding ribbon, is expensive ($75—$60 on **Amazon**). But I contend that it is worth the price. I would rather not attempt to translate the unique images into descriptive approximations. I prefer instead to use my words to urge the reader to **see for his or herself.** To me, the rest of the images found in the book images suggest an epic range of expressive styles; some figures resemble cave drawings, some remind of surrealism. It all amounts to an affirmation of the fundamental beauty of this holy human organ, something to never forget.

These unique works surely belong in a museum. Indeed, that is the opinion of DeFelipe. I was fortunate to be present at a small release event for the book that took place at last year's Society for Neuroscience conference in Chicago. At the end of his engaging talk, DeFelipe showed slides of an imaginary museum that would display the astounding work we had all just seen through the projector and which appears in the pages of the book. There were even, if I remember correctly, virtual ladies and gentlemen milling about the floor and admiring the featured art. The small conference room was struck, I believe, by the normalcy of the scenario. The message: this science *is* art. And I will say that I, for one, look forward to the day when I can visit an exhibit in a real museum.

*See the accompanying **gallery** of images from the book.*

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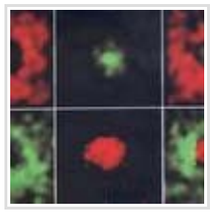

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