Cerebellum (2012) 11:457–487
DOI 10.1007/s12311-011-0331-9

REVIEW

Consensus Paper: Roles of the Cerebellum in Motor Control—The Diversity of Ideas on Cerebellar Involvement in Movement

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Published online: 13 December 2011

Abstract Considerable progress has been made in developing models of cerebellar function in sensorimotor control, as well as in identifying key problems that are the focus of current investigation. In this consensus paper, we discuss the literature on the role of the cerebellar circuitry in motor control, bringing together a range of different viewpoints. The following topics are covered: oculomotor control, classical conditioning (evidence in animals and in humans), cerebellar control of motor speech, control of grip forces, control of voluntary limb movements, timing,

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sensorimotor synchronization, control of corticomotor excitability, control of movement-related sensory data acquisition, cerebro-cerebellar interaction in visuokinesthetic perception of hand movement, functional neuroimaging studies, and magnetoencephalographic mapping of cortico-cerebellar dynamics. While the field has yet to reach a consensus on the precise role played by the cerebellum in movement control, the literature has witnessed the emergence of broad proposals that address cerebellar function at multiple levels of analysis. This paper highlights the diversity of current opinion, providing a framework for debate and discussion on the role of this quintessential vertebrate structure.

Keywords Cerebellum · Cortex · Nuclei · Purkinje neurons · Eye movements · Stability · Classical conditioning · Motor speech · Network · Grip force · Grasping · Predictive · Dysmetria · Torques · Timing · Synchronization · Excitability · Sensory · fMRI · Magnetoencephalography (MEG)

Introduction

Research on cerebellar functions has expanded tremendously during these last decades. Several new ideas have been proposed to explain the roles of the cerebellar circuitry in motor control. These concepts suggest that the cerebellum contributes to timing and sensory acquisition and is involved in the prediction of the sensory consequences of action. These theories explain to some extent the clinical deficits exhibited by cerebellar patients and which are characterized by disturbances in accuracy and coordination: disorders of eye movements, disorders of speech, disorders of limb movements, impairments of posture/gait as well as cognitive deficits (which are outside the scope of this article). The cerebellar structures controlling eye movements include the so-called oculomotor vermis (lobules VI and VII) and fastigius nucleus, crus I–II of ansiform lobule, flocculus and paraflocculus, uvula, and nodulus. Speech is controlled by the superior paravermal region, the intermediate cerebellar cortex, and the dentate nucleus. Limb movements are under the supervision of the dentate nucleus, the interpositus nucleus, the intermediate cerebellar cortex, and the lateral cerebellar cortex. Stance/gait is controlled by the medial and intermediate cerebellum. Cognitive operations are mainly controlled by the posterior lobe (posterolateral cerebellum) and cerebellar nuclei (mainly parts of dentate nuclei).

The primary objective of the present consensus paper is to summarize the key concepts which have been proposed to explain the roles of the cerebellar circuits, in the line of consensus papers of the journal. We focus the discussion on a state-of-the-art in the field of motor control, more particularly on human studies (with the exception of classical conditioning given its importance in the field and converging findings in human and animal studies). The cerebellum has traditionally been viewed as a motor control structure. While the roles now being proposed for the cerebellum continue to expand, including, for example, proposals for involvement in higher order cognitive function, ideas even for its role in traditional motor control have also been expanding. We therefore felt that it would be of value to the community to assemble in one place brief descriptions of current thinking about cerebellar involvement in motor function. To this aim, we have gathered contributions from experts in various areas of motor control, providing a range of different, sometimes even controversial viewpoints. Although a final consensus cannot be reached yet, we believe that it is likely that a new consensus on the function of the cerebellum will eventually emerge from some combination of the ideas presented here.

The Role of the Cerebellum in Oculomotor Control (D. Pelisson, C. Tilikete)

Our understanding of the cerebellar control of eye movements comes from neurophysiological data as well as from

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the results of focal lesions in primate models and patients with cerebellar lesions. The cerebellum is involved in all classes of eye movements and gaze fixation. Although not totally determined, two main anatomical subdivisions of the cerebellum correspond mainly to the control of different classes of eye movements, the vestibulocerebellum and the oculomotor cerebellum. The vestibulocerebellum (flocculus, paraflocculus, nodulus, uvula, tonsil, and cerebellar pyramid) is important for steady gaze holding, smooth pursuit, and the vestibulo-ocular reflex [1]; the oculomotor cerebellum (dorsal vermis—lobules VI and VII—and the underlying fastigial nucleus, as well as ansiform lobe—crus I and crus II) is mainly involved in the control of saccades but also contributes to smooth pursuit and vergence (Table 1). It has been shown in primate that the cerebellar hemispheric region around lobule VII is involved in the control of smooth pursuit and saccadic eye movements [2]. There is also a participation of the cerebellar paraflocculus in smooth pursuit eye movement control [3].

At a fundamental level, the specific cerebellar contribution, relative to most other oculomotor structures, is to ensure the best calibration of the eye movement system and to reduce eye instability. At a physiological level, this is achieved by a cerebellar side-loop control of sensorimotor transforms through inhibitory projections of Purkinje cells onto deep cerebellar and vestibular nuclei. Calibration is achieved both by immediate, online control and by an iterative (short- to long-term) sensorimotor adaptation process. The visuomotor aspect of this sensorimotor control is predominant and has received the great interest in the last decades. At a clinical level, analyses of eye movement disorders help to establish models of cerebellar dysfunction and give further insights in the specific cerebellar areas involved. In the following sections, we will illustrate the cerebellar role in the control of eye stability and in the online and adaptive control of eye movements.

Eye Stability Control

The control of eye stability corresponds to gaze holding processing, slow phase (VOR, smooth pursuit) instability control, and inhibition of unwanted saccades. The best insight into the role of the cerebellum in eye stability control is illustrated by the appearance of gaze-evoked nystagmus, periodic alternating nystagmus, and square wave saccadic intrusion (SWSI) following cerebellar dysfunction.

Gaze-evoked nystagmus occurs in the eccentric eye position in the orbit, showing centripetal slow phase followed by quick phases toward the desired eye position. It can occur in horizontal, vertical, or both dimensions and its occurrence is linked to a defective neural integrator [4]. While animal data suggested a major role of flocculus in the gaze-holding neural integrator network [5], recent data in patients with cerebellar lesions indicate that structures of the cerebellar vermis such as the pyramid, the uvula, and the tonsil are involved in the horizontal gaze-holding system [6].

Periodic alternating nystagmus (PAN) corresponds to a horizontal jerk nystagmus with regularly alternating beating phases. PAN results from ablation of the nodulus in monkeys [7], as well as lesions of the same areas in humans [8]. PAN probably arises from an alteration of a form of "memory" for persistent vestibular stimuli referred to as "velocity storage". The nodulus appears to govern velocity storage through inhibitory GABAergic projections to the vestibular nuclei [9, 10]. This hypothesis is reinforced by the dramatic GABAergic effect of baclofen in both monkeys and patients [11, 12] and by a case report showing PAN in the context of anti-GAD antibodies [13].

SWSIs consist of two consecutive saccades separated by approximately 200 ms [14]. Although they may occur in normal individuals, SWSIs appear in increased frequency in patients with spinocerebellar ataxia with saccadic intrusion [15] or in increased amplitude in ataxia-telangiectasia [16]. It is assumed that unwanted saccadic signals arriving at the fastigial nucleus via mossy fibers, which are normally suppressed by inhibition from the cerebellar cortex, would be expressed in cases of cortical cerebellar degeneration [15, 16].

Online and Adaptive Control of Eye Movement

Both the baseline gain and variability of eye movements are under cerebellar control, as well as their plastic modifications (adaptation, learning, and compensation) [17, 18]. Indeed, lesion studies demonstrate that eye movements can still be triggered with near normal latency but are often dysmetric (hypermetric if lesion confined to cerebellar cortex), are more variable, and can no longer be adaptively modified to new environmental conditions (see Table 1) [19–24]. In agreement with physiological data, this indicates that the cerebellar cortex exerts an inhibitory control which partly compensates for (1) moment-to-moment fluctuations (motor noise) of extra-cerebellar oculomotor drive signals and (2) sustained environmental (visual) or internal (physiological, pathological) alterations of baseline oculomotor behavior. When progressive re-calibration of eye movement gain is required, this inhibitory activity is modulated through plastic changes of synaptic efficacy (LTD and LTP) between parallel fibers and Purkinje cells, in agreement with the pioneering theory of Marr-Albus on cerebellar processing. However, the multiple plasticity loci involved within and outside the cerebellum and the origin

Table 1 Involvement of cerebellum in the different types of eye movements and *resulting deficits* (in italics)

	Vestibulocerebellum				Oculomotor cerebellum		Unknown topography	
	Flocculus/parafloccullus, uvula, tonsil, and cerebellar pyramid		Nodulus		Vermis VI and VII, fastigial nucleus			
Gaze holding	Sustains eccentric gaze-holding (eye velocity-to-position neural integrator)	*Gaze-evoked nystagmus*			Fine-tunes balance between saccadic generators	*Tonic gaze deviation*	Permanent fine-tuning of oculomotor fixation commands	*Pendular nystagmus*
	Inhibition of upward slow phase drift	*Downbeat nystagmus*						
Smooth pursuit	Sustains the pursuit response	*Impaired SP gain*			Initiates smooth pursuit	*Impaired SP onset*		
		Impaired VOR-suppression						
	Calibrates SP gain	*Impaired SP adaptation*						
VOR	Online modulation of dynamic VOR		Online modulation of the static (otoliths) VOR?	*Alternating skew deviation?*			Online modulation of the static (otoliths) VOR	*Positional upbeat nystagmus*
	Calibrates VOR gain			*Positional downbeat nystagmus*				
		Impaired VOR adaptation	Inhibition of VOR prolongation	*Periodic alternating nystagmus*			VOR inhibition	*High VOR gain*
Saccades	Calibrates saccadic pulse step match	*Post-saccadic drift (pulse-step mismatch)*			Calibrates saccadic amplitude	*Saccadic dysmetria*	Inhibition of unwanted saccades	*Saccadic intrusions*:
					Reduces motor noise (velocity fluctuations)	*Saccadic lateropulsion*		– *Square waves*
						Impaired saccade adaptation		– *Macrosquare waves jerks*
						Increased saccadic variability		– *Macrosaccadic oscillations*
								– *Flutter/opsolclonus*
Vergence					Helps to control vergence	*Esodeviation?*		

The vestibulocerebellum (flocculus, parafloccullus, uvula, tonsil, and cerebellar pyramid, and nodulus) is important for steady gaze holding, smooth pursuit, and vestibulo-ocular reflex, whereas the oculomotor-cerebellum (vermis lobules VI and VII, fastigial oculomotor region) is mainly involved in the control of saccades but also contributes to smooth pursuit initiation and vergence

and operating mode of the error signals leading to such plastic neural changes remain debated [23, 25–30]. At functional/computational levels, a current theory states that the cerebellum steers motor responses by implementing internal models of the controlled body part. First proposed for skeletomotor responses [31], this notion is also applied to all oculomotor responses used as models of sensorimotor plasticity, namely VOR, smooth pursuit, and saccadic eye movements [18, 32].

Classical Conditioning—Eyeblink Conditioning: Evidence in Animals (JM. Delgado-Garcia)

The classical conditioning of eyelid responses has a long trajectory going back to the 1930s of the past century [33–35]. Those early studies carried out in human volunteers provided basic information regarding the different types of eyelid response evoked by the conditioning (true conditioned responses, sensitization, pseudoconditioning, alpha responses, etc.) depending on the selected conditioned (CS) and unconditioned (US) stimuli or on their temporal relationships. For example, in delay conditioning, the US is presented in the presence of the CS and co-terminates with it, while in trace conditioning there is a time interval between the end of the CS and the beginning of the US. The latter has the advantage of allowing the formation of the conditioned response in the absence of any sensory stimulus [36, 37], although in this regard, it is frequently overlooked that sensory receptors are activated by changes in the stimulus presented to them and not by its sustained presence. Thus, delay conditioning could be considered a particular case of trace conditioning.

Gormezano's group and many others popularized the classical conditioning of the nictitating membrane/eyelid response in animals (mostly rabbits) during the 1960s [37]. In a seminal paper, Schneiderman et al. [38] had already noticed that the eyelid reflex can easily be conditioned using Pavlovian procedures (Fig. 1), although they did not mention that facial muscles belong to a special type of visceral muscle, a fact that could explain why eyeblinks are so easily conditioned as compared with other types of motor response involving skeletal muscles.

Indeed, both the orbicularis oculi (the muscle that closes the eyelids) and the retractor bulbi (the muscle retracting the eye in the orbit, allowing the passive displacement of the nictitating membrane in mammals) are peculiar in the sense that they are devoid of a stretch reflex (they have no proprioceptors). As a consequence, motoneurons receive no signal indicating the position of the lids on the eye [39]. Finally, these muscles have a constant mass (no extra weights on them), and their innervating motoneurons have no axon collaterals and control eyelid velocity only during

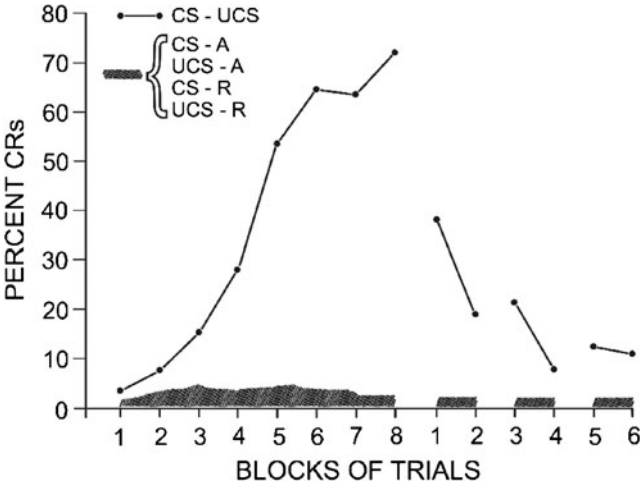


Fig. 1 Mean percentage of responses collected in rabbits during classical conditioning of the nictitating membrane response. The conditioned stimulus (*CS*) consisted of an 800-Hz, 72-dB tone lasting for 600 ms. The unconditioned stimulus consisted of a 100-ms air puff directed at the right cornea. Nictitating membrane responses were recorded with the help of a potentiometer attached to the ipsilateral nictitating membrane. Experimental groups were as follows: the CS–UCS group received paired CS–UCS presentations. CA-A and UCS-A groups received sole presentations of CS or UCS stimuli, respectively. CS-R and UCS-R groups received unpaired presentations of CS and USC stimuli. Figure taken with permission from [33]

reflexively evoked blinks [39]. Although the recording of nictitating membrane responses has provided valuable information about the biomechanics of eyeblink conditioning, it has been the use of the search coil in a magnetic field technique that has allowed a quantitative study of reflex and conditioned eyelid responses in humans [40], cats [41], and rabbits [42]. Recently, the magnetic distance measurement technique has enabled similar studies in the small eyelid of behaving mice [43]. Those quantitative studies of eyeblink kinematics have allowed the determination of the main sequence of eyelid responses [40–42] and of their oscillatory properties. The latter are dependent on eyelid mass and compliance [43] and are nicely tuned to the firing properties of facial motoneurons [39]. It should be stressed that a proper understanding of eyelid kinematics and of the firing properties of innervating facial and accessory abducens motoneurons is necessary to understand how acquired eyeblinks are generated and the functional possibilities offered by this motor system for the acquisition of new motor responses [44]. Another important requisite for understanding the organization of the eyelid motor system is knowing the location of the neural premotor system controlling spontaneous, reflex, and acquired eyelid responses. This was achieved recently using attenuated rabies virus injected as a transneuronal retrograde tracer in the orbicularis oculi muscle of the adult rat [45]. As expected, many brainstem, cerebellar, and cerebral cortex structures mediating reflex, voluntary, and limbic related

eyelid responses were labeled, indicating the neuronal complexity of this apparently simple motor system.

While a large number of neural regions are implicated in various aspects of eyelid responses, the cerebellum has been the primary focus in the study of eyeblink conditioning. Indeed, hundreds of research studies and reviews have been devoted to determining the involvement of cerebellar structures in the acquisition and storage of this type of associative learning [46–49]. In an influential series of studies, Thompson's group has popularized a basic brainstem–cerebellar circuit certainly involved in the generation and control of classically conditioned eyelid responses [46, 49] that is not completely in agreement with anatomical [45], kinematic [41], and electrophysiological and pharmacological [50, 51] findings. For example, the precise latency analysis (using both delay and trace conditioning paradigms) of identified cerebellar interpositus neurons indicates that they start firing after the beginning of the eyelid conditioned response [50]. Moreover, it is still under discussion whether cerebellar structures are involved in learning (i.e., in the acquisition and storage of newly acquired eyelid responses) or in the proper performance of eyelid responses independently of their reflex or acquired nature [51–54]. As illustrated in Fig. 2, learning and performance of conditioned eyeblinks can easily be differentiated in alert behaving cats [51]. Recently, it has been proposed [55] that the cerebellar output represented by the activity of interpositus neurons plays a modulating role in the dynamic control of eyeblink learned responses, i.e., they could be considered a phase-modulating device helping to reinforce, as well as to damp, the oscillatory properties of facial motoneurons (Fig. 3).

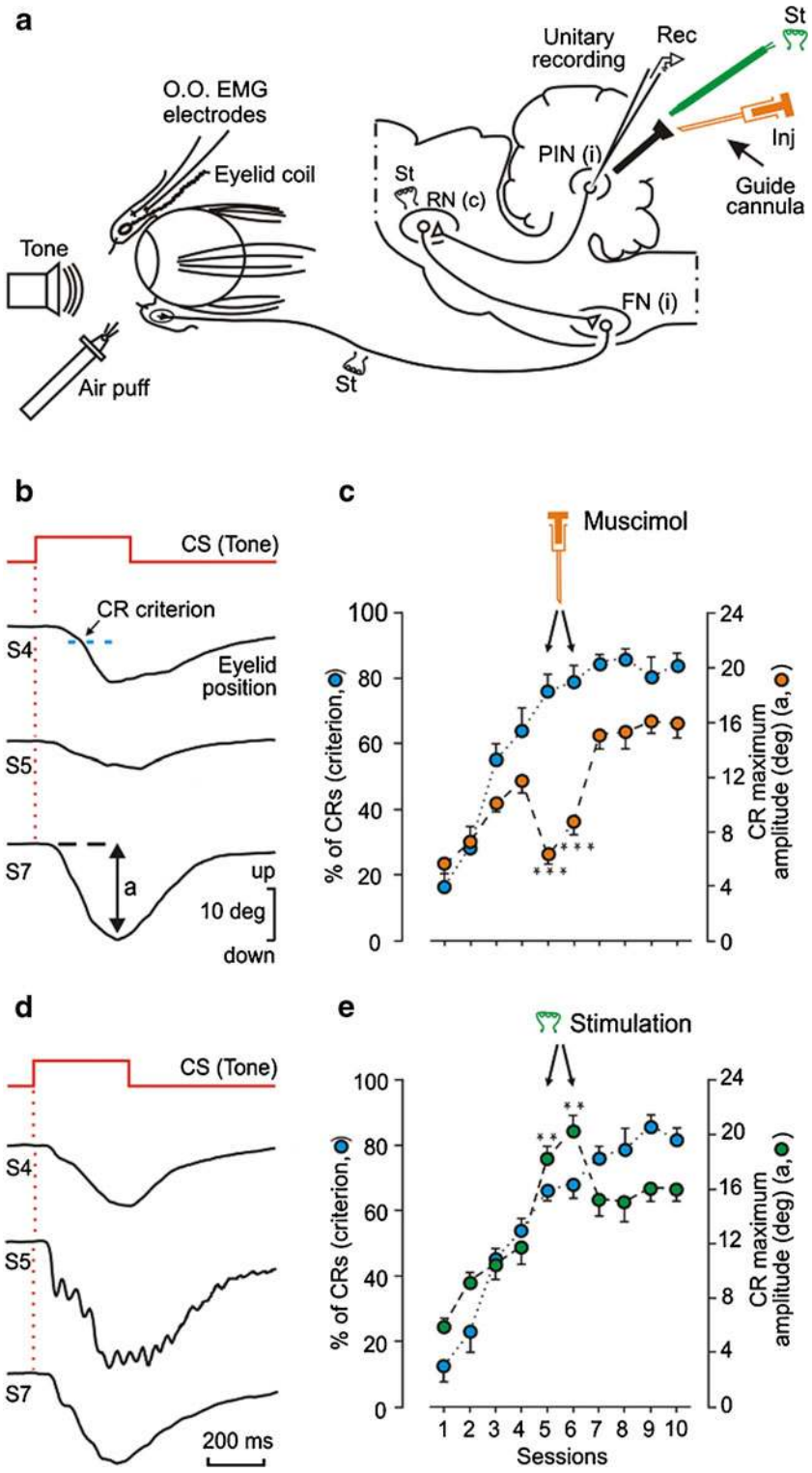
Even if the debate about the contribution of cerebellar circuits to the acquisition of new eyelid responses remains open for a while, we should keep in mind that many other brain structures, such as the hippocampus [44] or the amygdala [56], are also involved in this type of associative learning, and that, surprisingly, only a few studies have been devoted to the most important center for the generation of voluntary and acquired movements namely, the motor cortex [57].

Classical Conditioning—Eyeblink Conditioning: Evidence in Humans (M. Gerwig, D. Timmann)

The role of the cerebellum in eyeblink conditioning has been examined in great detail from the behavioral to the molecular level in animal models. It has been of early interest whether or not findings in animals can be translated to humans. Both cerebellar lesion and functional brain imaging data provide evidence that findings in humans are in very good agreement with those in other mammals [58, 59]. Most human studies examined delay eyeblink conditioning. Patients with various cerebellar disorders are impaired in their ability to acquire classically conditioned eyeblink responses. This is true for patients with cerebellar degeneration and patients with focal cerebellar disorders due to stroke or cerebellar tumors [60–63]. Acquisition of conditioned responses is impaired even after multiple sessions of conditioning (Fig. 4) [64, 65]. Whereas in patients with cerebellar cortical degeneration the incidence of conditioned responses (CR) is commonly close to the spontaneous blink rate, conditioned responses can be acquired to some extent in patients with focal cerebellar lesions [65]. Differences in lesion localization are a likely reason.

The use of high-resolution magnetic resonance imaging (MRI) has helped to outline the cerebellum-related neuronal networks in humans. Both human lesion and brain imaging studies indicate that the cerebellar cortex is critically involved in CR acquisition. Woodruff-Pak and coworkers found a significant correlation between cerebellar volume and the ability to acquire conditioned responses in healthy subjects [66]. A more recent study in healthy subjects showed that the number of acquired conditioned eyeblink responses was significantly related to the volume of the gray matter of the posterior lobe (including lobule VI), but

Fig. 2 Effects of muscimol injection in, and microstimulation of, the posterior interpositus nucleus on the percentage and amplitude of conditioned eyelid responses (*CRs*) collected from alert behaving cats. **a** Diagram illustrating the experimental design. Animals were implanted with electromyographic recording electrodes in the orbicularis oculi muscle (*O.O. EMG*) and with a chronic guide cannula in the posterior interpositus nucleus (*PIN*) allowing neuronal recording (*Rec*), microstimulation (*St*), and microinjection (*Inj*). Animals were also implanted with stimulating electrodes in selected brain sites for antidromic identification of recorded facial motoneurons and posterior interpositus neurons [46, 50]. Delayed eyeblink conditioning was achieved by the paired presentation of a 370-ms tone used as a conditioned stimulus (*CS*), followed 270 ms from its start by a 100-ms air puff as an unconditioned stimulus (*US*). **b** Representative examples of CRs evoked by the sole CS presentation, collected from the fourth, fifth, and seventh conditioning sessions. Muscimol (a $GABA_A$ agonist, 1.25 μg/kg) was injected 20 min before the fifth session. The *double-arrowed line* (*a*) indicates CR amplitude. **c** Quantitative analysis of data collected from three animals (mean ± SEM). Muscimol was injected before the fifth and sixth sessions. Note that, according to the selected CR criterion [*dashed blue line* in **b**], the expected percentage of CRs (*blue circles* and *dotted line*) was not modified by muscimol, but the amplitude of the evoked CRs (*red circles* and *dashed line*) was significantly decreased (***$p<0.001$; ANOVA). **d** Representative examples of CRs evoked by single CS presentations without (fourth and seventh sessions) and with (fifth session) microstimulation (20 Hz for 1 s; pulses of 50 μs and 50 μA) of the posterior interpositus nucleus. **e** Quantitative analysis of data collected from three animals (mean ± SEM). Microstimulation was applied during the fifth and sixth sessions in trials in which the CS was presented alone. Note that, according to the selected CR criterion, the expected percentage of CRs (*blue circles* and *dotted line*) was not modified by the microstimulation, but the amplitude of the evoked CRs (*green circles* and *dashed line*) was significantly increased (**$p<0.01$; ANOVA). Data collected from [46]. Figure reproduced with permission from [39]



not to the volume of the gray matter of the anterior lobe, the cerebellar white matter, or cerebrum [67].

More detailed information has been gained examining patients with focal cerebellar lesions. Early case reports and group studies have shown that eyeblink conditioning is reduced on the affected side in patients with unilateral cerebellar lesions [62, 68]. A study by Gerwig et al. [63] found that eyeblink conditioning was significantly reduced on the ipsilesional side in subjects with lesions (most of them due to stroke) within the common territory of the superior cerebellar artery (lobule crus I and above), but within normal limits on the contralesional side. In subjects

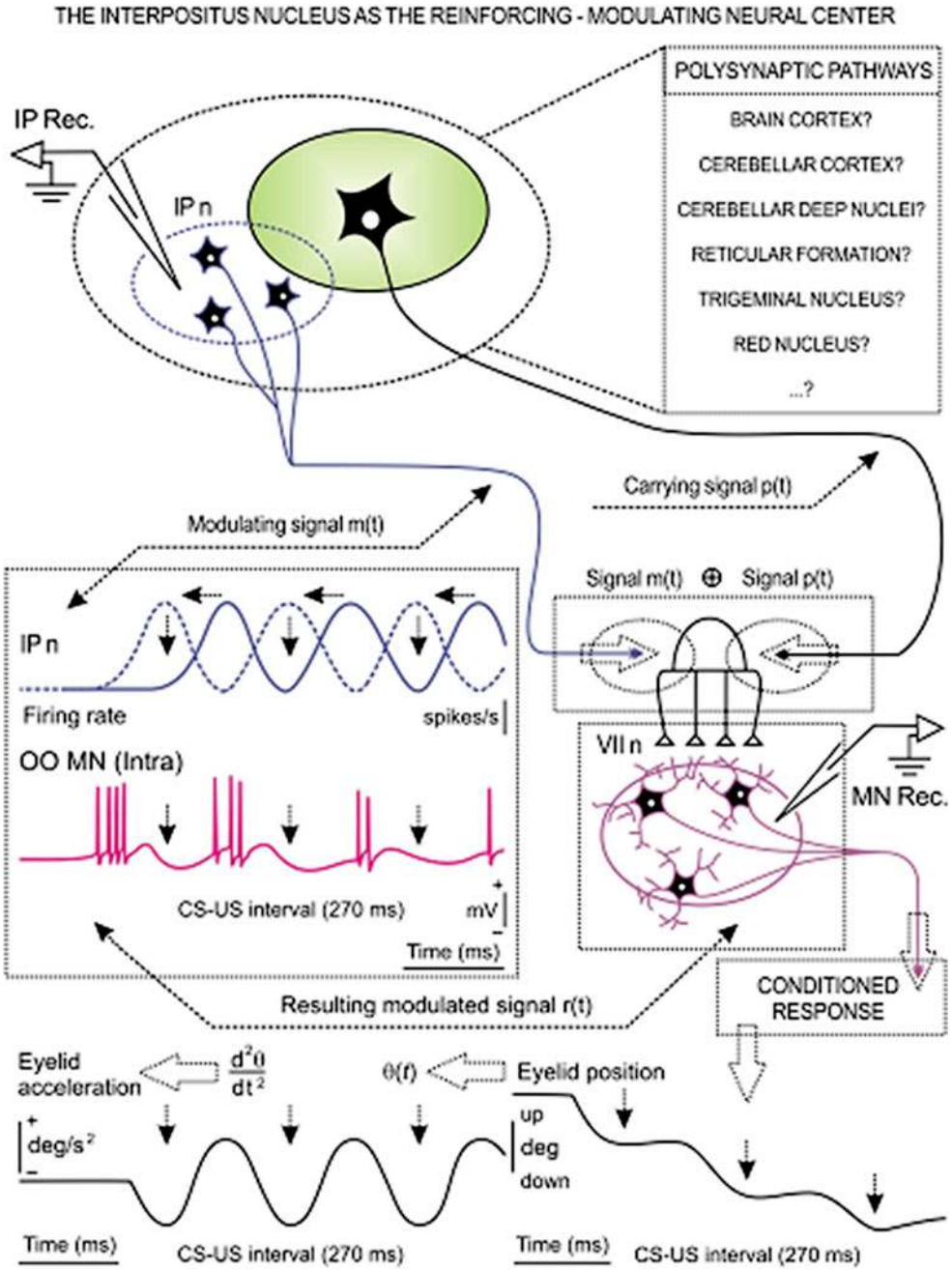


Fig. 3 Schematic representation of the reinforcing–modulating role of cerebellar interpositus neurons (*IP n*) during the acquisition of an associative learning task such as the classical eyeblink conditioning. This representation is based on data published elsewhere [23]. The experimental design is illustrated in Fig. 2. Neuronal inputs (*green set* of premotor nuclei) arriving at the orbicularis oculi motoneurons (*OO MNs*) and carrying eyeblink conditioned signals p(t) need the reinforcing–modulating role of cerebellar nuclei signals m(t). In order to be efficient, IP neuronal signals need to go through a learning process in order to become 180° out-of-phase with OO MN firing. Thus, IP neuronal activities (following a relay in the red nucleus) reach OO MNs right at the moment of maximum motoneuronal hyperpolarization [34], and IP neurons facilitate a quick repolarization of OO MNs, reinforcing their tonic firing during the performance of those classically conditioned eyelid responses. Abbreviation: *VIIn* facial nucleus. Figure reproduced with permission from [50]

with lesions restricted to the common territory of the posterior inferior cerebellar artery (crus II and below), no significant difference in eyeblink conditioning was observed comparing the affected and unaffected side. Voxel-based lesion-symptom mapping (VLSM) analysis revealed that learning rate was significantly reduced in subjects with focal lesions including superior parts of the posterior lobe, in particular hemispherical lobule VI [69]. Likewise, functional MRI studies (fMRI) report eyeblink conditioning-related activation of lobule VI in healthy subjects [70, 71]. Findings are in good accordance with animal data which emphasize the role of lobule VI [72]. Other groups, however, point out the importance of the anterior lobe (that is lobules I–V with a focus on lobule V; [73]).

As yet, there is little information about the importance of the cerebellar nuclei in humans. Animal experiments show that the interposed nuclei, but not the dentate or fastigial nuclei, are critically involved [74]. Human data are sparse because human lesion models with circumscribed damage of the cerebellar nuclei are lacking [75]. None of the fMRI studies has reported activations of the cerebellar nuclei during eyeblink conditioning, most likely because of methodological limitations [70, 71]. Recently improved methods of fMRI of the cerebellar nuclei may permit

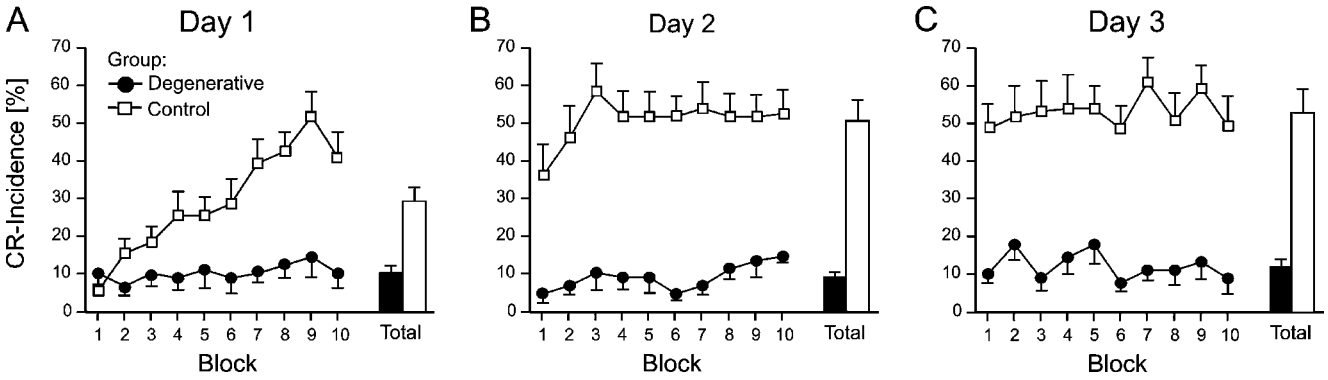


Fig. 4 **a**–**c** Acquisition of conditioned eyeblink responses across 3 days in patients with pure cerebellar degeneration compared to healthy controls. Mean percentage CR incidence and standard errors (SE) in paired trials (CS = tone; US = air-puff) are shown per block of ten trials and per session of 100 paired trials (total = mean total percentage CR incidence). In the group of patients, CR incidences were significantly reduced. No clear increase could be observed across the 3 days (adapted from [60])

investigation of interposed nucleus activation in the future [76].

Beyond acquisition, appropriate CR timing has been found disrupted in patients with cerebellar disorders [69]. CRs occur significantly earlier in subjects with cerebellar cortical degeneration and with lesions of superior parts of the cerebellar hemisphere compared to healthy controls. Disordered timing has also been reported in alcoholic patients and in abstinent chronic alcoholics in whom cortical degeneration of the anterior cerebellar lobe is to be expected [77]. Corresponding to animal findings of Mauk's group [73], VLSM analysis in focal cerebellar patients revealed that CR onset was significantly earlier in subjects with cortical lesions including parts of the ipsilateral anterior lobe, in particular hemispherical lobule V [69].

Good agreement between animal and human data and its comparatively simple application allow for universal usage of eyeblink conditioning as a model of cerebellar learning. Eyeblink conditioning can be used for direct comparison of cerebellar dysfunction in animal models of cerebellar disease and the corresponding human patient populations. For example, there are increasing numbers of mouse models of hereditary cerebellar disease. Furthermore, eyeblink conditioning is helpful to search for cerebellar dysfunction in various neurological diseases. In essential tremor [78], dystonia [79], fragile X syndrome [80], and neuropsychiatric disorders (including autism, schizophrenia, dyslexia, attention deficit hyperactivity disorder [81, 82]), impaired CR acquisition has been interpreted in favor of a cerebellar role in the pathogenesis of these disorders.

Cerebellar Control of Motor Speech (P. Mariën)

The articulation of speech is a highly complex process and a unique human capacity that poses high demands on the mechanisms of motor control. At the motor level, linguistically meaningful sound production in human communication involves an estimated 80 muscles (many of which are paired) to realize rapid, highly coordinated and smooth buccolabiolingual movements which are meticulously synchronized to laryngeal and respiratory activity. The production of speech involves an estimated 1,400 motor commands per second [83].

At least two distinct neural networks have been identified to subserve human speech sound production [84, 85]. The first network consists of a phylogenetically ancient motor pathway for primitive vocalizations such as innate vocal reactions to painful stimuli. This network encompasses the anterior cingulate gyrus and the adjacent mesiofrontal regions and projects via midbrain (tegmentum and periaquaductal gray), basal ganglia, and pons (central pattern generator) to cranial nerve motor nuclei in the lower brainstem that are responsible for the innervation of the vocal tract musculature. The second, more extensive neural network subserves more complex forms of motor speech production such as linguistically meaningful sounds, words, and phrases. At the cortical level, this second pathway involves the lateral and medial premotor regions—among which are the Broca's area and the supplementary motor area—the primary motor cortex and the anterior insula. At the subcortical level, the basal ganglia and the cerebellum are crucially involved in this network [86].

In his classic 1917 paper on the effects of gunshot wounds in victims of the First World War, Gordon Holmes described disturbed muscular control of speech production after cerebellar lesions and added evidence to the view that the cerebellum plays an important role in motor speech control [87]. Holmes characterized motor speech symptoms following cerebellar damage as typically slow, monotonous, staccato, scanned, indistinct, remarkable irregular, jerky, explosive, slurred, and labored. Darley, Aronson, and Brown designated these alterations in phonation and articulation as "ataxic dysarthria" and identified the imprecise production of consonants and vowels, irregular

articulatory breakdowns, excess and equal stress, and harsh voice quality as the cardinal symptoms of cerebellar motor speech disorder [88]. Holmes, as well as many investigators after him, maintained that the causative lesion for ataxic dysarthria could be situated in either one or both cerebellar hemispheres [87, 89]. By contrast, Lechtenberg and Gilman found that ataxic dysarthria mainly follows from damage to the superior anterior vermal and paravermal regions and also showed that motor speech deficits resulted more frequently from left than right cerebellar lesions [90]. However, anatomoclinical studies investigating the topographic correlates of ataxic dysarthria have not been able to provide a coherent picture with regard to lateralization nor localization of the causative lesion within the cerebellum [91, 92].

On the other hand, perceptual and parametric studies of ataxic dysarthria have consistently shown a reduction of the maximum speaking rate as well as a distorted coordination and slowed execution of articulatory movements [93, 94]. Based upon these findings, the functional contribution of the cerebellum to motor speech production has primarily been defined as a major regulator of the temporal, online sequencing and adaptation of overlearned, basic speech movement patterns (mental syllables) into linguistically larger segments such as words, phrases, and sentences during overt speech production [84, 92].

Functional neuroimaging studies of healthy persons and patients with cerebellar disorders substantially added to this view demonstrating crucial involvement of the fronto-cerebellar network at the prearticulatory stage of silent (covert, internal) speech as well [95]. In addition, a consistent lateralized distribution of metabolic or hemodynamic responses located in the prefrontal areas of the language dominant hemisphere and the anatomically connected contralateral cerebellar hemisphere has been observed during various conditions of internal speech processing [96, 97]. In line with these insights, clinical studies reported patients with apraxic speech disorders (such as developmental apraxia of speech and foreign accent syndrome) as well as patients with apraxic agraphia following disruption of the cerebello-cerebral network crucially implicated in the processing of oral and written language planning [98–102].

Involvement of the cerebellum in the sequencing phase of silent speech computation is in agreement with the recently acknowledged role of the cerebellum in a broad variety of nonmotor cognitive and linguistic functions. Indeed, during the last three decades, advances in the understanding of the neuroanatomy subserving the cerebello-cerebral network combined with evidence from functional neuroimaging, neurophysiological, and neuropsychological research have substantially extended the traditional view on the cerebellum from a mere coordinator of automatic and somatic motor functions to a topographically organized and highly specialized neural mechanism crucially implicated in a variety of nonmotor cognitive, linguistic, and affective processes [103–107].

Control of Grip Forces (D.A. Nowak)

The cerebellum plays a major role in the predictive timing and coordination of isometric grip forces when grasping and handling objects in the environment. The involvement of the cerebellum in predictive grip force control originates from its peculiar role in the anticipatory tuning of muscle activity during voluntary motor actions [108]. The exquisite control of grip forces when manipulating objects is an essential part of our daily motor repertoire. Skilled control of grip force involves different modes of control that rely on prediction and sensory feedback to different extents [109]. When we handle objects in the environment that exhibit stable properties, predictive control mechanisms can effectively be exploited. When, for example, the load of a handheld object is increased by a self-generated action, such as moving the arm to transport the object or dropping a weight from one hand into a receptacle held by the opposite hand, grip forces increase in parallel with load forces without an obvious time delay [110, 111]. When, on the other hand, we handle objects with unpredictable behavior, such as catching a weight that is unexpectedly dropped from another person into a handheld receptacle, sensory feedback provides the most useful source to signal a change in load with the consequence that grip forces tend to lag behind load [111].

Subjects with cerebellar disorders show deficits of predictive grip force control, whereas reactive control mechanisms are relatively unimpaired [112–115]. Figure 5 illustrates the control of grip forces during discrete upward and downward directed movements of a handheld object for three healthy control subjects in comparison to a subject with cerebellar agenesis [116]. Impaired predictive grip force control in cerebellar disorders has been documented for a variety of manipulative tasks, such as lifting an object, catching a weight, and transporting an object [112, 114, 115, 117, 118]. In particular, damage to the dentate nucleus and to the Purkinje cells of the cerebellar cortex has been associated with deficits in predictive grip force control [117].

Commonly, subjects with cerebellar disorders exert excessive grip force levels when grasping, lifting, and transporting objects in the environment [114, 115, 117]. The force overshoot observed in subjects with cerebellar pathologies has been interpreted to reflect an acquired strategy to ensure a stable grasp in situations the motor system works suboptimally [116]. In contrast, the timing

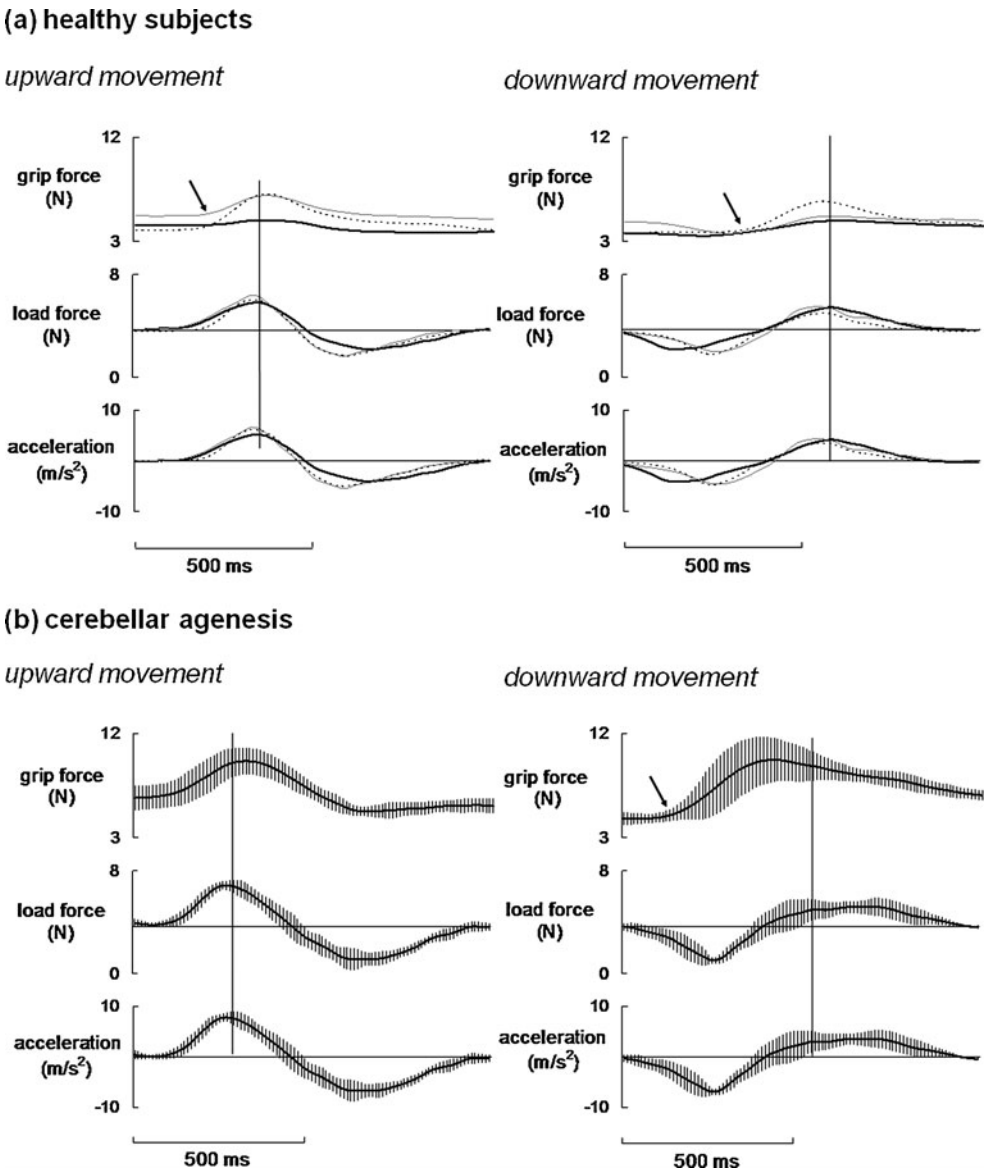


Fig. 5 Average data of grip force, load force, and acceleration obtained from vertical movements performed by three healthy subjects (**a**) (female, right-handed, aged 59, 63, and 65 years) and subject H. K. with cerebellar agenesis (**b**). Subjects moved a handheld instrumented object upward and downward. The handheld object incorporates a grip force sensor and three linear accelerations sensors registering acceleration in three dimensions including gravity. In healthy subjects, grip force starts to rise early in upward and late in downward movements (*arrows*). Grip and load force profiles change in parallel and peaks in load force coincide with peaks in grip force suggesting predictive force planning, regardless of movement direction. In H.K., the grip force profile does not exactly match the profile in load. Grip force starts to rise at movement onset, regardless of whether the movement is directed upward or downward (*arrows*). Peak grip force lags behind peak load force for upward movements, but precedes peak load force for downward movements. These findings indicate that H.K. was unable to plan and process the grip force output differentially to the direction-dependent loading requirements of the upcoming movement

deficits in grip force modulation reflect impaired prediction of external loads arising from voluntary object manipulation [112, 113, 115, 117]. However, the correlation between these impairments and clinical ataxia rating scales, such as the International Cooperative Ataxia Rating Score subscales [119], appears to be weak, implying that kinetic measures may serve as a valuable adjunct measure for testing dexterity in cerebellar disorders [115].

The predictive coupling between grip and load force profiles has been interpreted within the theoretical concept of *internal models* [109]. Figure 6 illustrates the theoretical concept of an *internal forward model* within the context of grip force control. Predictions of the consequences of voluntary motor actions are necessary as the cerebral motor cortex cannot respond on the basis of slowly evolving sensory and somatosensory feedback. The latter would produce essential time delays of around 100 ms [109]. Given the regular anatomical cytoarchitecture of the cerebellar cortex and the well-characterized functional circuitry with only one output cell and four main classes of interneurons, the cerebellum has been considered to incorporate such internal forward models [120–122]. The cerebellum may function similar to a *forward model* by using *efference copies* of motor commands to predict the sensory effects (*corollary discharge*) of voluntary actions. Accurate predictions reduce the dependence on time-delayed somatosensory feedback. Cerebellar circuitry would be necessary to learn how to establish accurate predictions using error information about the discrepancies between actual and predicted sensory consequences (*prediction error*) of voluntary actions. Given its anatomical connections, the cerebellum is well suited to compute expected sensory outcomes of voluntary motor actions. Data from functional brain imaging have provided

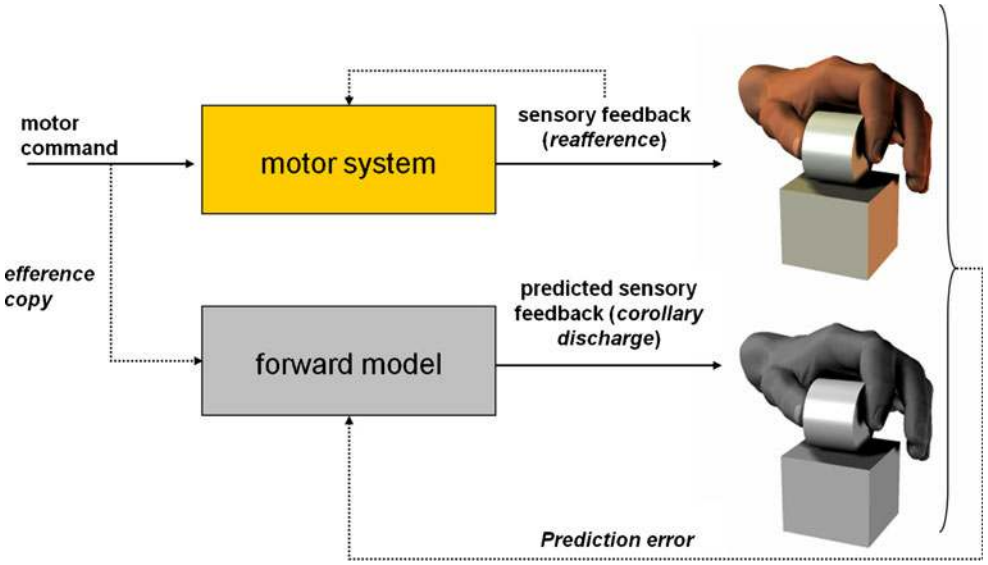


Fig. 6 Internal forward models enable a parallel modulation of grip force with the movement-induced loads when transporting a handheld object. The motor system generates a descending motor command that results in sensory feedback (reafference). A forward model of this system uses a copy of the descending motor command (efference copy) and generates an estimate of the sensory feedback likely to result from the movement (corollary discharge). The cerebellum computes an estimate of the sensory feedback. A mismatch between the predicted and actual sensory outcomes (prediction error) triggers force corrections along with an updating of the relevant internal models

additional support to the idea that the cerebellum is relevant for implementing the equivalent of internal forward models within the central nervous system [123–125].

Dysfunction of Voluntary Limb Movements in Cerebellar Patients (M. Manto, N. Oulad Ben Taib)

Limb movements in cerebellar patients are characterized by overshooting/undershooting, increased variability from trial to trial, impaired timing, overall slowness, and increased curvature of trajectories. Direction and gravity are two factors influencing the severity of these deficits [126]. Both movement initiation and termination are impaired. Errors in position, directional tuning, and velocity profiles are common, supporting the general hypothesis that the kinematic parameters of movements are affected in cerebellar disorders. Patients with cerebellar damage show difficulties with predictive motor timing [127]. Muscle tone may be decreased [128], although this is often subtle.

Control of Single-Joint Movements

Hypermetria is a classic sign of a lesion of the cerebellum or in the cerebellar connections. The term refers to the overshoot of a target when the patient makes a voluntary movement towards the target [129]. When a single-joint movement such as a wrist or elbow movement is performed quickly, a triphasic burst of electromyographic (EMG) activity can be identified: a first burst of activity in the agonist muscle launches the movement. This burst is followed by a second burst of EMG activity in the antagonist muscle to provide the braking torque [129]. This is often followed by a third burst at the level of the agonist muscle to reach the final position. The most prominent EMG defect associated with cerebellar hypermetria is a delayed onset latency of the antagonist activity [130, 131]. However, other defects have been identified, and cerebellar patients may show various combinations of the following elemental abnormalities: decreased intensities in both the agonist and the antagonist EMG activities, decreased rate of rise in the antagonist EMG activity, and inability to adapt appropriately the intensity of EMG activities to an increased inertia of the moving limb [132]. Indeed, hypermetria is larger when inertial loads are added to the moving hand, as a consequence of the inability to adequately tune the intensity of the antagonist activity. Cerebellar patients may also show impairments in the adaptation to external damping during fast reversal movements [133]. Dysmetria may be associated with a kinetic tremor, which predominates in visually guided tasks performed at slow or moderate velocities. Tremor may be obvious during maintenance of limbs against gravity.

Control of Multi-joint Movements

The investigation of unrestrained vertical arm movements executed at different movement velocities has shown that

hypermetria of multi-joint movements is associated with smaller peak muscular torques, and smaller rates of torque change at elbow and shoulder joints [134]. In patients performing forward pointing movements, peak muscular torques at the elbow are reduced during the initial phase of the movement when simultaneous shoulder joint anteflexion generates extension upon the elbow joint. Impairment in generating appropriate muscular torques significantly contributes to the patients' difficulties in controlling the mechanical consequences of dynamic interaction forces during multi-joint movements [134].

During throwing, patients with ataxia exhibit more variable hand trajectories and increased variability in timing/amplitude/velocity of finger opening [135, 136]. The increased timing variability of finger opening cannot be explained by an impairment in the generation of torques at the fingers level.

Lesion-Symptom Mapping for the Control of Limb Movements

Correlations between clinical/behavioral deficits associated with motor coordination as well as motor learning and high-resolution MRI have been investigated both in patients with degenerative disorders and in those with focal lesions [137]. In patients with cerebellar cortical atrophy, the deficits in limb movements correlate with the atrophy of the intermediate and lateral cerebellum. In case of acute cerebellar lesion, upper limb ataxia is correlated with lesions of lobules IV–VI, whereas lower limb ataxia is correlated with lesions of lobules III and IV, in agreement with the somatotopic organization of two homunculoid representations revealed by fMRI, with the more extended located upside down in the superior cerebellum [138]. Limb ataxia is correlated with lesions of the interposed and part of the dentate nuclei [139].

In terms of recovery of dysmetria following an acute cerebellar lesion, there is a trend toward a lower degree of recovery when cerebellar nuclei are involved. Lesions of the cerebellar nuclei are not fully compensated at any age and are independent of the pathology [139].

The Cerebellum and Timing (R. Ivry)

Understanding cerebellar function requires consideration of the temporal domain. The roots of this idea are found in the clinical literature. The cardinal feature of ataxia is the breakdown of the temporal patterning of coordinated movement. Patients with ataxia are unable to precisely control the timing essential for producing rapid movements [140] or coordinate dynamic interactions that arise in multi-joint movements [141].

These clinical observations inspired the experimental analysis of temporal control. Patients with cerebellar pathology have difficulty producing well-timed movements [142], especially if the damage encompasses superior cerebellar regions [143]. Similarly, cerebellar dysarthria is prominent for phonological features that rely on the precise timing of articulatory gestures; the deficit is less evident if the phonological contrasts are based on the configuration of the articulators [84, 144].

Reports of temporal processing deficits on perceptual tasks expanded the functional domain of cerebellar timing beyond motor control (Fig. 7). Patients with cerebellar degeneration have difficulty making perceptual judgments when the critical information requires fine temporal discrimination [142, 145]. Interestingly, this deficit is pronounced when the perceptual judgments are based on simple temporal features such as duration, but not for more complex rhythms, indicating that extracerebellar structures support abstract, hierarchical representations of time [146]. Cerebellar activation is also a consistent feature of neuroimaging studies of perceptual timing, although meta-analyses underscore the inconsistency of these data [147]. A cerebellar role in detecting violations of sensory expectancies is especially pronounced for temporal violations [148, 149].

Two issues have engendered considerable debate concerning how to characterize temporal processing within the cerebellum. The first centers on the distinction between event and emergent timing [150, 151]. Cerebellar pathology produces marked impairments on tasks in which movements are time-locked to specific events. Eyeblink conditioning serves as a model task of event timing; the animal learns to produce a singular response in anticipation of the unconditioned stimulus. Movements marked by the anticipation of precisely timed sensory inputs [152] or in which sequential transitions must be precisely coordinated [153] can also be viewed as event-based. In contrast, patients with cerebellar deficits show reduced deficits when temporal regularities are not associated with salient events [154], leading to the hypothesis that timing in such tasks is an emergent feature, reflecting the operation of other control parameters. For example, to produce continuous movements at a constant rate (e.g., circle drawing at 1 Hz), consistent timing can be achieved by maintaining a constant angular velocity.

The second issue centers on the question of absolute versus relative temporal representation. Computational models of cerebellar timing have focused on the representation of absolute intervals, for example, asking how an animal learns the precise interval between a CS and US. Models of absolute time naturally incorporate the idea that the temporal range of the cerebellum may be limited to the subsecond range. For longer intervals, extracerebellar structures either are sufficient, or interact with the cerebellum to provide a memory system for time [155, 156]. The

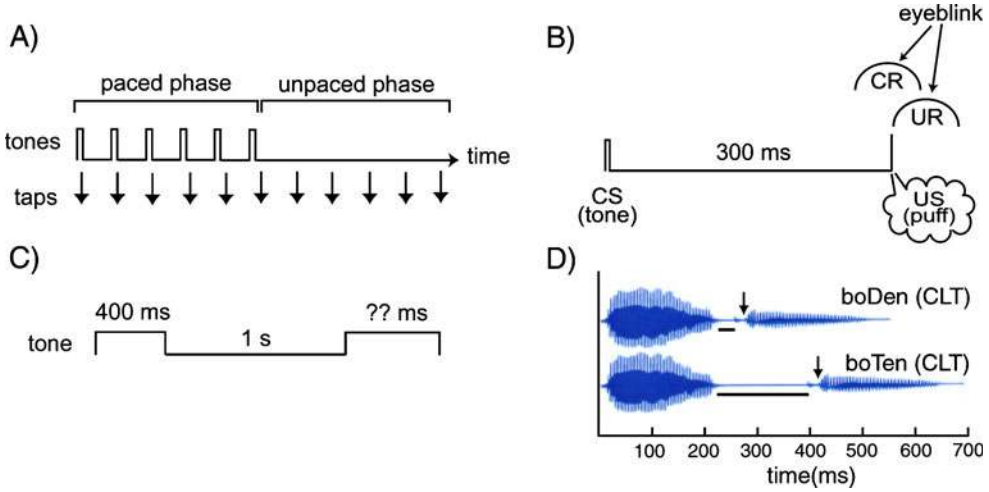


Fig. 7 Representative tasks associated with timing deficits in patients with cerebellar pathology. **a** Sensorimotor prediction task: SCA patients were highly variable in timing a button press to release a missile to intercept a moving target. **b** Temporal learning: the conditioned response is either abolished, takes longer to learn, or is produced without the appropriate delay. **c** A larger difference is required for the comparison interval. **d** Speech discrimination is disrupted when the phonetic contrast is based on the duration of a silent period (**a** from [122], **c** from [160], **d** from [140])

idea of absolute interval timing was at the core of Braitenberg's seminal conjecture concerning the cerebellum as a millisecond timer [157]. While experimental analyses revealed shortcomings with a fixed delay line model, subsequent computational studies have explored alternative mechanisms to provide interval-based representations [158]. Consensus is emerging from this work that temporal encoding arises from processing within the granular layer of the cerebellar cortex [159].

Alternatively, an orderly succession of states may serve as "trigger points" during the production of a skilled movement, even though the overall rate of the movement may vary from one instantiation to the next (Fig. 8). Models in which the cerebellum is viewed as a state estimator highlight how this structure imposes temporal regularities with relative rather than absolute timing [160, 161]. This formulation captures the flexible nature of skilled behavior, providing a compelling account of how the cerebellum contributes to tasks such as ball throwing [135], in which the action of one effector (e.g., the wrist) is dependent on the state of another effector (e.g., the rotating arm). The temporal processing capabilities of the cerebellum impose the dynamics that allow a desired action to unfold in a smooth, coordinated manner.

In summary, consensus holds for three core ideas concerning the cerebellum and timing. First, the represen-

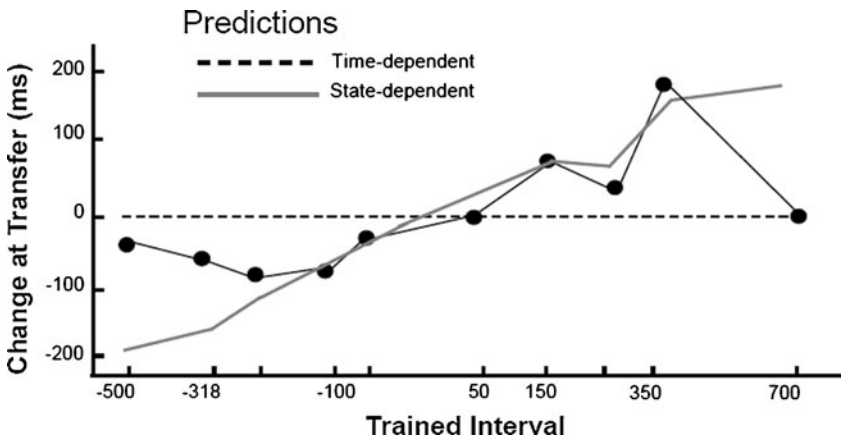


Fig. 8 Absolute and relative timing. Participants are trained to make an action composed of two parts, an arm reach and a thumb button press. During training, the reach lasts 350 ms and the button press either precedes the onset of the reach (negative values), occurs during the reach (50–350 ms), or occurs after the reach is terminated (700 ms). At transfer, the participant is told to slow down the reaching movement. When the actions are successive, the absolute timing between the components is maintained. When the actions are coordinated (overlap), the timing of the thumb press is delayed to maintain relative timing. fMRI revealed a cerebellar response for the coordination condition compared to either component alone (adapted from [156])

tation of time has proven to be a core concept for experimental and theoretical studies of the cerebellum. Second, while all brain activity is, at its core, about prediction, the cerebellum is critical for behaviors requiring real-time prediction. Third, activity in the granular layer of the cerebellar cortex is critical for temporal encoding.

We can also agree on issues that remain open questions: Are certain forms of temporal representation uniquely performed by specific brain structures such as the cerebellum, or is temporal encoding a ubiquitous and generic feature of neural activity [150, 162]? Does timing provide a characterization of the cerebellum at a functional level, or is accurate timing required for cerebellar-specific computations such as error detection? Are there unique features of cerebellar anatomy and physiology that support temporal processing [159]?

Sensorimotor Synchronization (M. Molinari)

Sensorimotor synchronization (SMS) is a form of referential behavior in which an action is coordinated temporally with a predictable external event—the referent [163]. Usually, the term *SMS* refers to a situation in which both the action and referent are periodic, such that the predictability of the referent arises from its regular recurrence.

Studies on the neurophysiological basis of SMS in humans have implemented various protocols. In general, testing is required to decode the time information from different sensory modalities to guide the motor response as movement timing (e.g., in tapping) or interception time (e.g., in reaching paradigms). Cerebellar involvement in sensory processing and time perception is well established [164, 165], and both areas focus on the cerebellum as the key structure in SMS.

Tapping protocols require one to produce a motor response in a time-locked manner with a sensory rhythmic stimulus. To achieve this goal, time information that is embedded in the sensory stimulus must be extracted and inserted into the motor output. This information must be processed to allow the motor commands to anticipate the sensory input—i.e., to synchronize the actions, the planning must be based on the prediction of an incoming input. Similarly, to intercept an object successfully, a motor system must be provided with all of the information that is needed to predict the interception point. Predictions that are based on sensory analyses constitute the crux in interpreting cerebellar processing for motor control learning when no SMS is required [166].

But how it is possible to predict something and how does cerebellar processing intervene? One explanation implicates cerebellar importance in sequence processing [167]. If events are organized in fixed sequences, then, after recognition of the initial elements, it would be possible to predict the elements that follow.

Convergent neuroimaging, neurophysiological, behavioral, and lesion data indicate the importance of cerebellar sequence recognition in SMS [168–170]. Neurophysiological data in humans have shed light on the cerebellar mechanisms of detecting expected and unexpected somatosensory events. In magnetoencephalographic (MEG) recordings, Tesche and Karhu [171] demonstrated that the cerebellar response to a time-locked somatosensory stimulus is higher when an expected stimulus is not presented compared to when it is perceived as expected. The importance of cerebellar processing in alerting the cerebral cortex to incoming sensory inputs has also been confirmed using time-based mismatch negativity (MMN) paradigms [148].

Cerebellar damage also impairs sequence recognition when the sequences are based on spatial, linguistic, or behavioral information [172]. Neurophysiological cerebellar function in discerning expected and unexpected conditions has been also demonstrated in a spatial MMN paradigm [173], in which the spatial location stimulus was changed at random within a time regular sequence of stimuli. Under this condition, the MMN cortical response developed only if cerebellar processing was preserved. Thus, cerebellar damage deprives the cerebral cortex of its capacity to react to changes in the spatial location of somatosensory stimuli.

The importance of recognizing the next item in a sequence and predicting what comes next based on experience has been also analyzed using ad hoc cart sorting tests that are based on spatial, verbal, or behavioral content. All patients with focal or atrophic cerebellar damage had impaired sequence detection, irrespective of the content; the sole differences in performance were related to the topography of cerebellar lesions [174]. In particular, behaviorally relevant scenes were ordered incorrectly by subjects with left cerebellar damage, and verbal sequences were ordered incorrectly by those with right cerebellar damage.

In a broader sense, SMS can be considered the ability to modulate motor behavior not only in the time domain but in general according to predictable environmental changes. At present, no direct experiments have been performed to analyze the cerebellar role in SMS to nontime-relevant stimuli. Nevertheless, cerebellar involvement in the detection of behaviorally relevant scenes [174] and its hypothesized importance in behavioural disturbances, such as autism [175] and schizophrenia [176], suggest that cerebellar synchronization functions must be considered in a wider scenario. If someone recognizes a known sequence of events, he can synchronize or adapt his behavior to a

specific context and thus promptly and correctly react to sensory stimuli. This hypothesis is particularly relevant, considering the holistic view of human motor cognition [177].

Such an approach stresses the idea that the same processes that mediate the production of actions mediate perceptual, conceptual, lexical, and behavioral processing. Within this framework, SMS and cerebellar processing can be considered the basis of human adaptation to environmental changes—not only at the motor level but for virtually all human abilities in general, given the wide range of cerebellar functional domains [178].

In closing, it is important to emphasize that SMS is achieved not only by processing within the cerebellum. Implicit SMS, at least in the time domain, can also be attained after cerebellar damage [179]. Similarly, precerebellar sensory processing for motor control has been recently and elegantly demonstrated in dorsal column nuclei [180].

Thus, as is often the case in neuroscience, SMS appears to be a more complex event than believed. SMS can link a motor response to a sensory stimulus in the absence of cerebellar processing. Conversely, the synchronization of human motor cognition with the environment, as perceived by our senses, requires the recognition of specific complex multisensory patterns. The cerebellum represents the only structure of the brain in which actual sensory information and previously experienced complex patterns can be compared and thus recognized. Cerebellar research is advancing rapidly, and soon, our knowledge of the cerebellar mechanisms that are involved in complex SMS will help us address pathologies, such as autism and schizophrenia.

The Cerebellum and Control of Corticomotor Excitability (AB. Conforto, SN. Farias da Guarda)

The cerebellum receives information from the contralateral motor cortex (M1), sensory cortex, and spinal cord. This information is integrated, processed, and relayed to the contralateral M1 [181]. The cerebellum has a putative facilitatory effect on excitability of the opposite M1 through dentothalamocortical projections [182]. Here, we review evidence from transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) studies, showing that cerebellar input regulates excitability of M1 in humans. The basic modes of action of TMS will not be discussed here (see also [183, 184]).

Cerebellar Modulation of M1 in Healthy Subjects

When TMS of M1 is preceded by TMS of the contralateral cerebellar hemisphere by 5–7 ms, motor-evoked potential (MEP) amplitudes decrease, compared to MEP amplitudes obtained by TMS of M1 alone. This phenomenon is called cerebellum–brain inhibition (CBI) and is likely mediated by excitation of Purkinje cells by TMS. Purkinje cells send inhibitory projections to deep cerebellar nuclei that in turn send excitatory projections to thalamic nuclei. Therefore, inhibition of the dentatothalamic excitatory projection leads to decrease in M1 excitability, reflected in decreased MEP amplitudes [185, 186].

Repetitive administration of pulses (repetitive TMS, rTMS) administered over several minutes can have effects that outlast the stimulation period. For example, 1-Hz rTMS often decreases neuronal excitability; 1-Hz rTMS of the cerebellum decreases CBI for 30 min [187]. A variant of rTMS is theta-burst stimulation (TBS) consisting of repetitive bursts of three TMS pulses delivered at a frequency of 50 Hz, every 200 ms. When administered continuously, TBS of the cerebellum also reduces CBI [188, 189].

In tDCS, anodal stimulation usually increases neuronal excitability while cathodal stimulation has the opposite effect [188]. Cathodal tDCS of the cerebellum decreases CBI and anodal tDCS enhances CBI [185]. It has been shown that peripheral electrical somatosensory stimulation increases contralateral M1 excitability reflected in increased MEP amplitudes in healthy humans and animals [190, 191]. In rodents, this effect is blocked by cerebellar lesions [191–193] indicating that the cerebellum facilitates this type of plasticity.

Modulation of M1 in Patients with Cerebellar Lesions

Resting motor threshold (rMT), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI) are measures of M1 excitability. When a subthreshold magnetic stimulus is followed 1–6 ms later by a suprathreshold stimulus delivered to the same M1, there is a decrease in M1 amplitude (SICI). When the interval is larger (10–15 ms), MEP amplitudes increase (ICF). When two suprathreshold stimuli are delivered at an interval of 50–200 ms, LICI is observed [194–196]. SICI is believed to be mediated by $GABA_A$ and LICI, by $GABA_B$ interneurons [197]. Table 2 summarizes TMS measures of excitability in patients with cerebellar lesions. In patients with unilateral cerebellar infarcts, SICI of the contralateral M1 is increased at an early phase (<2 weeks) [198] and decreases at later stages [198, 199].

Degenerative and paraneoplastic cerebellar ataxias lead to heterogeneous clinical syndromes with different abnormalities in corticomotor excitability. While Friedreich ataxia is an autosomal recessive disorder, spinocerebellar ataxias (SCA) include autosomal dominant, recessive, or X-

Table 2 Corticomotor excitability in cerebellar diseases

Measures of M1 excitability	Unilateral cerebellar infarct, early stage	Unilateral cerebellar infarct, chronic stage	SCA1	SCA2	SCA3	SCA6	FA	SCS	PCD
rMT	↑↓	n	↑	n	n	n	n	n	n
SICI	↑	↓	n	n	n	n	n	n	n
ICF	↓	n	n	↓	↓	n	n	n	n

M1 primary motor cortex, *rMT* resting motor threshold, *SICI* short intracortical inhibition, *ICF* intracortical facilitation, ↑ enhanced, ↓ reduced, *n* normal, *SCA* spinocerebellar ataxias, *FA* Friedreich ataxia, *SCS* sporadic cerebellar syndrome, *PCD* paraneoplastic cerebellar degeneration

linked disorders characterized by progressive degeneration of the cerebellum and its connections. There is a correlation between genetic defects and corticomotor excitability changes [200–202]. For instance, SICI is normal in patients with sporadic cerebellar syndrome and paraneoplastic cerebellar degeneration, but LICI is increased in both conditions [200, 201]. rMT has been found to increase in SCA1 and remains unchanged in other conditions.

Also, absence of CBI occurs in patients with lesions in the cerebellar efferent pathways from different etiologies such as SCA3, SCA6, paraneoplastic cerebellar cortical atrophy, and cerebellar stroke [203]. Therefore, even though some measures of cortical excitability are affected in different ways by conditions that affect the cerebellum, CBI absence is common to various syndromes that share defective cerebellar output.

Altogether, these results suggest that cerebellar output influences different neuronal populations in M1 and that timing and etiology of cerebellar lesions impact their effects on M1 excitability. Novel treatment strategies are expected to target specific abnormalities of M1–cerebellum interactions.

The Cerebellum and the Control of Movement-Related Sensory Data Acquisition (J. Bower)

The proposal that the cerebellum is directly and primarily involved in coordinating movement has been the dominant theory of cerebellar function since the mid-eighteenth century when Marie Jean Pierre Flourens observed that cerebellar ablation in rabbits resulted in the loss of motor coordination [204]. The majority of the mechanistic theories supporting this hypothesis since have assumed that cerebellar circuitry itself computes some function that then directly creates or modifies the patterns of muscle activations and synergies that underlie coordinated movement [205, 206]. In distinct contrast, we have proposed that cerebellar circuitry is not concerned with the coordination of smooth movement at all, but instead coordinates the acquisition of sensory data on which motor systems, and in fact, all other brain systems depend [166]. While in some, maybe even most brain systems, the cerebellum effects its control over sensory data acquisition through an influence on the physical position of sensory surfaces and thus through motoneurons (the extraoccular eye muscles as part of the vestibulo-occular reflex, for example), computationally, the cerebellum's influence on those motoneurons subtly controls the position of sensory surfaces (the retina for example in the case of the VOR) and, therefore, reflects a concern for the quality of the sensory data being obtained (in the case of the VOR minimizing retinal slip). Computationally, this control over sensory data acquisition is predicted to directly affect the efficiency and thus the processing power of other brain systems (the rest of the visual system in the case of the VOR) enhancing its performance (for the VOR, the maintenance of visual acuity with self movement). For the axial movements that have been assumed for 150 years to be coordinated by the cerebellum, this hypothesis therefore predicts that disruption in the timing or pattern of movements does not reflect a direct involvement of the cerebellum in calculating muscle synergies, but instead is a secondary consequence of the degradation in the quality of the sensory data motor cortex, the basal ganglia, the spinal cord, and the rest of the primary motor system used to coordinate patterns of muscle activation to produce coordinated movement.

The idea that the cerebellum is a sensory data acquisition and not a motor coordination device emerged from the study of the spatial pattern of tactile projections to the lateral hemispheres of the rat cerebellum [207] as well as the pattern of cerebellar cortical responses to those inputs [208]. The hypothesis, however, sheds a different light on several very basic cerebellar properties:

1. In order to continually assess the quality of sensory data, the cerebellum should receive direct and rapid projections from sensory structures collecting data relevant to movement. The spinocerebellar proprioceptive and tactile pathways are the most rapidly conducting pathways in the brain and provide extensive input to the cerebellum [209].
2. In order to coordinate sensory data acquisition, cerebellar output should directly influence the transduction

of sensory information at the earliest stages. Outputs from the cerebellum projecting via the red nucleus [210] directly influence the fusimotor system responsible for controlling sensory transduction in muscle spindles [211, 212].

3. Careful examination of specific movement-related effects of cerebellar lesions, like for example, the long known inability of cerebellar patients to respond to postural perturbations [213], should reveal specific deficits in the control of sensory surfaces either during or prior to movement onset. Experiments of this type have demonstrated a specific inability to use predictive feed-forward control to establish the correct "central sensory set" for upcoming movements [214].
4. This sensory acquisition theory also suggests that the particular influence of cerebellar deficits on complex multi-joint movements reflects those movements heightened requirement for the coordination of sensory data across multiple sensory surfaces, rather than a specific breakdown in active cerebellar involvement in motor control. Accordingly, the finding that cerebellar patients break complex movements into a series of simpler movements [141] can be viewed as an adaptive strategy to deal with the lack of coordinated sensory data.
5. In fact, the rather remarkable ability of motor coordination to recover from cerebellar ablations, which may be the best kept secret of cerebellar motor studies, we believe reflects the ability of the structures that are, in fact, responsible for motor coordination (motor cortex, the basal ganglia, the spinal cord) to develop new computational strategies to work around poorly coordinated sensory data at the cost that movements are slower, less complex, and less efficient. Consistent with this idea, the most commonly found clinical effect of cerebellar lesions is the general slowing down of behavioral execution [141, 215]. Again, the sensory acquisition theory predicts that this slow down reflects the additional computational time necessary to organize behavior using poorly coordinated sensory data, a prediction consistent with evoked potential studies [216].
6. Finally, the cerebellum receives projections from all known sensory surfaces and is structurally, and therefore almost likely computationally, uniform [164]. Accordingly, any proposed theory of cerebellar function will eventually need to extend to all sensory systems. The theory of sensory data acquisition clearly meets this standard, predicting that behavioral performance deficits associated with cerebellar removal or dysfunction will be manifested in all other sensory systems and attributable to disruptions in sensory data acquisition control (c.f. [173, 217]). Of course, it has been known for a many years that cerebellar lesions disrupt the performance of visual tracking systems, including the vestibular ocular reflex [218]. As mentioned briefly above, while executed through the activation of ocular motor muscles, these cerebellar-related mechanisms are functionally sensory, as they are responsible for increasing overall visual acuity by fine-tuning the position of the retina [219, 220]. No one has ever claimed that the cerebellum is involved in visual object recognition because disruption of the VOR results in a decrease in visual acuity. In a specific test of the idea that the cerebellum provides the same function for all sensory systems, it has recently been demonstrated that cerebellar patients have significant auditory deficits, for example, in pitch perception [221], even though data acquisition in the auditory system is not dependent on the movement of axial muscles. Again, it has never been suggested that the cerebellum is responsible itself for pitch perception. By direct analogy, it makes a little sense to suggest that the cerebellum is involved in coordinating smooth movements through influencing sensory processing.

In summary and put as simply as possible, the core question is whether the cerebellum itself computes how to make movements smooth and coordinated and drives motor neurons accordingly, or instead works to assure that the motor system has the best sensory data with which to calculate and execute behavior, including smooth and coordinated movements. While this distinction may at first seem somewhat subtle, it is not subtle at all with respect to the analysis of cerebellar cortical circuitry and what that circuitry actually computes [164], or with respect to understanding how the cerebellum is involved in the myriad and growing number of behaviors and systems beyond those traditionally associated with motor control now suggested to involve the cerebellum [106, 222].

Cerebro-cerebellar Interaction in Visuokinesthetic Perception of Hand Movement (N. Hagura, E. Naito)

Extracting the continuously changing spatial location of an effector during movement is essential for accurate motor control of that effector (limbs). The sensory afferent information the brain utilizes for inferring the state (position/movement) of the limbs is primarily the kinesthetic/proprioceptive information signaled by the firing of muscle spindles, cutaneous and joint receptors [223–229]. Also, visual information of the limb is often available to indicate its state to the brain [230–233]. Since sensory input from the two different sources is potentially conflicting, combination of visual and kinesthetic information is a

critical step for the brain to identify the unified spatial state of the limb.

Classically, it has been regarded that areas in the cerebral cortex take dominant role in this visuokinesthetic integration. Clinical studies have reported that brain lesions in frontal and parietal cortices, especially lesions in the right side, elicit severe deficit in body localization and ownership of the body [234–236]. Bimodal neurons found in these areas of nonhuman primates that respond to both tactile and visual information at the same spatial location also supported this view [237, 238]. However, it is still unclear whether and how the cerebellum is involved in this multisensory processing.

From the studies of motor control, evidence has been accumulated that the cerebellum is an important locus for the process of predicting the sensory consequence of action [31] and for the estimation of the effector state for online correction of action [160]. It has also been shown that cerebellar damage disturbs matching of visual and kinesthetic information when making continuous movements [239, 240]. From the sensory processing side, it is known that in nonhuman primates, visual [240–244] and kinesthetic [245–247] inputs reach the cerebellum, either indirectly via the cerebro-pontine-cerebellar pathway or directly via the spinocerebellar pathway. Since sensory function of the cerebellum has been also highlighted [248, 249], it is plausible to assume that the cerebellum is also involved in the visuokinesthetic integration process that enables humans to estimate the current bodily state. In particular, regarding the literature published in the motor control field, one may infer that the cerebellum is involved in the visuokinesthetic integration under a dynamical situation (during movement), where continuous online combination of the two sensory input channels is required. Results from a recent study [250] support this view and further suggest the importance of cerebro-cerebellar interaction during this computation.

In this study, healthy volunteers experienced kinesthetic illusion of hand flexion movement elicited by tendon vibration of wrist extensor muscle [251] while they viewed either flexion (CONG) or extension (INCONG) of their video-recorded hand motions (Fig. 9a). When the effect of visual velocity of hand motion on kinesthetic perception was examined in each condition (CONG or INCONG), the amount of illusory experience was graded by the visual velocities only in the CONG condition (Fig. 9b). Thus, the brain appeared to continuously match and combine visual and kinesthetic information, only when movement directions sensed by vision and kinesthesia were matched.

When brain activity was measured with fMRI, only the left posterolateral cerebellum was specifically recruited under the CONG condition (Fig. 10c, d), and the degree of left cerebellar activity was well correlated with the

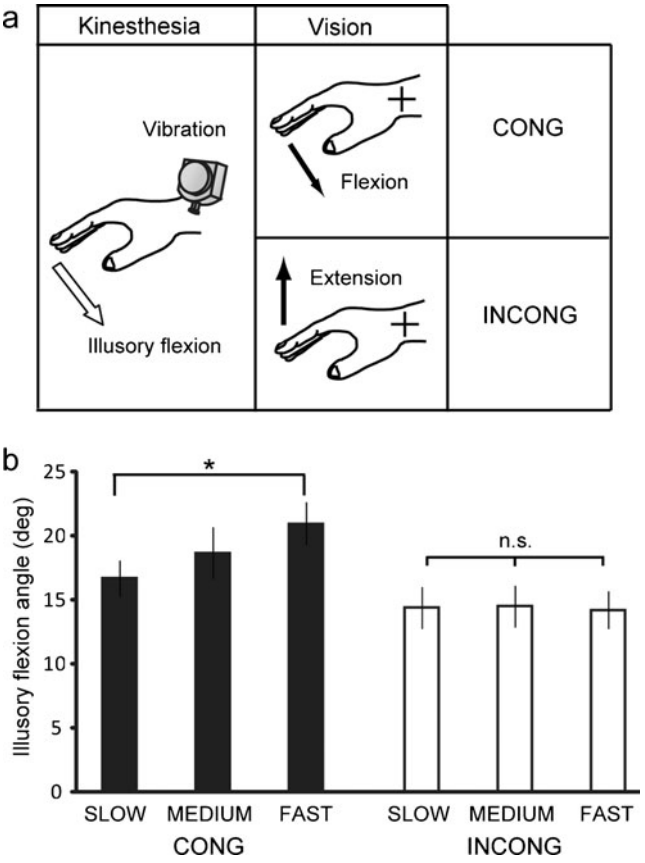


Fig. 9 Conditions (**a**) and behavioral results (**b**) in the experiment [245]. **a** Participants experienced illusory flexions of their right hands while viewing their video-recorded hand flexion (*CONG*) or extension motion (*INCONG*). *Crosses on the wrist joints* indicate fixation points. *Open arrow* indicates the direction of illusory movement, and *solid arrows* indicate the directions of visual hand motions. Three different velocities were used for each condition. **b** *Filled bars* represent the mean illusory angles across all participants under the CONG condition and *open bars* indicate those under the INCONG condition. *Error bars* indicate the standard errors of means across participants. $*p<0.05$

participants' perceived intensity of illusory hand movement under the CONG condition (Fig. 10c, e). This cerebellar activation was not observed when people experienced the illusion with their eyes closed [251]. Another finding was that the cerebellar activation was lateralized to the left irrespective of the hand (left or right) side (Fig. 10c). This finding contrasted with the right-dominant cerebral activations (Fig. 10a, b) normally observed during kinesthetic illusions irrespective of the left and right hands [251] and from the broad literature showing importance of the right cerebral cortex in bodily related sensory processing in humans [234–236]. From the nonhuman primate anatomical studies, it is now evident that the cerebral cortex and the cerebellum are mainly contralaterally interconnected (cerebellar projection to the cerebral cortex via the thalamus or projection from the cerebral cortex to the cerebellum via the

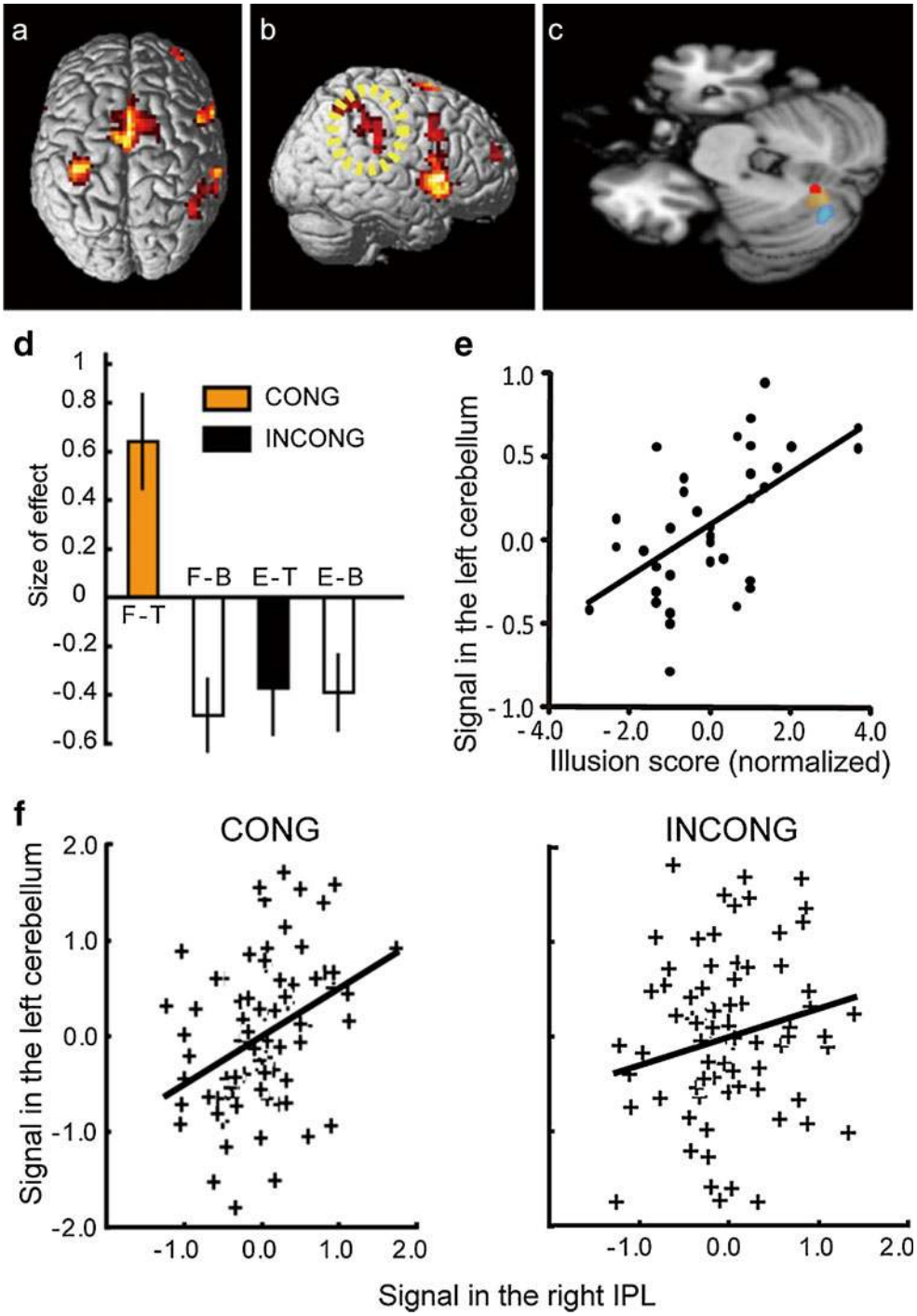


Fig. 10 Results from the fMRI experiments [245]. **a**, **b** Right-dominant cerebral activations (**a** *top view*, **b** *lateral view*) during visuokinesthetic processing in the CONG and INCONG conditions. **c** Left cerebellar activations exclusively under the CONG condition. *Orange* and *blue sections* correspond to the results obtained from the right and left hands, respectively. *Red section* represents the area where strength of activity correlated with the subjective experience of hand movement. The horizontal plane (z=−27) is displayed. **d** The size of effects of left cerebellar activation (*orange* in **c**) across conditions. *Bars* indicate the means of contrast parameter estimates (size of effect in arbitrary units) for the left cerebellar activation (−27, −69, −30) during the CONG (*orange bar*), INCONG (*black bar*), and other control conditions (*open bars*; see [245] for details). *Error bars* represent standard errors of means across participants. **e** Significant correlation between the behavioral ratings (illusion scores) and the left cerebellar activity (*red* in **c**; r=0.57, df=34, p<0.001 one-tailed). The illusion scores are mean-corrected. **f** Relationship of activities between the right IPL (*Dashed yellow circle* in panel **b**) and the left cerebellum in a representative participant, revealed by functional connectivity analysis. The regression slopes were 0.52 and 0.29 for the CONG and INCONG conditions, respectively. The activities (x-axis for right IPL; y-axis for left cerebellum) are mean-adjusted (arbitrary units)

pontine nuclei) [252–255]. Thus, the recruitment of the left cerebellum for this multisensory processing may be reflecting the communication with the bodily information processing areas of the right cerebral cortex. Functional connectivity analysis provided supportive data for this idea; we found that the activity of the left cerebellum enhanced its coupling with that of the right inferior parietal lobe (IPL; Fig. 10a, b), only when visual and kinesthetic information was combined (CONG; Fig. 10f).

The study demonstrated that the *left* cerebellum, working closely together with the anatomically connected high-order bodily region of the *right* parietal cortex, participates in online combination of exteroceptive (vision) and interoceptive (kinesthesia) information to maintain perceptual coherence of momentarily updated hand position, presumably, to maintain the unified bodily state. The cerebellum may play particularly important roles in visuokinesthetic combination when the bodily movement is sensed, allowing prediction

and updating of the bodily state, for online correction of ongoing action. The roles of the cerebellum in the build-up of action–perception linkage will be an important issue for future studies.

Functional Neuroimaging Studies (C. Habas)

Functional imaging studies (fMRI and PET) have substantiated the role of the cerebellum in motor control, automation, and learning (motor skill acquisition). Resting-state functional connectivity studies have showed that the (sensori-)motor cerebellar system is intrinsically connected and encompasses (Fig. 11) the sensorimotor, lateral premotor, supplementary motor, anterior cingulate, and insular cortices, striatum, ventral thalamus, red nucleus, and cerebellum including the dentate nuclei (DN) and cerebellar cortex [256]. The cerebellar motor cortex includes the hemispheres of lobules V/VI/VIII, especially their paravermian part, and the anterior vermis [256–259]. These cerebellar regions must correspond to the hand representation of the anterior (lobules V/VI) and posterior cerebellar homunculi (lobule VIII), revealed in fMRI studies [138, 260]. A third cerebellar homunculus has been postulated in the cerebellar pyramis, which is specifically activated on the right side during self-paced movements. Lobule VII can also be recruited during self-initiated and complex rhythmic movements [261, 262] and, in conjunction with lobule VIII, during different conditions of tool use [263]. Recently, another motor domain specifically devoted to ipsilateral and bilateral complex movements has been described in lobules VI and VIIA [264].

Specific activation of lobules V/VI/VIII is observed during simple right-handed finger movement tasks, such as flexion–extension or tapping [265], abduction–adduction [261], pronosupination [266], and index pointing towards a

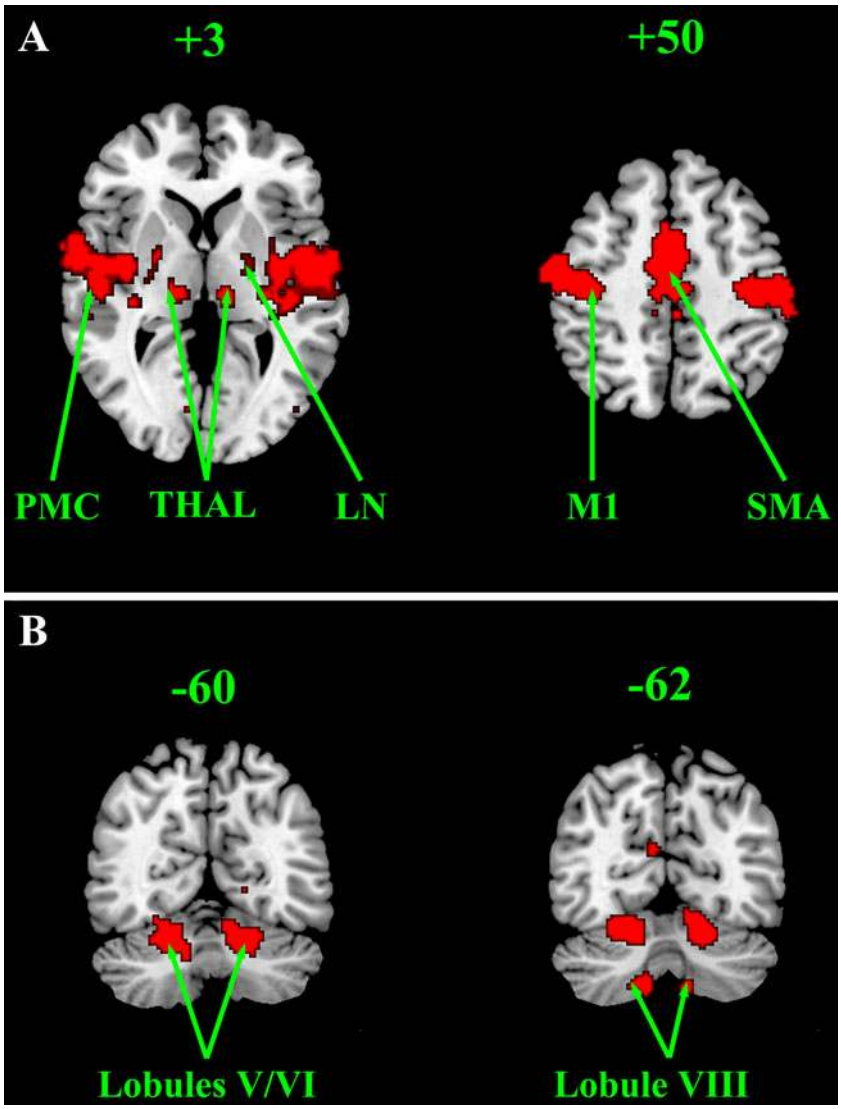


Fig. 11 The intrinsically connected motor network at rest (from [251]). **a** Axial slices (*Arabic numbers* indicate *z*-coordinates). **b** Coronal slices passing through the cerebellum (*Arabic numbers* indicate *y*-coordinates). Abbreviations: *LN* lentiform nucleus (pallidum), *M1* motor cortex, *PMC* lateral premotor cortex (clusters also include insula/claustrum), *SMA* supplementary motor cortex, *THAL* thalamus

visual target [267]. All kinds of movements are accompanied by anterior lobe activation (except oculomotor and phonation that specifically activated vermis of lobules VI/VII and lobule VI/crus I, respectively). However, the amount of cerebellar activation and the recruitment of dentate nuclei and posterior lobe are related to the complexity of the motor performance. First, for instance, lobule VIII [138, 261, 268, 269] and anterior and posterior vermis [266] are preferentially involved in unilateral or bilateral, simultaneous or rhythmic movements. Second, DN activation remained weak during simple motor task [270] and increases in parallel with the complexity of the task, reaching a maximum during tactile sensorimotor discrimination tasks (reviewed in [271]).

Cerebellar activation (especially, anterior lobe) is strongly correlated with (reviewed in [272, 273]) (1) movement frequency (in relationship with the premotor cortex [266]), (2) movement quantity, (3) speed [275, 276], (4) spatial and temporal complexity [267, 274], and (5) movement uncoupling [277]. Vermis of lobule VI is preferentially activated during discrete movements whereas its lateral part is activated in a similar manner during discrete and continuous movements [278]. Lobule V takes part in a state-dependent control during which a predicted state estimation of an effector is needed to coordinate actions of another [161]. Left lobule V activation is also increased with decreasing movement rate and strongly correlated with force error detection/correction [279]. The cerebellum appears to subserve spatiotemporal motor coordination and kinematical/dynamical implementation or control based on online sensory feedback for slow movements or on efferent copy for ballistic movements. Moreover, anterior lobe activations partially overlap during execution and imagination of the same movement, even if lobular VI(−VII) activation appears more posterior and lateral [280].

The cerebellum is differentially engaged in the successive phases of motor sequence learning (procedural memory) and automation. During the learning process, cerebellar activation progressively decreased while DN activation increased, suggesting transfer of plasticity of the motor engram from cortical to deep nuclear zones [281–283]. In the overlearning phase, DN activation diminished so that activation of the cerebellar motor activation is partly superseded by the striatal one. Lobule VII can be recruited during the late stage of the performance, likely due to executive requirement rather than motor control per se [265]. Therefore, increasing performance and movement automaticity is globally associated with decreasing anterior cerebellar activation. As activation of lobules V/VI and red nuclei is positively correlated with errors in performance, the anterior cerebellum may intervene in error-driven motor adjustments and learning [276].

In conclusion, the cerebellar motor system consists of an intrinsically connected network involved in kinematical, dynamical, and temporal planning and in error-driven online adjustments necessary to optimize movement performance, especially for complex, ballistic movements and during the early phases of motor learning. This cerebellar command can rely on sensory feedbacks during slow exploratory movements, or can remain independent of them and/or may subserve state estimation based on forward and inverse models. This network centered on lobules V/VI/VIII can also recruit neocerebellar regions (lobule VII) when executive/cognitive functions are required to execute very complex movements.

Magnetoencephalographic Mapping of Cortico-cerebellar Dynamics (C. Tesche)

Noninvasive neurophysiological methods have the capacity to reveal the dynamics of cortico-cerebellar interactions in both normal human subjects and patient populations with exquisite temporal resolution. Although scalp EEG recordings have long contributed to the understanding of motor planning and execution in the cerebral cortex, elucidation of cortico-cerebellar network dynamics has emerged only recently following the development of MEG arrays. Early recordings of isolated turtle cerebellum in vitro revealed strong neuromagnetic signals attributed to postsynaptic current flow in Purkinje cells [284]. Detailed whole-scalp MEG mapping of neuronal population dynamics elicited by median nerve stimulation demonstrated the feasibility of characterization and interpretation of both evoked and ongoing oscillatory activity in human cerebellum [171, 284–286].

Coherent oscillatory activity is believed to play a critical role in the sculpting and coordination of disparate neural populations in the sensorimotor system [287, 288]. Pre- and post-central cortical oscillations have been detected by MEG arrays in the alpha- (8–12 Hz), beta- (15–30 Hz), and high-frequency gamma-band (65–100 Hz) ([289]; for a review, see [290]). Changes in movement-related oscillatory activity begin as early as 1,500 ms before the initiation of a movement and endure for up to several seconds following cessation of movement. Specific sensorimotor areas participating to movement planning and execution may show increases in oscillatory power, whereas noninvolved areas typically display a reduction in power [291].

MEG has been used to characterize oscillatory activity in the motor system in normal individuals and patients with Parkinson's disease and hepatic encephalopathy ([292–294; for a review, see [295]). Data reveal that precise motor control is mediated by an 8-Hz oscillatory drive of spinal motor neurons that is coherent with oscillations in the

cerebellum, thalamus, and premotor and motor cortex. In parkinsonian resting tremor, a more extensive network, including the basal ganglia, posterior parietal cortex, secondary somatosensory cortex, and supplementary motor cortex, is recruited into coherent oscillation, with cortico-muscular entrainment at 8 and 16 Hz and coupling of sensorimotor areas emerging at 10 Hz. Abnormalities in oscillatory network level activity observed in patients with mini-asterixis due to hepatic encephalopathy include a slowing of cortico-muscular drive. These observations demonstrate that MEG can reveal abnormalities in cortico-cerebellar dynamics in patients with movement disorders.

An adaptive functional role for coherence within cortico-cerebellar networks in normal subjects is supported by the association of increased intercerebellar coupling and alpha- and beta-band coherence in bilateral cerebello-thalamo-cortical networks with reduced variability during rhythmic bimanual finger tapping [296]. In adults, the cerebellum and SMA are typically engaged in more difficult bimanual movements and auditory pacing tasks. Interestingly, children from 8 to 15 years old, who have less mature cerebello-frontal circuitry, also recruit SMA and cerebellum in the performance of simple unilateral flexion–extension tasks [297]. A detailed study of the maturation of coherence in the sensorimotor system of typically developing adolescents may provide insights into developmental transitions in cortico-cerebellar networks which falter in disorders such as autism and schizophrenia.

MEG responses to tactile stimulation have been recorded in adolescents with psychosis [297]. Differences in the modulation of alpha- and gamma-band activity between patients and controls were observed in post-central gyrus and in the left and right cerebellar cortex, supporting the notion that abnormal connectivity and function within cortico-thalamic cerebellar-cortical loops may be a contributing factor to the development of schizophrenia [298, 299]. MEG has also been used to characterize oscillatory activity and long-range synchronization in individuals with autism. Although analysis of waveforms recorded by individual MEG sensors do show differences in oscillatory activity and synchronization over the parietal and frontal cortex, measures of cerebellar dynamics and cortico-cerebellar coupling have yet to be extracted from these data [300].

Transcranial TBS of cerebellar vermis shows potential for the modulation of emotion and affect in individuals with schizophrenia [301]. The development of noninvasive transcranial stimulation for both research and clinical applications motivates continued efforts to image cortico-cerebellar dynamics within the broader context of sensory processing and attention, working memory, classical conditioning and emotional learning and affect in both normally developing children and adults and individuals with developmental disorders. Research studies have been initiated on attention to temporal cues [171, 302], musical training [303], decision making [304], the human mirror neuron system [305], and epilepsy [306, 307]. Clearly, much work remains to be done.

Conclusion

In this consensus paper, we have attempted to capture the diversity of the current opinions on the involvement of the cerebellum in sensorimotor control, by gathering contributions from a panel of experts. While a definite consensus statement on the roles of the cerebellum in motor control has not yet been reached, these contributions clearly highlight the broad range and diversity of current cerebellar studies.

The exact nature of the basic operations performed by the cerebellum remains unknown. Several major theories have emerged these last decades. The cerebellum copes with the highly complex nonlinear biomechanical features of the body. The hypothesis of Marr-Albus suggests that the climbing fiber input carries an error signal weakening the strength of a subset of parallel fibers/Purkinje neuron synapses in the cerebellar cortex, so that the cerebellum would gain the control of movement through trial-and-error practice. Because expectations and estimates of future motor states are essential to perform fast movements and due to the intrinsic time delay of sensory feedback related to motion, it has been suggested that the cerebellum contains internal models to emulate movements. Clumsiness and errors in motion would result from a distorted predictive control. Another influential theory relates to the inverse models that would be lodged in the cerebellum, the input being the aimed trajectory and the output the motor command. Both forward models and inverse models can be viewed as inter-related. Acquisition of a motor act would require forward models. The acquisition process itself would create an inverse model to allow an unconscious skilled movement.

What is the clinical relevance of these insights to the understanding of the exact cerebellar contributions in terms of cerebellar symptoms? The literature shows that the leading theories reviewed in this paper can explain to some extent the clinical deficits encountered in daily practice:

- Oculomotor deficits: disorders in timing
- Speech deficits: disorders in timing, sensory acquisition, and motor predictions
- Limb deficits: disorders in timing, sensory acquisition, sensorimotor synchronization, control of corticomotor excitability, visuokinesthetic cerebro-cerebellar interactions
- Ataxia of stance/gait: disorders in timing, sensory acquisition, and motor predictions

We would like to underline that these theories do not necessarily exclude each other. We have not discussed here the contributions of the cerebellum in cognitive operations. Analogies exist with the mechanisms underlying these deficits and those involved in motor control, the cerebellum encoding internal models reproducing the essential properties of mental representations in the cerebral cortex [308].

Conflict of Interest The authors declare that they have no conflict of interest.

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