The discovery of dendritic spines

Rafael Yuste

Our story starts in the spring of 1888, in Barcelona. At that time, this progressive city was undergoing a febrile creative period in literature, arts, architecture and industrial development, taking the leadership in the creation of modern Spain. It may not be a coincidence that a similar revolution in neuroscience was occurring in the relative isolation of the Laboratory of Histology of its Medical School. Working in solitude, we find the hero of our story: Santiago Ramón y Cajal, an Aragonese medical doctor, Professor of Histology and Pathological Anatomy, who had recently moved from a previous position in Valencia's Medical School.

On May 1, precisely the day of his thirty-six birthday, Cajal publishes a monograph in Spanish on the "Structure of the nervous centers in birds" in the first issue of a journal that he himself wrote, edited and financed (Ramón y Cajal, 1888). As he later said, the publication of this journal used up all his savings and prevented him and his wife from hiring domestic help to take care of their five children (Ramón y Cajal, 1923). Cajal had recently been taught the Golgi staining method by his friend and medical doctor Simarro, who had in turn learnt it from Ranvier in Paris. To a greater extent than any of his peers, Cajal had been struck by the beauty and power of the Golgi technique, particularly when applied to the embryonic nervous system, to reveal neuronal morphologies. In this brief communication, which included two figures, Cajal applies the Golgi stain to the cerebellum of some bird species, and describes that the surface of Purkinje cells " . . . appear bristling with thorns [*puntas*] or short spines [*espinas*]" (Ramón y Cajal, 1888) (Figure 1; see Favourite Sentences below). Thus, dendritic spines are described and named for the first time. As an aside, in this same publication he could not confirm the presence of anastomoses between axons and dendrites and thus proposed for the first time that neurons are independent units. This constituted the foundation of his "neuron doctrine", a theory opposed to the established "reticular theory" of Golgi, where neurons would form a syncitium, a continuous network of physically joined cells (see www.ibro.org/docs/Santiago and Shepherd, 1991).

Cajal was neither the first to use the Golgi method nor the first to observe spines. Indeed, other investigators such as Kölliker, Dogiel, Meyer and even Golgi himself, more established than Cajal and working in well-recognized centres of anatomical research at the time, altogether missed the spines or disregarded them as fixation artefacts or silver precipitates in the surface of neurons, and instead represented in their drawing smooth dendritic trees devoid of spines. Indeed, dendritic spines are still today clearly visible in Camillo Golgi's original sections (D. Purpura, p.c.), so obviously he chose to ignore them. These were not such unrealistic thoughts, considering that the Golgi method is notoriously capricious (and, still today, poorly understood), and that other structures such as dendritic varicosities were thought to be artefactual by Cajal himself (Ramón y Cajal, 1904). But on the particular topic of the real existence of dendritic spines, rather than buckle under the pressure of his contemporaries in field, Cajal pressed on and undertook as a personal crusade to demonstrate, in a flurry of publications, that spines were not only real, but also important. We should mention that in the popular culture of Spain, Aragonese people are notorious for being "single-minded and persistent". This is captured by a story of an Aragonese farmer (*baturro*) riding his donkey on the train tracks and, when faced with an incoming train at full speed and blowing its whistle to warn him, tells the train that "blow as much as you want, you are the one who needs to step out of the tracks". Single-mindedness and persistence apparently were combined in Cajal with superb observation capabilities and intuition. Indeed, Cajal credits his success in this and other instances to the combination of the "power of the will", good experimental techniques, laboriousness and plain common sense (Ramón y Cajal, 1923).

In his subsequent work on spines, Cajal showed in 1891 that they were not particular to birds but were also present in the dendrites of many neurons of the cerebral cortex of mammals (Ramón y Cajal, 1891) (Figure 2). He also speculated that spines receive axonal collaterals from other pyramidal cells, and thus serve as the main point of contact between axons and dendrites (Ramón y Cajal, 1894). This idea was based on the comparison between spines and intestinal villi: he argued that spines would extend tremendously the surface of the dendrites, and therefore dramatically increase their capability of receiving axons. In addition, Cajal argued that changes in spines could be involved in learning (Ramón y Cajal, 1891, 1893) and that physical changes in spines were associated with neuronal function, even to the point that they would grow with activity and retract during inactivity or sleep (Ramón y Cajal, 1899; see also http://www.ibro.org/docs/valverde.pdf). These ideas, one hundred years later, are still central to the study of the function of dendritic spines (Yuste and Bonhoeffer, 2001; Yuste and Majewska 2001).

In 1896 Cajal extended his observations of spines using a different method, the Ehrlich methylene-blue stain (Ramón y Cajal, 1896a; 1896b) and in subsequent years described with some detail spines in motor, visual, auditory and olfactory human cortices (Ramón y Cajal 1899a, 1899b, 1900a, 1900b). In 1904, he summarized his observations in his book *Histology of the Nervous System of Man and Vertebrates* (Ramón y Cajal, 1904), speculating that spines increase the surface area of dendrites and thus serve as a site of contacts between dendrites and axons, and noting that cells from more highly evolved animals are more spiny. Here he also assembled all his arguments that spines were not artefactual (Ramón y Cajal, 1904). Specifically, he argued that spines must be real because: 1. Spines are shown by different methods, such as the Golgi, Cox or Ehrlich stains; 2. They always arise in the same way, from the same regions; 3. Spines are never found in certain parts of the neuron (like the axon, soma or initial dendrites); 4. Spines do not resemble crystal deposits when viewed with higher-power apochromatic objectives; 5. Spine pedicles (necks) can be detected; 6. Spines are never stained with the neurofibrillary method. Finally, in his last monograph (Ramón y Cajal, 1933), Cajal describes at least three different types of axons that contact spines from cortical pyramidal neurons: (i) axonal collaterals from pyramidal cells; (ii) axons from interneurons (Golgi type II); and (iii) axons from other associative neurons.

In spite of this string of arguments and the combined weight of his evidence, Cajal's conclusions were not readily accepted, although eventually many of his contemporaries, such as Retzius, Schaffer, Edinger, Azolay, Berkley, Monti and Stefanowska, did confirm their appearance in their preparations (Ramón y Cajal, 1899). Cajal's proposal on the role of spines in connecting axons and dendrites would have to wait half a century for its confirmation. Indeed, Cajal was proven right in 1959 by Gray, using electron microscopy (Gray, 1959a, b). As to the specific function of the spine, one hundred and fourteen years after their discovery, it is still somewhat mysterious. Since synaptic connections can be made directly on dendritic shafts, spines must have an additional function, besides being recipient of synaptic inputs. Proposals range from connecting devices to minimize axonal wiring to biochemical or electrical compartmentalization (Peters and Kaiserman-Abramof, 1970; Swindale, 1981; Harris and Kater, 1994; Shepherd, 1996; Harris, 1999; Yuste *et al*,. 2000; Yuste and Majewska, 2001). In addition, confirming Cajal's (Ramón y Cajal, 1899) and Crick's (Crick, 1982) speculations, one of the most exciting recent findings has been the discovery that spines are constantly moving (Movie 1) (Fischer *et al*., 1998; Dunaevsky *et al*., 1999), although the purpose of this motility is still unclear (Bonhoeffer and Yuste, 2002). Nevertheless, from their strategic position in the nervous system, we cannot help but think that spines are essential for the function of the brain and that they must play a central role in any comprehensive theory of neuronal computations. As Cajal himself wrote, "the future will prove the great physiological role played by the dendritic spines"(Ramón y Cajal, 1904).

Department of Biological Sciences
Columbia University
New York, NY 10027
USA
Correspondence: rmy5@columbia.edu

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Favourite Sentences

First description of dendritic spines by Cajal:

"Also, the surface of the Purkinje cells dendrites appear bristling with thorns or short spines, which in the terminal branches are represented by light asperities. Early on we thought that these eminences were the result of a tumultuous precipitation of the silver; but the constancy of their existence and its presence even in preparations where the reaction appears with great delicacy in the remaining elements, incline us to consider them as a normal disposition" (S. Ramón y Cajal, Estructura de los centros nerviosos de las aves, *Rev. Tri. Hist. Norm. Pat*., 1888).

On the motility of axons, dendrites and spines:

" . . . because it is almost impossible to do experiments whose conditions approach the normal physiological state, during which the changes in position and form of the neuronal arborizations could be fleeting and erased" (S. Ramón y Cajal, 1899, *Textura del Sistema Nervioso del Hombre y de los Vertebrados*, Tomo II, Madrid: Imprenta y Librería de Nicolás Moya).

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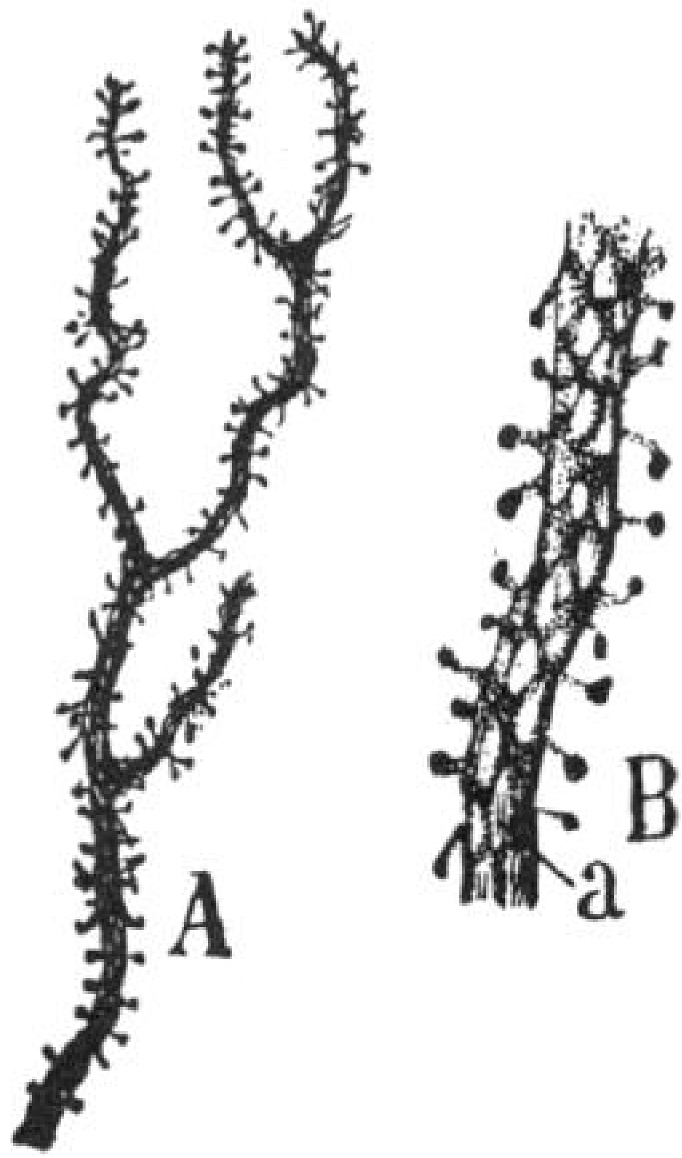


Figure 1

Low (A) and high (B) magnification views of dendritic spines from a cerebellar Purkinje cell, drawn by Cajal (Ramón y Cajal, 1899b).

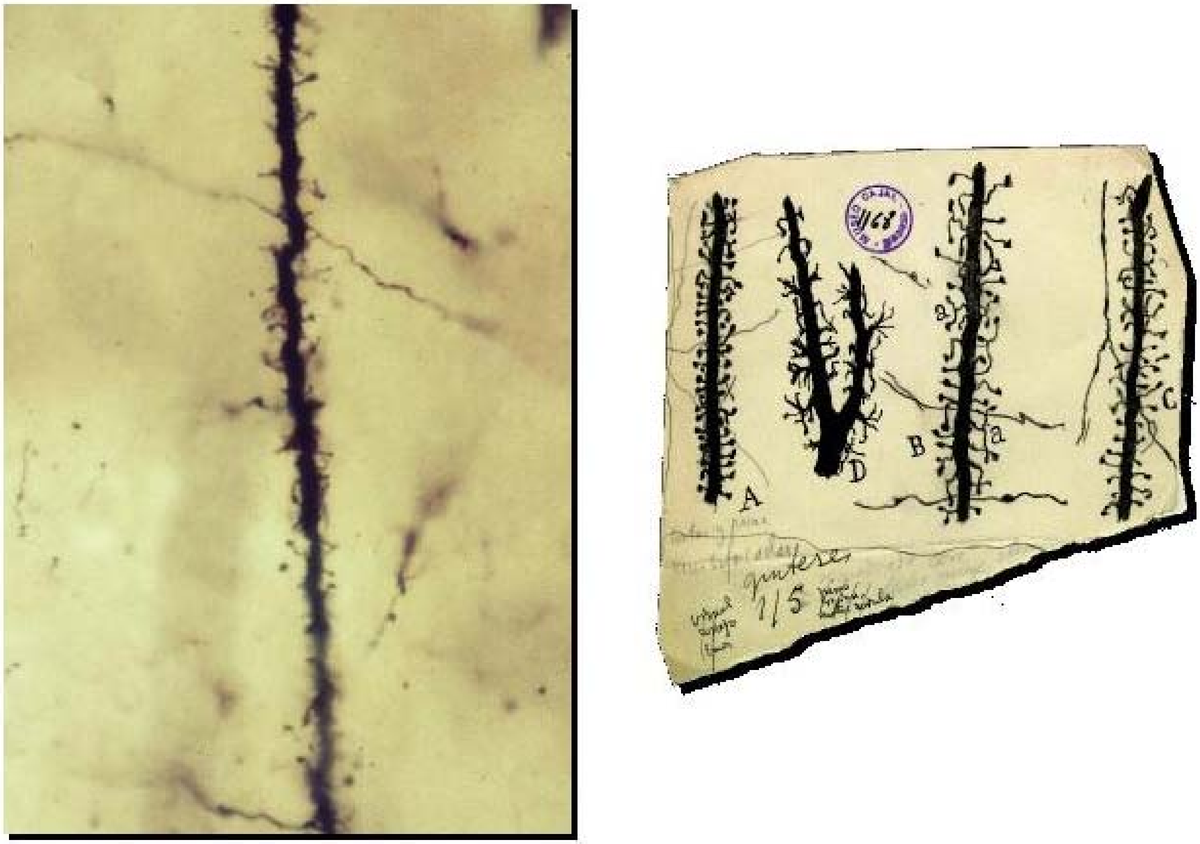
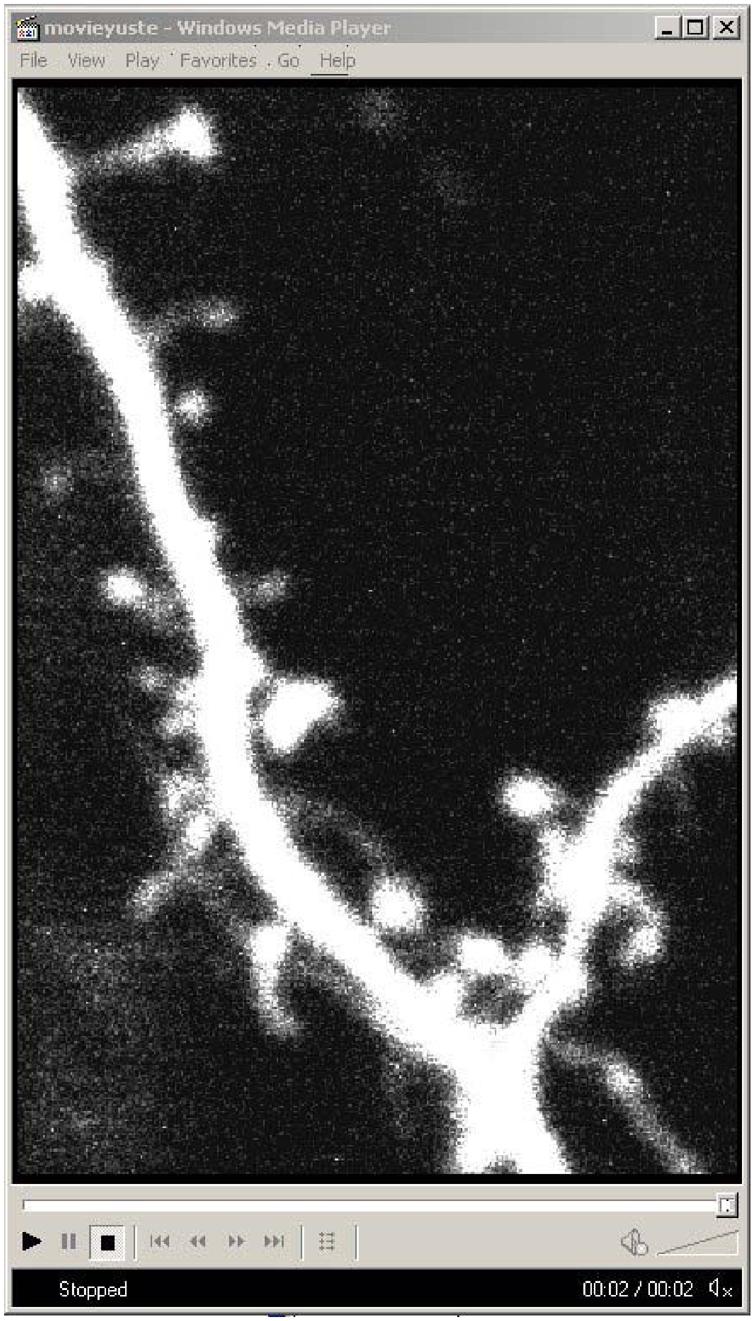


Figure 2

Left: Photomicrograph of an original Golgi preparation from Cajal. The image shows the apical dendrite of a pyramidal neuron with abundant spines (courtesy of Cajal Institute, Madrid).

Right: Drawings of different types of spines by Cajal. Note the large morphological diversity and their heterogeneity (courtesy of Cajal Institute, Madrid).



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Video sequence 1: Spine motility in a pyramidal neuron

Representative two-photon time-lapse sequence of a pyramidal neuron from a cultured neocortical brain slice. The neuron was transfected with EGFP at P1+15DIV and imaged at 17DIV with a custom-built two-photon microscope. The speeded-up sequence represents ~15 minutes of real time. Note the diversity in the morphological dynamics that dendritic spines can produce (Courtesy of Ayumu Tashiro, Columbia University; reprinted with permission from Bonhoeffer and Yuste (2002)).