Cajal BLUE BRAIN

CAJAL BLUE BRAIN PROJECT

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Cajal Blue Brain in Science

`*From the Connectome to the Synaptome: An Epic Love Story*'

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Special points of interest:

- A study carried out from the CCB Project is published in the prestigious scientific journal 'Science'
- Dissemination Activities: CBB participates in the X Science Week (2010).
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- CeSViMa: RES held the 4th User's Meeting at UPM

REVIEW

From the Connectome to the Synaptome: An Epic Love Story

Javier DeFelipe

A major challenge in neuroscience is to decipher the structural layout of the brain. The term "connectome" has recently been proposed to refer to the highly organized connection matrix of the human brain. However, defining how information flows through such a complex system represents so difficult a task that it seems unlikely it could be achieved in the near future or, for the most pessimistic, perhaps ever. Circuit diagrams of the nervous system can be considered at different levels, although they are surely impossible to complete at the synaptic level. Nevertheless, advances in our capacity to marry macro- and microscopic data may help establish a realistic statistical model that could describe connectivity at the ultrastructural level, the "synaptome," giving us cause for optimism.

What mysterious forces precede the appearance of the processes [dendrites and axon], promoting their growth and ramification, provoking the coherent migration of the cells and fibres in predetermined directions, as if obeying a wise architectonic plan, and finally establishing those protoplasmic kisses, the intercellular articulations [synapses] that appear to constitute the final ecstasy of an epic love story? —Santiago Ramón y Cajal (*Recuerdos de mi Vida*, Moya, Madrid, 1917)

Early Circuit Diagrams: The Neuron Doctrine and the Dynamic Polarization of Nerve Cells

From the outset of Cajal's studies in 1888 with the revolutionary method of Golgi, he provided strong support for his belief that dendrites and axons end freely in the nervous system and that they communicate by contact (*1*). This hypothesis contrasted with the most prevalent idea at the time, developed by Gerlach, that the elements of the nervous system formed a continuum (Fig. 1).

The existence of a continuous network would more readily explain the flow of currents, but how could this be possible through an infinitely interrupted and fragmented nervous system (Fig. 2)? Cajal proposed in 1891 that neurons showed a morphological and functional polarization in such a way that neurons could be divided in general into three functionally distinct regions: a receptor apparatus (formed by the dendrites and soma), the emission apparatus (the axon), and the distribution apparatus (terminal axonal arborization). This idea was based on the direction followed by impulses in certain regions of the nervous system in which their activity clearly reflected the anatomical routes the impulse followed, such as in the visual and olfactory systems (Fig. 3, left). Cajal's new ideas about the connections between neurons led to novel theories on the relationship between neuronal circuits and brain function. Indeed, this hypothesis gave rise to a new era in neuroscience and to the tracing of the first point-to-point connectivity maps of the nervous system (Fig. 3, right).

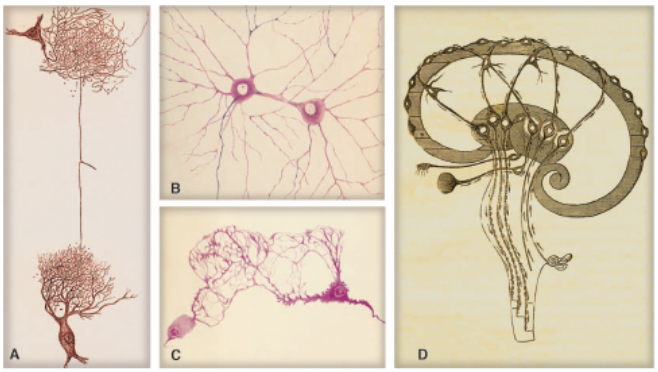

Fig. 1. In the reticular theory, the brain was thought to be made up of a mesh of nerve cell processes. **(A)** A drawing from Gerlach from 1872 showing two nerve cells from the spinal cord of the ox. According to Gerlach, nervous activity was driven through a network of neural elements formed by axons (axonal network) and dendrites (dendritic network). **(B** and **C)** Drawings of ganglion cells from the human retina and of cells from the dog's gall-bladder ganglia produced by Dogiel in 1893 and 1899, respectively. **(D)** Luys' schematic illustration from 1878 showing the processing of sensory-motor cerebral activity. [From (*26*)]

Visualization of the Synaptic Cleft: The Discovery of the Physical Separation Between Neuronal Processes

In the 1930s, it had been shown histologically that the terminal axonal bouton or synaptic specialization was separated by a "membranous synaptic barrier" (*2*, *3*). The large number of studies demonstrating this phenomenon resolved this issue for the vast majority of scientists; therefore, they turned their interest to other aspects of synaptic structure. At the areas of contact between the axon terminal and the soma or dendrite, only one membrane was visible (the synaptic membrane), presumably because the membrane of the pre- and postsynaptic elements were so close together that only a single membrane could be distinguished. Thanks to the introduction of transmission electron microscopy (TEM) in the 1950s, along with the development of methods to prepare nervous tissue for ultrastructural analysis, the nature of synapses was examined, confirming a critical aspect of the neuron theory: The pre-synaptic and the postsynaptic elements in both invertebrate and vertebrate nervous tissues are physically separated by a space of approximately 10 to 20 nm, the synaptic cleft (*4*, *5*). This essentially confirmed the observations and theories of Cajal.

Exceptions that Challenge the Neuron Doctrine and the Law of Dynamic Polarization

The appearance of new techniques to study the nervous system at the anatomical, physiological,

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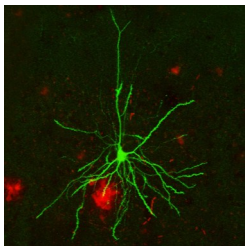
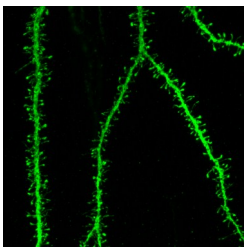
Professor Javier de Felipe, Full Professor at the Instituto Cajal (CSIC), Head of the Cortical Circuits Laboratory (UPM-CSIC) and Director of the Neurobiology area in the Cajal Blue brain Project (UPM-CSIC), has published in the prestigious journal Science the article entitled: '*From the Connectome to the Synaptome: An Epic Love Story*'

'From the Connectome to the Synaptome: An Epic Love Story'

Abstract
A major challenge in neuroscience is to decipher the structural layout of the cerebral microcircuits and how these circuits contribute to the functional organization of the brain. The term "connectome" has recently been proposed to refer to the highly organized connection matrix of the human brain. Later, this term was adopted to describe maps of neural circuits in general. In this article, the term 'connectome' is proposed to refer to the map of connections at the macroscopic and intermediate level or by using light microscopy, and the term 'Synaptoma' is introduced to refer to the set of interconnections established by neurons at synaptic level or ultrastructural level. For many scientists 'synaptoma' obtaining represents so difficult task that it seems unlikely it could be achieved in the near future or, for the most pessimistic, perhaps ever.
However, the author of this article is optimistic and suggests that the use of new tools for computational and structural analysis and following an appropriate strategy, a realistic statistical model may be established that could describe the layout of the cerebral circuits at the ultrastructural level, the "synaptome. Thus, that major challenge in neuroscience could be reached, since only by combining studies at all three levels, macroscopic, intermediate and ultrastructural, can we fully understand the structural plan of the brain as a whole.

Reference: *Science 26 November 2010: 1198-1201.*
DOI:10.1126/science.1193378





Cortical Circuits Laboratory (CCL), UPM-CSIC (Centro de Tecnología Biomédica, Campus de Montegancedo, UPM)
Cortical Circuits Laboratory (CCL) is located at the Campus de Montegancedo from the UPM and is leaded by Prof. DefElipe. CCL, created in 2008, is a joint research laboratory between the UPM and the Cajal Institute (CI) from CSIC (Spanish Council for Research), located at UPM. The CCL was created as a UPM experimental neuroscience unit, made up of researchers from the neuroscience field with large experience coming from the IC-CSIC, together with scientists from the Computer Science area from UPM. The CI has a long history of more than 100 years in which it has made many relevant contributions to the understanding of the structure and the function of the nervous system. CCL was created with the spirit of making the technological and the experimental studies of the brain and the nervous system converge. Main research line conducted by CI at the CCL is focused on the analysis of the microanatomic and neurochemical organization of the brain cortex, by means of a variety of techniques such as, the use of intracellular injections, histochemical and inmunocytochemical techniques for optical and electron microscopy, and 3D reconstruction methods. CCL is fully settled with the equipment needed to carry out the ongoing research activities. Also, because of its international dimension, CCL is currently collaborating with external research groups belonging to leaders universities and research centers on the field such us Columbia University (USA), Heidelberg University (Germany), The University of Cambridge (England) and others.

Other Contributions

PhD Thesis Defence
Theses reading during this period has been as follow:

Title: Estudio de la inervación perisomática neuronal en la corteza cerebral normal y en la enfermedad de Alzheimer. Doctorando**: Lidia Blazquez-Llorca** (Tesis co-dirigida con Virginia García-Marín). Universidad: Complutense de Madrid (Facultad de Biología), 2010. Calificación: Apto Cum Laude

Title: Optimización de procesos de adquisición de conocimiento en Biología Computacional. Doctorando**: Santiago Gonzalez Tortosa**. Directores: Víctor Robles, Fazel Famili. Universidad Politécnica de Madrid, 2010. Calificación: Cum Laude.

Cortical Circuits and Cognition: Cajal Blue Brain Project

2010 Science Week: Dissemination Activities in the Cajal Blue Brain Project.

Cajal Blue Brain Project participated in the X Science Week which was held in Madrid in November 8-21, 2010.

With the presentation entitled 'Cortical Circuits and Cognition: Cajal Blue Brain Project', CBBP participated in this event of Scientific Diffusion within the planned activities for the X Science Week in Madrid. The event was conducted not only to the scientific community but also to the public at large.

The event, organized by UCM (D. Carlos Pelta), took place on November 11, and consisted of several conferences followed by a round table. The presentation brought together more than one hundred attendances at the 'Colegio Oficial de Médicos de Madrid'.

The Vice President for Research of the Universidad Politécnica de Madrid, presented this event along with co-directors of the project Prof.: J. DeFelipe and Prof.: J. M. Peña, Neuroscience and Computational Science experts, respectively. The event also involved other experts from related fields such as D. M. Martín-Loeches (UCM-ISCIII), D. Kostadin Koroutchev (UAM), D. Fernando Maestú (UCM and CTB-UPM) and D. José Luis Muñiz (CIEMAT).

Prizes and Awards

Cajal Blue Brain Participants Prizes

BIOMAG-2010 MEG brain data analysis competition

The work "Classification of MEG data using a combined machine learning approach" by Roberto Santana, Concha Bielza and Pedro Larrañaga, members of the Cajal Blue Brain Project, received one of the prizes of the BIOMAG-2010 MEG brain data analysis competition. BIOMAG is an international conference devoted to research on biomagnetism, particularly its application to brain and heart study.
One of the current problems in the field is the determination, from the recorded MEG data, of which are the structural and functional relationships of the brain components.

The data analysis competition included three different problems. The first problem consisted of classifying a given stimulus from the analysis of recorded MEG data from four subjects. Six research groups from different countries participated of this problem two winners were declared, a group from Carnegie Mellon University and the group from the Cajal Blue Brain Project. There was not winner for the second problem and a group from the University College University of London won the prize for the third problem. The works that won the challenge were presented in a special session of the BIOMAG-2010 conference. The results are reported in MEG community web page (http://megcommunity.org/).

Comunidad de Madrid-Micro-videos 2010 Prize
Juan Morales, member of the Cajal Blue Brain Project, was awarded by CAM with the 2010 prizes on micro-videosMore information: http://www.madrimasd.org/lanochedelosinvestigadores/concurso-de-micro-videos/micro-videos-ganadores/?pag=ganadores

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CeSViMa

The Cajal Blue Brain Project is hosted by the Universidad Politécnica de Madrid (UPM) in the Scientific and Technological Park of Montegancedo Campus. Computational needs and support infrastructure required by CajalBBP are provided by two of the Research Centers of the Park, the Centro de Tecnología Biomédica (CTB) and the Centro de Supercomputación y Visualización de Madrid, CeSViMa, which is focused on the massive storage of information, high-performance computing and advanced interactive visualization.

More information: www.cesvima.upm.es

RES USER'S MEETING

The IV RES Users's Meeting (RES - Spanish Supercomputing Network) was held in Madrid on December 15th 2010.
The workday, organized by CeSViMa, took place at:

Rectorado, Universidad Politécnica de Madrid, Edificio A
Campus Ciudad Universitaria
C/Ramiro de Maeztu, 7 CP 28010 Madrid

Agenda

10.30h - Presentation of the Universidad Politécnica de Madrid *(Sr.D. Gonzalo León Serrano, Vice President for Research*
11.00h - Presentation of the Centro de Visualización y Visualización de Madrid, CeSViMa, *(Prof. Sr. D. Vicente Martín Ayuso, Director of* CeSViMa)
11.30h - Coffee Break
11.45h - Presentation of the Ministerio de Ciencia e Innovación
12.15h - RES General Presentation
12.45h - Chemistry, Science and Technology of Materials
13.15h - Biology and Life Science
13.45h - Break (lunch)
15.00h - Physics and Engineering
15.30h - Astronomy, Space and Earth Science
16.00h - Presentation of the Access Committee
16.30h - Presentation of the Users Committee
17.00h - Coffee Break
17.20h - Round Table with the Users Committee
18.00h - Conclusions and closure

More information: http://www.bsc.es/plantillaA.php?cat_id=681

Sponsorship