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Review

The cerebellar network: From structure to function and dynamics

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ABSTRACT

Since the discoveries of Camillo Golgi and Ramón y Cajal, the precise cellular organization of the cerebellum has inspired major computational theories, which have then influenced the scientific thought not only on the cerebellar function but also on the brain as a whole. However, six major issues revealing a discrepancy between morphologically inspired hypothesis and function have emerged. (1) The cerebellar granular layer does not simply operate a simple combinatorial decorrelation of the inputs but performs more complex non-linear spatio-temporal transformations and is endowed with synaptic plasticity. (2) Transmission along the ascending axon and parallel fibers does not lead to beam formation but rather to vertical columns of activation. (3) The olivo-cerebellar loop could perform complex timing operations rather than error detection and teaching. (4) Purkinje cell firing dynamics are much more complex than for a linear integrator and include pacemaking, burst-pause discharges, and bistable states in response to mossy and climbing fiber synaptic inputs. (5) Long-term synaptic plasticity is far more complex than traditional parallel fiber LTD and involves also other cerebellar synapses. (6) Oscillation and resonance could set up coherent cycles of activity designing a functional geometry that goes far beyond pre-wired anatomical circuits. These observations clearly show that structure is not sufficient to explain function and that a precise knowledge on dynamics is critical to understand how the cerebellar circuit operates.

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1. Introduction

At the end of the 19th century, the discoveries of Camillo Golgi and Santiago Ramón Y Cajal, both Nobel Prize for Medicine and Physiology in 1906 (Golgi, 1967; Ramón y Cajal, 1967), raised fundamental issues about the structure–function relationship in neuronal circuits. How do neurons contact each other? What are the precise numerical and topological relationships among them? The cerebellum early attracted the interest of the two scientists. Cajal in particular recognized that, in the granular layer, the granule cells and Golgi cells form densely packed aggregates of neurons receiving inputs from the mossy fibers and generating complex interactions in structures called glomeruli. The granule cells emit ascending axons reaching the molecular layer and forming the parallel fibers, contacting stellate and basket cell inhibitory interneurons, and the Purkinje cells. These send their output to the deep cerebellar nuclei, which generate the cerebellar output and convey it to other brain areas. It was also early recognized that the inferior olive sends climbing fibers to Purkinje cells. These elements form a highly ordered structure, suggesting that the relationship with function could be understood. However, although seminal experiments shed light on general aspects of responses elicited by peripheral stimulation, the functional impact of mossy fibers and the role of climbing fibers inputs remain the object of an open debate and are altogether still unclear. In a historical perspective, we highlight how the combination of electrophysiological and imaging techniques and computational network modeling allows now to reconstruct the spatio-temporal dynamics of the olivo-cerebellar system and to propose functional hypotheses going far beyond those inspired by the original anatomical analysis.

1.1. The historical context: the cerebellum and motor control

The cerebellum, literally “little brain”, has always strongly attracted the neuroscientific interest. Early functional hypothesis on the cerebellum preceded and then coevolved with the histological work of Camillo Golgi and Ramón y Cajal. At the beginning of the 19th century, Rolando (1809) proposed that the cerebellum was involved in motor functions but did not clearly distinguish a specific role of cerebellum in motor coordination. Then Flourens proposed a comprehensive hypothesis, based on ablation experiments, about the structure–function relationship of the major components of the central nervous system. “The properties or nervous forces are five: sensibility, motricity, life principle, coordination of

movements and locomotion, intelligence. Each of the forces resides in a specific organ. Sensibility in the posterior roots of the spinal cord, motricity in the anterior roots, life principle in the brainstem, coordination of locomotor movements in the cerebellum, and intelligence in the cerebral hemispheres.” (Flourens, 1858) A further step in elucidating cerebellar functions came from Luciani (1891), who made use of experimental and clinical observations. Luciani discovered that cerebellum ablation in dogs and monkeys caused atonia, asthenia, and astasia, forming a triad of symptoms still used for clinical diagnosis of cerebellar dysfunction. Thereafter, Gordon Holmes (1917, 1922) produced important clinical observations from soldiers wounded during the 1st world war and from patients with cerebellar tumors. He noted that many of these cases were associated with voluntary tremors and dyskinesia, leading to the modern concept of ataxia.

Thus, when Camillo Golgi and Ramón y Cajal began their histological analysis of the brain, the cerebellum was considered as a motor structure and, since then and for many years, several functional aspects of the cerebellar circuit anatomy have been interpreted within a motor control perspective. Only later, the importance of cerebellum in coordinating emotions and visceral functions in making sensory predictions and in elaborating certain aspects of cognition has been recognized (Bower, 1997; Ivry and Baldo, 1992). Given the homogeneity of the cellular and circuit organization, these new discoveries imply the existence of a basic cerebellar module developing a “general cerebellar algorithm”. The connectivity of numerous such modules with various cortical and subcortical centers would determine the diversity of function now attributed to the different parts of the cerebellum (Cermignani and Apps, 2010).

1.2. The insight from early histological observations: the cerebellum according to Golgi and Cajal

A major advancement toward understanding cerebellar circuit function came from the histological analysis. In 1873, Golgi announced the black reaction and in 1874 published the work entitled “On the fine anatomy of human cerebellum” (Golgi, 1874; Mazarrello, 2010), in which he described the whole cerebellar cytoarchitecture making basic hypotheses on cell connectivity and function. The work of Golgi completed the knowledge of the main cellular elements of the cerebellum: the Purkinje cells and stellate cells in the molecular layer, the granule cells and the Golgi cells (and also probably the Lugaro cells) in the granular layer (Galliano et al., 2010). In this work,

Golgi illustrated for the first time the structure of the Purkinje cells and of their dendritic processes. Then Golgi analyzed the prolongations of the various cerebellar neurons hypothesizing their functional role in a more comprehensive work, “On the fine anatomy of the central nervous system organs” (Golgi, 1885). Translating literally from his book:

“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 and hypothesized 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. Moreover, Golgi tried to give a role to the Golgi cells (which he called “big nervous cells”, the name “Golgi’schen Zellen” was introduced by Retzius, 1892): thinking about the fact that their impressive axonal plexuses do not go out of the cerebellum, he guessed that Golgi cells are local connective elements. Camillo Golgi also hinted to a possible relationship of the Golgi cells with a structure (“nucleo granuloso”) later named glomerulus by Ramón y Cajal. So, in 1885, the bases for understanding the cellular organization of the cerebellar cortex were revealed, and the observations were extended by several scientists (Fig. 1 reports drawings from the anatomist, Van Gehuchten, 1891; see also Fusari, 1883; Koelliker, 1891; Van Gehuchten, 1893).

Ramón y Cajal, by applying the black reaction invented by Golgi, proceeded through a systematic investigation of the “fine anatomy” of the cerebellum, to which he dedicated some works (Ramón y Cajal, 1888, 1889a,b) and many pages of his “Histology of the nervous system of man and vertebrates” (Ramón y Cajal, 1899, 1904, 1909, 1911, 1995). He extended the analysis of the granular layer neurons identifying four main components: small and abundant granule cells, large rare neurons different from granule cells, cytoplasmatic eosinophil islands (the glomeruli), and poor glial cells. Among the “large cells” group, he identified the Golgi cells and horizontal fusiform cells quite certainly corresponding to Lugaro cells. Moreover, he noticed “non-conventional large interneurons” probably including what we now call unipolar brush cells, synarmotic neurons, candelabrum neurons, and perivascular neurons (Ambrosi et al., 2007). Ramón y Cajal dedicated special attention to the cerebellar glomeruli, which he described as vacuolar dendritic cytoplasmatic islands containing granule cells dendrites, Golgi cells axonal collaterals, and mossy fibers rosettes. The cerebellar glomerulus appeared therefore as a structure in which mossy fibers and Golgi cells were able to contact and influence a huge number of granule cells. In the molecular layer, Ramón y Cajal described the Purkinje cells and differentiated the stellate from basket cells.

Moreover, he described the deep cerebellar nuclei and the inferior olive and their fundamental relationships with the Purkinje cells, revealing the parallel fiber organization and the

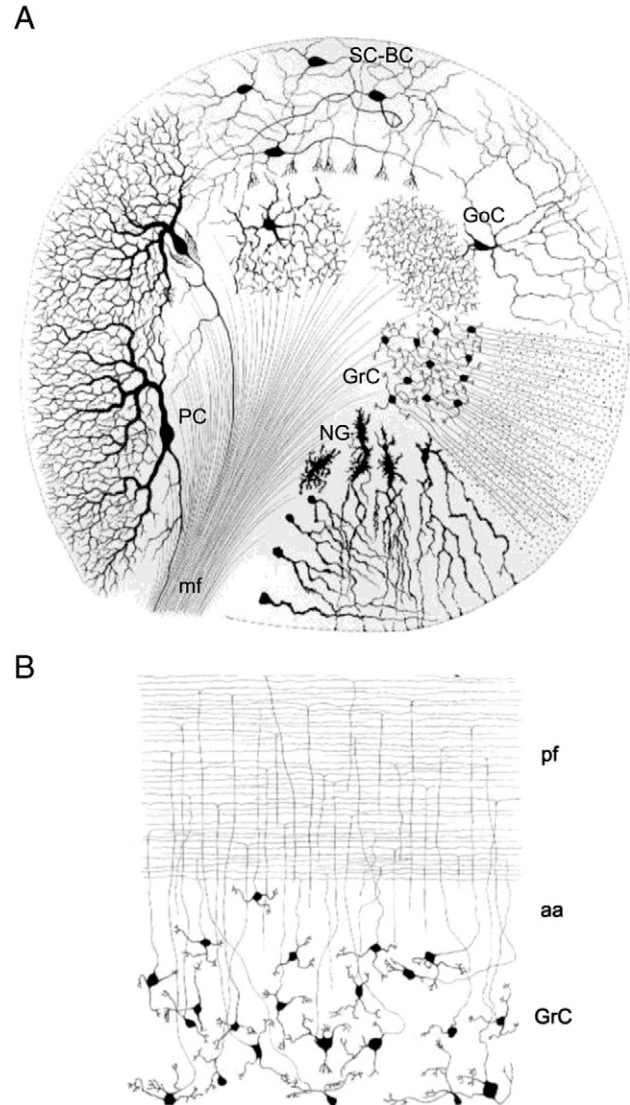


Fig. 1 – The elements of the cerebellar cortex at the time of the discovery. This drawing represents the main cellular elements of the cerebellar cortex revealed by Golgi staining at the end of the 18th century. (A) Cellular elements in a parasagittal section of a cerebellar folium, in which we can recognize Purkinje cells (PC), stellate and basket cells (SC/BC), Golgi cells (GoC), granule cells (GrC), mossy fibers (mf) and parallel fibers (pf: cut in this section), neuroglial cells (NG). The relationships between cellular elements are still poorly defined here but will become evident with Ramón y Cajal (1909, e.g., see figures 103 and 104 therein). Notably, BCs seem to make contacts onto PCs (arrow), but no relationships are defined yet between mfs and GrCs or between pfs and PCs, and the cerebellar glomeruli are not indicated. (B) This plate shows the granule cells, nicely depicting their dendrites and their ascending axon (aa) bifurcating into parallel fibers (pf). Clearly, while the most relevant elements are represented, the concepts of synapse and network are not yet well defined. From Van Gehuchten (1891).

climbing fiber connections. These observations have driven all subsequent studies aimed at understanding the structure–function relationships in the cerebellum and still provide inspiration to current research.

1.3. Early neurophysiology and the cerebellar theories: strength and weakness

A step ahead in the neurophysiology of the cerebellum occurred in the 1960s and 1970s through electrophysiological recordings *in vivo* and was summarized in seminal books (Eccles et al., 1967b; Palay and Chan-Palay, 1974; Ito et al., 1982). It was discovered that Golgi cells inhibit granule cells, providing the first demonstration of a central inhibitory neuron (Eccles et al., 1964). Then it was found that all the other neurons in the cerebellar cortex are inhibitory, with the exception of the granule cells. Therefore, the cerebellum appeared as an inhibitory loop controlling the deep cerebellar nuclei, in which excitation is conveyed to PC through the mossy fiber–granule cell–parallel fiber pathway and the inferior olive–climbing fiber pathway. The reaction times of the cellular elements to peripheral stimulation were described leading to the idea that the cerebellum worked as a timing computer (Eccles et al., 1973).

These ideas were synthesized by two main theories: Eccles proposed the Beam Theory (Eccles et al., 1967a; Eccles, 1973) and Marr and Albus the Motor Learning Theory (Marr, 1969; Albus, 1971; Fujita, 1982). Later on, Ito developed the forward controller theory (Ito, 1978, 1984, 1993, 2008), which considers the cerebellar function in the context of motor system control. Since then, the view of how the cerebellum operates has been crystallized on three main concepts: (1) the cerebellum operates by decorrelating the inputs and controlling gain in the granular layer and by detecting known patterns in Purkinje cells; (2) pattern recognition in Purkinje cells is regulated by memory storage at the parallel fiber–Purkinje cell synapse under climbing–fiber control; (3) when unfamiliar patterns are detected, the Purkinje cells change their firing rate and regulate activity in the DCN, thereby emitting the corrections signal required to control behavior.

Two main problems of the Marr–Albus–Ito theory are that some of its principles have not been demonstrated and that it does not explicitly consider timing as a critical element for cerebellar computation. Under a different perspective, the parallel fiber timing hypothesis maintained that different delays in parallel fiber activity would be critical for explaining cerebellar functioning (Braitenberg, 1967; Braitenberg et al., 1997). Although conduction delays are probably marginal, the timing issue is relevant and has been supported recently by electrophysiological data and cognitive experiments. The timing hypothesis is gaining particular relevance in front of the continuous afflux of new information on cellular and circuit dynamics (see below).

Other more abstract approaches have also been developed. The mathematical foundations of the Marr–Albus–Ito hypothesis have been investigated through the Adaptable Filter Theory (for a review, see Dean et al., 2010). The Tensor Network Theory implies that the cerebellum acts as a metric tensor establishing a geometry for the central nervous system motor hyperspace (Pellionisz and Llinas, 1979, 1980, 1982; Roy and Llinas, 2008).

1.4. Toward new concepts in cerebellar physiology

Recent experimental data indicate that the cerebellum operates in a much more complex manner than predicted by the Beam and Motor Learning theories, so that their operational principles largely based on anatomical observations can be disputed. Schematically, (1) the mechanisms of the granular layer go far beyond simple decorrelation (D'Angelo et al., 2009), (2) long-term synaptic plasticity does not occur only in the parallel fibers (Hansel et al., 2001; D'Angelo et al., 2009), (3) the IO operates as a complex timing system and not simply to control Purkinje cell plasticity (Jacobson et al., 2008). Moreover, the cerebellar neurons without any exceptions, and especially the Purkinje cells and the DCN cells, (4) have operative states that go far beyond the concept of firing rate regulation (Jacobson et al., 2009). This means that knowledge on the functioning of neuronal networks of the cerebellum is insufficient at the very least and that new experimental and computational tools are needed to investigate cerebellar network function and dynamics.

It is thus evident that the histological analysis of Golgi and Ramón y Cajal, combined with functional observations, opened remarkable questions for neuroscience. The cerebellum contains more than half the neurons of the whole brain (Herculano-Houzel, 2010) but only a limited number of neuronal types organized with a well-ordered architecture. It is fundamental for sensory–motor control but is now emerging as a central controller for emotional and cognitive functions probably exploiting the same computational modules (Gao et al., 1996; Bower, 1997; Ivry and Baldo, 1992). The cerebellum, despite its high number of cells with respect to the cerebral cortex (3.6:1; Herculano-Houzel, 2010) has little to do with consciousness, setting a definite difference between the two structures. In turn, whereas the cerebral cortex takes hundreds of milliseconds to elaborate a response, the cerebellum is extremely fast and reacts in milliseconds. So, what is the essence of cerebellar computations?

1.5. Functional dynamics of the cerebellar granular layer: beyond input decorrelation and gain control

A first example of how the anatomical observations of Golgi and Ramón y Cajal have opened the analysis of structure–function relationships concerns the granular layer. One of the most apparent aspects of histological analysis of the cerebellum is the combinatorial organization of the granular layer (Marr, 1969), which has inspired the hypothesis of signal decorrelation. This hypothesis originated from the observation that granule cells are much more numerous of the mossy fibers. Therefore, signals could diverge over many more lines than in the input, allowing decorrelation of common components. The Golgi cells could control transmission along these lines regulating transmission gain. However, two problems arise. First, signal decorrelation is probably only partly explained by the anatomical arrangement of the granular layer and could be enhanced by intrinsic neuronal responsiveness and synaptic plasticity. Secondly, additional properties not necessarily related to signal decorrelation could also be expressed in the granular layer circuit.

The granular layer has been recently shown to transform incoming signals by making use of specific cellular mechanisms controlling excitation, inhibition, oscillation, and plasticity

(different aspects are reviewed in [Farrant and Nusser, 2005](#); [D'Angelo, 2008](#); [D'Angelo and De Zeeuw, 2009](#)). A basic observation is that the mossy fibers generate spike bursts following punctuate sensory stimulation ([Chadderton et al., 2004](#); [Jorntell and Ekerot, 2006](#); [Rancz et al., 2007](#)). The analysis of responses to such bursts has inspired numerous subsequent developments. (i) By virtue of Golgi cell lateral inhibition, the granular layer response to mossy fiber bursts are spatially organized in center-surround, where excitation prevails in the center and by inhibition in the surrounding areas ([Mapelli and D'Angelo, 2007](#)). (ii) By virtue of Golgi cell feed-forward inhibition, the granular layer generates a time-window effect limiting the duration and intensity of the output ([Nieus et al., 2006](#), [D'Angelo and De Zeeuw, 2009](#)). (iii) By exploiting specific properties of NMDA and GABA receptors, the granular layer behaves as a high-pass filter allowing patterns over 50 Hz to be optimally transmitted ([Mapelli et al., 2010a](#)). (iv) By exploiting extended feed-back inhibition through Golgi cells, the granular layer can sustain coherent oscillations ([Maex and De Schutter, 1998](#)) synchronizing large granule cell fields ([Pellerin and Lamarre, 1997](#); [Hartmann and Bower, 1998](#)). Synchronous oscillations were also shown to exploit electrical junctions between Golgi cells ([Dugue et al., 2009](#)). The oscillations are enhanced when bursts are conveyed in the theta-frequency band due intrinsic cellular resonance ([D'Angelo et al., 2001](#); [Solinas et al., 2007a,b](#)). (v) In response to specific burst patterns, the granular layer generates long-term synaptic plasticity at the mossy fiber-granule cell synapse. Since induction is regulated by synaptic inhibition (which controls membrane depolarization and therefore the level on NMDA channel unblock and calcium influx), LTP dominates in the center and LTD in the surround of the response fields, consolidating specific geometries of activity. (vi) Finally, without requiring the burst activity regime, the granular layer can operate gain control operations exploiting tonic inhibition in the glomerulus ([Mitchell and Silver, 2003](#)). But how do these observations contribute to signal decorrelation and to extend our understanding of cerebellar functioning?

Using a realistic computational model of the granular layer ([Solinas et al., 2010](#)), it has been possible to evaluate the impact of cellular and synaptic dynamics on circuit computations. Burst stimulation of a small mossy fiber bundle results in granule cell bursts delimited in time (time windowing) and space (center-surround) by network inhibition. This burst-burst transmission shows marked frequency dependence configuring a high-pass filter with cutoff frequency around 100 Hz. The contrast between center and surround properties is regulated by the excitatory-inhibitory balance. The stronger excitation makes the center more responsive to 10- to 50-Hz input frequencies and enhances the granule cell output (with spike occurring earlier and with higher frequency and number) compared to the surround. Synaptic plasticity at the mossy fiber-granule cell relay, by exploiting changes in neurotransmitter cycling, can fine tune the transmission properties of the center-surround structure. The center by generating LTP reacts to spikes bursts over a broader input frequency range emitting new bursts with shorter delay and higher number of spikes compared to the surround (which is dominated by LTD).

An emerging novel hypothesis is that the granular layer network behaves as a complex set of filters operating in the

space, time, and frequency domains, and that this filter can be adapted through long-term synaptic plasticity and coordinated by theta-frequency oscillations. Thus, the original idea of input decorrelation may be extended to temporal dynamics of circuit activity and in particular to spike timing, an aspect that deserves specific future investigations.

1.6. *Transmission along the ascending axon and parallel fibers: not exactly beam formation*

Another example in which pure anatomical considerations proved insufficient to understand the underlying circuit dynamics is that of transmission of signals from the granular to the molecular layer. Ramón y Cajal showed that parallel fibers, after dividing into two opposite branches originating from the ascending axon of granule cells, travel transversally for millimeters contacting numerous Purkinje cells. This characteristic organization has inspired the idea that signals generated by granule cells are conveyed along the parallel fibers activating beams of Purkinje cells (the "Beam Theory": [Eccles et al., 1967b](#); [Braitenberg et al., 1997](#)). Activation of beams is indeed observed using parallel fiber stimulation (e.g., see [Vranesic et al., 1994](#); [Baginskaskas et al., 2009](#)). However, punctuate stimulation in vivo causes a prominent vertical activation of Purkinje cells overlaying the active granular layer areas ([Bower and Woolston, 1983](#); [Cohen and Yarom, 1998](#); [Hartmann and Bower, 2001](#); [Lu et al., 2005](#); [Rokni et al., 2008](#)). A possible explanation was that vertical activation could reflect either differential synaptic density or strength or differential spike delays along the ascending granule cell axon compared to parallel fiber synapses. The original proposal by Llinas on the ascending branch influence did not assume a difference in the strength of individual synapses of both types, but instead proposed a difference based on the timing of the inputs ([Llinas and Sugimori, 1980a,b](#)). This hypothesis was supported by the demonstration of the functional equivalence of the two inputs ([Isope and Barbour, 2002](#); [Walter et al., 2009](#)), although differences in terms of long-term synaptic plasticity have been reported ([Sims and Hartell, 2005, 2006](#)). Alternatively, differential properties of synaptic inhibition could be critical ([Cohen and Yarom, 1998](#); [Santamaria et al., 2007](#); [Bower, 2010](#)).

Clearly, solving the issue also depends on the development of appropriate recording and analysis methods. For instance, initially voltage-sensitive dye recordings did not allow one to determine the specific cellular components contributing to the signals (e.g., [Cohen and Yarom, 1998](#)) while a more strict correspondence has recently been achieved with high-resolution techniques and simultaneous imaging-patch clamp recordings in sagittal and coronal slices ([Mapelli et al., 2010a,b](#)). These investigations have revealed that optimal responses to mossy fiber input trains occurred for input frequencies over ~50 Hz in the granular layer and over ~100 Hz in the overlaying Purkinje cells. Conversely, Purkinje cell excitation along the parallel fibers occurred already at low frequency (<10 Hz) and did not improve with input frequency. The efficacy of GABA-A receptor-dependent inhibition increased passing from the granular to molecular layer and explained the different frequency-dependent responses in these subcircuits. Thus, while molecular layer mechanisms could enhance vertical transmission of high-frequency bursts, inhibitory systems in the molecular layer

would prevent diffusion of such amplified responses along the parallel fibers. This result indicates that both spots and beams of excitation can coexist although with different dynamic properties. It should be noted that another mechanism proposed to regulate gain at the mossy fiber–granule cell relay is based on tonic inhibition in the glomerulus (Mitchell and Silver, 2003; Arenz et al., 2008). This, however, may not be sensitive to rapid frequency changes between or during bursts.

1.7. *The olivo-cerebellar loop: not just error detection and teaching*

The histological observations have also profoundly influenced the interpretation of the olivary–cerebellar loops. By considering the different anatomical origin of parallel fibers and climbing fibers and their double innervation of Purkinje cell, it was assumed that climbing fibers, originating from the inferior olive play a fundamental role for motor learning (Marr, 1969; Albus, 1971; Ito et al., 1982). This anatomical contrast between the single convergence of a climbing fiber on each Purkinje cell and the massive number of parallel fiber inputs provided the sole basis for the Marr–Albus theory as explained in the chapter below (Ito, 1984). However, soon thereafter, new insight arose from the investigation of neuronal dynamics leading to an alternative hypothesis: the olivo-cerebellar loop may work as a timer for motor activity (Llinas, 1988; Welsh et al., 1995).

Recently, this alternative hypothesis has been expanded, considering the olivo-cerebellar loop as a generator of temporal patterns (Yarom and Cohen, 2002; Jacobson et al., 2008, 2009). This hypothesis postulates that the temporal patterns are encoded in the complex-spike trains and is based on three assumptions supported by experimental evidence: (1) inferior olivary neurons form a network of electrically coupled cells, where the coupling is modulated by inhibitory input from the DCN. Only in a network configuration, the neurons generate propagating waves of subthreshold oscillations. (2) The electrical synapses in the inferior olive operate only in the absence of inhibitory input from the deep cerebellar nuclei. Hence, olivary networks are dynamically and continuously reassembled by the activity pattern of the GABAergic projection neurons of the deep cerebellar nuclei. (3) Cerebellar Purkinje cells display bimodal dynamics of spiking activity (see below). These observations suggest that a request for specific patterns delivered via the mossy fiber system is translated into patterns of olivary activity, which can in turn reorganize activity in specific sections of the cerebellar cortex by sending climbing fiber signals to Purkinje cell organized in sagittal bands.

1.8. *Purkinje cell firing dynamics: much more than synaptic integration*

Histology inspired the first hypothesis about Purkinje cell functions, since these neurons collect signals generated from about 200,000 granule cells and may therefore operate as integrators. The prototype of this behavior, the ‘integrate-and-fire’ neuron, is far too simple compared to the unique features endowing Purkinje cells (De Schutter and Bower, 1994a,b). These neurons have a large dendritic tree processing synaptic inputs and a somatic compartment (including the initial

segment) responsible for action potential generation. While synaptic potentials, generated by both parallel and climbing fibers, can easily reach the soma, spikes cannot travel efficiently into the dendritic tree. Moreover, these neurons have a complex set of ionic channels distributed unequally over the compartments, generating a rich repertoire of electroresponsive properties including, bursting, rebounds, and pauses (Llinas and Sugimori, 1980a,b).

The Purkinje cells generate simple and complex spikes in response to parallel fiber and climbing fiber inputs. These synaptically driven events modulate a basal activity state generating bursts and pauses. Moreover, recent observations suggest the possibility that Purkinje cells operate as bistable elements (Loewenstein et al., 2005), although the occurrence of this observation *in vitro* as well as *in vivo* is still under debate (Schonewille et al., 2006; Yartsev et al., 2009). Membrane potential can switch between two stable levels, partially (but not strictly) under the control of simple and complex spikes. Current injections as well as synaptic inputs (either excitatory from parallel and climbing fibers or inhibitory from molecular layer interneurons) can bidirectionally shift the Purkinje cell states (Rokni et al., 2009). Moreover, neuromodulators such as serotonin (Williams et al., 2002) or CRF (corticotropin-releasing factor) have a significant impact on the ease and rapidity of the state transitions. Eventually, firing of simple spikes occurs exclusively during the depolarized state, with or without synaptic input.

Hence, a simplistic integrate-and-fire view is unacceptable for Purkinje cells. Rather, it is likely that their spontaneous firing sets the baseline activity of deep cerebellar nuclear neurons, that this activity is modulated by accelerating and decelerating firing frequency (burst–pause behavior) under control of synaptic inputs. In specific functional conditions, Purkinje cell responsiveness may be related to bistable activity states.

1.9. *Cerebellar long-term synaptic plasticity: beyond parallel fiber LTD*

Synaptic modification as a possible cellular basis of learning was initially proposed by the Italian psychiatrist Eugenio Tanzi and by Cajal, then by Sigmund Freud (for a review, see Mazzarello, 2010). However, a comprehensive theory on synaptic plasticity appeared on the scene many years later (Hebb, 1949). Marr (1969) and Albus (1971) predicted that cerebellar learning should occur with some form of plasticity between parallel fibers and Purkinje cells under control of climbing fibers. The climbing fibers originating from the inferior olive were assumed to play the role of a teacher, instructing the cerebellar cortex to modify its connectivity in order to cope with new motor demands. Parallel fiber–Purkinje cell “LTP” was predicted by Marr and reversed into “LTD” by Albus: LTD was in fact discovered more than a decade later by Ito (Ito et al., 1982). The resonance of this discovery can be compared to that of LTP in the hippocampus (Bliss and Lomo, 1973), which followed Hebb’s postulate on brain plasticity (Hebb, 1949). In 1984, J.C. Eccles said: “For me the most significant property of the cerebellar circuitry would be its plastic ability, whereby it can participate in motor learning, that is the acquisition of skills. This immense neuronal

machine with the double innervation of Purkinje cells begins to make sense if it plays a key role in motor learning... it could be optimistically predicted that the manner of operation of the cerebellum in movement and posture would soon be known in principle” (from the foreword to Ito, 1984). For more than a decade, the dominant idea had been that LTD was not just the most important but also probably the only relevant form of plasticity in the cerebellum. For instance, Marr (1969) explicitly negated the possibility that mossy fiber–granule cell synaptic weights could be modified by activity. He noted that “sooner or later all weights would be saturated” and so plasticity would be unuseful. Marr’s model does not include any mf-grc synaptic plasticity, although the subsequent extension due to Albus (1971) is more permissive. However, this view was challenged by new experimental facts.

Although parallel fiber LTD can be robustly reproduced *in vitro*, its demonstration *in vivo* has remained partial and its involvement in physiologically relevant behaviors has been questioned (Raymond et al., 1996; De Schutter, 1998; Coesmans et al., 2004; De Zeeuw and Yeo, 2005). In turn, several novel forms of plasticity have been demonstrated. Taking the move from the consideration that NMDA receptors, the main responsible of LTP induction in the brain (Bliss and Collingridge, 1993), are abundantly expressed in granule cells, experiments were undertaken demonstrating that LTP can indeed be generated by mossy fiber bursts at the mossy fiber–granule cell synapse (D’Angelo et al., 1999; Armano et al., 2000). In addition to LTP, mossy fiber–granule cell LTD was also demonstrated. LTP and LTD were related through a bidirectional learning rule based on intracellular calcium concentration changes driven by NMDA receptors (Gall et al., 2005; D’Errico et al., 2009) and showed a reciprocal spatial distribution (Mapelli et al., 2007) preventing the detrimental “saturation” of plasticity predicted by Marr. Once appropriately implemented into a model based on the Marr–Albus–Ito theory, mossy fiber–granule cell LTP and LTD proved able to improve motor learning and performance (Schweighofer and Ferriol, 2000; Schweighofer et al., 2001).

Mossy fiber–granule cell LTP was the first form of cerebellar long-term synaptic plasticity to be demonstrated following parallel fiber–Purkinje cell LTD. This finding was soon followed by numerous others revealing novel forms of plasticity at the parallel fiber–Purkinje cell synapse and at the Purkinje cell–DCN synapse (reviewed in Hansel et al., 2001; Ito, 2006). For all of these, the experimental results are now sufficiently clear to formulate appropriate learning rules and gating processes (e.g., see Schweighofer and Ferriol, 2000; Schweighofer et al., 2001; Coesmans et al., 2004; Hansel et al., 2006; D’Errico et al., 2009). Thus, the cerebellar network is plastic in a more extended sense than originally envisaged. The functional meaning of this extended plasticity in computational terms remains largely to be assessed.

The plasticity issue requires further comments. First of all, just because a synapse can be shown to be plastic does not necessarily mean that it is involved in “learning” in the classical sense. It is likely that at some level, all synapses in the brain are plastic, the question is for what functional purpose. For example, the classical parallel fiber–Purkinje cell LTD is Hebbian and supervised in nature, while the aforementioned mossy fiber–granule cell LTP and LTD are Hebbian but

unsupervised, with fundamentally different impact on learning and behavior. In fact, as far as we can understand, plasticity in the granular layer could tune the response timing of specific granule cells and therefore the activation patterns of Purkinje cells rather than “motor learning” directly. Secondly, some forms of LTD appear to be trans-synaptic. That makes cerebellar learning, if it happens, explicitly not Hebbian. The apparent fact that active parallel fiber synapses can influence the weights of inactive parallel fiber synapses is a fundamental problem for traditional theories of cerebellar Purkinje cell learning (Hansel et al., 2001).

1.10. Cerebellar synchrony, oscillations, and resonance

Although Golgi had no tools for understanding network functions, he had the intuition that a “network” structure was required in order to explain brain functioning. In modern terms, we would say that neuronal activities are locally coordinated through specific membrane and synaptic mechanisms.

The first hints that the cerebellum might generate coordinated activities were raised by the discovery of gap junctions (the molecular correlate of the electrical synapses) in the inferior olive between olivary neurons and in the molecular layer between stellate cells (Sotelo and Llinas, 1972; Mann-Metzer and Yarom, 2000). More recently, gap junctions have been observed in the granular layer between Golgi cells (Dugue et al., 2009; Vervaeke et al., 2010). It was then observed that, as well as other major systems of the brain (like the thalamo-cortical system), also the olivo-cerebellar system can generate rhythmic activities (reviewed in D’Angelo, 2008; De Zeeuw et al., 2008). In addition, intrinsic neuronal properties can contribute to generate oscillations: the inferior olivary neurons can generate theta-frequency oscillations, and recently, a similar property has been found in Golgi cells (Dieudonne, 1998; Forti et al., 2006).

Low-frequency oscillations are fundamental for several neurophysiological processes, including sensory–motor control, the formation of memories and sleep (for a review, see Buzsaki, 2006). Sensory–motor control is based on 6- to 9-Hz oscillations (Gross et al., 2005) spreading through a cerebro-cerebellar loop involving cerebral cortical areas (prefrontal cortex, PFC; premotor cortex, PMC; primary sensory–motor cortex, S1-M1; posterior parietal cortex, PPC), cerebellum, thalamus, and back to the cerebral cortex (Schnitzler et al., 2009). The fundamental operations controlled by cerebro-cerebellar loop are explained through the “timing hypothesis” (the temporal goal is a requisite component of the task representation, Timmann et al., 1999) and the “sensory prediction” hypothesis (match between the predicted and actual sensory outcome of motor commands, Ebner and Pasalar, 2008; Timmann et al., 1999; Ivry et al., 2002; Ivry and Spencer, 2004; Spencer and Ivry, 2009). The proposed functions of the cerebro-cerebellar loop include motor sequence generation, sensory–motor control, switching of attention and decision making. Some circuit elements of the cerebro-cerebellar loop can intrinsically generate and sustain the rhythm while others are probably entrained by circuit activity. These two mechanisms, entraining and being entrained, are probably not disjointed because large-scale brain oscillations are collective processes, in which coalitions of neurons

transiently reinforce their reciprocal interaction (Buzsáki, 2006). Voluntary movement causes oscillatory activity in the prefrontal areas, which then propagates to the PMC, S1-M1, PPC and is then relayed to the cerebellum (through pontine nuclei). The cerebellum may therefore initially be entrained and then participate to reinforce theta-band oscillations in the cerebro-cerebellar loop.

Both the granular and molecular layer can be entrained into theta-frequency cycles driven by the cerebral cortex (Courtemanche et al., 2009; Ros et al., 2009). The granular layer spike patterns, once recognized by Purkinje cells, could set up theta-frequency oscillations in specific subsection of the inferior olive–Purkinje cell–deep cerebellar nuclei system (see above). Due to climbing fiber branching, this activity would affect specific groups of Purkinje cells located along the sagittal axis. The parallel fibers (which can reliably transmit at low frequency, see above) could drive into the theta-frequency Purkinje cell beams located along the transverse axis. The final effect would be a positive interference of theta-frequency activity in Purkinje cells that lie at the intersection between the transverse (parallel fiber-driven) and sagittal (climbing fiber-driven) groups. This mechanism could provide the necessary coherence for multiple inputs occurring in different regions of the cerebellum, extending the concepts of congruence of climbing and mossy fiber signals (Brown and Bower, 2002; Kistler and De Zeeuw, 2003).

1.11. Recapitulation: what remains of the early intuitions from structure?

As was clearly expressed by Arbib and colleagues (Arbib et al., 1998; Arbib and Erdi, 2000), the three key elements for understanding brain circuit functions are “structure, function, and dynamics”. What is amazing when looking backward to the discovery of cerebellar neurons and fibers is the intuition that Golgi and Cajal had on the general properties of the cerebellum. Clearly, they could not imagine the complexity of neuronal and circuit dynamics. But their struggle oscillated between two poles, the role of single neurons and that of the circuit they are part of. Historically, first Golgi observed the morphological characteristics of nerve cells and heralded the so-called reticularist hypothesis, while Cajal subsequently became the paladin of the neuron doctrine, the pillar of modern neuroscience. That network interactions are fundamental is now very clear, obviously in a way different from what Golgi believed: in other words, he proposed a wrong explanation for a right question (Kruger, 2007; Kruger and Otis, 2007; Galliano et al., 2010). This struggle led to hypothesize the existence of the synapses and to found the neuron doctrine more than to reveal the intimate functions of the cerebellum. In fact, subsequent history of cerebellar investigations has been characterized by several “morpho/functional discrepancies” (Bower, 1997, 2002; Rokni et al., 2008) based on assumptions derived from the pure anatomical observation. These interpretations concerned the role of mossy, parallel, and climbing fibers, along with that of the main neurons, granule, and Purkinje cells. After more than one century, investigations making use of sophisticated electrophysiological, imaging, and computational techniques are opening new views on how the cerebellar structure may operate.

REFERENCES

- Albus, J., 1971. The theory of cerebellar function. *Math. Biosci.* 10, 25–61.
- Ambrosi, G., Flace, P., Lorusso, L., Girolamo, F., Rizzi, A., Bosco, L., Errede, M., Virgintino, D., Roncali, L., Benagiano, V., 2007. Non-traditional large neurons in the granular layer of the cerebellar cortex. *Eur. J. Histochem.* 51 (Suppl 1), 59–64.
- Arbib, M.A., Erdi, P., 2000. Precis of neural organization: structure, function, and dynamics. *Behav. Brain Sci.* 23, 513–533 discussion 533–571.
- Arbib, M.A., Erdi, P., Szentagothai, J., 1998. *Neural organization: structure, function, and dynamics*. MIT Press, Cambridge, MA, USA.
- Arenz, A., Silver, R.A., Schaefer, A.T., Margrie, T.W., 2008. The contribution of single synapses to sensory representation in vivo. *Science* 321, 977–980.
- Armano, S., Rossi, P., Taglietti, V., D’Angelo, E., 2000. Long-term potentiation of intrinsic excitability at the mossy fiber-granule cell synapse of rat cerebellum. *J. Neurosci.* 20, 5208–5216.
- Baginskis, A., Palani, D., Chiu, K., Raastad, M., 2009. The H-current secures action potential transmission at high frequencies in rat cerebellar parallel fibers. *Eur. J. Neurosci.* 29, 87–96.
- Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361, 31–39.
- Bliss, T.V., Lomo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* 232, 331–356.
- Bower, J.M., 1997. Is the cerebellum sensory for motor’s sake, or motor for sensory’s sake: the view from the whiskers of a rat? *Prog. Brain Res.* 114, 463–496.
- Bower, J.M., 2002. The organization of cerebellar cortical circuitry revisited: implications for function. *Ann. NY Acad. Sci.* 978, 135–155.
- Bower, J.M., 2010. Model-founded explorations of the roles of molecular layer inhibition in regulating purkinje cell responses in cerebellar cortex: more trouble for the beam hypothesis. *Front. Cell. Neurosci.* 4.
- Bower, J.M., Woolston, D.C., 1983. Congruence of spatial organization of tactile projections to granule cell and Purkinje cell layers of cerebellar hemispheres of the albino rat: vertical organization of cerebellar cortex. *J. Neurophysiol.* 49, 745–766.
- Braitenberg, V., 1967. Is the cerebellar cortex a biological clock in the millisecond range? *Prog. Brain Res.* 25, 334–346.
- Braitenberg, V., Heck, D., Sultan, F., 1997. The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav. Brain Sci.* 20, 229–245 discussion 245–277.
- Brown, I.E., Bower, J.M., 2002. The influence of somatosensory cortex on climbing fiber responses in the lateral hemispheres of the rat cerebellum after peripheral tactile stimulation. *J. Neurosci.* 22, 6819–6829.
- Buzsáki, G., 2006. *Rhythms of the brain*. Oxford University Press US, New York.
- Buzsáki, G. (Ed.), 2006. *Rhythms of the Brain*. Oxford University Press, USA.
- Cerminara, N.L., Apps, R., 2010. Behavioural Significance of Cerebellar Modules. *Cerebellum*.
- Chadderton, P., Margrie, T.W., Hausser, M., 2004. Integration of quanta in cerebellar granule cells during sensory processing. *Nature* 428, 856–860.
- Coemans, M., Weber, J.T., De Zeeuw, C.I., Hansel, C., 2004. Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber control. *Neuron* 44, 691–700.
- Cohen, D., Yarom, Y., 1998. Patches of synchronized activity in the cerebellar cortex evoked by mossy-fiber stimulation: questioning

- the role of parallel fibers. *Proc. Natl Acad. Sci. USA* 95, 15032–15036.
- Courtemanche, R., Chabaud, P., Lamarre, Y., 2009. Synchronization in primate cerebellar granule cell layer local field potentials: basic anisotropy and dynamic changes during active expectancy. *Front. Cell. Neurosci.* 3, 6.
- D'Angelo, E., 2008. The critical role of Golgi cells in regulating spatio-temporal integration and plasticity at the cerebellum input stage. *Front. Neurosci.* 2, 35–46.
- D'Angelo, E., De Zeeuw, C.I., 2009. Timing and plasticity in the cerebellum: focus on the granular layer. *Trends Neurosci.* 32, 30–40.
- D'Angelo, E., Rossi, P., Armano, S., Taglietti, V., 1999. Evidence for NMDA and mGlu receptor-dependent long-term potentiation of mossy fiber-granule cell transmission in rat cerebellum. *J. Neurophysiol.* 81, 277–287.
- D'Angelo, E., Nieus, T., Maffei, A., Armano, S., Rossi, P., Taglietti, V., Fontana, A., Naldi, G., 2001. Theta-frequency bursting and resonance in cerebellar granule cells: experimental evidence and modeling of a slow K^+ -dependent mechanism. *J. Neurosci.* 21, 759–770.
- D'Angelo, E., Koekkoek, S.K., Lombardo, P., Solinas, S., Ros, E., Garrido, J., Schonewille, M., De Zeeuw, C.I., 2009. Timing in the cerebellum: oscillations and resonance in the granular layer. *Neuroscience* 162, 805–815.
- De Schutter, E., 1998. Dendritic voltage and calcium-gated channels amplify the variability of postsynaptic responses in a Purkinje cell model. *J. Neurophysiol.* 80, 504–519.
- De Schutter, E., Bower, J.M., 1994a. An active membrane model of the cerebellar Purkinje cell II. Simulation of synaptic responses. *J. Neurophysiol.* 71, 401–419.
- De Schutter, E., Bower, J.M., 1994b. An active membrane model of the cerebellar Purkinje cell. I. Simulation of current clamps in slice. *J. Neurophysiol.* 71, 375–400.
- De Zeeuw, C.I., Yeo, C.H., 2005. Time and tide in cerebellar memory formation. *Curr. Opin. Neurobiol.* 15, 667–674.
- De Zeeuw, C.I., Hoebeek, F.E., Schonewille, M., 2008. Causes and consequences of oscillations in the cerebellar cortex. *Neuron* 58, 655–658.
- D'Errico, A., Prestori, F., D'Angelo, E., 2009. Differential induction of bidirectional long-term changes in neurotransmitter release by frequency-coded patterns at the cerebellar input. *J. Physiol.* 587, 5843–5857.
- Dieudonne, S., 1998. Submillisecond kinetics and low efficacy of parallel fibre-Golgi cell synaptic currents in the rat cerebellum. *J. Physiol.* 510 (Pt 3), 845–866.
- Dugue, G.P., Brunel, N., Hakim, V., Schwartz, E., Chat, M., Levesque, M., Courtemanche, R., Lena, C., Dieudonne, S., 2009. Electrical coupling mediates tunable low-frequency oscillations and resonance in the cerebellar Golgi cell network. *Neuron* 61, 126–139.
- Ebner, T.J., Pasalar, S., 2008. Cerebellum predicts the future motor state. *Cerebellum* 7, 583–588.
- Eccles, J.C., 1973. The cerebellum as a computer: patterns in space and time. *J. Physiol.* 229, 1–32.
- Eccles, J., Llinàs, R., Sasaki, K., 1964. Golgi cell inhibition in the cerebellar cortex. *Nature* 204, 1265–1266.
- Eccles, J.C., Ito, M., Szentagothai, J., 1967a. The cerebellum as a neural machine. Springer-Verlag, Berlin, Heidelberg, New York.
- Eccles, J.C., Ito, M., Szentagothai, J., 1967b. The Cerebellum as a Neuronal Machine. Springer-Verlag, Berlin, Heidelberg, New York.
- Farrant, M., Nusser, Z., 2005. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. *Nat. Rev. Neurosci.* 6, 215–229.
- Flourens, P., 1858. De la vie et de l'intelligence. Garnier, Paris.
- Forti, L., Cesana, E., Mapelli, J., D'Angelo, E., 2006. Ionic mechanisms of autorhythmic firing in rat cerebellar Golgi cells. *J. Physiol. Lond.* 574, 711–729.
- Fujita, M., 1982. Adaptive filter model of the cerebellum. *Biol. Cybern.* 45, 195–206.
- Fusari, R., 1883. Sull'origine delle fibre nervosa dello strato molecolare delle circonvoluzioni cerebellari dell'uomo: Atti della Reale Accademia delle Scienze di Torino, 19, pp. 47–51.
- Gall, D., Prestori, F., Sola, E., D'Errico, A., Roussel, C., Forti, L., Rossi, P., D'Angelo, E., 2005. Intracellular calcium regulation by burst discharge determines bidirectional long-term synaptic plasticity at the cerebellum input stage. *J. Neurosci.* 25, 4813–4822.
- Galliano, E., Mazzarello, P., D'Angelo, E., 2010. Discovery and rediscovery of the Golgi cells. *J. Physiol.* 3639–3655 588.19.
- Gao, J.H., Parsons, L.M., Bower, J.M., Xiong, J., Li, J., Fox, P.T., 1996. Cerebellum implicated in sensory acquisition and discrimination rather than motor control. *Science* 272, 545–547.
- Golgi, C., 1874. Sulla fine anatomia del cervello umano: Archivio Italiano per le Malattie Nervose, 2, pp. 90–107.
- Golgi, C., 1885. Sulla fina anatomia degli organi centrali del sistema nervoso. Reggio Emilia, Calderini.
- Golgi, C., 1967. The neuron doctrine. Theory and facts. : Nobel Lecture (1901–1921). Elsevier Publishing Company, Amsterdam, pp. 189–217.
- Gross, J., Pollok, B., Dirks, M., Timmermann, L., Butz, M., Schnitzler, A., 2005. Task-dependent oscillations during unimanual and bimanual movements in the human primary motor cortex and SMA studied with magnetoencephalography. *Neuroimage* 26, 91–98.
- Hansel, C., Linden, D.J., D'Angelo, E., 2001. Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. *Nat. Neurosci.* 4, 467–475.
- Hansel, C., de Jeu, M., Belmeguenai, A., Houtman, S.H., Buitendijk, G.H., Andreev, D., De Zeeuw, C.I., Elgersma, Y., 2006. α CaMKII Is essential for cerebellar LTD and motor learning. *Neuron* 51, 835–843.
- Hartmann, M.J., Bower, J.M., 1998. Oscillatory activity in the cerebellar hemispheres of unrestrained rats. *J. Neurophysiol.* 80, 1598–1604.
- Hartmann, M.J., Bower, J.M., 2001. Tactile responses in the granule cell layer of cerebellar folium crus IIA of freely behaving rats. *J. Neurosci.* 21, 3549–3563.
- Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. Psychology Press, London.
- Holmes, G., 1917. The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain* 40, 461–535.
- Holmes, G., 1922. On the clinical symptoms of cerebellar disease and their interpretation. *Lancet* 1, 1177–1182.
- Isope, P., Barbour, B., 2002. Properties of unitary granule cell→Purkinje cell synapses in adult rat cerebellar slices. *J. Neurosci.* 22, 9668–9678.
- Ito, M., 1978. Recent advances in cerebellar physiology and pathology. *Adv. Neurol.* 21, 59–84.
- Ito, M., 1984. The Cerebellum and Neural Control. Raven Press, New York.
- Ito, M., 1993. Movement and thought: identical control mechanisms by the cerebellum. *Trends Neurosci.* 16, 448–450 discussion 453–444.
- Ito, M., 2006. Cerebellar circuitry as a neuronal machine. *Prog. Neurobiol.* 78, 272–303.
- Ito, M., 2008. Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304–313.
- Ito, M., Sakurai, M., Tongroach, P., 1982. Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells. *J. Physiol.* 324, 113–134.
- Ivry, R.B., Baldo, J.V., 1992. Is the cerebellum involved in learning and cognition? *Curr. Opin. Neurobiol.* 2, 212–216.
- Ivry, R.B., Spencer, R.M., 2004. Evaluating the role of the cerebellum in temporal processing: beware of the null hypothesis. *Brain* 127, E13 author reply E14.
- Ivry, R.B., Spencer, R.M., Zelaznik, H.N., Diedrichsen, J., 2002. The cerebellum and event timing. *Ann. NY Acad. Sci.* 978, 302–317.

- Jacobson, G.A., Rokni, D., Yarom, Y., 2008. A model of the olivo-cerebellar system as a temporal pattern generator. *Trends Neurosci.* 31, 617–625.
- Jacobson, G.A., Lev, I., Yarom, Y., Cohen, D., 2009. Invariant phase structure of olivo-cerebellar oscillations and its putative role in temporal pattern generation. *Proc. Natl Acad. Sci. USA* 106, 3579–3584.
- Jornfelt, H., Ekerot, C.F., 2006. Properties of somatosensory synaptic integration in cerebellar granule cells in vivo. *J. Neurosci.* 26, 11786–11797.
- Kistler, W.M., De Zeeuw, C.I., 2003. Time windows and reverberating loops: a reverse-engineering approach to cerebellar function. *Cerebellum* 2, 44–54.
- Koelliker, A., 1891. The minute anatomy of the spinal cord and cerebellum demonstrated by Golgi's method. *J. Anat. Physiol.* 25, 443–460.
- Kruger, L., 2007. The sensory neuron and the triumph of Camillo Golgi. *Brain Res. Rev.* 55, 406–410.
- Kruger, L., Otis, T.S., 2007. Whither withered Golgi? A retrospective evaluation of reticularist and synaptic constructs. *Brain Res. Bull.* 72, 201–207.
- Llinas, R.R., 1988. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science* 242, 1654–1664.
- Llinas, R., Sugimori, M., 1980a. Electrophysiological properties of in vitro Purkinje cell dendrites in mammalian cerebellar slices. *J. Physiol.* 305, 197–213.
- Llinas, R., Sugimori, M., 1980b. Electrophysiological properties of in vitro Purkinje cell somata in mammalian cerebellar slices. *J. Physiol.* 305, 171–195.
- Loewenstein, Y., Mahon, S., Chadderton, P., Kitamura, K., Sompolinsky, H., Yarom, Y., Hausser, M., 2005. Bistability of cerebellar Purkinje cells modulated by sensory stimulation. *Nat. Neurosci.* 8, 202–211.
- Lu, H., Hartmann, M.J., Bower, J.M., 2005. Correlations between purkinje cell single-unit activity and simultaneously recorded field potentials in the immediately underlying granule cell layer. *J. Neurophysiol.* 94, 1849–1860.
- Luciani, L., 1891. Il cervelletto: nuovi studi di fisiologia normale e patologica, Firenze, Coi tipi dei successori Le Monnier.
- Maex, R., De Schutter, E., 1998. Synchronization of golgi and granule cell firing in a detailed network model of the cerebellar granule cell layer. *J. Neurophysiol.* 80, 2521–2537.
- Mann-Metzer, P., Yarom, Y., 2000. Electrotonic coupling synchronizes interneuron activity in the cerebellar cortex. *Prog. Brain Res.* 124, 115–122.
- Mapelli, J., D'Angelo, E., 2007. The spatial organization of long-term synaptic plasticity at the input stage of cerebellum. *J. Neurosci.* 27, 1285–1296.
- Mapelli, J., Gandolfi, D., D'Angelo, E., 2010a. Combinatorial responses controlled by synaptic inhibition in the cerebellum granular layer. *J. Neurophysiol.* 103, 250–261.
- Mapelli, J., Gandolfi, D., D'Angelo, E., 2010b. High-pass filtering and dynamic gain regulation enhance vertical bursts transmission along the mossy fiber pathway of cerebellum. *Front. Cell. Neurosci.* 4, 14.
- Marr, D., 1969. A theory of cerebellar cortex. *J. Physiol.* 202, 437–470.
- Mazzarello P. (2010) Golgi, a Biography of the Founder of Modern Neuroscience. (transl. A. Badiani and H. Buchtel). New York: Oxford University Press.
- Mitchell, S.J., Silver, R.A., 2003. Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron* 38, 433–445.
- Nieus, T., Sola, E., Mapelli, J., Saftenku, E., Rossi, P., D'Angelo, E., 2006. LTP regulates burst initiation and frequency at mossy fiber-granule cell synapses of rat cerebellum: experimental observations and theoretical predictions. *J. Neurophysiol.* 95, 686–699.
- Palay, S.L., Chan-Palay, V., 1974. Cerebellar cortex: cytology and organization. Springer-Verlag, New York.
- Pellerin, J.P., Lamarre, Y., 1997. Local field potential oscillations in primate cerebellar cortex during voluntary movement. *J. Neurophysiol.* 78, 3502–3507.
- Pellionisz, A., Llinas, R., 1979. Brain modeling by tensor network theory and computer simulation. The cerebellum: distributed processor for predictive coordination. *Neuroscience* 4, 323–348.
- Pellionisz, A., Llinas, R., 1980. Tensorial approach to the geometry of brain function: cerebellar coordination via a metric tensor. *Neuroscience* 5, 1125–1138.
- Pellionisz, A., Llinas, R., 1982. Space-time representation in the brain. the cerebellum as a predictive space-time metric tensor. *Neuroscience* 7, 2949–2970.
- Ramón y Cajal, S., 1888. Sobre las fibras nerviosas de la capa molecular del cerebelo. *Rev. Trim. Histol. Norm. Patol.* 1, 33–42.
- Ramón y Cajal, S., 1889a. Sur l'origine et la direction des prolongations nerveuses de la couche moléculaire du cervelet. *Internat. Mschr. Anat. Physiol.* 7, 12–31.
- Ramón y Cajal, S., 1889b. Sobre las fibras nerviosas de la capa granulosa del cerebelo. *Rev. Trim. Histol. Norm. Patol.* 1, 107–118.
- Ramón y Cajal, S., 1899. *Textura del sistema nervioso del hombre y de los vertebrado: estudios sobre el plan estructural y composición histológica de los centros nerviosos adicionales de consideraciones fisiológicas fundadas en los nuevos descubrimientos*. Madrid: Moya.
- Ramón y Cajal, S., 1904. *Textura del sistema nervioso del hombre y de los vertebrado: estudios sobre el plan estructural y composición histológica de los centros nerviosos adicionales de consideraciones fisiológicas fundadas en los nuevos descubrimientos*. Madrid: Moya.
- Ramón y Cajal S. (1909) *Histologie du système nerveux de l'homme et des vertèbres* (transl., L. Azoulay). Paris: Maloine.
- Ramón y Cajal S (1911) *Histologie du système nerveux de l'homme et des vertèbres* (Transl, L. Azoulay). Paris: Maloine.
- Ramón y Cajal S., (1967). *The Structure and Connections of Neurons*. (1901–1921): Elsevier Publishing Company, Amsterdam, 1967, pp. 220–253.
- Ramón y Cajal S. (1995) *Histology of the Nervous System of Man and Vertebrates* (Transl. N. Swanson and L. Swanson). New York: Oxford University Press.
- Rancz, E.A., Ishikawa, T., Duguid, I., Chadderton, P., Mahon, S., Hausser, M., 2007. High-fidelity transmission of sensory information by single cerebellar mossy fibre boutons. *Nature* 450, 1245–1248.
- Raymond, J.L., Lisberger, S.G., Mauk, M.D., 1996. The cerebellum: a neuronal learning machine? *Science* 272, 1126–1131.
- Retzius, G., 1892. Kleinere Mittheilungen von den Gebiete der Nervenhistologie: Biologische Untersuchungen (Neue Folge) IV, pp. 57–66.
- Rokni, D., Llinas, R., Yarom, Y., 2008. The morpho/functional discrepancy in the cerebellar cortex: looks alone are deceptive. *Front. Neurosci.* 2, 192–198.
- Rokni, D., Tal, Z., Byk, H., Yarom, Y., 2009. Regularity, variability and bi-stability in the activity of cerebellar purkinje cells. *Front. Cell. Neurosci.* 3, 12.
- Rolando, L., 1809. Saggio sulla vera struttura del cervello dell'uomo e degl'animali e sopra le funzioni del sistema nervoso Sassari, Sassari, Stamperia da S.S.R.M. Privilegiata.
- Ros, H., Sachdev, R.N., Yu, Y., Sestan, N., McCormick, D.A., 2009. Neocortical networks entrain neuronal circuits in cerebellar cortex. *J. Neurosci.* 29, 10309–10320.
- Roy, S., Llinas, R., 2008. Dynamic geometry, brain function modeling, and consciousness. *Prog. Brain. Res.* 168, 133–144.
- Santamaria, F., Tripp, P.G., Bower, J.M., 2007. Feedforward inhibition controls the spread of granule cell-induced Purkinje cell activity in the cerebellar cortex. *J. Neurophysiol.* 97, 248–263.
- Schnitzler, A., Munks, C., Butz, M., Timmermann, L., Gross, J., 2009. Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. *Mov. Disord.* 24, 1629–1635.

- Schonewille, M., Khosrovani, S., Winkelman, B.H., Hoebeek, F.E., De Jeu, M.T., Larsen, I.M., Van der Burg, J., Schmolesky, M.T., Frens, M.A., De Zeeuw, C.I., 2006. Purkinje cells in awake behaving animals operate at the upstate membrane potential. *Nat. Neurosci.* 9, 459–461 author reply 461.
- Schweighofer, N., Ferriol, G., 2000. Diffusion of nitric oxide can facilitate cerebellar learning: a simulation study. *Proc. Natl Acad. Sci. USA* 97, 10661–10665.
- Schweighofer, N., Doya, K., Lay, F., 2001. Unsupervised learning of granule cell sparse codes enhances cerebellar adaptive control. *Neuroscience* 103, 35–50.
- Sims, R.E., Hartell, N.A., 2005. Differences in transmission properties and susceptibility to long-term depression reveal functional specialization of ascending axon and parallel fiber synapses to Purkinje cells. *J. Neurosci.* 25, 3246–3257.
- Sims, R.E., Hartell, N.A., 2006. Differential susceptibility to synaptic plasticity reveals a functional specialization of ascending axon and parallel fiber synapses to cerebellar Purkinje cells. *J. Neurosci.* 26, 5153–5159.
- Solinas, S., Forti, L., Cesana, E., Mapelli, J., De Schutter, E., D'Angelo, E., 2007a. Computational reconstruction of pacemaking and intrinsic electroresponsiveness in cerebellar Golgi cells. *Front. Cell. Neurosci.* 1, 2.
- Solinas, S., Forti, L., Cesana, E., Mapelli, J., De Schutter, E., D'Angelo, E., 2007b. Fast-reset of pacemaking and theta-frequency resonance patterns in cerebellar golgi cells: simulations of their impact in vivo. *Front. Cell. Neurosci.* 1, 4.
- Solinas, S., Nieuwenhuis, T., D'Angelo, E., 2010. A realistic large-scale model of the cerebellum granular layer predicts circuit spatio-temporal filtering properties. *Front. Cell. Neurosci.* 4, 12.
- Sotelo, C., Llinas, R., 1972. Specialized membrane junctions between neurons in the vertebrate cerebellar cortex. *J. Cell Biol.* 53, 271–289.
- Spencer, R.M., Ivry, R.B., 2009. Sequence learning is preserved in individuals with cerebellar degeneration when the movements are directly cued. *J. Cogn. Neurosci.* 21, 1302–1310.
- Timmann, D., Watts, S., Hore, J., 1999. Failure of cerebellar patients to time finger opening precisely causes ball high-low inaccuracy in overarm throws. *J. Neurophysiol.* 82, 103–114.
- Van Gehuchten, A., 1891. La structure des centres nerveux. La moelle épinière et le cervelet. *Cellule* 7, 79–122.
- Van Gehuchten, A., 1893. Le système nerveux de l'homme. *Lierre: Van In.*
- Vervaeke, K., Lorincz, A., Gleeson, P., Farinella, M., Nusser, Z., Silver, R.A., 2010. Rapid desynchronization of an electrically coupled interneuron network with sparse excitatory synaptic input. *Neuron* 67, 435–451.
- Vranesic, I., Iijima, T., Ichikawa, M., Matsumoto, G., Knopfel, T., 1994. Signal transmission in the parallel fiber-Purkinje cell system visualized by high-resolution imaging. *Proc. Natl Acad. Sci. USA* 91, 13014–13017.
- Walter, J.T., Dizon, M.J., Khodakhah, K., 2009. The functional equivalence of ascending and parallel fiber inputs in cerebellar computation. *J. Neurosci.* 29, 8462–8473.
- Welsh, J.P., Lang, E.J., Sugihara, I., Llinas, R., 1995. Dynamic organization of motor control within the olivocerebellar system. *Nature* 374, 453–457.
- Williams, S.R., Christensen, S.R., Stuart, G.J., Hausser, M., 2002. Membrane potential bistability is controlled by the hyperpolarization-activated current I(H) in rat cerebellar Purkinje neurons in vitro. *J. Physiol.* 539, 469–483.
- Yarom, Y., Cohen, D., 2002. The olivocerebellar system as a generator of temporal patterns. *Ann. NY Acad. Sci.* 978, 122–134.
- Yartsev, M.M., Givon-Mayo, R., Maller, M., Donchin, O., 2009. Pausing purkinje cells in the cerebellum of the awake cat. *Front. Syst. Neurosci.* 3, 2.