



Santiago Ramon y Cajal and Neuron Doctrine

Santiago Ramon y Cajal ve Nöron Doktrini

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Summary

Santiago Ramon y Cajal's emergence in the world of science has led to a new era in neuroscience. He was the founder of modern neuroscience with the neuron doctrine he revealed. He showed that nervous system was not a continuum network structure as it is believed to that day, but consists of individual cell as in all other tissues. His contribution to modern neuroscience was not limited to the neuron doctrine, he also contributed to neuronal morphology, communication and development. All of these contributions was honored with a shared Nobel Prize Award with Camillo Golgi in 1906, for their studies on the nervous system. Santiago Ramon y Cajal, was a scientist with unusual observation and interpretation talents, who pushed the conditions until the end to access to information and share his findings in the underdeveloped scientific environment of Spain. Besides, he was involved in scientific breakthroughs of his country. Ramon y Cajal was not only a scientist but also a multi-faceted personality; a passionate chess player, gymnast, a very talented painter and photographer.

Keywords: Santiago Ramon y Cajal, neuron doctrine, neuroscience, reticular theory

Öz

Santiago Ramon y Cajal'ın bilim dünyasında ortaya çıkışı sinir bilimlerinde yeni bir dönem açmıştır. Ortaya koyduğu nöron doktrini ile modern sinirbilimin kurucusu olmuştur. Sinir sisteminin o güne kadar inanılan şekliyle süreklilik gösteren bir ağ yapısında değil, diğer tüm dokulardaki gibi tek tek hücrelerden oluştuğunu göstermiştir. Modern sinir bilime katkısı sadece nöron doktrini ile sınırlı kalmamış, nöronal morfoloji, haberleşme ve gelişim ile ilgili katkılarda da bulunmuştur. Tüm bu katkıları 1906 yılında "sinir sisteminin yapısı konusundaki çalışmaları" için Camillo Golgi ile ortak olarak Nobel Ödülü'ne layık görülmesi ile onurlandırılmıştır. Santiago Ramon y Cajal yetiştiği İspanya'nın bilimde geri kalmış ortamında, bilgiye ulaşmak ve bulgularını paylaşmak için koşulları sonuna kadar zorlayan, sıradışı gözlem ve yorumlama yeteneğine sahip bir bilim insanıdır. Bunun yanında ülkesinin bilimsel atılımlarında yer almıştır. Ramon y Cajal sadece bir bilim insanı değil aynı zamanda çok yönlü bir kişiliktir. Tutkulu bir satranç oyuncusu, jimnastikçi, çok yetenekli bir ressam ve fotoğrafçıdır.

Anahtar kelimeler: Santiago Ramon y Cajal, nöron doktrini, sinirbilim, retiküler teori

Introduction

When Scjleiden and Schwann proposed Cell Theory in 1838, all living beings were accepted to consist of one or multiple cells, and the cell was the basic unit of life. However, due to the insufficiency of imaging and coloring, brain tissue was exempted from this theory and was thought to have a single anastomosis. In 1871, German scientist Joseph van Gerlach proposed the Reticular Theory (Figure

1). According to this theory, grey matter consisted of a dense network that was formed by condensation of thin filaments. These thin filaments were thought to form nerve fibers and these fibers formed white matter and passed into the medulla spinalis. Gerlach also suggested that central nerve endings did not freely terminate; instead they continued with protoplasmic extensions (1).

The Reticular Theory was challenged after the introduction of the Golgi staining method, which was developed by Camillo

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Golgi. The most important feature of this method was random staining of approximately 5% of nerve cells, which allowed evaluation of a single neuron and unmyelinated axons within the complex and dense nervous tissue. Recognition and widespread use of this method was made possible by Spanish scientist Santiago Ramon y Cajal (2).

Cajal was born in Spain on May 1st, 1852. He started medical education in 1869 in Zaragoza University and graduated in 1873, the same year in which he joined the Spanish Army as a doctor. He was in with the army in 1874 during the Cuban war of independence against Spain. He returned to Spain in 1875 because he contracted tuberculosis and malaria and then started to work as an anatomy assistant in Zaragoza University, from where he had graduated. Cajal's first meeting with a microscope occurred in the same year when he observed blood flow in a live frog's foot. He was so impressed with the views from the microscope that he decided to establish a microscope laboratory as a complementary method to descriptive anatomy just after he returned to Zaragoza (3).

Cajal attained the position of temporary assistant professor in 1877 with his doctorate thesis "Pathogenesis of Inflammation." In 1883 he was appointed to Valencia University as Professor of General and Descriptive Anatomy and he concentrated heavily on microscopic evaluations (Figure 2). Two years later, a large cholera outbreak emerged in Valencia. Due to insufficient treatment methods, this outbreak caused great destruction and the city governor assigned Cajal to find a vaccine against cholera. At that time, a scientist suggested a live vaccination technique but

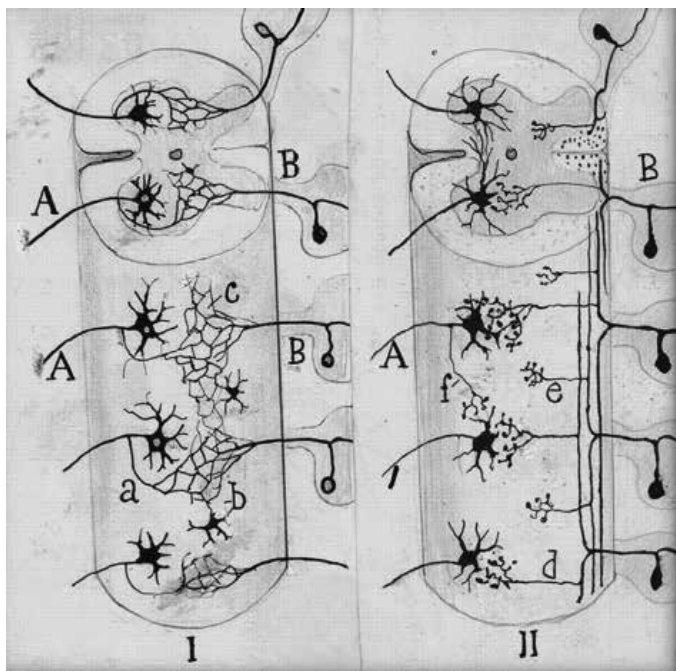


Figure 1. Drawing of Cajal to explain the differences between Reticular Theory (I) and Neuron Doctrine (II), 1917. A: Anterior roots, B: Posterior roots, a: Collateral of motor root, b: Short axons that form continuous network according to Golgi's reticular theory, c: Diffuse intercellular network, d: Long collaterals making connections with motor cells, e: short collaterals, f: motor root collateral (16)

Cajal demonstrated that vaccination with dead bacteria served the purpose and recommended this technique. This technique achieved success. Unfortunately, this achievement of Cajal's is not known across the world. As a reward to suppression of this outbreak, the municipality presented Cajal with newest model Zeiss microscope (4). This was an important step for Cajal's scientific studies because he had obtained the hardware that would help him compete with other scientists across the world.

During the early years of his career, Cajal's studies focused on the pathogenesis of inflammation, microbiology of cholera, and the structure of epithelial cells and tissue. His focus later changed to the nervous system. In 1877, he went to Madrid to attend a committee that would decide upon the assignment of an anatomy professor, and he visited anatomy professor Luis Simarro's laboratory. There he saw brain tissue stained with the Golgi method and he was very impressed by the images. He immediately started to work using this method; a new world opened for Cajal after his chance meeting with the Golgi method, fourteen years since its introduction. He then started working on brain structure at Barcelona University where he was appointed as Chairman of Histology, Histochemistry, and the Department of Pathological Anatomy (5).

Cajal improved the Golgi method by double precipitation and chose the right structures to evaluate, which enabled him to see details that could not be seen by other researchers using the same



Figure 2. Santiago Ramon y Cajal. Valencia University, 1885 (17)

method. He could stain deeper into tissues such that he could work with thicker sections and follow courses of axons. He started to work on common voles because he did not have much money; however, this problem turned into an advantage. Even though he was working on small scale brains he was able to visualize long axon endings. Another well-thoughtout detail was working on embryonic tissues. He predicted that adult brain tissue would be dense and complicated, whereas embryonic tissue, which is at an earlier period of development, would be simpler. Moreover, the low rate of myelination in embryonic nervous tissue enabled evaluation of neurons as a whole because the Golgi method stained unmyelinated extensions (3). All of these correct choices allowed Cajal to forge ahead of other scientists working with the same method on nervous tissue. In addition, his ability to reconstruct whole components he saw under the microscope in his mind and then draw onto paper enabled him to draw all layers and links of a neuron as a whole while it was still very hard to see a complete neuron (6).

Working heavily on the nervous system, Cajal published his findings in several Spanish and European journals. One of the obstacles he faced was that Spanish scientists lacked a place of significance in the world of science, which caused their studies to go unnoticed (7). While continental Europe developed during the modernization period, Spain stuck to feudalism under hegemony of the Catholic Church and was late to make bourgeois revolutions. This delay caused Spain to fall behind the rest of Europe and become isolated. Other scientists in Europe were not aware of Cajal's findings as a result of this isolation. Another difficulty of making science in Spain was the scarcity of knowledge entering Spain, much the same as the dearth of leaving wisdom. University libraries would not buy journals in languages other than Spanish so Cajal had to buy them with his limited salary. He examined figures in articles and tried his best to understand the footnotes with his French and limited German.³ His remoteness from other discoveries enabled him to develop his own theory without being affected by others' views (eg. Reticular Theory). Insisting on sharing his findings, Cajal took it upon himself to publish the quarterly journal *Revista Trimestral de Histología Normal y Patológica* and wrote his findings in this journal. He posted this journal to famous scientists in Europe but again he was not taken into consideration (3).

He published his first article on the concept of nerve cell "Structure of Avian Nerve Centers" in his journal in 1888. In this article, he demonstrated for the first time that all extensions of nerve cells freely terminate unlike the anastomotic-structured view in Reticular Theory and he suggested that nerve cells communicate with each other by contacts, not by continuation. In addition, he described dendritic spines for the first time ever (8).

Cajal's findings went unnoticed by the scientific world till he attended the Congress of the German Anatomy Society in Berlin in 1889. In that period, congresses were the most important events where scientists came together and discussed their findings such that they became aware of other centers' findings. Famous scientists from many countries attended these annual meetings. Cajal realized that congresses were good opportunities to share his findings with everyone and bringing his slides with him, he went to Berlin in 1889. During this meeting he met the famous German scientist Albert von Kölliker to whom he showed his slides.

Kölliker was very impressed by these images and discussed Cajal's across Germany, translated his important articles into German and published these articles in his own journal, and then learned Spanish to read Cajal's studies as soon as they were published (9). After this point, Cajal was known all over the world.

Neuron doctrine rapidly became validated by histologic evidence presented by Cajal. During these years, much data was collected showing that neurons were separate elements. This view was previously proposed by His, Nansen, and Forel, but had never been demonstrated until that time. In 1891, Waldayer used the term "neuron" for the nerve cell and Neuron Theory was proposed using Cajal's findings. In 1897, Sherrington used the term 'synapse' for the first time in his physiology textbook. Thus, Reticular Theory was terminated and Neuron Doctrine, which is still valid today, took its place. A breakthrough occurred in neurosciences and modern neuroscience was born (10).

Cajal's contribution to neuroscience was not limited to the Neuron Doctrine. He described the axonal growth cone in embryonic tissues for the first time and 2 years later he proposed neurotropism hypothesis. He described dynamic polarization and demonstrated that information had a direction of flow in neurons (Figure 3). He asserted that pyramidal neurons were the most important cells of neuronal cortical circuits and described them as 'butterflies of the soul' (8).

After Cajal's findings were heard worldwide and Neuron Doctrine was established, he was invited to universities to present his findings, and he received many rewards and honorary doctorates. In the Croonian Lecture he delivered in 1892 he spoke of the Cerebral Gymnastics hypothesis for the first time. This hypothesis actually considers a concept we know as neuroplasticity today. In this lecture, Cajal stated that through exposure to different stimuli, neuronal connections would increase and therefore brain capacity would improve. He developed his hypothesis after his observations in species that were phylogenetically and evolutionally at varying steps; he demonstrated that evolutionary development was associated with increasing complexity of dendrites. He published his first theoretical article 'General Perspectives on the Morphology of a Nerve Cell' in 1894 in which he frankly proposed that neural connections may increase plasticity in response to continuous stimuli (11).

After his studies Cajal was honored with a Nobel Prize in Physiology or Medicine together with Camillo Golgi for their contributions to the 'structure of the nervous system' (12). Speeches at the prize-giving ceremony shed light on the nature of scientific development. Golgi still supported Reticular Theory while Cajal's Neuron Theory represented a revolution in neuroscience. After he received the Nobel Prize, his scientific research continued extensively till his death in 1934 and he also contributed to the development of science in Spain (7).

Cajal was a multifaceted personality in addition to being a scientist. In addition to publishing more than 200 scientific articles he wrote several books to guide young scientists and to endear science to the public (13). He was a passionate chess player. Additionally, he was an amateur gymnast and a hunter. He contributed to photography in the field of Random Point Stereography (14), and he was among the first few to use color photography (15). He had been a talented drawer since his childhood. This drawing skill may have been the reason for his

love of anatomy and histology, and may have enabled him to see details under the microscope that could not be seen by others and then draw what he saw in detail at a time when microscope photography was not available (3).

When we look at Santiago Ramon y Cajal's life we see an extraordinary scientist who challenged limitations to acquire knowledge, share his findings, and to contribute to the scientific achievements of his nation in the underdeveloped scientific milieu of Spain. An exceptional man with a multifaceted personality who made enormous contributions towards the creation of a theory that is still valid today.

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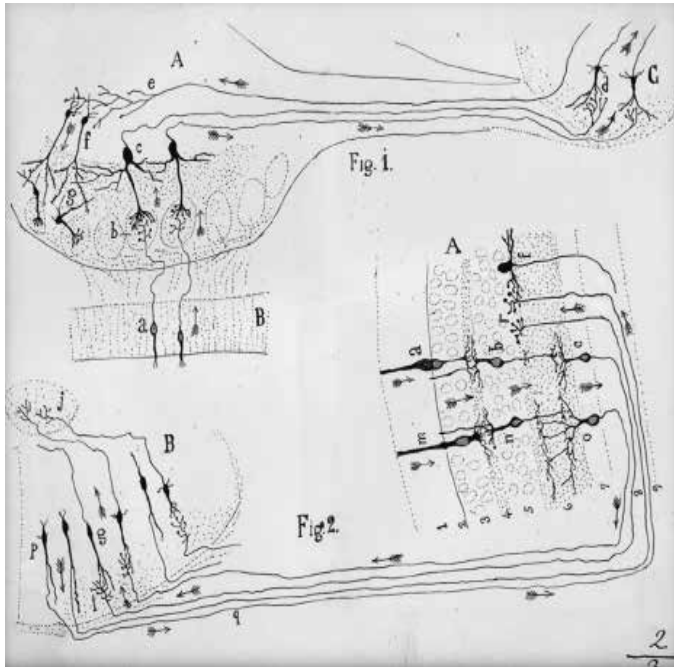


Figure 3. Cajal's drawing that shows direction of flow (arrows) in visual and olfactory systems in order to support Dynamic Polarization Law (16)

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