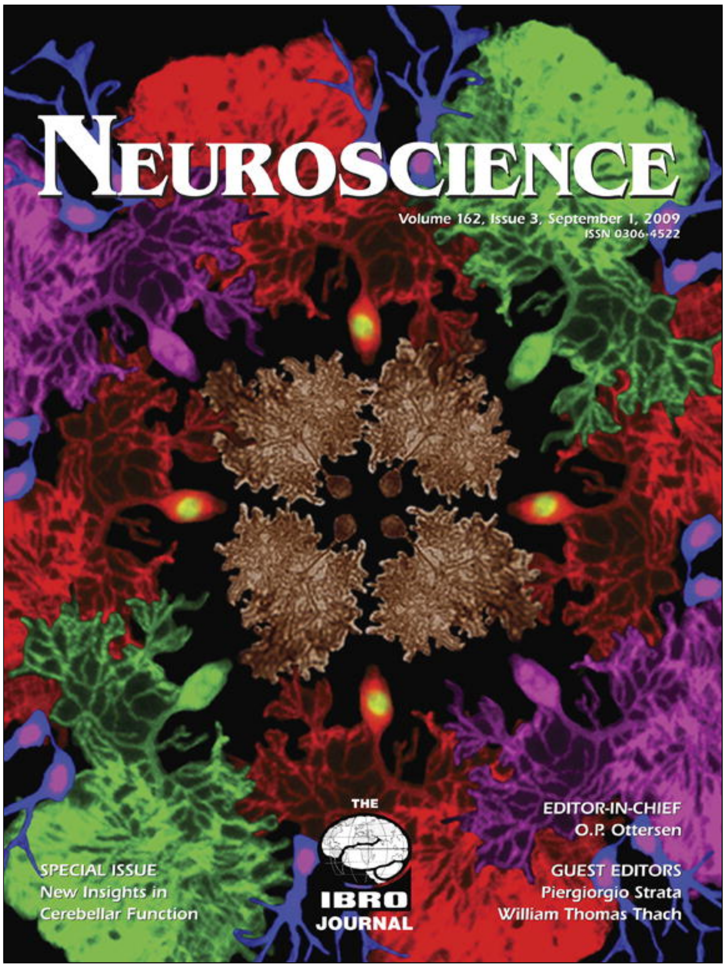
NEUROSCIENCE
Volume 162, Issue 3, September 1, 2009
ISSN 0306-4522
THE
IBRO
JOURNAL
EDITOR-IN-CHIEF
O.P. Ottersen
SPECIAL ISSUE
New Insights in
Cerebellar Function
GUEST EDITORS
Piergiorgio Strata
William Thomas Thach

Neuroscience 162 (2009) 805–815

REVIEW

TIMING IN THE CEREBELLUM: OSCILLATIONS AND RESONANCE IN THE GRANULAR LAYER

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Abstract—The brain generates many rhythmic activities, and the olivo-cerebellar system is not an exception. In recent years, the cerebellum has revealed activities ranging from low frequency to very high-frequency oscillations. These rhythms depend on the brain functional state and are typical of certain circuit sections or specific neurons. Interestingly, the granular layer, which gates sensorimotor and cognitive signals to the cerebellar cortex, can also sustain low frequency (7–25 Hz) and perhaps higher-frequency oscillations. In this review we have considered (i) how these oscillations are generated in the granular layer network depending on intrinsic electroresponsiveness and circuit connections, (ii) how these oscillations are correlated with those in other cerebellar circuit sections, and (iii) how the oscillating cerebellum communicates with extracerebellar structures. It is suggested that the granular layer can generate oscillations that integrate well with those generated in the inferior olive, in deep-cerebellar nuclei and in Purkinje cells. These rhythms, in turn, might play a role in cognition and memory consolidation by interacting with the mechanisms of long-term synaptic plasticity.

Key words: cerebellum, granular layer, oscillations, resonance, granule cells, Golgi cells.

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The olivo-cerebellar system processes sensorimotor signals to rapidly control fine movement coordination and to store memories of past procedures (Eccles et al., 1967; Ito, 1984). Moreover, a role of the cerebellum in cognitive functions has been reported by several groups (Schmahmann, 2004; Leiner et al., 1993; Sacchetti et al., 2004; Ito, 1993; Schmahmann and Caplan, 2006; Allen et al., 2004). The cerebellum has a regular anatomical matrix structure (Fig. 1), which inspired the first comprehensive models of cerebellar functions such as the motor learning theory (Marr, 1969; Albus, 1971; Fujita, 1982). The concepts of these theories still provide classic references, but at the time they were based on relatively limited knowledge of the functional properties of neurons and synapses involved. It was not until the potential roles of the Golgi cells were considered in detail that the granular layer was proposed to process input temporal patterns (Fujita, 1982; Chapeau-Blondeau and Chauvet, 1991) and generate internal oscillatory dynamics (Maex and De Schutter, 1998; Medina and Mauk, 2000).

In recent years, important achievements were made on cellular and synaptic properties of the olivo-cerebellar circuit. The key elements that turned out to be relevant for models on cerebellar processing include the precise time patterns of spikes in the various neurons and the distribution of long-lasting synaptic plasticity inside the network (Hansel et al., 2001; De Zeeuw and Yeo, 2005). These elements are functionally related throughout the entire circuit and they influence one another without almost any exception (Casado et al., 2002; Coesmans et al., 2004; Nieus et al., 2006; Jörntell and Hansel, 2006; Steuber et al., 2007). More recent works attempt to address the issue as to how the network properties of the cerebellar system processes precisely the sequences of the timed signals and how it enforces the required internal dynamics (D'Angelo, 2008; Jacobson et al., 2008; De Zeeuw et al., 2008; D'Angelo and De Zeeuw, 2009). One of the intriguing properties in this respect is the capability of the olivo-

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Abbreviations: DCN, deep-cerebellar nuclei; IO, inferior olivary; LTD, long-term depression; LTP, long-term potentiation; UBC, unipolar brush cell; VN, vestibular nuclei.

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doi:10.1016/j.neuroscience.2009.01.048

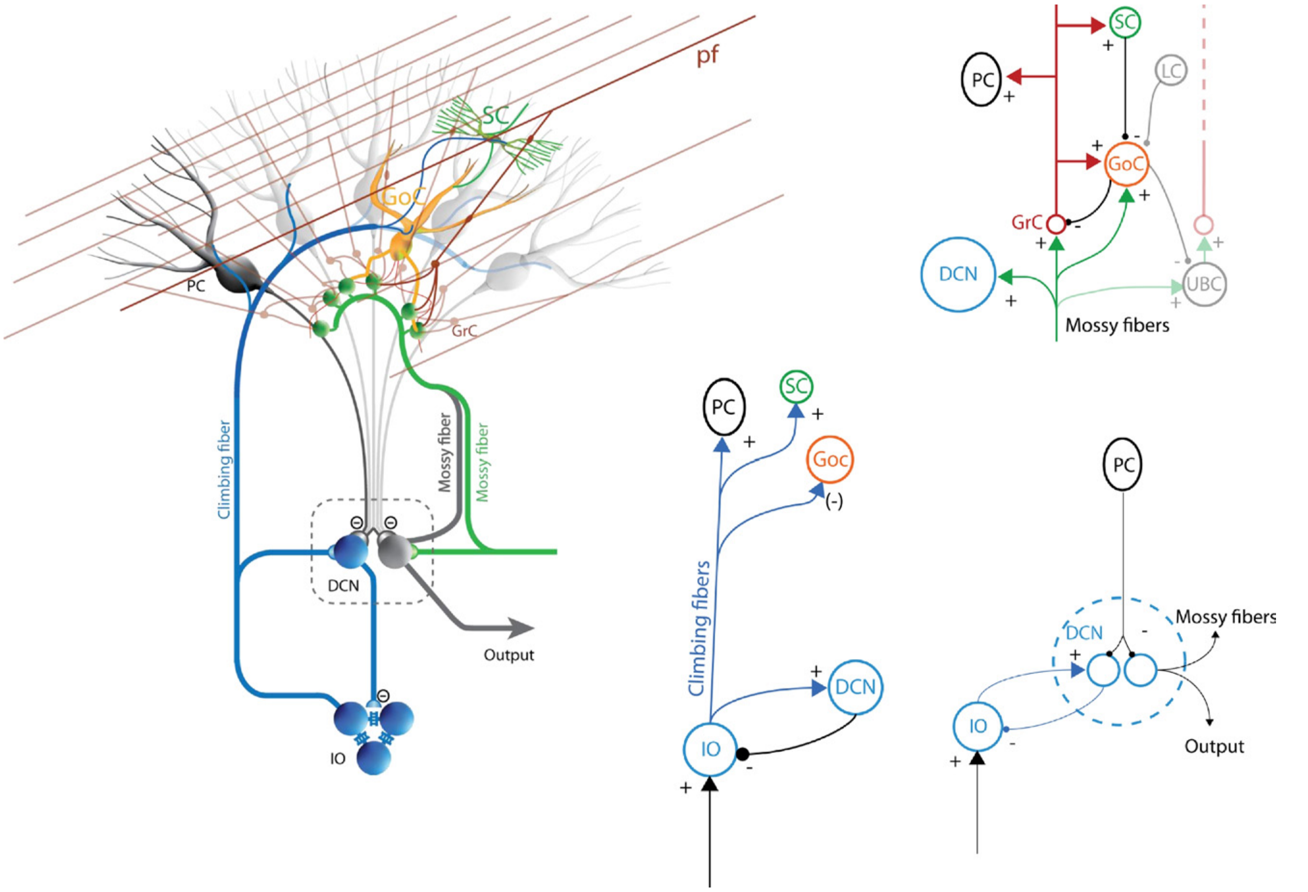

Fig. 1. The organization of a cerebellar module. This schematic drawing shows the most relevant connections within a cerebellar module. The cerebellar module is made of a series of connections, in which different circuit elements communicate in closed loops and are contacted by the same afferent fiber set. The mossy fibers contact granule cells (GrC) and DCN cells which, in turn, receive inhibition from the same common set of Purkinje cells (PC). Moreover, the IO cells emit climbing fibers that contact DCN and PC, which also project to the same DCN cells. For convenience, the circuit can be divided in three sections illustrated schematically in the insets. The top-right inset also shows a Lugaro cell (LC) and a UBC, this latter typical of the vestibulocerebellum. Note that connections exist between the climbing fiber and mossy fiber sections, although these have often been considered as separated.

cerebellar network to show oscillatory activities. Question remains which network factors cause the cerebellum to generate particular internal rhythms and to operate at preferential frequency bands, and what the functions of these oscillations might be (Buzsáki, 2006; De Zeeuw et al., 2008).

Although the EEG of the cerebellum is not used in daily clinical practice, experimental analysis has revealed that the cerebellum, in humans, can express all series of rhythms encompassing the theta, alpha, beta, gamma and very high frequency (VHF) bands (Dalal et al., 2008; Gross et al., 2002). These rhythms are likely to arise to a large extent from electric fields generated in the molecular layer (Isope et al., 2002; Cheron et al., 2008; de Solages et al., 2008; Middleton et al., 2008), but the granular layer is likely to contribute as well to at least some of these rhythms (for review see De Zeeuw et al., 2008). Extracellular field recordings in freely behaving animals have shown that large granular layer areas can oscillate in synchrony demonstrating remarkable coherence in the 7–25 Hz frequency range (Pellerin and Lamarre, 1997; Hartmann and Bower, 1998; Courtemanche et al., 2002; Courtemanche and Lamarre, 2005; Schnitzler, 2005; Schnitzler and Gross, 2006). In keeping with this, granular layer neurons are well equipped with appropriate membrane channels favoring activity in this band (D'Angelo et al., 2001; Solinas et al., 2007a,b). Moreover, computational modeling has predicted that the granular layer can generate theta-frequency oscillations (Kistler and De Zeeuw, 2003) and may also undergo cycles of activity at relatively higher frequencies (up to 40 Hz; Maex and De Schutter, 1998).

Interestingly, all these frequencies have been observed in muscular responses either as tremor or through EMG spectral analysis and are somehow species-specific. For example, eyelid oscillates at ~10 Hz in humans, ~20 Hz in cats and 25–30 Hz in rats, guinea pigs (Gruart et al., 2000) and mice (Koekkoek et al., 2002). Therefore, the cerebellum may be able to sustain oscillations at different frequencies to synchronize with other areas of the brain involved in sensorimotor control (Domingo et al., 1997; Gruart et al., 1997; Sanchez-Campusano et al., 2007).

While we recently focused on the interplay between timing and plasticity in shaping the granular layer response to external inputs (D'Angelo and Dezeeuw, 2009), here we will consider the cellular and functional properties of the granular layer and their implications for oscillations and resonance in the olivo-cerebellar system as a whole. Given the difficulties in classifying and comparing brain oscillations across brain regions, species or behaviors (Buzsáki, 2006), in this review we will refer to low-frequency oscillations when considering those between 7 and 25-30 Hz and to high-frequency oscillations when considering those occurring above 30 Hz.

ANATOMO-FUNCTIONAL PROPERTIES OF THE OLIVO-CEREBELLAR CIRCUIT

The cerebellum is organized in modules including cortical microcomplexes (De Zeeuw et al., 1994; Brown and Bower, 2001; Voogd et al., 2003; Pijpers et al., 2006). The understanding of circuit mechanisms can be conceived by addressing the connectivities within an individual module and the relation between the various modules (Fig. 1). Each module receives two major kinds of inputs, one from the mossy fibers and another from the climbing fibers. These inputs ultimately converge onto Purkinje cells, which eventually inhibit the deep cerebellar nuclei, representing the sole output of the circuit. Virtually all connectivities among neurons and interneurons in the cerebellar cortex occur within individual modules. The intracortical connections between modules occur prominently via the parallel fibers, apart from the Lugaro cell axons running along the parallel fibers and contacting different inhibitory neurons (including Purkinje cells, Golgi cells and stellate cells; Lainé and Axelrad, 1998; Dieudonné and Damoulin, 2000; Dean et al., 2003). Moreover, at the cerebellar input, common mossy fibers can activate more lobules and a single olivary neuron also usually reaches different modules even at a considerable distance (for review see De Zeeuw et al., 1998; Voogd et al., 2003). Here for clarity of presentation, we dissect the olivo-cerebellar system into three principal sub-circuits and we discuss their relationship accordingly.

The mossy fiber input and the granular layer

The mossy fibers provide one of the major inputs to the cerebellum and mediate sensorimotor and higher cognitive inputs via dedicated pathways running through the spinal cord, brainstem and cerebral cortex (Ito, 1984). The properties of the mossy fiber firing pattern appear to depend on the specific characteristics of the particular input source and the actual stimulus status. For example, during slow head rotations, the vestibular input is represented through a linear encoding of mossy fiber spike rates, typically in the 0–40 Hz range (Arenz et al., 2008; Bagnall et al., 2008); the trigeminal input tends to generate spike bursts in response to transient stimuli causing corresponding bursts in granule cells (Chadderton et al., 2004; Rancz et al., 2007); and the oculomotor eyeball input as well as joint input appears to produce both bursts and tonic discharges related to changes in position (van Kan et al., 1994; Kase et al., 1980). Since many of the sensory systems nuclei, pontine nuclei and cortical efferents also include neurons capable of both phasic and tonic discharge (e.g. see Ghez, 1991; Schwarz and Thier, 1999; Möck et al., 2006), the combined capacity is probably rather common in mossy fiber signaling, even though some spiking patterns may only become apparent during a particular status of the stimulus.

Signals coming into the cerebellum through the mossy fibers are processed in the granular layer network, which includes a feed-forward inhibitory loop (mossy fiber→Golgi cell→granule cell) and a feedback inhibitory loop (mossy fiber→granule cell→Golgi cell→granule cell). Here, with the intervention of the inhibitory circuits and synaptic plasticity, mossy fiber spikes are recoded into new spatiotemporally organized sequences by granule cells and Golgi cells exploiting their specific electroresponsive properties, which are specialized for sustaining bursting and repetitive activity on specific frequency bands (D'Angelo et al., 2001; Mapelli and D'Angelo, 2007; D'Angelo, 2008; Solinas et al., 2007a,b) (Fig. 2). Four relevant aspects of this processing are:

a. Granular layer processing is fast and precise; output spikes are emitted within milliseconds exploiting fast synaptic and excitable mechanisms (Silver et al., 1992; D'Angelo et al., 1995; Cathala et al., 2005).
b. Specific input patterns, under the guidance of inhibitory circuits, can induce bidirectional NMDA receptor-dependent long-term synaptic plasticity at the mossy fiber–granule cell synapse (D'Angelo et al., 1999; Armano et al., 2000; Rossi et al., 2002; Maffei et al., 2002; Sola et al., 2004; Gall et al., 2005; Mapelli and D'Angelo, 2007). Long-term potentiation (LTP) and probably also long-term depression (LTD) are expressed presynaptically (Sola et al., 2004; D'Errico, Prestori and D'Angelo, unpublished observations), and as such they may have a prominent impact on timing through their control of repetitive neurotransmitter dynamics, i.e. short-term facilitation and depression (Nieus et al., 2006).
c. By controlling first spike delay, LTP would allow spikes to fall inside the window set by Golgi cells feed-forward inhibition, while LTD would drive the granule cells response beyond the window limit ("window-matching" effect; D'Angelo, 2008; D'Angelo and De Zeeuw, 2009). By doing so, the granular layer operates a spatiotemporal filtering of signals and a spatiotemporal redistribution of activity, which can eventually lead to computational operations involving coincidence detection and pattern separation (Mapelli J, Gandolfi D and D'Angelo E, unpublished observations).
d. The granule cells are resonant and the Golgi cells are pacemaking and resonant at low frequency ($<$10 Hz *in vitro*, but probably higher *in vivo*; Vos et al., 1999; D'Angelo et al., 2001; Solinas et al., 2007a,b). The granular layer can be entrained in repetitive synchronous discharges in the 7–25 Hz range (Pellerin and Lamarre, 1997; Hartmann and Bower, 1998; Courtemanche et al., 2002; Courtemanche and Gross, 2005).

Thus together, these four elementary aspects of granular

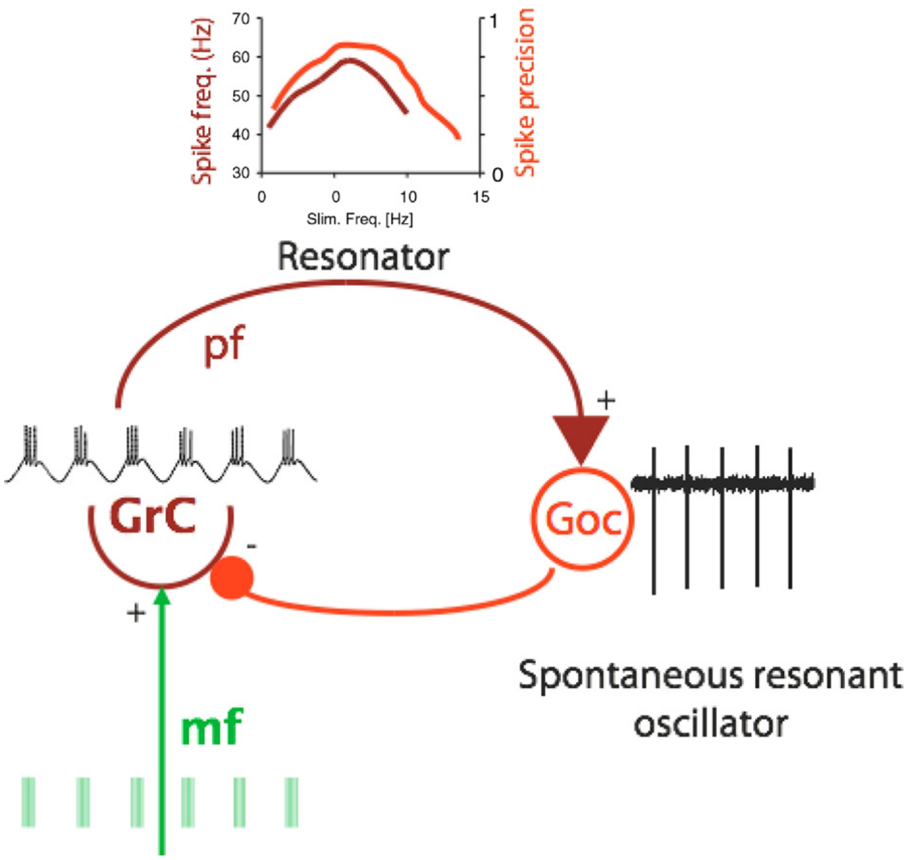

Fig. 2. The cellular basis for low-frequency oscillations and resonance in the cerebellar granular layer. The granule cell (GrC) and the Golgi cell (GoC) are endowed with ionic currents that allow the emergence of theta-frequency resonance. Granule cell intrinsic excitability is enhanced in the 4–10 Hz frequency range, and Golgi cells show enhanced responses and precision at the same frequencies. Moreover, Golgi cells show pacemaker activity and phase reset with the corresponding characteristic period. This circuit is therefore appropriately designed to generate enhanced responses when, for example, the mossy fiber input would occur in theta-burst patterns. Experimental traces have been redrawn from D'Angelo et al. (2001); Forti et al. (2006) and Solinas et al. (2007b).

layer processing show that this layer is in principle well equipped to control the absolute timing and phase of oscillations and resonance (Fig. 2). This control is of fundamental importance since every subsequent computation in the cerebellum will depend on it. Granule cell spike patterns are further processed in Purkinje cells, induce long-term synaptic plasticity at the parallel fiber–Purkinje cell synapse and activate molecular layer interneurons.

The climbing fiber input, Purkinje cells and the molecular layer

A second major input to the cerebellar cortex comes from the inferior olive through the climbing fiber system. The inferior olive itself receives inputs from many brain regions that form, in fact, directly or indirectly a source for one of the mossy fiber inputs (for review see De Zeeuw et al., 1998). The olivary neurons have a propensity to oscillate (Llinás and Yarom, 1981; Chorev et al., 2007; Khosrovani et al., 2007; Van Der Giessen et al., 2008), and their climbing fiber activities can produce theta-frequency patterns in the cerebellar cortex by directly innervating the dendritic arbors of Purkinje cells and inhibitory interneurons, including stellate cells (Barmack and Yakhnitsa, 2008) and possibly Golgi cells (Xu and Edgley, 2008). In fact, in Purkinje cells, climbing fiber activities are able to exert a very powerful phasic excitation through the complex spike (Miall et al., 1998). The complex spike signal may carry an error in motor performance and as such it might be used as an instruction for generating synaptic plasticity at the parallel fiber to Purkinje cell synapse (Ito and Kano, 1982; Coesmans et al., 2004). Moreover, climbing fibers can exert a tonic inhibitory action (Montarolo et al., 1982), which has been assumed to be due to collaterals to interneurons. Recently, Szapiro and Barbour (2007) have provided a mechanistic explanation to this observation by demonstrating that interneurons are affected by glutamate spillover from the climbing fibers.

The Purkinje cells have their own processing mechanisms, which also rely on intrinsic electroresponsive properties and synaptic plasticity. Their most relevant computational aspects are:

a. Purkinje cells are spontaneously active (30–50 Hz) and their discharge is modulated by inputs from the olivary neurons, granule cells, and molecular layer interneurons. Following the original observations by Adrian and Matthews (1934), it was recently shown that the molecular layer can sustain synchronous high-frequency (100–200 Hz) oscillations entraining the Purkinje cells (de Solages et al., 2008; Middleton et al., 2008). Thus, the granular layer patterns need to be precisely synchronized in order to efficiently affect Purkinje cells activity.

b. Purkinje cell synapses are sites of plasticity, including for example LTD and LTP at the parallel fiber to Purkinje cell synapse (Coesmans et al., 2004), LTD at the climbing fiber to Purkinje cell synapse (Hansel et al., 2001), and LTP at the interneuron to Purkinje cell synapse (Kano, 1995). For alternative interpretations see Llinas et al. (1997).
c. Purkinje cells may act as perceptrons exploiting their plasticity capabilities for pattern recognition (Brunel et al., 2004).
d. Purkinje cells may communicate through spike pauses modulating the interspike intervals over milliseconds (Steuber et al., 2007; Hoebeek et al., 2005; Shin et al., 2007). In this respect, it is relevant to note that under particular forms of anesthesia, but less so in the awake state, Purkinje cells show extensive bistable up-and-down states lasting over much longer time periods of hundreds of milliseconds to seconds (Loewenstein et al., 2005; Schonewille et al., 2006; Jacobson et al., 2008).

Thus, apart from a direct inhibitory feed-forward control imposed by the molecular layer interneurons (stellate and basket cells), the dynamic firing properties of the Purkinje cells are presumably tightly controlled by both the climbing fiber and the parallel fiber system, which have probably impact on all four aspects described above.

The deep-cerebellar neurons and the cerebellum output stage

The Purkinje cells form the only output of the cerebellar cortex and they inhibit the cells of the vestibular nuclei (VN) and deep-cerebellar nuclei (DCN), which ultimately convert the activities of the microzones and those of the mossy fiber and climbing fiber collaterals into the final cerebellar output (Fig. 1). The VN and DCN are thus at a key location within the cerebellar network. Their projection neurons can be divided into at least two main groups: those that inhibit the inferior olivary (IO) cells presumably regulating their coupling and oscillations (De Zeeuw et al., 1989, 1998; Jacobson et al., 2008) and those that exert a more direct control on the ultimate motor output (Fig. 3). In fact, while the role of inhibitory interneurons has not been demonstrated convincingly in freely behaving animals yet, principal neurons can be divided into types A and B, which modulate their firing in relation to activation of agonist or antagonist muscles (Gruart et al., 2000; van Kan et al., 1993). The most relevant properties of the DCN neurons are the following:

a. DCN neurons are intrinsically active at frequencies ranging from a few Hz to tens of Hz (Uusisaari et al., 2007). In general, the intrinsic dynamics of the cells generate silent pauses and often rebound excitation, producing alternating phases of activity depending on the strength and length of the inhibition induced by the Purkinje cells (Uusisaari et al., 2007). The projecting GABAergic and non-GABAergic DCN cells can be distinguished based on their synaptic currents; the synaptic currents in the GABAergic cells have lower amplitude, lower frequency and slower kinetics than those of the non-GABAergic cells (Uusisaari and Knöpfel, 2008). Therefore, the GABAergic cells appear better designed for conveying phasic spike rate information, whereas the larger non-GABAergic cells relay more faithfully tonic spike rate.
b. The DCN and VN neurons may act as one of the main substrates of downstream motor memory storage (Lisberger and Sejnowski, 1992; Wada et al., 2007; Ito, 2006). This hypothesis is supported by the fact that the synaptic strength of their inputs as well as their active membrane properties can be readily modified (Telgkamp and Raman, 2002; Aizenman et al., 1998; Aizenman and Linden, 2000). Interestingly, as predicted by a recent model of the cerebellar nuclei neurons and their Purkinje cell and mossy fiber collateral inputs (De Zeeuw et al., 2008), Pugh and Raman (2008) showed that the extent of plasticity varies with the relative timing of synaptic excitation evoked by the mossy fiber collaterals and the hyperpolarization induced by the Purkinje cells activity.

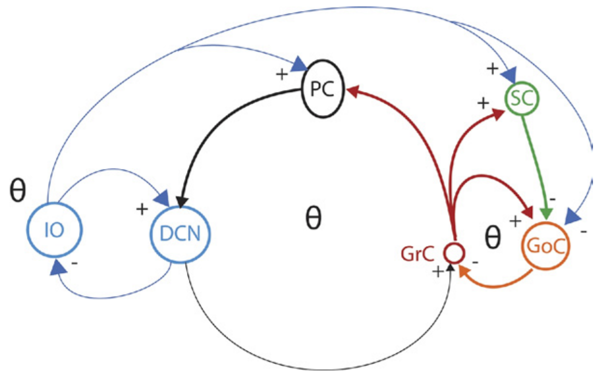

Fig. 3. Multiple loops involved in controlling cerebellar low-frequency activity. Due to the intrinsic resonance of neurons in the granular layer loop (GC–GoC), to signal reentry from the DCN, and to oscillatory activity in the IO complex, the olivo-cerebellar circuit demonstrates a design suitable to operate within a dominant frequency band of ~10 Hz. GrC, GoC, PC, mf and cf. indicate granule cells, Golgi cells, Purkinje cells, mossy fibers and climbing fibers, respectively. While the backbone of the circuit summarizes classic knowledge on the cerebellum (e.g. see Eccles et al., 1967), some less known connections like those from climbing fibers to the SC and GoC (Shibata et al., 1998; Barmack and Yakhnitsa, 2008) and from the DCN to GrC (Buisseret-Delmas and Angaut, 1989; Trott et al., 1998) may also play an important role for the overall network synchronization and phase-locking.

Thus, one can hypothesize that the synchronous oscillations in the Purkinje cell activities together with plasticity at the mossy fiber–DCN and the Purkinje cell–DCN synapses form the main mechanistic tools to control the activity in the DCN output neurons, and that different sets of neurons in the DCN are sensitive for oscillations at different frequency ranges (for details about hypothesis see De Zeeuw et al., 2008).

There are, in addition, several connections between these three main subcircuits. Activity of the inferior olive can be conveyed through the climbing fiber→stellate cell→Golgi cell circuit (Dumoulin et al., 2001; Szapiro and Barbour, 2007; Barmack and Yaknitza, 2008). Moreover, Golgi cells may also be inhibited directly through metabotropic receptor activation by the climbing fibers, as proposed by Xu and Edgley (2008). Finally, some mossy fibers can originate from the DCN (Trott et al., 1998). Thus, activity of the IO and DCN can be reverberated in the granular layer. Interestingly, the interaction between the two main subsystem can exert complex effects on spike discharge and on synaptic plasticity in Purkinje cells (Miall et al., 1998; Hansel et al., 2001).

As a whole, one can conclude that all circuit subsections make their own contribution to oscillatory activity in the cerebellum and eventually interact through several internal connection loops. Importantly, the granular layer is the starting point for the activities generated in several of the other circuit sections.

SPECIAL PROPERTIES OF GRANULAR LAYER NEURONS

Both the granule cells and Golgi cells have complex dynamic properties, which can influence granular layer temporal patterns. Granule cells, in addition to generating repetitive nonadapting spike discharge in response to a continuous stimulus (D'Angelo et al., 1995, 1998; Brickley et al., 1996), can enhance spike burst generation and resonate in a low-frequency band (between 4 and 10 Hz) (D'Angelo et al., 2001; Magistretti et al., 2006). High-frequency bursting (Chadderton et al., 2004; Jörntell and Eckerot, 2006; Rancz et al., 2007; Barmack and Yakhnitsa, 2008) as well as collective low-frequency oscillations (Hartmann and Bower, 1998; Pellerin and Lamarre, 1997; Lu et al., 2005) characterize indeed granule cell responses *in vivo*. Golgi cells show an even more complicated set of excitable properties including pacemaking, rebound excitation and burst discharge (Dieudonné, 1998; Forti et al., 2006), whose mechanisms have recently been elucidated to a considerable extent (Solinas et al., 2007a,b). The pacemaker oscillation usually also occurs at low frequency (between 4 and 10 Hz) and spikes triggered by incoming synaptic inputs can reset the phase of such ongoing intrinsic oscillations. The response to brief repetitive depolarization generally starts with a doublet or triplet of spikes and subsequently resonates at a faster, stronger and more precise rhythmic activity at the theta-frequency band. Importantly, most of these properties can be traced *in vivo* in that Golgi cells under these conditions too are spontaneously active and show precise temporal response patterns to punctuate stimulation, which include fast bursts followed by a silent pause corresponding to phase-reset (Vos et al., 1999; Simpson et al., 2005; Holtzman et al., 2006a,b).

The importance of bursting could be related to the need of generating reliable and strong responses to the high-frequency bursts of impulses entering the granular layer through the mossy fibers (Vos et al., 1999; Chadderton et al., 2004; Jörntell and Eckerot, 2006; Rancz et al., 2007). Bursts are intensified by specific ionic mechanisms including the resurgent Na current, whose contribution becomes particularly efficient when cell excitation is intense (Magistretti et al., 2006; Solinas et al., 2007a). As a consequence, the response of those granule cells that are intensely activated will be prized with the generation of a burst, whose duration is limited by a brisk feed-forward inhibition caused by a similar burst in the Golgi cell. On this basis one may anticipate that erratic spikes in the mossy fibers will not be efficiently transmitted, so that the burst-burst mechanism would indeed play a role for secure transmission along the mossy fiber pathway (e.g. see Rancz et al., 2007).

The dynamic properties of the granule cells and Golgi cells described above are reflected in the composition of their conductances. While they both contain the sodium, calcium and potassium currents responsible for repetitive firing regulation, bursting and resonance, it is only the Golgi cells that express the specific conductances required for pacemaking, phase resetting and rebound excitation (Table 1). An important consideration is that Golgi cell rhythmic activity at 4–10 Hz can be linearly biased by injected currents (Dieudonné et al., 1998; Forti et al., 2006; Solinas et al., 2007a,b), so that different frequencies may be generated under continuous synaptic bombardment. Indeed, spontaneous activity of Golgi cells *in vivo* shows a range of values from 4 up to 30 Hz (Vos et al., 1999; Holtzman et al., 2006a,b). Despite this variability, however, resonance would remain unaltered, since it depends on the specific channels expressed in the membrane rather than on the bias input current. Therefore, Golgi cells can provide a flexible background firing while maintaining a stable resonance frequency.

The granule cell–Golgi cell loops are probably regulated by other neurons including the stellate cells, the IO cells, Lugaro cells and, in the vestibulocerebellum, the unipolar brush cells (UBC) (Fig. 1, inset: for further details see D'Angelo, 2008; D'Angelo and Dezeeuw, 2009). UBCs are organized to redistribute and perpetuate excitation. Although the investigation of UBC responses to mossy fiber inputs is still incomplete (for the original report see

Table 1. Major ionic currents that regulate granule and Golgi cell excitability (D'Angelo et al., 2001; Forti et al., 2006; Solinas et al., 2007a,b)

	Granule cell	Golgi cell
High-frequency doublets	Na-r	Na-r
Spike delay	K-A	K-A
Resonance	Na-pK-slow	Na-pK-slow
Pacemaking		Na-p/K-slow/K-AHP/h
Phase-reset		K-AHP
Rebound excitation		h/LVA

Abbreviations: Na-p, persistent Na current; Na-r, resurgent Na current; K-A, A-current; K-slow, slow (M-like) potassium current; K-AHP, apamine-sensitive calcium-dependent potassium current; h, h-current; LVA, low-voltage-activated calcium current.

Rossi et al., 1995), UBCs have been shown to generate either tonic or burst discharge or even to present intrinsic oscillations depending on resting potential (Diana et al., 2007; Russo et al., 2007) by exploiting the properties of an h-current and a low voltage activated calcium current. UBCs, like granule cells, are inhibited by Golgi cells (Dugue et al., 2005) and could be tuned on a low-frequency band (S. Masetto, P. Perin, L. Bottà, and E. D'Angelo, unpublished observations). Lugaro cells (Fig. 1, inset) are normally silent but specifically inhibit Golgi cells upon serotoninergic activation, thereby providing a mechanism to regulate the extent of granular inhibition in relation to internal states (e.g., attention, arousal, reward) of the CNS (Dieudonné and Dumoulin, 2000; Geurts et al., 2003).

OSCILLATIONS AND RESONANCE IN THE GRANULAR LAYER

Low-frequency granular layer oscillations

Regular synchronous oscillations in the low frequency (7–25 Hz) range were reported over large granular layer fields *in vivo* during periods of resting attentiveness in rats and monkeys (Hartmann and Bower, 1998; Pellerin and Lamarre, 1997). The low-frequency preference of the granular layer denotes the ability of the granular layer to tune toward similar patterns conveyed by afferent structures. Low-frequency oscillations, specifically in the theta band, pervade sensorimotor processing (Llinás, 1988; Llinás et al., 1997; Gross et al., 2002; Schnitzler and Gross, 2005). For instance, whisking in rodents occurs at ~10 Hz, so that the same frequency is probably reverberated into the cerebellum both through the sensorimotor cortex and the sensory afferent pathways as a consequence of movement. A remarkable coherence between low frequency oscillations in sensorimotor cortex and cerebellum has been indeed observed in the rat and monkey (O'Connor et al., 2002; Courtemanche et al., 2002).

The theta-band seems predominant in the cerebellum and the tendency of neurons in the granular layer to operate in the theta-band does not stand alone (Fig. 3). At least two other loops within the same system may operate largely within the same frequency range. First, the recurrent circuitry passing through the DCN may reactivate the granular layer in about 100 ms (Kistler and De Zeeuw, 2003; see also Porrill and Dean, 2007) (Fig. 3). Since mossy fibers are also emitted by DCN neurons (Trott et al., 1998), the theta frequency tuning of the granular layer may evolve so as to raise the sensitivity to recurrent DCN inputs, which presumably represent an efference copy of the cerebellar motor output. Second, many of the activities in olivo-cerebellar modules formed by the inferior olive, DCN and Purkinje cells, are dominated by the pace generated in the neurons of the olive, which also tend to oscillate and fire in the theta-band (Llinás and Yarom, 1981; De Zeeuw et al., 1998; Kitazawa and Wolpert, 2005; Chorev et al., 2007; Khosrovani et al., 2007). Thus, since the Golgi cells presumably receive various direct and indirect inputs (either excitatory or inhibitory) from the climbing fibers derived from the olive (see above; Sugihara, 2006; Barmack and Yakhnitsa, 2008; Xu and Edgley, 2008) (Fig. 3), the granular layer may also tune toward the dominant frequencies of the olivo-cerebellar modules. Finally, it should be noted that the theta frequency preference of the cerebellar network matches that of certain input patterns coming from extracerebellar areas, which provide inputs to sources of both the mossy fiber and climbing fiber system. For instance, vibrissal activations and movements in rodents occur at about 10 Hz and give rise to projections to both the pontine nuclei and inferior olive (Kleinfeld et al., 2006) as well as directly from the trigeminal nucleus to the cerebellum (Bower and Woolston, 1983; Morrissette and Bower, 1996). Taken together, one can conclude that the theta-band operations in the granule cell layer can be readily integrated with those of other cerebellar and extracerebellar theta-band activities.

Prediction of high-frequency granular layer oscillations

In addition to elaborate slow 7–25 Hz oscillations, the granular layer may be able to generate oscillations at higher frequency. There are two main circuit loops suggesting that this could indeed be the case.

Golgi cell inhibition of granule cells can rapidly arrest signal transmission along the mossy fiber pathway. *Feedforward inhibition* (mossy fiber→Golgi cell→granule cell) operates rapidly (Kanichay and Silver, 2008), usually allowing the time for just a couple of spikes to cross the mossy fiber→granule cell relay. This effect was called "time-windowing" (D'Angelo and De Zeeuw, 2009). The time window is typically of about 5 ms and allows the granule cells to fire one to two spikes in response to a single mossy fiber stimulus (Mapelli and D'Angelo, 2007). During a continuous stimulation, *feedback cell inhibition* (granule cell→Golgi cell→granule cell) can depress signal transmission along the mossy fiber→granule cell pathway with a longer delay. Computational modeling predicts that, in the presence of a continuous input, this mechanism can give rise to oscillations, since once granule cells are excited, they activate the Golgi cell switching excitation off. When the inhibitory action is terminated, the cycle can restart generating oscillation at frequencies depending on the cell and synaptic time constants of the circuit (around 40 Hz in Maex and DeSchutter, 1998).

Double inhibition from the molecular layer (granule cell→stellate cells→Golgi cell→granule cell) can reduce Golgi cell activity (Barmack and Yakhnitsa, 2008). Computational modeling suggests that this mechanism could be important to stabilize high-frequency oscillatory cycles, since the excitability of granule cells would be raised after each excitation/inhibition cycle favoring re-excitation (J. A. Garrido, E. Ros, R. R. Carrillo, E. D'Angelo, unpublished observations).

Unfortunately, the MEG demonstration of the gamma band oscillations in the human cerebellum could not indicate their layer of origin (Dalal et al., 2008; Gross et al., 2002) and high-frequency granular layer oscillations remain to be demonstrated experimentally (e.g. using local field potentials).

Why are oscillations in the granular layer important?

From this review, it emerges that granular layer oscillations may play a critical role in cerebellar activity.

Low-frequency oscillations are fundamental for several neurophysiological processes, including motor control, the formation of memories and sleep (for review see Buzsáki, 2006). Low-frequency activity was shown to correlate with that in the cerebral cortex, and may therefore represent a suitable band for communication between cerebellum and the thalamo-cortical system (O'Connor et al., 2002). Moreover, it may provide a binding element between the two main functional sections of the cerebellar cortex, i.e. mossy fiber and the climbing fiber input systems. The disruption of appropriate control mechanisms in the olive and DCN allows low-frequency oscillations to prevail at the DCN output stage causing muscle tremor, as it occurs with harmaline application and in essential tremor in humans (Llinás, 1988). Muscle tremor occurs at ~10 Hz for larger muscles, and is also species-specific ranging from about 7 Hz to 25–30 Hz (Gruart et al., 2000; Koekkoek et al., 2002). Therefore, low-frequency patterns may have important yet incompletely understood roles in cerebellar control, opening new fields for future research.

Low-frequency oscillations are essential for signal processing at high rate (for review see Buzsáki, 2006). Since the afferent inputs are largely encoded with 5-ms precision in the 1st spike delay (Johansson and Birznieks, 2004), the same accuracy in the time-window matching process seems needed for efficient elaboration of incoming information. The repetition of these time-windows during protracted stimulation is predicted to generate high-frequency oscillations in the granular layer, providing a coherent framework for data processing over large granular layer fields. This periodic output may then be sampled by Purkinje cells, which also have a high-frequency regimen of activity and provide precise timing of Purkinje cells simple spike activity over the same scale (Hoebeek et al., 2005; Shin et al., 2007). The high-frequency sampling based on oscillating background could be important if the Purkinje cell works as a perceptron, allowing signal sampling over very short time windows and improving pattern recognition (Brunel et al., 2004). The repetition of spikes emitted by granule cells in the gamma frequency band may also be important to implement other physiological processes. First, parallel fiber–Purkinje cell release probability is usually low (except for ascending axon synapses, Isope and Barbour, 2002; Sims and Hartell, 2006), so that short high-frequency bursts can ensure efficient transmission through short-term parallel fiber–Purkinje cell facilitation. Secondly, there are forms of parallel fiber–Purkinje cell LTD which require doublets (Casado et al., 2000, 2002), so that persistent changes could be induced only at those synapse that receive high-frequency inputs. The demonstration of high-frequency oscillations in the granular layer remains an interesting challenge for future cerebellar investigations.

CONCLUSION

In conclusion, available evidence suggests that both slow and fast granular layer oscillations could have specific roles in cerebellar signal processing. While high-frequency oscillations may support millisecond-scale timing in granular layer activities preparing signals for Purkinje cells and allowing fast and precise elaboration of single motor acts, low-frequency oscillations may support repetition or coordination of complex motor sequences. Indeed, the granular layer demonstrates a theta-frequency preference that is indicative of the existence of such higher-order dynamics, and anatomical and functional evidence suggests that these could involve entire cerebellar modules. This low-frequency activity may be important for coordinating cerebellar communication with the sensorimotor cortex correlating with processes like learning, arousal and attention.

Note added in proof

During publication of this paper, a report has appeared showing that gap-junctions among Golgi cells play an important role for low-frequency oscillations and resonance in the cerebellum granular layer. (Dugué GP, Brunel N, Hakim V, Schwartz E, Chat M, Lévesque M, Courtemanche R, Léna C, Dieudonné S. (2009) Electrical coupling mediates tunable low-frequency oscillations and resonance in the cerebellar Golgi cell network. Neuron 61: 126–139.)

Acknowledgments—The authors thank for discussion about aspects of the present work F. Hoebeek, P. Rossi, L. Forti, F. Prestori, J. Mapelli, S. Diwakar, E. Cesana, and D. Gandolfi. This work was supported by the joined EU project SENSOPAC (to E.D., C.I.D.Z. and E.R.), by the EU project CYBERRAT and the CNISM project NEUROIMAGE (to E.D.), and by the Prinses Beatrix Fonds, Zon-MW and Neuro-Bsik (Senter) in the Netherlands (to C.I.D.Z.).

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(Accepted 24 January 2009)
(Available online 31 January 2009)