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REVIEW

Oscillations, Timing, Plasticity, and Learning in the Cerebellum

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Abstract The highly stereotyped, crystal-like architecture of the cerebellum has long served as a basis for hypotheses with regard to the function(s) that it subserves. Historically, most clinical observations and experimental work have focused on the involvement of the cerebellum in motor control, with particular emphasis on coordination and learning. Two main models have been suggested to account for cerebellar functioning. According to Llinás's theory, the cerebellum acts as a control machine that uses the rhythmic activity of the inferior olive to synchronize Purkinje cell populations for fine-tuning of coordination. In contrast, the Ito–Marr–Albus theory views the cerebellum as a motor learning machine that heuristically refines synaptic weights of the Purkinje cell based on error signals coming from the inferior olive. Here, we review the role of timing of neuronal events, oscillatory behavior, and synaptic and non-synaptic influences in functional plasticity that can be recorded in awake animals in various physiological and pathological models in a perspective that also includes non-motor aspects of cerebellar function. We discuss organizational levels from genes through intracellular signaling, synaptic network to system and behavior, as well as processes from signal production and processing to memory, delegation, and actual learning. We suggest an integrative concept for control and learning based on articulated oscillation templates.

Keywords Purkinje cell · Golgi cell · Plasticity · Learning · Motor control · Inferior olive · Oscillation

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Introduction

When addressing the issue of learning, it has become important to use a dynamic hierarchical framework that includes the different organizational levels that are involved from genes to behavior (i.e., synapses, neurons, network circuitry, systems) [1, 2] and, in parallel, the different related processes, such as oscillation/timing, plasticity, memory, delegation, and proper learning [3–5] (Fig. 1). In this scheme, gene and oscillation/timing occupy the first basic level upon which the other organizational levels and processes may be hierarchically built [6].

Neuronal oscillations and coherent relations between neuronal events are of major importance in this self-organizing structure [7]. For example, the long-term potentiation (LTP) (a key element for memory and learning) elicited in the hippocampus occurs only if the conditioning stimuli are applied in phase with intrinsic theta oscillation [8, 9]. Another example concerns the theta-phase precession in hippocampal place cells [10–12] that assumes temporal coding in the brain and the cross-frequency coupling between gamma and theta oscillation involved in sensory and memory processing [13]. This process documented elsewhere in the CNS might have implications for future research in the cerebellum.

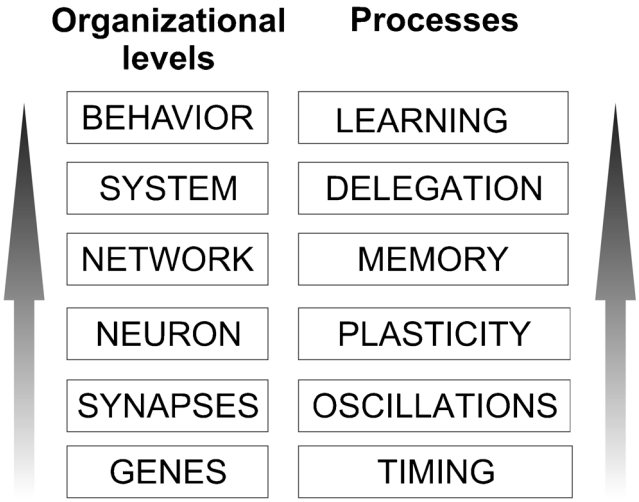

Fig. 1 Simplified framework of a hierarchical dynamic system for behavioral learning. *Bottom–up* representation includes the different organizational levels that are involved from genes to behavior paralleled by the different related processes

In this review, we follow this dynamical scheme to outline current understanding of the cerebellum in the general field of learning. This issue has been the subject of a long debate between two main positions that have sculpted the experimental work on the cerebellum for the last 40 years. Ito and his followers have regarded the cerebellum as a *learning machine* [14] while Llinás and his followers have contested this and have rather considered the cerebellum as a *control machine* [15–18]. The number of experimental evidences increases, supporting one or the other of these divergent positions, which also leaves some possibilities for new emerging positions. We try to confront and integrate the different classical viewpoints in order to propose a tentatively unifying platform for future explorations of cerebellar physiology.

The Cerebellum as a Neuronal Machine

The cerebellum has exerted universal attraction and has been regarded as a *neuronal machine* [19, 20] ever since the early descriptions by anatomists, clinicians, and neuroscientists. Inspired by its electrophysiological work on the spinal cord, Eccles adopted an efficacious strategy based on electrical stimulation and microelectrode exploration for revealing the basic operational mode of the cerebellar circuitry. This 50+-year-old characterization has remained valid and has been reinforced by increasing documentation of cerebellar functions and functioning relying on ever-refined technological and conceptual approaches [21–23].

Based on the pioneering clinical studies and experimental observations realized after WWI [24–27], the cerebellum has been mainly considered as a neuronal machine involved in motor coordination, muscle tone, and reflex regulation. The cardinal motor signs of cerebellar disorders are summarized under the term ataxia, which is characterized by incoordination of limb and eye movements, gait, posture, and dysarthria. This clinical complexity is attributed to cerebro-cerebellar interactions represented by multiple closed-loop pathways passing through the thalamus and the basal ganglia [28–31].

In addition to this motor domain, another closed-loop circuit between non-motor cortical areas and the cerebellum has been documented [32–34]. The latter supports cerebellar involvement in various aspects of sensorimotor [35], cognitive, and affective processing, as illustrated by neuropsychological and neuroimaging studies [36–38]. Therefore, a cerebellar cognitive affective syndrome has been suggested in parallel to ataxia. It manifests itself as impaired visuo-spatial, executive, and linguistic abilities, affective disturbance and psychiatric features, which can be conceptualized as a dysmetria of thought [39].

Such broadening of the perspective on the cerebellum beyond the classical motor involvement also resonates with paleontological studies highlighting a reciprocal relationship between the cerebellum and each of 14 neocortical regions that are crucial to human cognitive evolution [40]. Interestingly, in the model proposed by Weaver [41], the increased cognitive efficiency of humans in the late Late Pleistocene and Holocene is due to expanded cerebellar capacity. This has been suggested to have allowed efficient processing of cognitive operations without an increase in net brain volume in recent human evolution [41].

The preservation of the crystal-like circuit organization of the cerebellum throughout vertebrate phylogeny [14, 42, 43] has prompted neuroscientists to search for a single basic operation underlying all cerebellar functions. It must be noted that 40 years on, no such single operation has been found to date, despite clear evidence of implication of the cerebellum in integration of multiple inputs, coordination of both input and output signals, and short- as well as long-term encoding of experience [44, 45]. In addition, while cerebellar damage provides some clues about the function of the cerebellum, no single operation has been found [46–48].

Learning to Walk: a Cerebellum Performance

One of the reasons explaining why no single operation has been found is because different regions of the cerebellum have specific functions, such as the control exerted by the vermis on the static and dynamic balance, the rhythmic activity of the flexor/extensor muscles, and the adaptive control made by the lateral and intermediate regions on the limb placement [49, 50]. These cerebellar specializations have been grossly established by early clinical [26] and experimental observations [27]. Namely, in the *atrophie paléo-cérébelleuse primitive* where the Purkinje cells (PCs) of the vermis

degenerate, the major impairments of the posture and gait instability (titubation) contrast with conserved voluntary control of the upper limb and isolated lower limb movement.

When revisiting plasticity at the developing climbing fiber–Purkinje cell (CF–PC) synapses, Bosman and Konnerth [51] pointed out that the establishment of the mature form of the mammalian cerebellum roughly corresponds to the moment at which the animal starts to stand upright and walk, an idea already suggested in the nineteenth century [52]. This event is now associated with the end of the developmental competition between the two major afferent inputs (i.e., mossy and climbing fibers) on the PC, which is the sole output neuron of the cerebellar cortex. Notwithstanding the conservation of the cerebellum structure from non-human species to human, bipedal locomotion can be viewed as a distinctive feature requiring a strong motor learning demand at an early developmental age in humans. In order to achieve independent walking, which is universally considered as a "milestone" event in locomotor development, toddlers must find a compromise between postural stability for the erect posture against gravity and the dynamic control of the body and limbs for forward progression [53]. Whereas carrying out the very first walking steps requires full concentration, a basic coordinative template of the lower limb segments rapidly emerges and evolves toward (semi-)automated walking and later to fine adjustment [53, 54]. This development allows the toddler more freedom for accomplishing volitional acts. Bipedality is thus challenging, but it also appears to confer a selective advantage [55] in facilitating the transfer of basic tasks (such as walking) from the cerebral cortex to "lower" centers such as the cerebellum and basal ganglia, allowing the cortex to finely process new, unpredictable events [56].

Today, gait impairments are used to quantify cerebellar ataxia both in animal [57–61] and human studies [62, 63]. The precise timing of the EMG bursts and the intersegmental coordination are perturbed in patients with cerebellar ataxia in such a way that the vertical ground reaction force is abnormal, producing heel-strike instability [61]. These authors report that this abnormal timing (prolonged EMG activity) is reminiscent of the pathological picture present in the upper limb movement [64, 65] and during early development of locomotion [53, 66]. In some way, these ataxic alterations represent what the other parts of the CNS at the exception of the cerebellum have not been able to compensate, in spite of the possibility to learn other types of motor behaviors. This also indicates that even though the memory of the cerebellar learning may be stored outside of the cerebellum, some important elements of learned behaviors, such as locomotion skill, need to pass through a normal cerebellum. This poses the problem or the role of the cerebellum as a learning or a control system.

The Cerebellum as a Control or a Timing Machine

Another central idea considers the cerebellum not as a *learning* but as a *control* machine. The difference is not only semantic but supported by two main trends of fundamental thinking and experimental evidences [16, 17]. The first one originates in the rhythmic oscillatory activity of the electrically coupled inferior olive (IO) neurons assuming an oscillatory template to the olivo-cerebellar loop and the second from the immediate modulation of the PC simple spike (SS) by the CF inputs [67].

Based on the 10-Hz rhythmic oscillatory activity [68, 69] of the electrically coupled IO neuron [70, 71], Llinás et al. [72] have proposed that the CF imposes to the cerebellum a timing function in motor coordination. This hypothesis was further supported by numerous evidences reinforcing the idea that this rhythmic imprint originated in the IO acts also as a spatial organizer (via the CF) of the cerebellar circuit [73]. The developmental evolution of this rhythmic imprint involves the olivo-cerebellar system on both sides of the loop assuming the emergence of behavioral plasticity [74, 75] such as in the case of the classical conditioning of the eyeblink reflex. In addition, the IO input has a significant role in the regulation of the firing properties of the PC and consequently in the maintenance of the dynamic properties of the cerebellar motor control. For example, after chemical destruction of the IO, the PCs doubled their SS firing rate, and the spike rate became more regular and linked to the oscillation of the background [76] as those reported in ataxic mice [77–79] where the complex spike (CS) wave form and Ca^{2+} homeostasis are altered.

The IO input plays thus a global and a local role on the cerebellum. The global aspect is related to a general timing function [17] while the local aspect concerns a regulating action on the intrinsic properties of the PC by means of their urge Ca^{2+} influx. The climbing fibers primarily contact the more proximal portion of the PC dendritic tree and provide the major excitatory action on the PC (1500 climbing fiber–PC synaptic contacts) [80]. The mature PC receives this excitatory input from only one IO neuron, giving rise to the well-recognizable CS [81, 82] and the induced pause in the spontaneous SS firing of the same PC. In order to better understand the origin of the CS, simultaneous somatic and dendritic patch–clamp recordings have been made [83]. These authors demonstrated that all spikelets in the CS are generated in the axon and relatively independent of the dendritic Ca^{2+} spikes. They proposed the existence of two functional roles of the CF input which activates (1) a dendritic compartment responsible for the duration of the SS pause and able to trigger dendritic plasticity by means of Ca^{2+} influx and (2) an axosomatic compartment acting as an independent generator of the CS burst transmission toward PC targets in the deep cerebellar nuclei.

Delegation, Learning, and Memory

Transmission of signals from one side of the olivo-cerebellar loop to another one poses the general problem of delegation of neuronal competences from one part of the CNS to another, raising the question of the form of memory traces. In other words, how could a same network store and use memory of automated items, and participate in new learning processes at the same time? If memory is a widely distributed dynamical process with hot spots or privileged nodes in the network [84], it seems unlikely that a static mechanism uniquely localized in one part of the system could support this function. Rather, the process of delegation could correspond to a dynamic shift from one node to another one along the learning time. This type of functional delegation of automaticity by one part of the CNS to another was also proposed for the cerebellum itself [85], in which PC learning is transferred to the deep cerebellar nuclei (DCN) [86, 87]. Medina and Mauk [88] showed that the DCN circuit, which is mainly composed of mossy and climbing fiber inputs, was unable to retain memorized elements in the presence of background activities, except when it received learned PC input. The DCN circuit could then keep the memory trace, which remained resistant to ongoing activities in the network. In this system, PC activity can be seen as exerting a plasticity rule on to the DCN [88].

Delegation of automated motor task can also result in sharing competencies between different neural structures. For example, this was recently illustrated by a robotic manipulation task simulated by such a distributed system [89]. In this theoretical scheme, the association cortex elaborates the desired kinematics in body coordinates that are transmitted to both the motor cortex and the cerebellum. The torque commands are then produced in the motor cortex by using an inverse dynamics arm model. In parallel, the olivo-cerebellar system generates corrective torques after comparative computation between the desired commands and the final output commands made in the inferior olive and transmitted to the cerebellum by the climbing fiber error signals. The signals coming from the motor cortex and the cerebellum are summed up in the red nucleus and then sent to the robotic arm. In this model, learning and control processes are thus inextricably linked and distributed in different loci interconnected by long loop pathways.

The delegation process also exists within single neurons, and even at the level of the bidirectional cascade of molecular events that extend from the neuronal membrane to nuclear genes [90, 91]. Interestingly, increased transcription of microRNA implicated in protein regulation of PC plasticity has been demonstrated following sustained optokinetic stimulation inducing an increase in the climbing fiber input to the flocculus [92, 93]. However, in spite of the attractiveness of the cytoplasmic polyadenylation element binding protein (CPEB) mechanism, there has only been one published study of the contribution of CPEB in cerebellar plasticity [94]. These authors engineered mice expressing CPEB1 with phosphorylation sites mutated to alanine (mCPEB1-AA) exclusively in the PC. They demonstrated that although mCPEB1-AA mice showed no gross morphological changes in the cerebellum and normal synaptic transmission, long-term depression (LTD) at the parallel fiber–PC (PF–PC) synapses was altered and the mice showed ataxia. These results demonstrate that CPEB1 is implicated in PC plasticity and pave the way for future identification of the memory trace in very specific dendritic spines of the PC or in the other neurons of the cerebellum.

The Cerebellum as a Learning Machine

The idea that the cerebellum is the memory site for new motor skills through plasticity of PF–PC synapses originates in the proposal of Marr [95] and Albus [96] and was later consolidated by the fact that the olivary-mediated CF inputs, associated to an error signal, induce a long-term depression (LTD) at the PF–PC synapse [97].

As Ito [98] proposed for the vestibulo-ocular reflex adaptation, the CF plays the role of a "teacher" that signals errors and disturbances in sensorimotor function. By acting in conjunction with mossy fiber input (which acts into the PC via the parallel fiber synaptic termination), the CF signal triggers a massive Ca^{2+} input playing a determinant element for subsequent plasticity. This motor error input indexed by the presence of the complex spike (CS) would weaken the PF–PC synapses allowing improvement of motor performance.

Cerebellar LTD was first demonstrated in response to conjunctive stimulation of the vestibular nerve and the IO in the decerebrated rabbit by Ito et al. [99] and in response to conjunctive PF and IO stimulation by Ito and Kano [97]. Subsequently, Ekerot and Kano [100] reproduced the same LTD effect in the anesthetized and decerebrated rat. Later, the same authors specified that the maximal effectiveness for inducing LTD was obtained for a time interval between the CF and the PF stimulation of 125 to 250 ms and that the conjunctive stimulation given at 4 Hz induced a stronger LTD than those obtained at 1–2 Hz [101].

Repetitive stimulation of the climbing fiber as it is predicted in the case of peripheral mismatch or error (sensorimotor conflicts) produces a PF–PC synapse LTD sustained by a well-defined physiological mechanism, including implication of metabotropic glutamate receptors subtype 1 (mGluR1) [102–104], protein kinase C (PKC) [105, 106] resulting in clathrin-mediated internalization of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [107] and the activation of both postsynaptic α-calcium/calmodulin-dependent protein kinase II and nitric oxide-cyclic GMP-protein kinase G cascade [108–110]. More recently, the

interaction of protein interacting with C-kinase 1 (PICK1) and casein kinase II substrate in neurons (PACSIN) for the internalization of the AMPA is found to be critical for LTD expression in cultured PC [111]. However, in spite of the biological foundation of these elements and the fact that PF–PC LTD has been confirmed in decerebrate animals [97, 100, 112] and in the anesthetized mouse [113], the existence of LTD in awake animals has only been proved recently [114]. Much insight into cerebellar physiology has been gained through markedly different approaches. Studies conducted on slice provide access to specific aspects that are severed from wide network activity. The latter can be studied in vivo, but there too, there are marked differences between cerebellar physiology in the anesthetized vs the awake animal. In addition, there is evidence that cerebellar learning involves more than PC–LTD [115–118]. Therefore, it appears absolutely essential to verify the applicability of findings across approaches.

Recent views and experimental evidences [119, 120] propose that CS configuration, namely the number of spikelets which are directly related to the number of spikes in the CF [121], plays a major role in PC motor learning. During "trials over trials" learning of pursuit eye movement, Yang and Lisberger [120] demonstrated that a longer duration of CS related to a greater number of spikelets induced stronger learning responses indexed in the magnitude of SS firing depression than medium or short CS duration. In contrast, the SS silent period triggered by the CS did not affect the learning. Interestingly, it was recently demonstrated [122] in awake mice that the climbing fiber-triggered calcium signals are enhanced when it was elicited by a sensory event allowing a strong modulation of cerebellar plasticity. The majority of brain operations necessitate the cerebellum assistance to provide exact timing of multiple signals coming from the sensory systems [123] and their integration in the cerebral cortex. This multi-dimensional computation would also require a timing plasticity allowing motor sequence ordering, detection of error, and sensory prediction [23, 124, 125]. Very recently, it was demonstrated that the L7-PP2B mice presenting impaired PC intrinsic plasticity were severely impaired in learning of an object localization task requiring a precise timing [126]. This is of particular interest considering that the ability to produce adequate responses to sensory stimuli was preserved in this mutant. Based on these findings, these authors suggested an important role of cerebellum–cerebrum interaction in cognitive task necessitating a strict temporal tuning.

Whisker Pad Stimulation: a New Way Toward Plasticity

In the convergence of approaches to cerebellar physiology, the importance of awake animal studies must be particularly underlined as it appears to be closest to ecological applications in human functioning and disease. Several paradigms have been developed to study plasticity in this context, based on sensory stimulation, such as visual pursuit [87], adaptation of the vestibulo-ocular and optokinetic reflex [92, 93], the blink reflex [1, 3], and response to other peripheral stimuli. Among these, cerebellar changes induced by whisker pad stimulation have emerged as a promising paradigm for studying the linking between neuronal firing and local field potential in the context of synaptic plasticity.

When the whisker pad is stimulated by an air puff [127, 128] or by electrical pulses delivered in the control situation at a random rate (~0.1 Hz) or at 8 Hz (for inducing LTD) (Fig. 2a) [114], the PC of the Crus II zone presents a highly reproducible firing comprising an early SS response shortly followed by a CS. Figure 2 illustrates the precise timing events in both the firing of a PC (Fig. 2b) and a Golgi cell (Fig. 2c) and the related local field potential (LFP) components evoked by a single electrical stimulation of the whisker pad. Interestingly, the Golgi cell spikes occur shortly before the simple spikes (SS) of the PC followed by the CS. The Golgi cell spikes arrive before or during the N2 component while the PC SS arrive during the N2 and or the N3 component (Fig. 2d). In order to better understand the physiological origin of these LFP components, in-depth penetrations were performed (Fig. 3). When the microelectrode penetrated the molecular layer perpendicularly with respect to the surface, the negative polarity of N2 and N3 components were conserved until the PC layer was approached (Fig. 3(A–C)). This was revealed by the occurrence of PC firing (Fig. 3(B)), the N3 amplitude progressively decreased, and just beneath the PC layer, the N3 component suddenly changed into a positive component (Fig. 3(C)) peaking at the exact latency as the previous negative peak. Intriguingly, we have observed such an inversion only for the N3 component and not for the N1 and N2 components. In addition, when an electrical stimulation was made on the PF beam just before the stimulation of the whisker pad, only the amplitude of the N3 component was decreased (Fig. 3(D)). This collision test indicated that the sensory signals contributing to the N3 travel along the PF beam. This was interpreted in the following way and illustrated by the diagram of Fig. 3(E): (1) the postsynaptic generator of N3 may be produced by PC dipoles vertically oriented with the negative pole situated in the superficial part of the dendrite arborization explaining the reversal of N3 into P3 [81] and (2) the origin of N2 is more complex and could correspond to the granular and Golgi cell activity [19] directly followed by the action of an ascending axon–PC synapse [129].

The fact that N2 and N3 LFP components related to the PC spiking are delayed during at least 30 min after 8 Hz conditioning stimulation of the whiskers pad (Fig. 3(A)) reinforces the existence of a plasticity mechanism acting on the time constraint. Interestingly, this timing plasticity is absent in the mouse presenting a PC-specific ablation of the large-

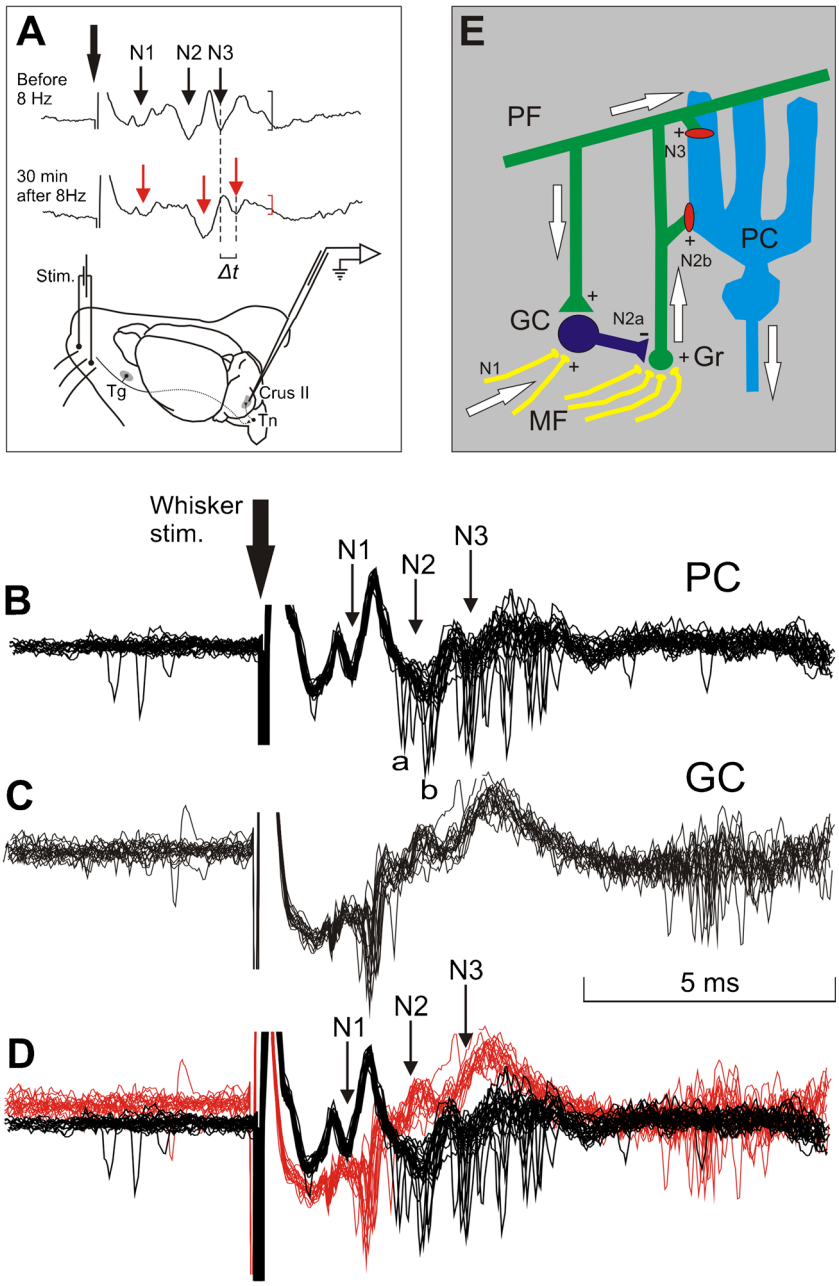

Fig. 2 Experimental design and electrophysiological response to electrical stimulation of mouse whiskers. **a** Animals were prepared for chronic recordings of local field potentials and unitary extracellular activity in the Purkinje cell layer of the Crus I/II area. Facial dermatomes of the whisker region were electrically stimulated with a pair of needles under the skin (*Stim.*) Evolution of the LFP components (*N1*, *N2*a,b, *N3*) before and after the 8-Hz LTD-inducing protocol. The *gray* and *red areas* represent the N3 amplitude before and after the 8-Hz LTD-inducing stimulation. The *dashed line* indicates delayed peak of the N3. **b** Superimposition of single traces including the *N1*, *N2a,b*, and *N3* LFP components and the simple spikes (SS) of a *PC*. **c** Superimposition of concomitant Golgi cell spikes. **d** Superimposition of the LFP+SSPC (*black*) and the Golgi cell firing (*red*). **e** Diagram explaining the origins of *N1*, *N2a*, *N2b*, and *N3* (see text for more details). *MF* mossy fibers (*yellow*), *GC* Golgi cell (*dark blue*), *PC* Purkinje cell (*blue*), *Gr* granule cell (*green*), *PF* parallel fiber (*green*). The signal fluxes are indicated by the *white arrows*. The synapse of the ascending axon of the granule cell and the synapse of the parallel fiber on the PC are represented by the *red ellipses*. *Vertical arrows* in **a** and **b** represent the electrical stimulation of the whisker pad

conductance voltage- and Ca^{2+}-activated K^+ (BK) channels (while the decrease in N3 amplitude is inconsistent) [130]. This indicates the implication of BK channels in the timing plasticity of the PC. This is in accordance with the crucial role played by these channels on the rhythmic imprint of the PC firing on the final control of movement and on ataxia [127, 131]. This timing plasticity is conserved in the *mdx* mouse model of Duchenne muscular dystrophy, while the amplitude depression (LTD) of the N3 component is absent (C. Prigogine, J. Márquez-Ruiz, B. Dan, and G. Cheron, personal communication). Interestingly, the PC of the *mdx* mice is concerned with the deletion of the dystrophin gene, resulting in disorganization of the GABAA receptor stabilization and clustering at postsynaptic densities of their inhibitory synapses [132]. This clustering disruption impairs the function of these inhibitory synapses and leads to a decreased inhibitory input of the PC and increased SS firing rate in alert *mdx* mice [133]. The absence of LTD on the N3 amplitude may be explained by an imbalance in PC excitatory inhibitory input altering the LTD process but conserving N2–N3 timing plasticity. This shows that the two types of plastic changes of the LFP, namely N2–N3 time shift and N3 amplitude decrease, involve different mechanisms.

Another proposal which could be made in relation to the N2 and N3 origins (Fig. 3(E)) is that ascending axon and PF synapses serve a fundamentally different role [16]. The

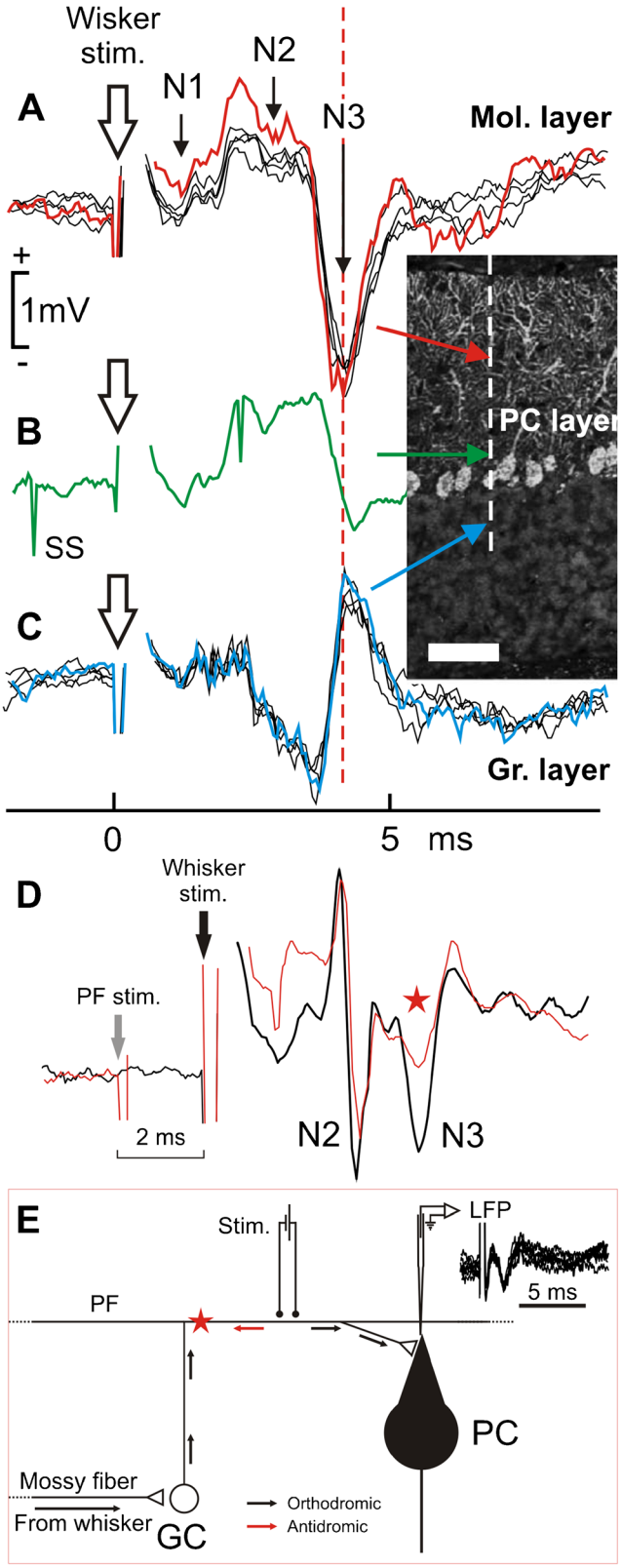

Fig. 3 Depth profile analysis of the LFP induced by electrical stimulation: inversion of the N3 LFP component and collision testing. *A* LFP recorded in the molecular layer (*Mol. layer*). *N1*, *N2*, and *N3* components are indicated. *B* LFP recorded near the PC layer where simple spikes (*SS*, *green trace*) were recorded. At this level, indexed by the occurrence of PC firing, the N3 amplitude decreased (see for comparison the superimposition of the LFP traces recorded in the molecular layer. *C* LFP recorded just beneath the PC layer showing the polarity inversion of the N3. The *white arrow* indicates electrical whisker stimulation. The *vertical dotted line* indicates N3 latency along different depths. *D* Superimposition of the average LFP (n=10 stimulations) in control (*black trace*) and during the collision (*red trace*, *red star*). The *gray vertical arrow* indicates the direct stimulation of the PFs while the *black vertical arrow* indicates the peripheral stimulation of the whisker pad. *E* Diagram of the neural pathways concerned in the direct stimulation (*Stim.*) applied on the top of the parallel fiber (*PF*). This stimulation produced a negative LFP (*superimposed traces* on the *right corner*) recorded by a microfiber placed in the dendritic arborization of Purkinje cells (*PC*). The *small arrows* indicate the propagation of the orthodromic action potentials (*black arrows*) and the antidromic action potentials (*red arrow*) producing collision (*red star*). The peripheral input coming from the whisker pad is transmitted to the granule cells (*GC*) via the mossy fiber. (*Adapted from* Márquez-Ruiz and Cheron [114])

ascending axons are mainly hard-wired, resistant to LTD [134, 135], and play the role of event detectors. In contrast, the PF demonstrate short- and long-term synaptic plasticity [97, 136–138] playing a modulating role. Based on this functional dichotomy—innate control (for the ascending granule cell axons) and acquired control (for the parallel fibers)—Rokni et al. [16] elegantly defend the idea that the cerebellum should be regarded as a control machine rather than a learning machine. Their main arguments are that the control capabilities of behavior are an innate ability achieved through synapses along the ascending axons and that it is not acquired by learning. In fine, a fine-tuning of this control system performed through the plastic capabilities of the parallel fiber–Purkinje cell synapses [16] allows them adaptive optimization.

Cerebellar Oscillations as a Key to Understanding Function

Cerebral oscillations play a crucial role in sensorimotor and cognitive behavior [6, 139]. Their emergence results from a subtle tuning between excitatory and inhibitory synapses and the interplay between the cortex and the thalamus [140]. However, in spite of the presence of synchronization of local field potential (LFP) oscillations in 10–25 Hz frequency range between the cerebellum and the primary somatosensory and motor cortex during active and passive expectancy [141], the role of cerebellar oscillations remains largely unknown.

Many analogies between the cerebrum and the cerebellum may indicate that common physiological mechanisms might promote oscillation in both entities. Among those, the presence of gap junctions would facilitate the emergence of fast oscillation [142]. In addition, the presence of intrinsic oscillatory properties in thalamic neurons [140] and in the IO neurons [143], respectively, in the case of the cerebral and cerebellar cortex and the existence in both cases of a

closed feedback loop between them play in favor of a general mode of operation. However, reverberating connections between excitatory neurons between cortical regions in short- and long-range distances are only present in the cerebral cortex and not in the cerebellum organized in rostro-caudal modules [144].

Another striking difference between cerebral and cerebellar cortices is that most of the synapses within the cerebral cortex are excitatory, while the only excitatory cells in the cerebellar cortex are represented by the granular cells transmitting their input in the molecular layer via the parallel fiber synapses [145] (at the exception of the unipolar brush cell lying in the vestibulocerebellum). All the other five types of cerebellar neurons are inhibitory and all of the recurrent connections are GABAergic. In spite of this particular circuitry, cerebellar oscillations exist in the awake condition under the form of local field potentials (LFP) and may be related to cerebellar functions. Now if we consider that learning represents one of these functions, oscillation may be viewed as reflecting a timing organization facilitating the packaging of information treatment [140]. Contrasting with the increased interest in cerebral gamma oscillations in perceptual binding, selective attention, memory [146–149], and the beta–gamma oscillation in the sensorimotor cortex [150–152], no such physiological functions are so strongly allocated to the cerebellar oscillations.

The search for a functional significance of cerebellar oscillation has been traced by Llinás work performed on the olivocerebellar system (see [19] for a review). The intrinsic properties of the electronically coupled IO neurons [71, 153] form a basic oscillatory template presenting subthreshold oscillations at 6–12 Hz upon which a burst of axonic spikes may emerge around the depolarizing phase of the oscillation [154] (Fig. 6). The number of spikes in the burst depends on the phase [121] and or amplitude [155] of the subthreshold oscillations.

In a recent review, Courtemanche et al. [165] highlighted the importance of the 4–25-Hz rhythmic oscillatory activity in the granular cell layer which could be considered in parallel to the basic oscillatory template imposed by the IO [15] as one of the major rhythmic activities of the cerebellum recorded in the form of waxing and waning spindles when the animals remained immobile in an attentive or passive expectancy [141, 157–160]. These oscillations are regulated by the firing activities of the Golgi [166] and Lugaro cells [167, 168] and play an important role in the spatiotemporal organization of the mossy fibers' input (LFP synchronization of the granule cells into the parasagittal module) [160, 165, 169].

In the context of fast oscillation (160–200 Hz), it is important to note that large-amplitude 160-Hz LFP oscillation have been described for the first time in calcium binding knockout mice [77] (Fig. 4a, b, d) and in a mouse model for Angelman syndrome [78] (Fig. 4c, e). These evidences have restarted the scientific interest for the pioneering observation of Adrian [172] about the existence of low-amplitude 200-Hz oscillations on the surface of the cerebellum in decerebrate and anesthetized preparations. The major interest is to better understand the role played by these fast oscillations [173]. However, the 160-Hz LFP oscillation recorded in the different mouse models presenting cerebellar ataxia (calcium binding knockout [77], Angelman syndrome model [78], and FAS model [79]) does not exist in WT mice. It is different from the 200-Hz oscillation described by de Solages et al. [162] which is not clearly visible in the LFP but only represented by a small deflection in the FFT spectrum (Fig. 4 of de Solages et al. [162]). In order to obtain a clear peak at this frequency, de Solages et al. [162] have added GYKI 52466 (an AMPA receptor blocker) or WIN 55,212-2 (a cannabinoid CB1 receptor activator). As mentioned by these authors, the possibility exists that the fast LFP oscillation recorded in the different mutants is a pathological form of a physiological 200-Hz rhythm resulting from a functional synchrony of the PC. Indeed, electrophysiological evidences (generation by PC, synchronization with PC) and pharmacological behavior (suppression of the high-amplitude 160-Hz LFP by gabazine [77, 78] (Fig. 4c) and the 200-Hz power by picrotoxin [162])—two antagonists of GABAergic synapses—play in favor of a continuum between a basic physiological rhythm to an exaggerated, pathological form disturbing the basic function of the cerebellum. The fact that it is possible to produce a fast LFP oscillation (~100 Hz) in a cerebellar slice [170, 174] when nicotine was added to the bath and that it was suppressed by the gap junction blockers (carbenoxolone) as in the mutant 160-Hz LFP oscillation [77, 78] (Fig. 4c) reinforces the idea that different physiological processes basically exist in the cerebellar cortex for promoting such fast rhythmic activities implicated in PC synchronization but in a moderate and restrictive way.

At least, five different factors are implicated in the control of 160 Hz oscillation: (1) the calcium homeostasis of the PC [77, 175]; (2) an increased excitatory input from the parallel fiber as in the case of the calretinin (Cr) knockout mice, for which the restoration of Cr in the granular cells suppresses the 160-Hz LFP oscillation [59]; (3) the control exerted by the Golgi cells firing on the amplitude of the 160-Hz LFP [77] (Fig. 5c, d); (4) the gap junctions [77, 170, 174] (Fig. 4f), and (5) the action of the PC collaterals on the PC synchronization [162, 177].

Interestingly, spontaneous synchrony between PCs along the PF beam has only been reported in the normal awake cerebellum for a very short distance or only during a motor task [163]. In addition, simple spike firings of PCs distant of about 300 μm on the parallel fiber beam are not spontaneously synchronized in the wild-type animal [77, 178]. In contrast, when strong LFP oscillations (~160 Hz) emerge in different pathological models, a significant synchrony between PCs in

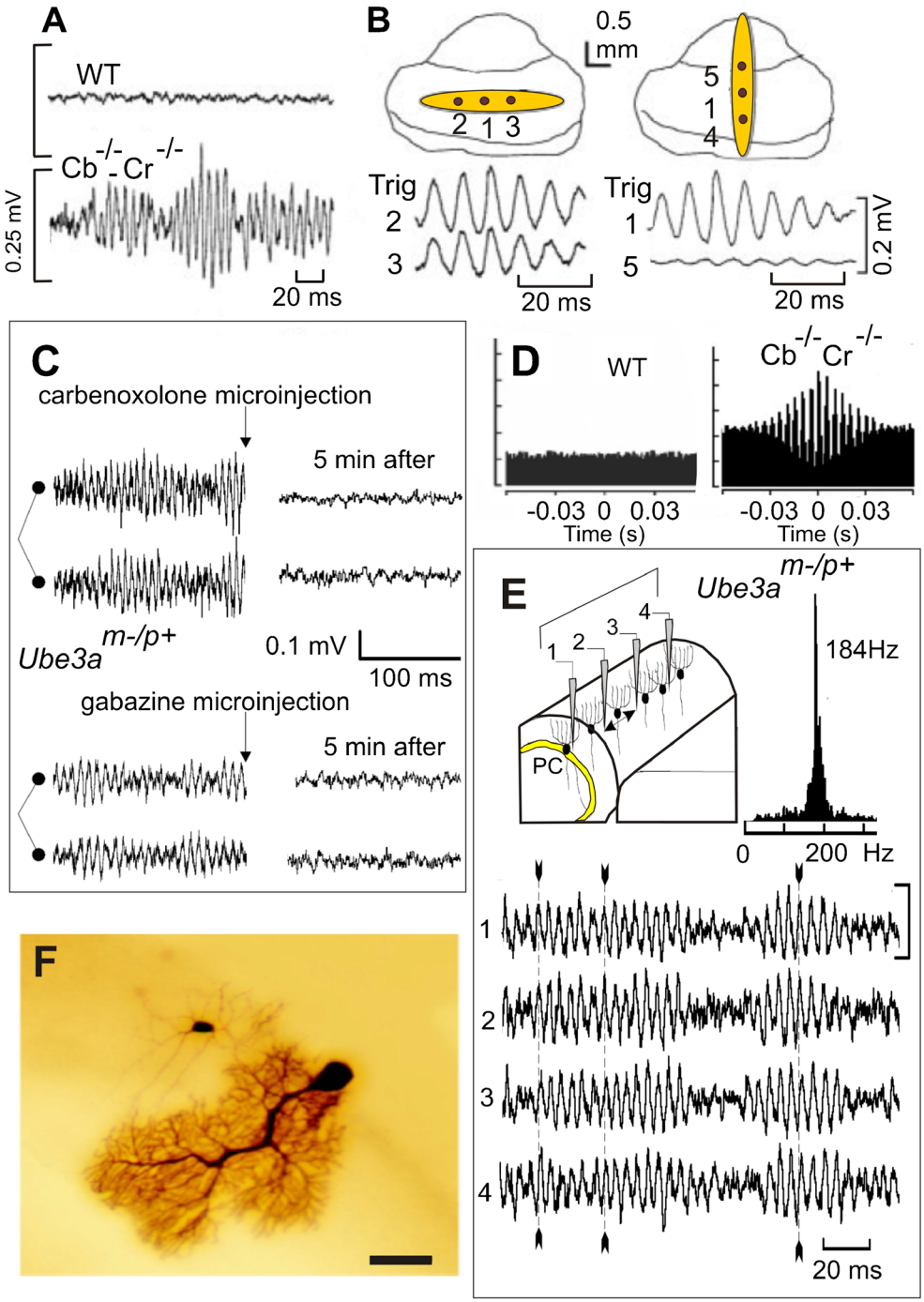

Fig. 4 Emergence and spatial coherence of high-frequency oscillations in the cerebellum of $Cb^{-/-}$–$Cr^{-/-}$ mice. **a** Sample records of LFP oscillation from wild-type mice (*WT*; *top trace*) and $Cb^{-/-}$–$Cr^{-/-}$ mice (*bottom trace*). **b** Spatial coherence of LFP oscillation was analyzed by recording simultaneously from electrodes aligned along the longitudinal [*left*, *tracts 2*, *1*, *3* (0.5 mm apart)] or rostro-caudal (*right*, *tracts 4*, *1*, *5*) axis of a folium. Pair traces (*left*), using LFP oscillation recording *2* as a trigger (*Trig*) for a wave-triggered average, show coherent oscillations of the same period and without any significant phase delay, whereas for pair traces (*right*), using channel *1* as a trigger, no oscillatory pattern was visible (*modified with permission from* Cheron et al. [77]). **c** Effects of carbenoxolone and gabazine microinjections on the 160-Hz LFPO in $Ube3^{am-/p+}$ mice. Raw LFPO recordings with 250 μm distanced microelectrodes before (*left*) and 5 min after (*right*) carbenoxolone (*upper traces*) or gabazine (*lower traces*) microinjections. **d** Cross-correlograms of SSs from PC pairs multirecorded along a PF beam (0.5 mm apart) in WT mice and $Cb^{-/-}$–$Cr^{-/-}$ mice, demonstrating PC synchronization along the PF beam in the mutant (*modified with permission from* Cheron et al. [78]). **e** Emergence of high-frequency LFPO in the cerebellum of $Ube3^{am-/p+}$ mice. Sketch of microelectrode placement along a parallel fiber beam. Adjacent electrodes are distant by 250 μm. Sample LFPO records at four sites. *Dashed lines* indicate synchronization. Fast Fourier transform of recording labelled 1 in peaked at 184 Hz. **f** Hetero-cellular dye coupling illustrated by biocytin diffusion between a Purkinje cell and an inhibitory interneuron via presumed gap junctions. Note that the injection was performed only into the PC during extracellular high-frequency oscillations induced on slice preparation [170]. *Scale bar*: 20 μm (*with permission of* Akemann et al. [171])

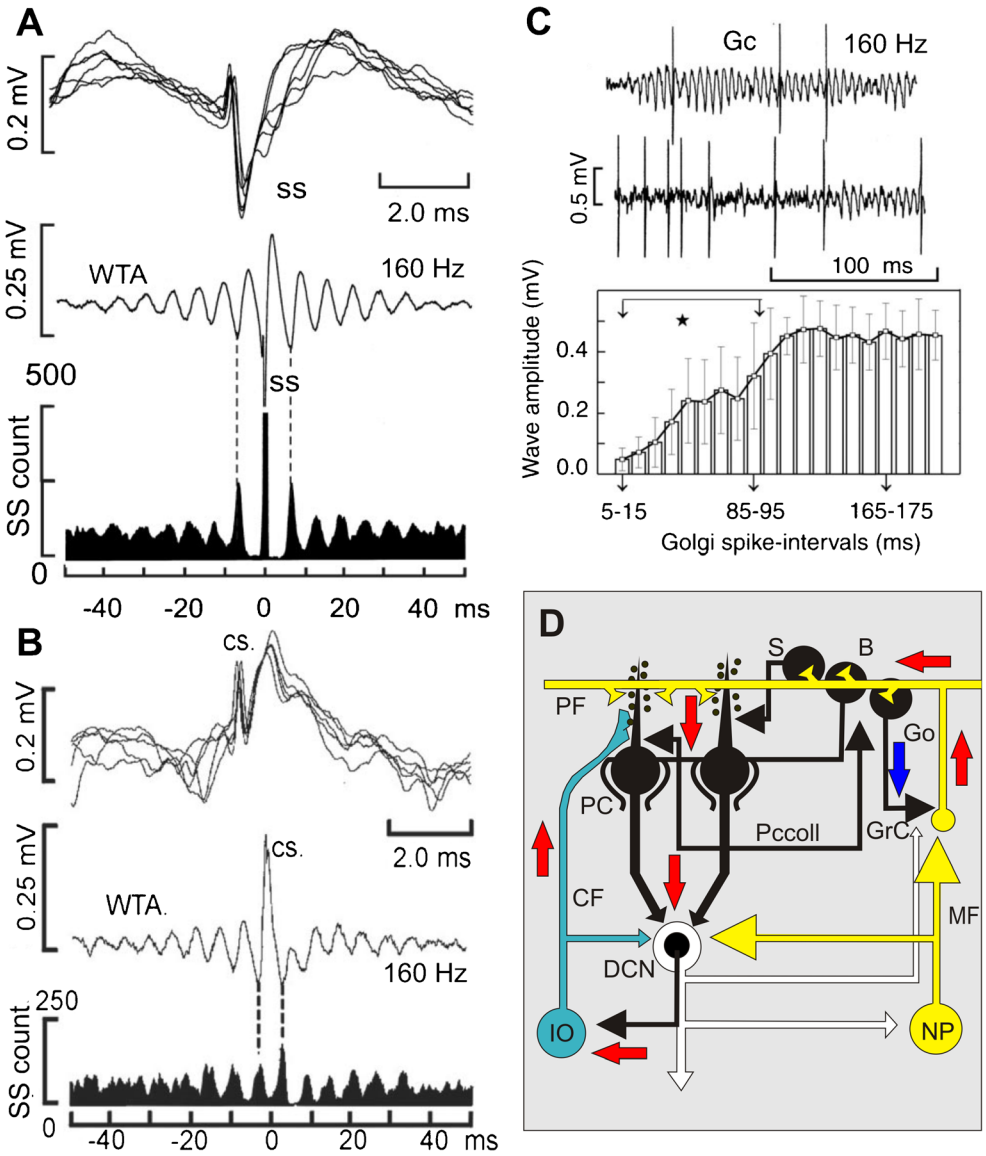

Fig. 5 Temporal relationships between LFP oscillation and PC and Golgi cell firing. **a** Simultaneous recordings by the same electrode of an isolated PC and a 166-Hz LFP oscillation were made. Shown is the superimposition of single traces (n=6) (*top*). The wave-triggered average (*WTA*) of the LFP oscillation using PC SSs as a trigger (n=1000) (*middle*) is displayed. An *SS* autocorrelogram, with a central peak truncated (*bottom*), has the same rhythmicity as the WTA trace. The *dashed lines* indicate the correspondence between the depth of the first two side waves and the first two side peaks of the SS autocorrelogram. **b** Temporal relationships between LFP oscillation and PC cell firing. The same procedure as in **a** was performed with the trigger adjusted on the CS of the same PC. Superimposition of averaged traces (n=6) confirmed the recurrent occurrence of the CS in the ascending phase of the LFP oscillation (*top*). The *WTA* shows the presence of 166 Hz oscillation around the *CS* (*middle*). The SS cross-correlogram has the same rhythmicity as the WTA trace. The *dashed lines* indicate the correspondence between the depth of the first two side waves and the first two side peaks of the SS autocorrelogram. **c** Temporal relationships between LFP oscillation and Golgi cell (*Gc*) firing; *top* single trace recordings of Gc spikes and LFP oscillation; *bottom* quantitative relationship between LFP oscillation amplitude and Gc interspike intervals demonstrates a Gc firing-associated suppression of LFPO (ANOVA; p<0.00001). *Arrows* indicate selected Golgi spike intervals. (*modified from* Cheron et al. [78]). **d** Schematic circuitry of the cerebellar cortex (*inspired by* Voogd and Glickstein [176]) showing the reverberating pathway implicated in the emergence of the 160-Hz oscillation, the phase locking of the CS (see *red arrows*), and the inhibition exerted by the Golgi cell (see text for more details)

phase with a fast LFP oscillation is recorded over a larger distance along the beam and not in the direction of the rostro-caudal module [77] (Fig. 4b, d and Fig. 5e).

In order to explain the emergence of this abnormal rhythm along the parallel fiber beam, the following mechanism has been proposed [164]: the increase of PC rhythmicity facilitates LFP oscillation if already present and the increased LFP oscillation would secondarily recruit rhythmic PCs. This would constitute a positive feedback loop where the fast oscillation is the cause and the consequence of PC synchronicity. The synchronization of a critical number of rhythmic PCs would be at the basis of the emergence of a local oscillating field which

would itself synchronize other neighboring PCs [179]. A similar feedback mechanism has been suggested in neocortical ripples, which are probably implicated in seizure initiation [180–182].

The PC output is also transmitted to neighboring PCs by axon collaterals (Fig. 5e) [183]. These recurrent pathways transmitting PC output reveal another important substrate for synchronization. This idea has been now reinforced by experimental evidences [177, 183] demonstrating the functional existence of such reciprocal PC connections. As pointed out by Orduz and Llano [177], the averaged delay of 1.56 ms between the pre-synaptic action potential and the recurrent collateral IPSC predicts a preferred oscillation frequency close to ~160 Hz (156 Hz). They also proposed that, as the 160-Hz oscillation is minimal in WT mice but emerged in mice deficient for calbindin [77, 175], Ca^{2+} buffering plays a major role in the gain control of this inhibitory connection between PCs.

The important perturbation of the basic functioning of the operational unit formed by the rostro-caudal organization of the cerebellum may explain the learning deficit observed in the presence of 160-Hz oscillation. In the mouse model of the fetal alcohol syndrome (FAS) presenting decreased voltage-gated calcium currents because of a decreased expression of the γ-isoform of protein kinase C, 160–200 Hz LFP oscillation is present and accompanied by ataxia, deficit in motor learning (rotarod, runwalk and eye blink conditioning) and reversal of the parallel fiber–PC LTD into an LTP (slice recordings) [79]. More recently, we have reported that in *Ube3a*$^{m-/p+}$ mice (Angelman syndrome) after an 8-Hz LTD-inducing protocol, the cerebellar LTD (reduction of the N3 amplitude and delayed latency) is missing and that the LTD induced in the barrel cortex following the same whisker pad stimulation in WT mice is reversed into a LTP in the *Ube3*$^{am-/p+}$ mice [184]. This later observation opens the possibility that the abnormal 160-Hz oscillation disturbs not only the normal PC operation but also the DCN and consequently the other targets of the cerebellum such as the cerebral cortex. As pointed out by Traub and Whittington [142], a first clue to the answer to this possibility was provided from recordings of deep cerebellar neurons in the isolated brainstem–cerebellar preparation when an electrical stimulation in the white matter has induced rhythmic IPSPs at about 83 Hz in deep cerebellar nuclear neurons [185]. This demonstrates the possibility for the transmission of fast oscillation between PC and DCN neurons (Fig. 6). Another experimental evidence is given by the fact that in case of the emergence of the 160-Hz LFP oscillation, the CS arrives always on the repolarizing phase of the oscillation [77] (Fig. 5b), indicating that the generation mechanism of the CF activation in the IO is influenced via the DCN by the 160-Hz oscillation present in the PC layer. Such type of phase locking between CS and cerebellar LFP oscillation was also reported in case of beta oscillation present in $BK^{-/-}$ mice and inducing important ataxia [104]. The capacity of the IO to control the up and down state of the PC [186–189] was recently confirmed during the 600-Hz up state paradoxically characterized by low-amplitude SS [190]. Indeed, the CF can initiate this 600-Hz episode and also switch it into the down state. In addition, during the 600-Hz up state, the CS frequency was increased, indicating that the high SS frequency transmitted by the PC axon increases their inhibition on the DCN, which in turn reduces inhibition of the IO, *in fine* producing an increase in CS firing. Not only the mode of PC firing but also their synchronicity (independent of the firing rate) may "paradoxically" induce an increase of the DCN firing rate [191, 192].

In summary, these experimental evidences demonstrate that the oscillatory activities present in the cerebellar cortex are able to sculpt the DCN activity and from there the entire operation of the olivo-cerebellar loop, the thalamo-cortical-ponto-cerebellar loop, and finally the motor neuron entities by the rubrospinal and pyramidal pathways (Fig. 6). We may thus suggest an integrative concept of control and learning based on articulated oscillatory templates.

A fine-tuning of the multiple mechanisms is necessary in order to avoid the emergence of pathological LFP oscillations extended from the lower beta band (in case of tremor induced by harmaline [193]), beta (in case of BK channel deletion [127]), and fast oscillations (in case of calcium binding protein deletion [77, 175], Angelman syndrome [78], and FAS [79]). In all these situations, we suggest that ataxia is present because the fine-tuning of the cerebellar timing organized by different oscillatory templates is perturbed. In reminiscence of the complex relationships between motor learning and PF–PC LTD (see for more details the recent reviews [194–196]) showing that motor learning can occur without LTD, if in all of the mutants expressing 160–200-Hz LFP oscillation ataxia is present, the relationship with LTD plasticity is more complex. In the calbindin knockout mice (slice preparation), the PF–PC LTD is normal [197]; in FAS mice (slice preparation), the LTD is reversed into a LTP [79] while acute ethanol impairs LTD (slice preparation) [198] and in Angelman syndrome the LTD (N3 component recorded in alert mice) is absent [184].

Conclusion

The classical theories that were proposed to explain cerebellar functioning have produced a considerable body of evidence at numerous physiological levels, including through the use of recent technologies that were not available when these theories were originally conceived. Newer paradigms have highlighted major phenomena such as calcium signaling, oscillatory behaviors, and specifics about spiking and membrane plasticity. Despite the long-standing tensions between the motor learning and the motor control theories, emerging findings

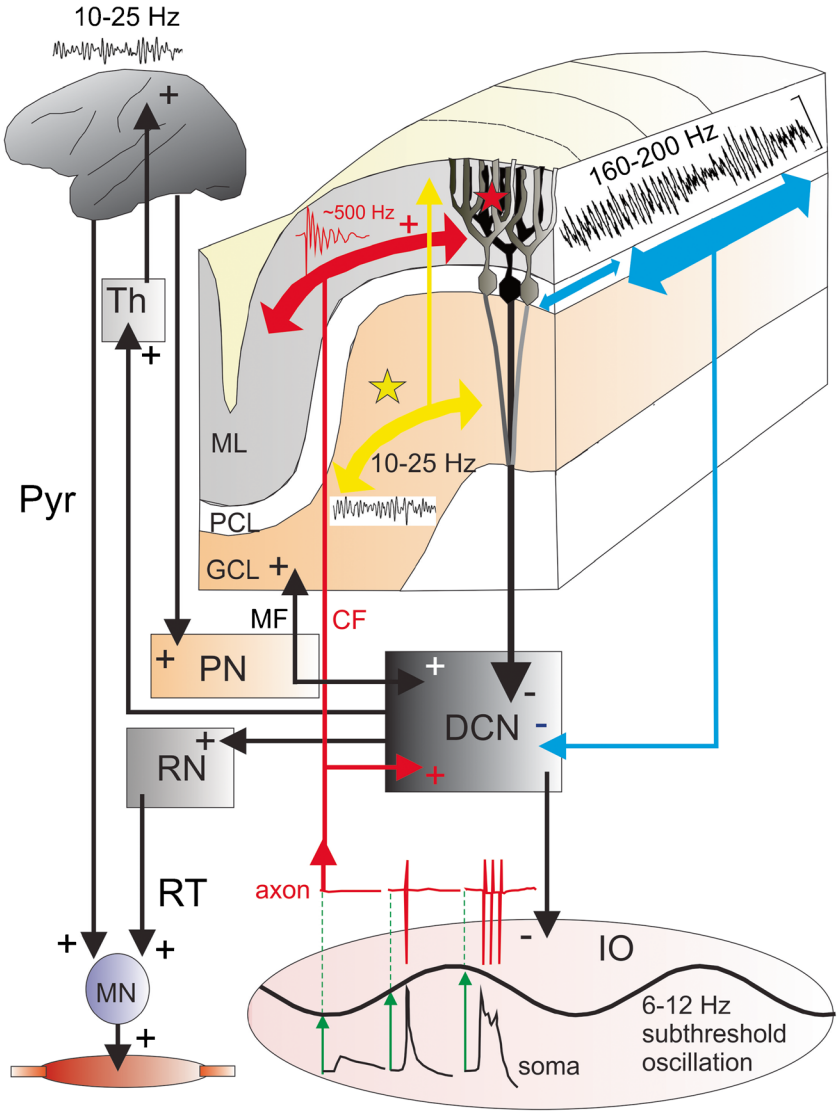

Fig. 6 Integrative concept of cerebellar control and learning based on articulated oscillation templates. In the inferior olive (*IO*), the basic oscillatory template emerges from the intrinsic properties of the electronically coupled IO neurons [71, 153] presenting subthreshold oscillations at 6–12 Hz upon which a burst of axonic spikes fire around the depolarizing phase of the oscillation [154]. The phase [121] and or amplitude [155] of the subthreshold oscillations determine the number of spikes in the burst. This modulation of IO output (*red*) by subthreshold oscillations is illustrated by data from [121] (with permission). Three EPSPs (recorded on the soma) triggered by single synaptic stimuli timed to arrive at different phases of the oscillation (*green vertical arrows*) producing no spike, or one or three spikes at the axon level depending on the oscillation phase. At the PC level, this CF excitation produces the CS presenting an intra-burst spikelet frequency of ~500 Hz [156]. This element is a key factor for PC plasticity (*red star*) [72, 73]. The synchronization of the PC by the CF is realized in the plane of the rostro-caudal module (*red curved arrow rostro-caudally oriented*) [15, 73]. Mossy fiber (*MF*) project in the granule cell layer (*GCL*) where 10–25-Hz LFP oscillation is recorded when animals are immobile in expectancy [141, 157–160] (illustrated oscillation from [141] with permission). This GCL oscillation is synchronized across the parasagittal module (*yellow curved arrow*) and with the 10–25-Hz oscillation in the cerebral cortex [141]. The GCL is also an important locus for timing plasticity [124] (*yellow star*). As the PCs are the sole output of the cerebellar cortex, the PC network including the interneurons of the molecular layer (*ML*) forms a hierarchically integrated template of the diverse rhythmical influences that then converge onto the deep cerebellar neurons (*DCN*), i.e., about 11 PCs to 1 DCN neuron [161]. Then, the DCN imposes its proper rhythm to the different cerebellar targets in the thalamus (*Th*) and red nucleus (*RN*) with a final influence on pyramidal (*Pyr*) and rubrospinal (RS) tracts on the motor neurons (*MN*). In the physiological situation, small-amplitude 200-Hz activity [162] and PC synchronization at a short distance along the parallel fiber beam are described [163] (*small blue arrow*). Eventual pathological high-frequency (160–200 Hz) oscillations (*large blue arrow*) synchronized over a long distance along the parallel fiber beam may disturb the activity of the rostro-caudal modules and the DCN output inducing ataxia [164]

suggest that these models could be integrated to account for important aspects of cerebellar function. These likely go beyond motor control to include cognitive, emotional, and verbal processing. We suggest an integrative concept for control and learning based on articulated oscillation templates involving multiple levels of the CNS for functional plasticity.

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Conflict of Interest The authors state that potential conflicts of interests do not exist about the present manuscript.

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