DISCOVERY AND REDISCOVERIES OF GOLGI CELLS

1, 4 Elisa Galliano, 3 Paolo Mazzarello, 1, 2 Egidio D’Angelo
1 Department of Physiology, University of Pavia, Italy
2 Brain Connectivity Center, IRCCS C. Mondino, Via Mondino 2, I-27100 Pavia, Italy.
3 University Museums System and Department of Experimental Medicine, University of Pavia, Italy
4 Department of Neuroscience, Erasmus MC, Rotterdam, The Netherlands

dangelo@unipv.it

ABSTRACT

When Camillo Golgi invented the black reaction in 1873 and first described the fine anatomical structure of the nervous system, he pointed his attention on a “big nerve cell” that later took his name, the Golgi cell of cerebellum (“Golgi’schen Zellen”, Gustaf Retzius, 1892). The Golgi cell was proposed as the prototype of type-II interneurons, which form complex connections and exert their actions exclusively within the local network. Santiago Ramón y Cajal (Nobel Prize with Golgi in 1906) proceeded through a detailed description of Golgi cell morphological characteristics but the functional insight remained very limited for many years. The first rediscovery happened in the Sixties, when neurophysiological analysis in vivo revealed that Golgi cells are inhibitory interneurons. This finding promoted the development of two major cerebellar theories, the “Beam theory” by John Eccles and the “Motor Learning theory” by David Marr, in which the Golgi cells regulate the spatial organization and the gain of input signals to be processed and learned by the cerebellar circuit. However, the matter was not set and a series of pioneering observations using single unit recordings and electron microscopy raised new issues that could not be fully explored until the Nineties. Then, the advent of new electrophysiological and imaging techniques in vitro and in vivo demonstrated the cellular and network activities of these neurons. Now we know that Golgi cells, though complex systems of chemical and electrical synapses, effectively control the spatio-temporal organization of cerebellar responses. The Golgi cells regulate the timing and number of spikes emitted by granule cells and coordinate their coherent activity. Moreover, the Golgi cells regulate the induction of long-term synaptic plasticity along the mossy fibre pathway. Eventually, the Golgi cells transform the granular layer of cerebellum into an adaptable spatio-temporal filter capable of performing several kinds of logical operation. After more than one century, Golgi’s intuition that the Golgi cell, as a local interneuron, had to generate complex ensemble effects at the network level finds therefore its demonstration.
DISCOVERY OF GOLGI CELLS

On 16 February 1873 a relatively unknown physician wrote to a friend these words: “I spend long hours at the microscope. I am delighted that I have found a new reaction to demonstrate even to the blind the structure of the interstitial stroma of the cerebral cortex. I let the silver nitrate react with the pieces of brain hardened in potassium dichromate. I have obtained magnificent results and hope to do even better.” (Mazzarello, 2010). This was the first known recording of the invention of the “black reaction”, a real breakthrough for brain structure research. The author of this letter was Camillo Golgi (1843-1926; Fig. 1) and for this invention he won the Nobel Prize for Physiology and Medicine on 1906. At the time of this contribution Golgi was physician in charge in a hospital for chronic patients at Abbiategrasso, thirty kilometers from Pavia, in the North of Italy. He afterwards became professor of General Pathology and Histology at the University of Pavia. Using his extraordinary method, Golgi undertook a systematic scientific exploration of the complex nervous system architecture, starting his ambitious scientific adventure with the study of the cerebellum.

The Golgi cell in the first description by Camillo Golgi

In 1874 Camillo Golgi published the work “On the fine anatomy of human cerebellum” (Golgi, 1874), in which he described the Purkinje cells dendritic tree and the whole cerebellar cytoarchitecture. Among the various cell types, Golgi described two kinds of “big nerve cells” in the granular layer:

“... always in the granular layer, with the silver nitrate method, I verified not only the beautiful characteristics of the nerve cell that lay here (characteristics that somebody denies), but I also underlined their exact dimensions, shapes, dispositions and ramifications...
Speaking about their shape, they are really various, but we can roughly distinguish two main groups, that is: 1. long and narrow cells irregularly fusiform, with the maximum diameter parallel to circumvolution’s surface; 2. irregularly round or polygonal cells, with round corners, quite laterally flattened, similar to some others laying in the deep layers of cerebral cortex, with the maximum diameter transversally placed in respect to the direction of granular layer, and so perpendicular to the circumvolution’s surface. Both these types have a large number of prolongations (extensions). […]
More than once from a single nervous prolongation of one of these cells, I saw the formation, cause of the fine and repeated subdivisions in all directions, of a complicated filaments’ interlacement, going from the periphery of the granular layer in both lateral directions, widespread for more than 200 μm.
For what concerns their position, we can say that these gangliar cells are present at the same level at the periphery of the granular layer, close to Purkinje cells, in the middle of the layer, and also in the deepest parts; sometime it is possible to see some of them in the medullary rays, where the nervous fibres are still parallel or they have just started diverging.”

In this description, it is probable that the first type of cell was the Lugaro cells (named after Ernesto Lugaro 1870-1940, who provided a detailed description of them). Moreover, there are no doubts that the second cell type is the one that now bears the name of Golgi, i.e. the “Golgi cell” (Fig. 1-3). Even today, the most relevant criterion to recognise the Golgi cell is the presence of its impressive axonal plexus (Dieudonne et al., 1998; Forti et al., 2006), so well highlighted by Golgi himself and so influential in the elaboration of the reticularist theory.

Golgi’s functional hypothesis on the Golgi cell

After this first hint to the cerebellar structure, Golgi developed a systematic investigation on the whole central nervous system, which he collected in 1885 in a comprehensive work with the
title “On the fine anatomy of the central nervous system organs” (Golgi, 1885). In the chapter of this book dedicated to the cerebellum, Golgi resumed his previous detailed morphological description and went further on considering the course of the cytoplasmatic prolongations of the various cerebellar cell types hypothesizing their functional role.

“It seems obvious to me to consider the cells whose prolongations go directly to form a nervous fibre, as organs with a direct influence on peripheral parts; they would likely be organs connected with motor activity. The other cells, about which I am sure to exclude a direct connection with the fibres that go from the periphery to the centre, seem to me organs connected to sensory activity, or even with automatic actions. In the filaments emanating from the nervous prolongations of this second category of cells, it is easy to recognise a central communication way between the distinct categories of nervous elements.”

Golgi noticed that Purkinje cell axons project out of the cerebellum (these fibres form indeed the sole cerebellar cortex output), so he hypothesised for these cells a motor function. He did not find a similar extra-cerebellum projection from granule cells, so he ascribed them to the sensory or “automatic” function: modern evidences backed his deduction up, because it is in the granular layer that mossy fibres present inputs to cerebellar circuit, while Purkinje cells provide the output and can influence movement (e.g see Bower, 1997). Moreover Golgi tried to give a role even to the big nervous cells: thinking about the fact that their impressive axonal plexuses do not go out of the cerebellum, he guessed that these cells (actually the Golgi cells) are connectional elements in the network. Camillo Golgi also hinted to a possible relationship of the Golgi cells with a structure (“nucleo granuloso”) later named glomerulus (see below). In his Nobel Prize Lecture, while classifying the first and second nerve cells types, Golgi presented a picture of the Golgi cell considering it as “one of the most characteristic examples of the way in which the nerve process of the second type of cells [i.e. those with short local prolongations] behaves” (Golgi, 1967).

As explained below, this intuition has found a certain support in recent anatomo-functional analysis revealing the critical role of Golgi cells in local network regulation.

Golgi cells and the cerebellar network according to Santiago Ramón y Cajal

Following the introduction of the black reaction other histologists - namely the Italian Romeo Fusari, the Swiss Albrecht von Kölliker, the Belgian Arthur van Gehuchten and especially the Swedish Gustaf Retzius - observed the Golgi cells of the cerebellum (Fusari, 1883; Retzius, 1892; Van Gehuchten, 1891). Retzius, in particular, published very clear and detailed drawings of these cells and described them in a paragraph of a work devoted to the histology of the nervous system. Retzius in 1892 introduced the terminology “Golgi’schen Zellen” (Golgi cells) to indicate this type of neurons. But the most extended description of the Golgi cells came with the great Spanish histologist Santiago Ramón y Cajal, who shared the Nobel Prize with Camillo Golgi in 1906.

Ramón y Cajal was one of the first and main users of the black reaction. By applying this new method, he proceeded through a systematic investigation of nervous elements. This work resulted in a fascinating and exhaustive treatment of the “fine anatomy” of central nervous structures: the cerebellum, of course, was included. Ramón y Cajal dedicated some works (Ramón y Cajal, 1888; 1889a; 1889b) and an entire chapter of his “Histology of the nervous system of man and vertebrates” (first edition in Spanish 1899, 1904; French edition 1909, 1911; English edition, 1995) to the cerebellar granular layer, in which he identified four main components: granule cells (small and abundant), cytoplasmatic eosinophil islands (glomeruli), poor glial cells, large neurons different from granule cells. Among the “large cells” group, he identified subgroups: stellate cells (ordinary or with long axon) that he named Golgi cells following Retzius’s terminology, horizontal fusiform cells (which are quite certainly Lugaro cells), and displaced stellate cells (heterogeneous group still today not well characterized, and identified as “non-conventional large interneurons”; in
this group we can include unipolar brush cells, synarmotic neurons, candelabrum neurons and perivascular neurons, besides Lugaro cells; Ambrosi et al, 2007).

Ramón y Cajal proceeded with a detailed description of Golgi cells morphological characteristics, looking at soma, dendrites and axon, and confirming what Camillo Golgi had observed before. By considering localization and soma, he identified them as big stellate or polygonal neurons, present everywhere in the granular layer but more abundant in the region close to Purkinje cells (compared to which are smaller and more stellate-like). Golgi cells have a big nucleus, pale and eccentric, with a big spherical nucleolus; their cytoplasm is abundant and contains scarce and small Nissl bodies. Dendrites depart from the soma in any direction (determining the stellate shape) and some, as Retzius pointed out, reached the plexiform or molecular layer with spines that contact granule cells axons. The dendritic tree is not placed on a unique plane as for Purkinje cells but, as precisely described by Golgi (Golgi, 1974, 1885, 1903) and then confirmed by Kölliker, van Gehuchten, Retzius and Ramón y Cajal (Kölliker, 1890, 1891; 1896; Retzius, 1892; van Gehuchten, 1891, 1893; Ramón y Cajal, 1888, 1889a, 1889b, 1899, 1904, 1909, 1911, 1995), it is displaced, ascending and disorganized. The axon of these cells is peculiar: thick and almost similar to a dendrite, it has an initial bifurcation and a large number of collaterals, forming a real axonal plexus which, with varicose and hook-like endings contacting an enormous number of granule cells inside glomeruli. Depending on the position of the Golgi cell in the granular layer, its axon can be descending (cell close to Purkinje cells), tangential (cell close to white matter) or going in any direction (cell in the middle of the granular layer); the axon length and the arborization degree of the axonal plexus are markers used to distinguish different subtypes of Golgi cells.

It is very interesting to focus on Ramón y Cajal’s description of cerebellar glomeruli, because it is almost the same we are now able to produce with much more powerful histological techniques. He described the glomeruli as vacuolar dendritic cytoplasmatic islands, without nuclei, underlying that they are not cells. Glomeruli, Ramón y Cajal continued, contain granule cells dendrites, Golgi cells axonal collaterals and mossy fibres rosettes. In summary, the cerebellar glomerulus is a structure in which mossy fibers and Golgi cells are able to contact and influence a huge number of granule cells. Ramón y Cajal’s account, extraordinarily detailed, continues with the description of the other large neurons present in the granular layer and with the comparative and developmental histology of the cerebellum. What emerges from his work is a clear interest for cerebellar neurons, particularly for the small granule cells and for the large stellate cells discovered by Camillo Golgi.

FROM SIXTIES TO NINETIES: FIRST FUNCTIONAL DESCRIPTIONS OF GOLGI CELLS

In the course of the first sixty years of the Twentieth century the Golgi cells were usually only quoted in the anatomical handbooks without adding new inferences about their putative physiological function. Their first rediscovery happened in the Sixties, thanks to improved histological and functional measurements leading to new hypothesis on the cerebellar circuit. The basic design of the cerebellar cortex and, inside it, of Golgi cell anatomical and functional connectivity was defined (Palay and Chan-Palay, 1974). Golgi cells were shown to receive excitatory inputs from mossy fibres and parallel fibres (the granule cell axons) and to give inhibitory outputs to granule cells into the glomeruli. Each granule cell receives 3–4 inhibitory synapses on different dendrites (Hamory and Somogyi, 1983; Jakab and Hamori, 1988). The Golgi cell – granule cell synapses consist of small boutons located proximally to the granule cell dendritic endings, which, in turn, receive the excitatory mossy fibre terminals. Both the mossy fibre and Golgi cell terminals, together with several tens of granule cell dendrites (see Palkovits et al., 1971; Ito, 1984), are included into the cerebellar glomerulus. Observations that are not often mentioned are that the glomerulus includes Golgi cell basal dendrites (Hamori and Szentagothai, 1966) and
that the climbing fibers send collaterals to the Golgi cell (Scheibel and Scheibel, 1954). Another surprising observation that was predictive of most recent discoveries on temporal coherence in the inhibitory cerebellar network (see below), was that electrotonic coupling occurred among basket cells and Golgi cells (Sotelo and Llinas, 1972).

A breakthrough about Golgi cell function happened indeed in 1964, when R. Llinas and S. Sasaki in Sir J.C. Eccles’s laboratory discovered the inhibitory nature of the Golgi cell (Eccles et al., 1964). This was in fact the first example of inhibitory feedback to be assigned to a particular neuronal element. Feedback inhibition of motoneurons, known as Renshaw cell inhibition (Renshaw, 1946) was originally described 25 years before the actual cell type responsible was identified anatomically (Jankowska and Lindstrom, 1971). With the subsequent elaboration of the so called “beam theory”, Eccles proposed an interpretation of Golgi cell’s function (summarized in Eccles et al., 1967): the Golgi cell was considered to inhibit granule cells through two mechanisms, feedforward and feedback. By causing a strong inhibition in granule cells close to the core of mossy fibre activity, Golgi cells would improve the spatial discrimination of the inputs that reach the cerebellar cortex. However, this theory lacked of some critical elements: first, it was uniquely based on anatomy and disregarded circuit dynamics. Secondly, beam formation was uniquely attributed to lateral inhibition generated by basket stellate inhibitory innervations on Purkinje cells and had nothing doing with the Golgi cell / granule cell circuit. Thirdly, it made the assumption that Golgi cells generated a random inhibitory feedback. These are clearly three oversimplifications that have subsequently been reconsidered leading to reevaluate the connectivity and functional role of Golgi cells and of the entire cerebellar circuit (see below).

David Marr, one of the fathers of neurocomputation, in 1969, proposed his own theory to explain cerebellar functioning, which is known as “Motor-learning theory”. He defined, on theoretic basis, a computational role for Golgi cells. According to Marr, Purkinje cells are liable for the learning of motor patterns carried by mossy and climbing fibres to granular layer. The number of patterns that can be learned at the Purkinje cell level decreases together with the increase of the amount of active parallel fibres per input. It is so necessary that one element of the circuit acts as regulator of the codon size, which represents the number of granule cells activated by a beam of mossy fibers. The Golgi cell is in an ideal position to play this role. Thus, Marr predicted that Golgi cells would be able to regulate granular layer excitability, and so the amount of information that can be elaborated, transmitted and learned.

Despite the Beam and Motor Learning theories were quite attractive and seemed to provide a comprehensive explanation for the whole cerebellum and for the Golgi cell inside it, the investigation of cellular dynamics and of detailed connectivity patterns moved its first steps leading to new results and mining the plausibility of the two theories. The contrast between the simplified Golgi cell connectivity proposed by the two theories and the morphological observations on the cerebellar glomerulus was striking. The very specific gating nature of the inhibitory feedback was investigated (Precht and Llinas, 1969) showing that the activity of a given granule cell/Purkinje cell set was more powerfully inhibited by homonymous activation of mossy fibers (in that case from the vestibular system) than from mossy fibers innervating the same granule cells from the contralateral vestibular nerve. This indicated that Golgi cell inhibition was probably glomerulus specific and not a random inhibitory feedback, as originally supposed. Moreover, as explained, potentially important observations like those on electrotonic coupling and on the fine structure of glomerular organization were not considered. These observations, which address the real nature of the issue, have found their continuation in the single cell recordings and detailed computational models developed in the last two decades (see below).

**GOLGI CELLS: THE STATE OF THE ART**
A new trend in Golgi cell investigations arrived in the Nineties, when cerebellar neurons begun to be recorded in acute slice preparations using the patch-clamp recording technique. Moreover, single unit Golgi cell activities were recorded in vivo, the connectivity of these neurons has been revisited and their histochemical and functional properties redefined (Figs 4-8) generating the current view of Golgi cell connectivity and function. At the same time, the interest for brain dynamics has raised (Buzsàky, 2006) and the cerebellum has been subjected to intensive investigations aimed at understanding its involvement in timing and sensory expectation (Spencer et al., 2007) involving both the spheres of sensory motor programming and cognition (Ivry and Spencer, 2004).

**Backing-up Golgi’s predictions on local Golgi cell connectivity**

Although the basic morphology and connectivity identified by Camillo Golgi are still actual [“… irregularly round or polygonal cells, with round corners, quite laterally flattened...”, Golgi (1874)], several major advancements have appeared. In a quantitative description recently reported by Barmack and Yakhnitsa (2008), Golgi cells in vivo showed relatively large (10–20 µm) soma. The axonal plexus extended with a parasagittal organization, branching within the granule cell layer for ~650 µm sagittally and for ~180 µm medio-laterally. The dendrites showed variable morphology and often two-four dendrites emerged as thin processes from a single point in the soma and terminated with several varicosities.

The fact that Golgi cells may be heterogeneous [“... Speaking about their shape, they are really various... For what concerns their position, we can say that these gangliar cells are present at the same level at the periphery of the granular layer, in the middle of the layer, and also in the deepest parts.”, Golgi (1874)] has also been revisited. Five distinct subpopulations of Golgi cells were distinguished by Simat and colleagues (2007) based on neurochemical phenotype, cell shape, size, and location in the granular cell layer. The majority of Golgi cells are in fact both GABAergic and glycinenergic (80%), some are specifically GABAergic (15%), and some specifically glicinenergic (5%). Whereas, in general, granule cell inhibition is only GABAergic, in the vestibulo-cerebellum Golgi cells inhibit the granule cells by releasing GABA and the Unipolar Brush Cells (UBCs) by releasing glycine. Moreover, Geurts et al. (2001, 2003) found various expressions of certain biochemical markers (rat-303, calretinin, mGluR2, somatostatin). The Golgi cells may thus contribute to distinct cerebellar sub-circuits, although no remarkable differences in their intrinsic excitability have emerged (Forti et al., 2006).

It is important to note that Golgi postulates a local connectivity (Golgi, 1874), which has been subsequently redefined and analyzed in detail (Eccles et al., 1967; Palkovits et al., 1971; Palay and Chan-Palay, 1974; Ito, 1984). Functional studies (Figs 4-6) have shown that Golgi cell activity can be influenced both by mossy fibers, parallel fibers and climbing fibers and by molecular layer interneurons (Eccles et al., 1967; Vos et al., 1999a; Holtzman et al., 2006a, 2006b, 2009; Xu et al., 2008; Barmack and Yahnktsa, 2008; Ros et al., 2009). Tactile punctuate stimulation readily activates the Golgi cells generating a first rapid spike response through sensory mossy fibers, a second spike is then conveyed through cortico-cerebellar pathways and further spikes are possibly conveyed through the parallel fibers. However, while a physiological analysis has been performed for the granule cell → Golgi cell (Dieudonne, 1998; Bureau et al, 2000), stellate/basket cell → Golgi cell (Dumoulin et al., 2001) and Lugaro cell → Golgi cell (Dieudonné and Dumoulin, 2000) connections, the nature of connections from mossy fibers and climbing fibers to Golgi cells remains largely to be determined. Recent results indicate that the mossy fiber → Golgi cell connection is glutamatergic and rapidly and efficiently excites the Golgi cell (Kanichai and Silver, 2008) but several issues remain unanswered. Do all mossy fiber synapses originate from glomerular connections? Do granule cells form their main connections with the Golgi cell through the parallel fibers or are there also en passant synapses along the ascending axon? Are the afferent synapses formed by mossy and parallel fibers functionally equivalent? Concerning the climbing fiber → Golgi cell connection (Scheibel and Scheibel., 1954; Shinoda et al., 2000), despite climbing fibers
are excitatory on Purkinje cells they have an inhibitory effect on the Golgi cells. This can occur in at least two different ways (Xu and Egley, 2008), i.e. (i) by activating the stellate cells, which in turn inhibit the Golgi cells, or (ii) by activating mGluR2 glutamate receptors on Golgi cell dendrites, which activate an inward rectifier current preventing depolarization (Watanabe et al., 2003). And what is the impact of the electrical junctions formed by Golgi cells (Sotelo and Llinas, 1972)?

Clearly much remains to be done before a complete view of Golgi cell functional connectivity can be drawn. A more detailed explanation on functional synaptic connectivity and a survey on the receptors involved at the different synapses can be found below and in Box. 2.

**How local Golgi cell connectivity may determine function**

Camillo Golgi understood that morphology and local connectivity had to reflect into the function that a single nerve cell plays in the local network as well as in the economy of the whole nervous system (Golgi, 1967). We consider here 6 main observations reconnecting the structure of the Golgi cell to its function.

As observed in Figs 1-3 and 4A (see also Dieudonne, 1998; Forti et al., 2006; Barmak and Yakhnitsa, 2008), the Golgi cell axonal plexus extends exclusively in the granular layer and, through thin branches, can form secondary plexuses in the same or even in neighboring laminae (e.g. see Eccles et al., 1967). The broader extension of axon than basal dendrites provides the basis for lateral inhibition, whose functional impact has recently been demonstrated by multi-electrode array recordings and voltage-sensitive dye (VSD) imaging (Mapelli and D’Angelo, 2007; Mapelli et al., 2009, 2010; Fig.6).

In some Golgi’s original drawings the axonal fields of Golgi cells overlap (e.g. see Fig. 2-3), although in subsequent drawings the Golgi cell axonal fields appear well isolated (e.g. see Eccles, 1967; Ramon y Cajal 1995; Ito, 1984). This overlap would be important to allow the combinatorial inhibition of granule cells and has recently been observed using fluorescent staining in vivo; see Barmak and Yakhnitsa, 2008). Consistently, the analysis of Golgi cell – granule cell neurotransmission has recently shown that each granule cell receives inhibition from different Golgi cells, implying overlapping of the axonal fields (Mapelli et al., 2009).

In Golgi’s drawings, the terminal endings of Golgi cell axons generate hand-like structures matching the size and separation distance of the glomeruli (Figs 1-2 and Golgi, 1967), a fact even more evident in subsequent drawings by Ramón y Cajal (1889a). The presence of robust GABA receptor-mediated spillover responses to Golgi cell axon stimulation, which indicates diffusion of GABA onto neighboring dendrites (Rossi and Hamann, 1998), suggests that Golgi cell terminals can inhibit clusters of granule cells sending their dendrite in the same glomerulus (Mapelli et al., 2009).

A feature that was already evident in Golgi’s drawings and clearly described by Ramón y Cajal is that, at variance from Purkinje cells, the structure of Golgi cell dendrites is not rigorously organized in a plane but rather it is more irregular and tri-dimensional. Thus, Golgi cells may not be suited to detect ordered time sequences transmitted through the parallel fibers (Braitenberg et al., 1997). These observations combined with recent electrophysiological and modeling data support the view that Golgi cells can both precisely respond to topographically organized inputs and perform an extended spatio-temporal integration of parallel fiber information modulating their basal activity state (Vos et al., 2000; DeSchutter and Biaalije, 2001; DeSchutter, 2002).

Another fact is that, in Golgi’s and Ramón y Cajal’s drawings, the axonal plexus of Golgi cells is always shown in parasagittal sections. This implicates that the Golgi cell axon expands preferentially in the parasagittal plane, as subsequently confirmed by confocal imaging (Barmak and Yakhnitsa, 2008). The axonal organization is in matching with the parasagittal distribution of mossy fiber ramifications (Sultan, 2001). Moreover, the entire Golgi cells, comprised of their axon and dendrites, are segregated into parasagittal compartments for zebrin-2, aldolase C, NOS and other markers of granular layer neurons and Purkinje cells (Sillitoe et al., 2008). This observation is
related to a major issue of cerebellar organization, in which mossy fiber inputs coherently activate certain granular layer areas, certain sets of Purkinje cells and specific portions of the olivo-nuclear complex thus forming structural and functional modules (Brown and Bower, 2001; Voogd et al., 2003; Pijpers et al., 2006; Apps and Hawkes, 2009). Therefore, it seems that Golgi cells, through mossy fiber (and potentially climbing fiber) inputs to their dendrites, are wired within microcircuits involving specific cortico-nuclear modules, while through their parallel fiber connections can be interconnected with multiple modules.

Finally, the presence of gap-junctions among the inhibitory interneurons (stellate, basket and Golgi cells) was early observed both within and across classes (Sotelo and Llinas, 1972). The role of this inhibitory syncytium, which may facilitate the synchronization of vast areas of the cerebellar cortex, has only been recently addressed. The functionality of gap-junctions between stellate cells (Mann-Metzer and Yarom, 2000) and between Golgi cells (Duguè et al., 2008) has been demonstrated using double-patch recordings, while low-resistance electrical communication between molecular layer interneurons and Golgi cells remains to be demonstrated. Clearly, low-resistance electrical connections between Golgi cells have the potentials, together with other mechanisms (D’Angelo et al., 2008), of enhancing the local coherence of cerebellar activity.

Golgi cell physiology: dynamic properties and network entrainment

A completely new view on the Golgi cell has been opened by electrophysiological recordings in vitro and in vivo (Figs 4-6).

Electrophysiological patch-clamp recordings in vitro (see Box 2) have shown that the Golgi cell is a pacemaker neuron that fires autonomously at 1-10Hz (Dieudonné, 1998; Forti et al., 2006; Fig. 7A). When perturbed, it shows discharge adaptation, post-inhibitory rebound and afterhyperpolarization (Fig. 7A-B). In addition, Golgi cells are resonant around their oscillation frequency, making them suitable to enhance responses in the theta-frequency band (Solinas et al., 2007a,b; Fig. 7C). Rhythmic activity is also observed in vivo both in awake (cat: 2 to <50 Hz, Edgley and Lidierth, 1987; monkey: 10–80 Hz, Miles et al. 1980) and anaesthetized animals (rat: 2 to 30 Hz, Schulman and Bloom, 1981; Vos et al. 1999a; Holtzmann et al., 2006a,b), probably as a reflection of pacemaking modulated by synaptic activity. It has been recently proposed that electrical coupling between Golgi cells could be critical to allow the emergence of low-frequency pacemaking, at the same time synchronizing oscillations in neighboring Golgi cells (Fig. 5A; Duguè et al., 2008). Golgi cells show “loose synchrony” over hundreds of micrometers along the coronal axis (Volny-Luraghi et al., 2002; Tahon et al., 2005), possibly reflecting synchronization along the parallel fiber beam and feed-back inhibition onto granule cells (Vos et al., 1999b).

The mossy fiber inputs occur in two main modalities, namely protracted frequency-modulated discharges and short high-frequency bursts (Chadderton et al., 2004; Kase et al., 1980; Van Kan et al., 1993; Jorntell and Eckerot, 2006; Rancz et al., 2007). Accordingly, the Golgi cells present two well defined response modalities. First, Golgi cells can follow peripheral signals in a continuous fashion modulating their frequency with the intensity of the stimulus (Miles et al., 1980; Edgley and Lidierth, 1987). Secondly, Golgi cells respond to punctuate stimulation with a short burst of spikes. The bursts occur very rapidly (in about 10 ms upon facial stimulation) and consist of 1-3 well timed spikes in short sequence (Fig. 4B; Vos et al., 1999a; Holtzman et al., 2006a). The first spike corresponds to the trigeminal input (trigemino-cerebellar mossy fibers), the second spike to sensory-motor cortical input (cortico-ponto-cerebellar mossy fibers), the third one may reflect the parallel fiber input. Following the bursts, the Golgi cell generates a long-lasting inhibitory period (Fig. 4B; Holtzman et al., 2006a,b; 2009; Xu et al., 2008) or silent pause (Vos et al., 1997) lasting for about 100 ms, probably reflecting both intrinsic membrane properties and synaptic inputs (Fig. 7A-B; Solinas et al., 2007a,b).

The entrainment of Golgi cells into local and extracerebellar networks is observed in different cases (Figs 4-5). In states of restive attentiveness and active expectancy (Pellerin and Lamarre, 1997; Hartmann and Bower, 1998; Courtemanche et al., 2009), the granular layer shows
rhythmic activity in the theta-frequency band. In the anesthetized animal, Golgi cells can generate repeated bursts along with granule cells during the “up” phase of the slow delta-frequency cortical oscillations (Ros et al., 2009). Golgi cells can contribute to tune the granular layer toward this slow frequency band through the feedback inhibitory loop (Maex and De Schutter, 1998), their resonant properties (Figs 7-8; Solinas et al., 2007; Solinas et al., 2009) and electrical synapses (Duguè et al., 2009).

In summary, the Golgi cell, by shifting from a rhythmic discharge to an event-drive state on behavioral demand (D’Angelo, 2008), can both entrain and be entrained in network oscillations demonstrating an intimate relationship with both local and long-range circuits (cf. Buzsaki, 2006).

**Multiple inhibition mechanisms contribute to global network computation**

The Golgi cells take part to granular layer processing through multiple inhibitory mechanisms:

(i) Golgi cells generate *phasic* and *tonic inhibition* (Mapelli et al., 2009; Crowley et al., 2009). This latter occurs through neurotransmitter spillover causing slow and diffused responses within the glomerulus (Brickley et al, 1996; Rossi & Hamann, 1998) and inhibiting numerous granule cells altogether.

(ii) Golgi cells organize granular layer responses in center-surround exploiting *lateral inhibition*. The center-surround organization, once occurring over partially overlapping activation fields, generates combinatorial responses (Mapelli et al., 2009) resembling coincidence detection and spatial patterns separation predicted by the Motor Learning Theory (Marr, 1968; Albus, 1971).

(iii) Golgi cells enhance coherent oscillations in the granular layer network. Oscillations occur through *feedback inhibition* and coherence emerges from the fact that Golgi cell inhibition extends over large granule cell fields. The intrinsic Golgi cell excitable properties, including pacemaking and resonance, may tune oscillations on the theta band complementing the theta-frequency resonance of granule cells (D’Angelo et al., 2001; Lombardo and D’Angelo, unpublished observations).

(iv) Golgi cells determine a time-window through which granule cell spikes are allowed to pass in response to mossy fiber bursts. This occurs through *feed-forward inhibition*, which limits the duration and intensity of granule cell excitation (Kanichai and Silver, 2008; D’Angelo and De Zeeuw, 2009).

(v) Golgi cells regulate the gain at the mossy fiber-granule cell relay during prolonged input bursts by exploiting *tonic inhibition*, which regulates granule input resistance and spike threshold (Mitchell and Silver, 2003).

(vi) Golgi cells, by regulating granule cell depolarization through a *shunting inhibition* mechanism, control NMDA channel unblock and the induction of mossy fiber – granule cell long-term synaptic plasticity in response to repeated mossy fiber bursts (Mapelli and D’Angelo, 2007:).

These properties suggest that Golgi cell inhibition can allow the granular layer to operate as an adaptable spatio-temporal filter (Dean et al., 2010) capable of regulating delay, controlling gain, enhancing contrast and combining multiple afferent input fields (D’Angelo and De Zeeuw, 2009). These mechanisms have been interpreted through mathematical models incorporating the main neurophysiological properties of Golgi cells (Solinas et al., 2010; Fig. 7-8). And by being embedded into the granular layer, the Golgi cell operates as hidden neuron in a multi-layered network that could provide extended computational capabilities to the whole cerebellum (Mapelli et al., 2009). How these mechanisms contribute to setting-up cerebellar computation as a whole remains a challenge for future research.
THE DISCOVERY OF CAMILLO GOLGI: A RETROSPECTIVE VIEW AND FUTURE DEVELOPMENTS

One of the major issues raised by the Nobel Prize dissertations in Stockholm in 1906 concerned the complexity of brain structural organization (Ramón y Cajal, 1967; Camillo Golgi, 1967; Box 1). Ramón y Cajal was undisputedly the paladin of the neuron theory according to which the nervous tissue is composed, like any other tissues, of single independent cells. On the other hand Camillo Golgi was impressed by the complexity of the brain and thought that it was not possible to account for brain performance by simple point-to-point connectivity. Based on the observations made with the black reaction, 15 years before Ramón y Cajal, he proposed a reticularist theory known as “diffuse nervous net”. This states that the axonal prolongations of nerve cells were fused (or intimately interlaced) in a diffuse web along which the nervous impulse propagated (Kruger, 2007; Kruger and Otis, 2007; Mazzarello, 2007, 2010). The debate between neuronists and reticularists, which was at the origin of modern neuroscience, was a fundamental clash of ideas between the 18th and 19th century. In the end, Ramón y Cajal’s neuronal theory of the nervous system triumphed and it is now considered the fundamental paradigm of brain organization. Golgi, in turn, gave a wrong answer to a real question, i.e. the difficulty to conceptualizing complexity with simple point-to-point connectivity. Golgi envisioned multiform dynamical and interacting fields of activity, as much as modern neural network theory is predicting even if, of course, in a different way (Rieke et al., 1997; Buzsaki, 2006).

The Golgi cell provides an intriguing example of this duality in that, while maintaining well defined single neuron properties, this neuron can coordinate (and be entrained into) activity of large granular layer fields. The Golgi cell makes extensive connections with the rest of the cerebellar network, receiving inputs from both the mossy fiber and the climbing fiber system (comprising granule cells, stellate cells, basket cells, inferior olivary cells, Lugaro cells) and sending outputs to the granular layer (comprising both granule cells and UBCs). Moreover, the presence of gap-junctions has been proposed to form a Golgi cell electrical syncytium (Sotelo and Llinas, 1972; Duguè et al., 2009), raising a puzzling analogy with the “protoplasmic syncytium” envisaged by Golgi. Eventually, the Golgi cells may be able to coordinate the activity of large granule cell fields with extracerebellar structures (like the thalamo-cortical system) on appropriate frequency bands and to contribute to rhythmicity and to the representation of time in the cerebellum and in cortico-cerebellar loops (Ivry and Spencer, 2004). Therefore, the Golgi cell fully represents a kind of nerve cell which revitalizes, under a new light, the discussion on the relationship between single neurons and the networks they are part of.

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Fig. 1. Camillo Golgi, the black reaction and the Golgi cell. (A) Camillo Golgi, Nobel Prize for Physiology and Medicine (1906). Camillo Golgi (1843-1926) invented the “black reaction”, that allowed him and many other scientists to visualize the fine structure of the nervous system. “... I have found a new reaction to demonstrate even to the blind the structure of the interstitial stroma of the cerebral cortex. I let the silver nitrate react with the pieces of brain hardened in potassium dichromate. I have obtained magnificent results ....” (from a letter to a friend, 16 February 1873; Mazzarello, 2010). (B) In this picture, Golgi shows reconstruction of a Golgi cell. Note the precise description of the basal and apical dendrites and of the large axonal plexus, the hallmark of the Golgi cell. [Gangliar cell in the (neonatal) cat cerebellar cortex (TABLE XIV, Opera Omnia, Golgi, 1903). “Such cells are part of the granular layer and, in the cat and rabbit, when the black reaction succeeds, can be seen in a considerable amount. – Most ramifications of the protoplasmatic prolongations (in black) reach the superior border of the molecular layer. – The nervous prolongation (in red), with repeated subdivisions becoming finer and finer, creates an extremely complicated interlacement of fibers. These, in the vertical plane, spread from one to the other border of the granular layer, and in the width of the granular layer mix up with the interlacements resulting from subdivisions of neighbouring cells of the same type (see Table XVII). This cell is one of the most remarkable specimens among those that are described as second type cells in the text. Regarding the cerebellum, such a cell should be to compared to the one represented in Table XV (a Purkinje cell), representing one of the most remarkable specimens of the first type of cells.” Translated from Opera Omnia (Golgi, 1903).]
**Fig. 2. The spatial relationship between multiple Golgi cells.** Note that no restriction is imposed to axons, which spread and overlap into the granular layer, that apical dendrites ramify in the molecular layer without specific orientation, and that basal dendrites ramify in the granular layer over a surface smaller than that occupied by the axon. In this figure, the fundamental features of the Golgi cell are captured. [Fragment of a (neonatal) cat cerebellar convolution (vertical section). (TABLE XVII, Opera Omnia, Golgi, 1903). “The drawing is specifically made to show shape, disposition, ramification laws, localization and relationships of the large gangliar cells of the granular layer. Protoplasmatic prolongations branch dichotomously in a very different way compared to Pukinje cells. The most distal extensions of the branches often reach the molecular layer peripheral limit. Nervous prolongations, with their fine and repeated subdivisions, form a complicated interlacement so that it results impossible to follow the course of single prolongations. Such interlacement does not seem to have borders either toward the inside the granular layer or toward the molecular layer. Thus, several of these interlacements obviously mix up to form a complicated plexus.” Translated from Opera Omnia (Golgi, 1903)].
**Fig. 3. The relationship between Golgi cells and granule cells.** Granule cells largely exceed in number the Golgi cells and are much smaller (Purkinje cells are distinctly shown in the background). Therefore a Golgi cell can innervate several granule cells laying within their axonal plexus, capturing another fundamental feature of the granular layer organization. (*Fragment of a rabbit cerebellar convolution (vertical section).* (TABLE XIX, *Opera Omnia*, Golgi, 1903). “This drawing was specifically made to illustrate the granular layer. – The so-called granule cells look like nervous cells with a globose shape, really small and equipped with 3, 4, 5 or even 6 prolongations, among which just one has the features of nervous prolongation (the nervous prolongation is just outlined, red thread). Prolongations, that seems to be correct to name protoplasmatic, even if they appear slightly different from other gangliar cells’ prolongations, end up with a small granulous mass, towards which neighbouring granule cells’ prolongation often converge. In the region in which the granular layer converts into the molecular layer, two large cells are drawn. These are placed laterally and differ from Purkinje cells for the cell body shape, for the way of branching of their protoplasmatic prolongations and, overall, for the very different organization of the nervous prolongation. – These two large cells are of the same type of the ones already illustrated in Tables XIV and XVII.” Translated from *Opera Omnia* (Golgi, 1903).)
Fig. 4. Golgi cell activity in vivo. (A) The Golgi cell shows rhythmic background activity in vivo (from Holtzman et al., 2006a). (B) Peripheral sensory stimulation elicits bursts of activity (from Holtzman et al., 2006a). Each burst is usually composed by 2-3 spikes and is followed by a long-lasting inhibitory period (or silent pause in Vos et al., 1997). (C) During locomotion, the Golgi cell is entrained into repetitive activity cycles, during which its frequency is modulated.
**Fig. 5.** Golgi cell network entrainment. (A) The Golgi cell spikes are in phase with the local field potential of the granular layer (Duguè et al., 2008). (B) Golgi cells can show rhythmic entrainment with the UP-DOWN states characterizing neocortical activity (Ros et al., 2009). The different behavior in A and B may reflect different functional states or simply the fact that the trace in A may be part of an UP state as shown in B.
Fig. 6. Control of granular layer spatio-temporal dynamics by Golgi cell inhibition. (A) Stimulation of a mossy fiber beam elicits local field potentials in the granular layer, which can be composed by more spikes generated in sequence by granule cells. Activation of the feed-forward inhibitory Golgi cell loop limits spike emission (time-window effect; from Mapelli and D’Angelo, 2007). (B) Stimulation of a mossy fiber beam elicits local field potentials in the granular layer, which are surrounded by lateral inhibition generated by Golgi cells (center-surround effect; from Mapelli and D’Angelo, 2007).
Fig. 7. *The electrical activity of Golgi cells*. The Golgi cell shows response dynamics, which can support the cycles of activation and inactivation observed in various functional conditions (see Figs 5 and 6). (A) The Golgi cell *in vitro* shows (1) pacemaker activity at around 7 Hz. In response to depolarization (2), the Golgi cell shows high-frequency discharge with frequency adaptation. In response to hyperpolarization (3), the Golgi cell shows sagging inward rectification, followed by (4) rebound excitation. Burst of activity are followed by (5) a silent pause. (B) Demonstration of the silent pause following a burst response to a mossy fiber stimulus (arrows in the inset). (C) When stimulated with pulses repeated at different frequencies, the Golgi cell shows enhanced responses (faster and higher frequency spikes) at the resonant frequency of 6 Hz. The tracings are simulated from the models of Solinas et al. (2007a,b, 2010) and reproduce response behaviors reported in Dieudonné (1988), Forti et al. (2006) and Solinas et al (2007a,b).
**Fig. 8. The physiological consequences of Golgi cell activation.** Golgi cell activation has complex consequences on granular layer responses. (A) A burst in a group of mossy fibers (mf) generates stronger and faster granule cell responses in the center than in the surround of a granular layer field (the red profile represents the excitatory/inhibitory balance in a granular layer field activated by a group of mfs and regulated by Golgi cells – drawn after Mapelli and D’Angelo, 2007). (B) A mf theta-burst stimulation (TBS) in a group of mfs generates more effectively LTP in the center and LTD in the surround of the granular layer field. (C) The raster plot shows that a diffused random stimulation of the mfs generates a coherent response of the granule cells (GrC) and of the Golgi cells (GoC). Synchronization is due to parallel fiber feed-back inhibition. Crosscorrelograms (CCH) are shown for two GoCs and for all the granule cells and the Golgi cells in the network revealing their coherence. Data elaborated from the model of Solinas et al. (2010).
BOX 1

NETS VERSUS NODES: THE CONTROVERSY BETWEEN GOLGI AND CAJAL

In the mid 70s, when Golgi began his investigation, the prevailing morphological theory of the brain was that of a reticular dendritic net of “connective vessels” extending and interlinking across the nervous tissue. Instead Camillo Golgi, supported by his observations with the black-reaction, believed that were the axons to be interconnected in a net. However Golgi did not make any definitive statement on the precise mode of that connection: in some of his writings he tended to consider a direct fusion of axon prolongations, in others he left open the possibility that groups of nerve cells did not form direct anastomoses but only an intimate functional web through the interlacing of they axons. Beside the exact histological intercellular connection, Golgi adhered to the physiological idea of a diffuse interactions among nerve centres.

In 1886 there was a turning point in concepts concerning the nervous system structure. The Swiss anatomist Wilhelm His theorized that the nerve-cell body and its processes formed independent units. Another Swiss scholar, August Forel, reached similar conclusions in 1887. The same year a Spanish psychiatrist, Luis Simarro Lacabra, returned to Madrid from Paris equipped with the latest literature and histological preparations. Simarro Lacabra was visited by Santiago Ramon y Cajal, a young professor at the University of Valencia. Cajal observed the preparations made with the black reaction and remained breathless. He suddenly started an extensive investigation of the nervous system using the Golgi method and, looking at the preparations with the new neuronistic ideas in mind, he soon agreed with the Swiss hypothesis and became “the champion of neurons”.

The emergence of “neuronism” drove Golgi to even more deeply identify with “reticularism”, in favor of which he wrote a paper in 1891. On the other side, Cajal continued to produce evidence in favor of neuronism. This was the situation when, in 1906, the Karolinska Institute of Stockholm announced the Nobel prize award to Golgi and Cajal. This seemed the great opportunity to recompose the scientific rivalries of the previous 16 years. Unfortunately, the confrontation between the two scientists became even worse after the Nobel prize lecture, in which Golgi strongly attacked the neuronist theory. The Nobel lecture was a disaster for Golgi and, consequently, a triumph for Cajal.

Adapted from:
BOX 2

The molecular level of organization: Golgi cell channels and receptors

Far from what Golgi could imagine, the intricate connectivity and the excitable dynamics of the Golgi cell are supported by an even further complexity of ionic channels and receptors (for previous reviews see Farrant and Nusser, 2005; Geurts et al., 2003) providing mechanisms suitable for regulating circuit dynamics and homeostasis. Most relevant factors are the expression of specific receptor sub-types coupled to neurotransmitter spillover in the cerebellar glomerulus.

The main excitatory inputs to Golgi cells are glutamatergic, with AMPA and NMDA receptors at the mossy fiber–Golgi cell relay (Kanichay and Silver, 2006; L. Forti et al., unpublished observation) and AMPA, NMDA and kainate receptors at the parallel fiber–Golgi cell relay (Bureau et al., 2000; Dieudonné, 1998; Misra et al., 2000). Whether NMDA receptors contribute to regulate Golgi cell excitability or are involved in some forms of plasticity remains to be determined. The inhibitory inputs to Golgi cells are both GABAergic and glycinergic. GABAergic inputs are provided by stellate and basket cells (Dumoulin et al., 2001), while mixed GABAergic/ glycinergic inputs are formed by the Lugaro cells (Dieudonné and Dumoulin, 2000; Dumoulin et al., 2001).

The main output from Golgi cells is GABAergic and inhibits the granule cells in the cerebellar glomeruli. The IPSCs consist in a fast and a slow component (Rossi et al., 2003) determined by differential receptor subtypes and localization (Farrant and Nusser, 2005). Different combinations of α1 and α6 subunit-containing receptors with ancillary subunits regulate synaptic response kinetics conferring specific sensitivity to ambient GABA concentration and spillover in the spillover in the glomerulus (Brickley et al., 1999, 2001; Hadley and Amin, 2007; Nusser et al., 1998; Rossi and Hamann, 1998; Tia et al., 1996). Thus, in addition to determining phasic inhibition, Golgi cells contribute to regulate the basal granule cell input conductance by maintaining a tonic GABA concentration level inside the glomerulus (Brickley et al., 1996; Chadderton et al., 2004). The tonic level of GABA, which is also regulated by non-vesicular release and by the rate of GABA re-uptake in glial cells (Rossi et al., 2003) by binding high-affinity receptors (Tia et al., 1996), can control the gain of the mossy fiber–granule cell relay (Mitchell and Silver, 2003). Acetylcholine can increase non-vesicular GABA release from the Golgi cells contributing to set the ambient GABA level in the glomerulus and tonic inhibition of granule cells (Rossi et al., 2003; see below).

Although the main effects of Golgi cells on granule cells are mediated by GABA, Golgi cells also co-release glycine at their synaptic terminals (Dugué et al., 2005). Granule cells do not express glycine receptors, but it is attractive to speculate that glycine plays a role in regulating activation of granule cell NMDA receptors on their glycine binding site. Conversely, both GABA and glycine receptors are expressed in UBCs, in which Golgi cell activity generates mixed GABAergic/glycinergic responses (Dugué et al., 2005). Interestingly, serotonin activates the Lugaro cells, thereby regulating Golgi cell inhibition (Dieudonné and Dumoulin, 2000).

Metabotropic receptors play also an important role in the Golgi cell circuit. The mGluR2 receptors on Golgi cell dendrites enhance an inward rectifier K-current reducing the response following intense granule cell – Golgi cell transmission (Watanabe and Nakanishi, 2003). Metabotropic receptor also sustain cross-talk between mossy fiber and Golgi cell terminals in the glomerulus: mGluR2 receptor activation on Golgi cell presynaptic terminals inhibits GABA release (Mitchell and Silver, 2000b), while GABA-B receptor activation on mossy fiber terminals inhibits glutamate release (Mitchell and Silver, 2000b). Golgi cells functions are therefore deeply integrated with those of the cerebellar glomeruli allowing to fine tune their response dynamics depending on functional demand.

The mechanisms of Golgi cell electroresponsiveness have been summarized in a previous review (D’Angelo, 2008). A combination of electrophysiological, pharmacological and modeling
experiments (Forti et al., 2006; Solinas et al., 2007a,b) has revealed the basis of pacemaking, bursting, adaptation and rebound excitation and phase-reset. A set of ionic channels, including the $h$-current, raises membrane potential into a critical region. Here, near-threshold oscillations are generated involving a persistent Na-current, the $M$-current and an apamine-sensitive AHP (afterhyperpolarization) K-current. The same ionic mechanism allows fast phase-reset after a perturbation. In response to a stimulus, the resurgent Na-current favors generation of doublets, then adaptation is generated by the M-current and AHP-current. Finally, following an hyperpolarization, the $h$-current and a low-threshold Ca-current cause rebound excitation. Although the investigation of specific ionic currents in Golgi cells is far from complete, present knowledge provides a coherent mechanism through which the Golgi cell simultaneously controls pacemaking and response elicited by depolarization and hyperpolarization.