Cerebellar Physiology

Jasmine Pickford and Richard Apps

Abstract The cerebellum is typically associated with motor control although there is now extensive evidence that its involvement extends into other domains including cognitive processing. The cerebellum contains a highly regular neural organization, but exactly how this circuitry contributes to its diverse functions remains unclear. Patterns of inputs to and outputs from the cerebellum, together with intracerebellar connections, add layers of complexity to cerebellar computations that can differ between anatomically and physiologically defined modules. Different modules are therefore likely to be specialized for different functions, for example in balance and locomotion versus reach-to-grasp. However, the unifying role of the cerebellum in the control of motor and cognitive behavior may be to serve as a prediction device, refining these predictions based on actual outcomes, to enhance behavioral performance.

Keywords Cerebellum · Purkinje cell · Climbing fiber · Mossy fiber · Cerebellar nuclei · Module · Motor · Learning · Prediction

1 Introduction

This chapter aims to provide an overview of the physiology of cerebellar circuits as a framework for the consideration of other chapters in this book. The physiology of the cerebellum has been studied intensively for over a century. A step change in understanding occurred in the 1960s with the pioneering work of Eccles and colleagues, who electrophysiologically characterized the intricate neuronal circuitry of the cerebellum and thus provided a physiological foundation upon which many future studies were based (Eccles et al. 1967). Given the huge subject area, it is beyond the scope of this chapter to consider all aspects in detail. Instead, the aim is

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to provide an up to date introduction for those unfamiliar to the topic (and those that welcome a refresher), with a focus on cerebellar physiology in relation to voluntary behavior. This provides the foundations for understanding the etiology of cerebellar disease including the focus of this book, namely ataxia, which is defined as the impaired coordination of voluntary muscle movement (Ashizawa and Xia 2016). The reader is directed to previous reviews for further details (e.g., Middleton and Strick 1998; Garwicz 2002; Llinás et al. 2002; Apps and Garwicz 2005; Ito 2006; Courtemanche et al. 2013; Jörntell 2017; D'Angelo 2018).

The current chapter will consider cerebellar physiology in the context of neural circuit loops, including olivo-cortico-nuclear connections, local cerebellar cortical circuits, and reciprocal patterns of input and output connectivity with other brain structures. As a consequence of these circuit loops, rhythmicity and synchronicity appear to be important physiological features of the cerebellum. Evidence is also accumulating to indicate that physiology is non-uniform across cerebellar regions, so caution should be made in assuming the same information transform occurs throughout the cerebellum.

The chapter will also explore how physiology translates to behavior, and evidence is presented that the cerebellum acts as a feedforward controller to modulate behavior. Generally speaking, the cerebellum is thought to contain internal models of effector systems that allow it to refine ongoing behaviors without waiting for sensory feedback (Wolpert et al. 1998). As such, the cerebellum is likely to control behavior by generating predictions about future behavioral outcomes that are updated based on the comparison of actual and expected outcomes (Hull 2020). Similar predictive mechanisms may apply across motor and cognitive domains, allowing the cerebellum to optimize the many types of behavior in which it is now known to be involved.

2 Basic Cerebellar Structure

2.1 Gross Cerebellar Structure

In order to understand cerebellar physiology, it is necessary to first consider cerebellar anatomical organization. Broadly speaking, the cerebellum has two major subdivisions: the cerebellar cortex and cerebellar nuclei (CN). The cerebellar cortex is highly convoluted and encapsulates the CN, which are situated deep within the cerebellum and are thus often referred to as the deep cerebellar nuclei. From medial to lateral, each half of the cerebellum can be classified into three longitudinal compartments—the vermis, paravermis (intermediate), and hemispheres—and across all compartments the cerebellar cortex has the same basic trilaminar structure, composed from inner to outermost by the granule cell layer, the Purkinje cell (PC) layer, and the molecular layer (Fig. 1).

The granule cell layer contains granule cells (the most numerous neuronal cell type in the nervous system), Golgi cells, unipolar brush cells (UBCs), Lugaro cells,

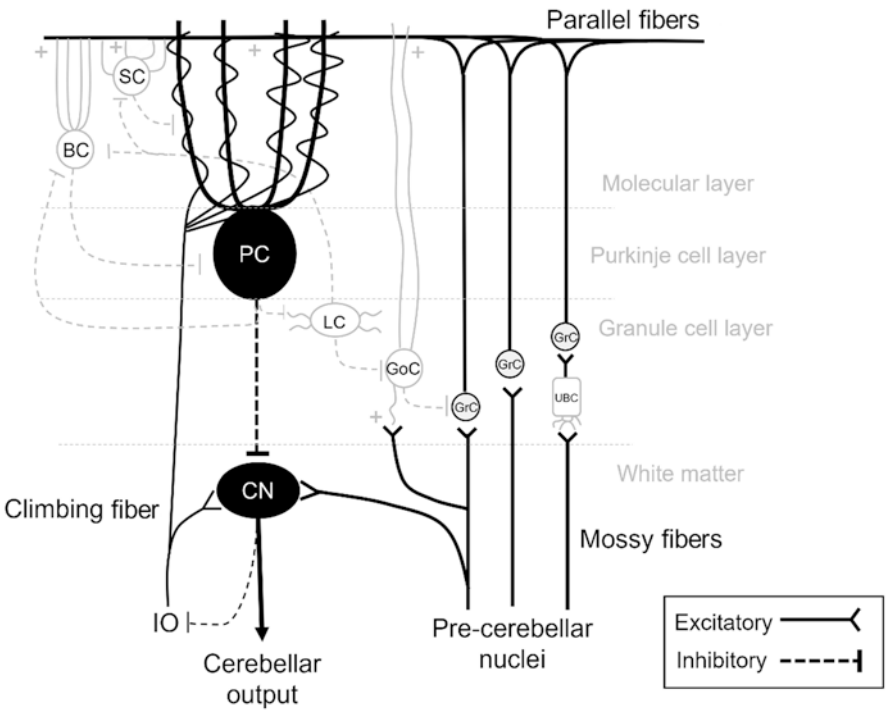

Fig. 1 Simplified cerebellar circuitry. Inputs to the cerebellum are mainly from mossy fibers and climbing fibers. Mossy fibers synapse onto granule cells (GrCs) that form bifurcating axons known as parallel fibers. Purkinje cells (PCs) receive inputs from parallel fibers and climbing fibers and their main target is the cerebellar nuclei (CN). Other local neurons are also present in the molecular and granule cell layers of the cerebellar cortex. Nucleo-cortical connections, candelabrum cells, and Bergmann glia are not shown. Abbreviations: BC basket cell, GoC Golgi cell, GrC granule cell, IO inferior olive, LC Lugaro cell, SC stellate cell, UBC unipolar brush cell

and a subgroup of Lugaro cells known as globular cells (Lainé and Axelrad 2002). The PC layer contains PCs—the only output neuron of the cerebellar cortex—and candelabrum cells (a type of interneuron: Lainé and Axelrad 1994), as well as Bergmann glia—astrocytes that contribute to cerebellar information processing (De Zeeuw and Hoogland 2015). Finally, the molecular layer contains interneurons including stellate cells and basket cells (Fig. 1). Granule cells and UBCs are excitatory, whereas all the other types of neurons in the cerebellar cortex are thought to be inhibitory.

In terms of cerebellar output there are three major subdivisions of the CN located in each half of the cerebellum, from medial to lateral: the medial (fastigial), interpositus (anterior and posterior divisions), and lateral (dentate) nuclei, which receive topographically organized cortico-nuclear inputs from PCs in the overlying vermis, paravermis, and hemispheral cortex, respectively (Voogd 1967; Voogd and Glickstein 1998).

2.2 *Cerebellar Inputs*

Climbing fibers and mossy fibers form the two major synaptic inputs to the cerebellum and both are excitatory (glutamatergic). In addition, there are several, far less studied, neuromodulatory inputs that project with varying patterns and densities throughout the cerebellum.

2.2.1 Basic Anatomy of Climbing Fiber Projections and Olivo-Cortico-Nuclear Circuits

Climbing fibers originate from a single brainstem nucleus, the inferior olive, which in turn receives widespread inputs from the spinal cord, brainstem, CN, and higher centers including the motor cortex (Llinas et al. 2004). Climbing fibers make direct synaptic contact with cerebellar cortical PCs, and the physiological consequences of this intimate connectivity are discussed later in Sect. 3.1. Several climbing fibers originate from each inferior olive neuron (on average approximately seven per neuron in rats), but each PC is only innervated by a single climbing fiber in the adult rat (Sugihara et al. 1999). The stem axon of individual olive neurons therefore branches to provide climbing fiber input to multiple PCs that are arranged mainly in the rostrocaudal axis (Apps and Garwicz 2005). On their path to the cerebellar cortex, olivary axons also form collateral inputs onto CN neurons (Fig. 1), typically forming between one and six collaterals terminating in a particular nucleus (Sugihara et al. 1999).

Small populations of neurons located within different subnuclei of the inferior olive give rise to climbing fibers that target a specific rostrocaudally orientated "zone" of PCs in the cerebellar cortex (Fig. 2, Apps and Garwicz 2005). These zones can be identified both anatomically and physiologically, with each zone typically one to three millimeters in mediolateral width but extending for many millimeters in the rostrocaudal axis (Apps and Hawkes 2009). The PCs in each cortical zone provide a convergent cortico-nuclear inhibitory projection to neurons in a specific region of the CN, thereby forming multiple, olivo-cortico-nuclear connections termed "modules" (Fig. 2, Apps and Garwicz 2005; Apps and Hawkes 2009).

This modular organization extends to nucleo-olivary projections arising from the same region of CN that provides inhibitory feedback to the originating olivary subnucleus via GABAergic projections (Fig. 2). As a result, PCs can influence their own climbing fiber inputs by modulating the inferior olive neurons from which the climbing fibers arise, via CN neurons (as shown in paravermal regions by Chaumont et al. 2013). Individual cerebellar modules are thought to subserve different functions (Horn et al. 2010, although see Cerminara and Apps 2011). For example, the vermal A module is associated with head movements, balance, and postural control; the paravermal C modules are involved in limb movements, including grasping; and the lateral D2 module is involved in predicting target motion during visually guided movements (Fig. 2c; Cerminara and Apps 2011). It is important, however, to

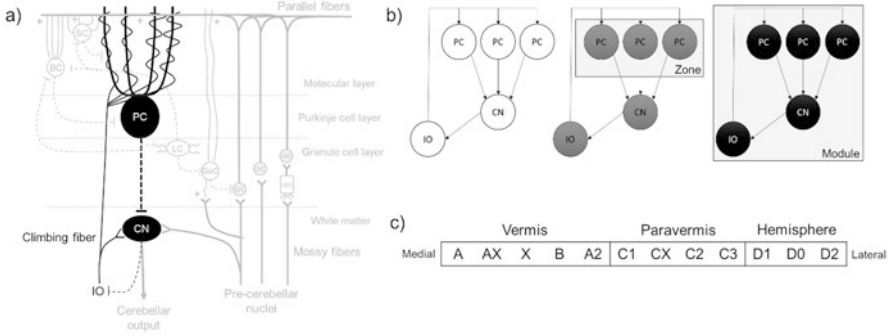

Fig. 2 Cerebellar zones and modules. (**a**) Olivo-cortico-nuclear circuit within the cerebellar circuitry (see Fig. 1 for abbreviations); (**b**) Purkinje cells (PCs) receiving common inferior olive (IO) climbing fiber inputs form a "zone," and these PCs together with their IO input and cerebellar nuclei (CN) output regions form a "module"; (**c**) Modules defined in rats in each half of the cerebellum from medial to lateral

emphasize that individual modules are not likely to be restricted to specific functions, not least because of the various interactions that can occur between them (see below).

The cortical component of some modules can be further divided into microzones that contain PCs with similar climbing fiber receptive fields (e.g., Andersson and Oscarsson 1978; Ekerot et al. 1991). Microzones and their microcomplex connections with the CN and inferior olive are thought to represent the basic functional units of the cerebellum (Apps and Hawkes 2009).

2.2.2 Basic Anatomy of Mossy Fiber Projections

In stark contrast to the climbing fiber system, mossy fibers arise from multiple brain nuclei distributed throughout the central nervous system, including all segmental levels of the spinal cord, numerous brainstem nuclei, but most notably the basilar pontine nuclei (which receive inputs primarily from the neocortex; Llinas et al. 2004). Mossy fibers branch widely in the cerebellar cortex, usually in the rostrocaudal dimension, and in the rat follow a similar pattern of termination as climbing fibers in the overlying molecular layer, although their organization is less precise (Voogd et al. 2003; Pijpers et al. 2006). This suggests that broadly speaking, mossy fiber termination patterns adhere to the modular organization of the olivo-cortico-nuclear system, and that these projections are targeted to certain functions rather than forming a diffuse, generalized input. However, given that mossy fibers have collaterals in the mediolateral plane they may be able to influence multiple modules (Shinoda et al. 1992; Wu et al. 1999), and mossy fiber projections may also vary within a given module as demonstrated in the C1 zone of the rat (Herrero et al. 2002, 2012).

Mossy fibers synapse onto granule cells in the granule cell layer and many also form excitatory collateral inputs to CN neurons on their route to the cortex (Fig. 1). Mossy fiber collaterals arising from a given axon may target different divisions of the CN, again suggesting that mossy fiber inputs are not universally aligned with climbing fiber inputs to the cerebellum (Wu et al. 1999). Granule cell axons bifurcate to form parallel fibers that contact many PCs in the long axis of individual cerebellar folia and so multiple cerebellar modules can be connected via common parallel fiber inputs (Valera et al. 2016; Binda et al. 2016).

A subset of mossy fibers (approximately 5% in cat) arise from the CN and provide a nucleo-cortical feedback projection to the cerebellar cortex, targeting the granule cell layer (Houck and Person 2014). While some of these neurons target areas of the cerebellar cortex that provide reciprocal PC cortico-nuclear projections, others target regions of the cortex from which they receive no input, thereby forming an additional route for modules to interconnect (Trott et al. 1998a, b). In mice, a proportion of the nucleo-cortical connections arise from collaterals of the large glutamatergic projection neurons in the CN (Houck and Person 2015) and are thought to act as an internal amplification system to assist associative learning (Gao et al. 2016). In addition, a subpopulation of nucleo-cortical neurons, also described in mice, are inhibitory and target Golgi cells in the granule cell layer, thereby allowing disinhibition of cerebellar cortical circuits (Ankri et al. 2015).

2.2.3 Neuromodulatory Inputs

As well as climbing fiber and mossy fiber glutamatergic inputs, neuromodulatory afferents targeting the cerebellum release either serotonin, noradrenaline, acetylcholine, dopamine, or histamine (Schweighofer et al. 2004). These inputs differ in their pattern of termination and are not uniformly distributed throughout the cerebellum. Far less is known about their physiology but they may have roles in regulating cerebellar development (Oostland and van Hooft 2013), synaptic transmission and plasticity (Lippiello et al. 2015), and modifying cerebellar activity throughout different stages of the sleep–wake cycle (Brown et al. 2001; Jaarsma et al. 1997).

2.3 Non-uniformity in Cerebellar Anatomy

The preceding sections outline the classical, orderly microcircuit organization of the cerebellum, characterized by olivo-cortico-nuclear loops. However, it is becoming increasingly clear that there are also important regional variations in anatomy that confer differences in physiological properties. In particular, it has long been known that a variety of molecular markers are differentially expressed throughout the cerebellar cortex, providing anatomical and physiological subdivisions. Most notable among these markers is zebrin II (also known as aldolase C), which in some regions of the cerebellar cortex is expressed in subsets of PCs forming a highly

characteristic and reproducible pattern of stripes, with alternating positive and negative rostrocaudally oriented bands of expression.

Zebrin II colocalizes with several other markers, such as phospholipase Cβ3, excitatory amino acid transporter 4 (EAAT4), and metabotropic glutamate receptor 1a (mGluR1a), while some markers are present only in zebrin II-negative PCs, such as phospholipase Cβ4. This pattern of protein distribution appears to be present in the cerebellum of all birds and mammals, including humans, and in some regions of the cerebellar cortex has been found to correspond to the organization of both mossy fiber and climbing fiber inputs (Apps and Hawkes 2009). This relationship between molecular signature and anatomical circuits extends to PC cortico-nuclear projections, suggesting a common spatial organization of cerebellar cortical inputs, PC phenotype, and cortico-nuclear outputs (Apps and Hawkes 2009).

Another important example of non-uniformity is the distribution of UBC cerebellar cortical interneurons. These are glutamatergic, located in the granule cell layer (Fig. 1), and are found mainly in the vermis and flocculonodular lobe where they provide feedforward amplification of cerebellar inputs. Since these regions of the cerebellum are known to be involved in the regulation of body, head, and eye position, UBCs are thought to serve a specific cellular function within these cerebellar regions relating to these behaviors (Mugnaini et al. 2011). In mice, PC collaterals to UBCs preferentially inhibit UBCs expressing metabotropic glutamate receptor 1 (mGluR1), adding an extra level of heterogeneity even within regions containing UBCs (Guo et al. 2021).

3 Cellular Physiology

3.1 Cortical Circuits

3.1.1 Inputs to the Granule Cell Layer

Granule cells account for over half of all neurons in the human brain (Herculano-Houzel 2010). Their primary input is from mossy fibers, which terminate in structures called glomeruli, with an average of four glutamatergic mossy fiber inputs to each granule cell (Eccles et al. 1967). The structure of a glomerulus allows glutamate released from one mossy fiber terminal to spillover onto neighboring granule cell dendrites within the glomerulus, which may improve efficacy of neurotransmission (DiGregorio et al. 2002). Transmission at mossy fiber–granule cell synapses is thought to be highly secure, with stimulation of a single mossy fiber at high frequencies evoking granule cell firing in vivo (Rancz et al. 2007). Other studies, however, suggest that synchronous input from multiple mossy fibers is required to evoke granule cell firing, and that subthreshold signals are filtered out (Jörntell and Ekerot 2006). These differences in synaptic efficacy may be the result of a number of possibilities, including regional variations (see Sect. 2.3) and the nature of the inputs being encoded.

Mossy fibers transmit sensorimotor, proprioceptive, and contextual information, with inputs from different body parts represented in different cerebellar regions in line with the somatotopic organization of the cerebellum (see Sect. 4.1; Arenz et al. 2009). Granule cells may receive input from multiple modalities; for example vestibular, visual, and eye-movement-related signals converge on individual granule cells in the flocculus of mice (Arenz et al. 2008). This means that granule cells transmit distinct outputs that depend on the specific combination of inputs they receive rather than acting as a simple relay, thereby enriching sensory representations for further cerebellar processing (Chabrol et al. 2015). The granule cell layer is thought to facilitate pattern separation through the connections of single mossy fibers to many granule cells, and their output is passed to PCs via parallel fibers (granule cell axons).

Granule cells have also been shown to encode non-sensorimotor, predictive information. They are able to encode the expectation of reward (Wagner et al. 2017), and also encode an acquired conditional response following eyeblink conditioning training (Giovannucci et al. 2017). This suggests that prediction is apparent even at the input stages of information processing within the cerebellar cortex.

Golgi cells, found in the granule cell layer, provide inhibition to granule cells and receive excitatory input from both mossy fibers and parallel fibers (Fig. 1). Golgi cells therefore provide both feedforward inhibition (as a result of their mossy fiber inputs) and feedback inhibition (via granule cell axon and parallel fiber inputs) to their target granule cells (D'Angelo 2008).

3.1.2 Parallel Fiber Inputs to the Molecular Layer

Granule cell axons bifurcate to form parallel fibers that extend along the molecular layer (Fig. 1, Sect. 2.2.2). Parallel fibers are slowly conducting but evoke rapid excitatory responses in all neurons in the molecular layer, including PCs, molecular layer interneurons (MLIs), and the dendrites of Golgi cells (Jirenhed et al. 2013). Owing to the large number of granule cells, each PC is estimated to be contacted by around 150,000 parallel fiber synapses (Zang and De Schutter 2019), although many of these may be functionally weak or silent (Isope and Barbour 2002). The parallel fiber–PC synapse is an important site of plasticity, which is discussed further in Sect. 3.4.1.

Parallel fiber inputs to MLIs provide feedforward inhibition onto PCs, which can modulate the efficacy of parallel fiber inputs (Binda et al. 2016). Maintenance of the excitatory–inhibitory balance of PC inputs is important for cerebellar functioning, given silencing MLIs' changed firing patterns of PCs, increasing simple spike rate and regularity, and impaired locomotor behavior (Jelitai et al. 2016). Basket cells and stellate cells are both subtypes of MLIs, and they may have different impacts on PC signaling. Removing GABAergic transmission from basket cells of behaving mice was shown to increase simple spike rate in PCs while decreasing complex spike rate; the same manipulation in stellate cells increased the regularity of simple spikes and increased complex spike rate (Brown et al. 2019). Therefore, MLI subtypes are likely to have different roles in cerebellar information processing.

3.1.3 Purkinje Cell Simple Spikes and Complex Spikes

Climbing fibers provide an incredibly powerful excitatory synaptic input to PCs and as a result generate unique action potentials known as complex spikes (Fig. 3; Eccles et al. 1966; Thach 1967). While the simple spikes generated by a PC resemble typical action potentials (duration one to two milliseconds), complex spikes generated by the same PCs are longer in duration (approximately 10 milliseconds on average) and consist of an initial large sodium-dependent component followed by a variable number of smaller, calcium-dependent components known as spikelets (Fig. 3; Eccles et al. 1966). Simple spikes are generated both intrinsically and as a result of mossy fiber–parallel fiber inputs, and occur at a wide range of firing frequencies, ranging from 19 to 95 Hz in vivo (mean 44 Hz; Armstrong and Rawson 1979) and 1 to 148 Hz (mean 38.8 ± 2.4 Hz) in vitro, even in the absence of synaptic inputs (Hausser and Clark 1997).

By contrast, complex spikes arise solely as the result of climbing fiber input. They occur at approximately 1 Hz in the awake animal, and their occurrence causes a subsequent pause in simple spike firing, the duration of which may relate to the number of spikelets in the complex spike (Fig. 3; Burroughs et al. 2017). The secondary components of a complex spike can reach frequencies of 500–600 Hz (Campbell and Hesslow 1986) and vary considerably in number, but typically each complex spike has three or four spikelets (Burroughs et al. 2017). MLIs, which form inhibitory connections with PCs (Fig. 1), have been shown in rat cerebellar slices to

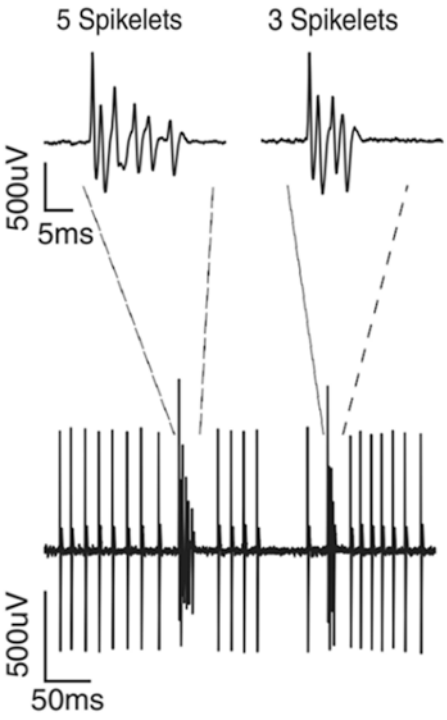

Fig. 3 An example extracellular recording from a single Purkinje cell showing complex spikes and simple spikes. The number of spikelets within a complex spike is variable, as shown in the insets. (Modified from Burroughs et al. 2017)

also receive inputs from climbing fibers as a result of glutamate spillover (Szapiro and Barbour 2007), so as well as providing direct excitatory inputs to PCs, climbing fiber inputs may also produce feedforward inhibition.

Inferior olive neurons, the origin of climbing fibers, are electrotonically coupled via gap junctions that synchronize their activity (Leznik and Llinás 2005). Synchronous activation of climbing fibers is thought to be important for the initiation and coordination of movement in mice (Hoogland et al. 2015), and greater complex spike synchrony increases the amplitude of complex spike-induced short-latency inhibitory and long-latency excitatory responses in CN neurons of anesthetized rats (Tang et al. 2019). Coupled PCs, as determined by correlations in complex spike occurrence, also have increased likelihood of simple spike synchrony (Wise et al. 2010). In addition, the number of spikelets in a complex spike correlates with synchronization (Lang et al. 2014), and the variability in spikelet number suggests that complex spikes are not an "all-or-nothing" event but instead convey information (Zang and De Schutter 2019). Thus, the complex spike activity of PCs, particularly when synchronized, can result either directly or indirectly in changes in cerebellar output, which in turn has the potential to influence behavior. The role of complex spikes and simple spikes in behavior is further discussed in Sect. 5.3.4.

3.1.4 Purkinje Cell Targets Within the Cerebellar Cortex

In mice, PCs have been found to directly inhibit other cell types in the cerebellar cortex via axon collaterals in the parasagittal plane, including neighboring PCs, MLIs, and Lugaro cells (Witter et al. 2016), thereby regulating their own inputs. In terms of cerebellar cortical non-uniformity, there may also be regional differences in how PCs regulate their own feedback. For example, PC axon collaterals directly inhibit granule cells in localized regions of the cerebellum related to eye movements and vestibular processing (lobule X, ventral paraflocculus, and flocculus; Guo et al. 2016). As well as these local synaptic connections, studies in mice have also shown that climbing fiber synapses to one PC can generate large negative extracellular signals that suppress simple spikes in neighboring PCs via ephaptic coupling (Han et al. 2020). This means that a single climbing fiber may in fact influence multiple local PCs, which may, in turn, promote firing of cerebellar output neurons due to synchronous disinhibition.

Connections between cells of the same type are a common feature in the cerebellum. As well as PCs targeting other PCs as described above, the same principle also holds true for cerebellar cortical interneurons. MLIs and Golgi cells are connected to the same cell type by both electrical (gap junction) and chemical (GABAergic) synapses (Mann-Metzer and Yarom 1999; Rieubland et al. 2014)—the former promoting synchronization in Golgi cells (Dugué et al. 2009). The extent to which this reciprocity is important for cerebellar function requires further investigation.

3.2 Purkinje Cell Control of Cerebellar Nuclei

PCs are the sole output of the cerebellar cortex, projecting to either the CN or vestibular nuclei, and are therefore central to cerebellar information processing. They are inhibitory, using GABA as a neurotransmitter, and form the main synaptic input to CN neurons with approximately 60% of synaptic boutons in the CN arising from PC axons (Ito 1984). Other synaptic inputs to CN are mainly from glutamatergic climbing fiber and mossy fiber collaterals (Fig. 1). In mice, excitatory climbing fiber collateral inputs to CN neurons resulting from olivary stimulation have been shown to be overridden by climbing fiber-induced inhibition via the PC pathway (Lu et al. 2016), suggesting that PC inhibition is the dominant CN input.

PC complex spikes in vivo have been shown to exert a strong and long-lasting inhibitory effect on activity in some CN neurons, although in others there is an excitatory–inhibitory sequence. Andersson and Oscarsson (1978), who first identified microzones in the B zone of the cat cerebellum, showed that lateral vestibular nuclear neurons were activated by collaterals of climbing fibers projecting to PCs providing inhibition to the same group of neurons. Therefore the same climbing fiber axons can produce excitation of CN neurons via direct collateral inputs followed by indirect inhibition via PC inputs (Blenkinsop and Lang 2011).

In young rat cerebellar slice preparations, hyperpolarizing currents (mimicking PC inhibition) are able to reduce spontaneous activity of CN neurons and subsequently elicit a rebound depolarization (Aizenman and Linden 1999). In mice this depolarization is thought to underlie rebound increases in CN firing rate that occur in vivo following trains of stimuli delivered to the cerebellar cortex or the inferior olive (Hoebeek et al. 2010). Similarly, in cat, synchronous climbing fiber activation evoked by electrically stimulating the peripheral receptive field results in substantial inhibition of CN neurons followed in some cases by rebound responses, suggesting this may be an important feature of the olivo-cortico-nuclear system (Bengtsson et al. 2011). However, it remains a matter of debate whether rebound firing occurs under physiological conditions because it has been less reliably observed in vivo as compared to in vitro investigations, and often involves non-physiological patterns of stimulation (Alvina et al. 2008; Witter et al. 2013).

Other studies argue that asynchronous PC inputs suppress CN firing while synchronous activity can entrain nuclear firing to PC inputs (Person and Raman 2012a, b), with single stimuli to the cerebellar cortex in rodents evoking precisely timed action potentials without changing firing rate (Hoebeek et al. 2010). The net effect of PC inhibition on individual CN neurons therefore likely depends on the degree of PC synchrony together with the level of PC–CN convergence (Tang et al. 2016). Further study is required to clarify how these factors contribute to cerebellar functions, and to determine if the mechanisms of PC to CN signaling are consistent throughout the cerebellum.

The nature of PC influence on the CN is also complicated by the presence of multiple cell types within the CN, including: (1) large glutamatergic neurons projecting to extracerebellar targets to provide powerful and short-latency excitatory

connectivity, notably with the thalamus and red nucleus, to influence motor and premotor areas; (2) small GABAergic projection neurons, which are the origin of the topographically organized nucleo-olivary inhibitory projection mentioned above (Uusisaari and Knopfel 2011); (3) glycinergic premotor output neurons in the medial nucleus (Bagnall et al. 2009); (4) inhibitory projection neurons of the interpositus nucleus, which have been recently described in mice, with inputs to regions including the pontine nuclei, medullary reticular nuclei, and sensory brainstem structures, such as the external cuneate nucleus, cuneate nucleus, parabrachial nuclei, and vestibular nuclei (Judd et al. 2021); (5) a heterogeneous population of local interneurons including an inhibitory population with a mixed GABAergic and glycinergic phenotype (Husson et al. 2014), and a non-GABAergic (putatively glutamatergic) population (Uusisaari and Knopfel 2012); and (6) nucleo-cortical neurons, which project to the cerebellar cortex and can be inhibitory or excitatory as outlined in Sect. 2.2.2 (Ankri et al. 2015; Houck and Person 2014).

There is evidence that the effects of PC inhibition on CN neurons may depend on cell type. In vivo recordings in mice suggest that glutamatergic cells of the medial nucleus respond to the rate and timing of PC inputs, with synchronous PC activation entraining CN neuron activity, whereas GABAergic neurons respond to mean population firing rates and may therefore encode PC inhibition differently (Özcan et al. 2020). A key outstanding question is how different cell types across the nuclei respond to their synaptic inputs, and how they interact with one another to shape CN output.

3.3 Zebrin Stripes

Several important physiological differences have been found in vivo in rodents between zebrin II positive (Z+) and negative (Z–) PCs (see Sect. 2.3). Firstly, simple spike firing rates are higher on average in Z– PCs than Z+ PCs (Zhou et al. 2014; Xiao et al. 2014). Secondly, the climbing fiber-evoked pause in simple spike firing is shorter in duration in Z– PCs (Xiao et al. 2014). And thirdly, the regularity of simple spike firing rates is greater in Z– PCs (Zhou et al. 2014; Xiao et al. 2014). These systematic differences in simple spike activity are thought to be due to the presence of the transient receptor potential cation channel C3 (TRPC3) in Z– PCs, since blocking these channels pharmacologically reduces simple spike firing rates in Z– but not Z+ PCs (Wu et al. 2019). Mice with loss of TRPC3 function show impaired eyeblink conditioning, a form of cerebellar learning that occurs in cerebellar cortical regions associated with Z– PCs, whereas compensatory eye movement adaptation, related to Z+ regions, remains intact (Wu et al. 2019). This suggests important differences in function of Z+ and Z– PCs, reinforcing the notion that cerebellar cortical physiology is not uniform.

Complex spike firing rates are also higher on average in Z– PCs than in Z+ PCs. Moreover, complex spikes have a longer half-width, implying a larger number of spikelets, and larger spike area in Z+ PCs (Zhou et al. 2014). Z+ PCs in vitro display

prolonged excitation following climbing fiber activation due to terminals in Z+ regions having larger pools of release-ready vesicles and enhanced multi-vesicular release, thus triggering longer-duration complex spikes with a greater number of spikelets (Paukert et al. 2010). However, the same phenomenon was not observed in vivo with Z+ and Z– PCs having similar distributions of spikelet number (Tang et al. 2017). Z+ PCs also show a greater variety of simple spike responses following a complex spike (Zhou et al. 2014), which may be related to differences in mossy fiber–granule cell–parallel fiber inputs, MLI inputs, and/or differences in PC intrinsic excitability.

The systematic differences in zebrin expression in the cerebellar cortex are also retained in some regions of the CN. The lateral, posterior interpositus and caudal medial nuclei contain terminals of Z+ PCs, whereas the anterior interpositus and rostral medial nucleus receive Z– PC terminations (Sugihara 2011). It might be expected that by comparison to Z+ PCs, Z– PCs cause more inhibition in their target CN neurons due to their higher firing rates and therefore Z– PC targets would have lower firing rates; however, recent research suggests the opposite. In awake adult mice, firing rates are consistently lower in CN neurons receiving input from Z+ PCs than those with input from Z– PCs (Beekhof et al. 2021). Identifying the reason(s) for this difference could enhance our understanding of how information is processed in cerebellar modules related to different behaviors.

In addition to Z+ and Z– PCs having distinct physiology, there is also evidence that zebrin stripes can act together in functional pairs; in the pigeon vestibulocerebellum, pairs of Z+ and Z– bands form functional units in relation to patterns of optic flow, e.g., self-rotation about the vertical axis (Graham and Wylie 2012). It remains to be determined exactly how zebrin II-related differences in physiology relate to differences in output, and ultimately function, throughout the cerebellum.

3.4 Synaptic Plasticity

3.4.1 Parallel Fiber–Purkinje Cell Synaptic Plasticity

Plasticity in the cerebellum was first studied at the parallel fiber–PC synapse, where long-term depression (LTD) was found to be induced by paired stimulation of parallel fibers and climbing fibers in vitro (Marr 1969; Albus 1971; Ito and Kano 1982). Ito et al. (1982) showed that LTD at this synapse could be induced in vivo by coincident stimulation of the sources of mossy fibers and climbing fibers, the vestibular nerve and inferior olive respectively, to the flocculus in decerebrate rabbits.

The mechanisms of LTD are described in detail in a review by Hoxha et al. (2016). In brief, parallel fiber–PC LTD requires postsynaptic calcium influx resulting from climbing fiber input together with intracellular release of calcium resulting from activation of mGluR1 by glutamate released from parallel fibers (which also activates AMPA receptors). The increase in intracellular calcium leads, via a biochemical cascade involving protein kinase C, in the endocytosis of postsynaptic AMPA recptors in PCs. This renders the PC less responsive to parallel fiber inputs.

Long-term potentiation (LTP) can also be induced at this synapse by stimulation of parallel fibers alone, typically at 1 Hz, which leads to insertion of AMPA receptors into the postsynaptic membrane (Salin et al. 1996; Lev-Ram et al. 2002). This type of stimulation results in relatively low levels of intracellular calcium compared to the LTD protocol described above, promoting activation of protein phosphatases and binding of N-ethylmaleimide-sensitive factor to AMPA receptors, leading to the stabilization of these receptors in the postsynaptic membrane (Hoxha et al. 2016). In fact, both LTD and LTP can occur at most synapses within the cerebellum through a variety of mechanisms (for reviews, see Mapelli et al. 2015; Gao et al. 2012).

Parallel fiber–PC synaptic transmission is dysfunctional in rodent models of spinocerebellar ataxia, for example because of abnormal regulation of mGluR1 (SCA1, SCA5) or deficient release of glutamate from parallel fibers (SCA27, Hoxha et al. 2016). Physiological functioning of this synapse is therefore central to normal cerebellar function and genetic causes of ataxia may lead to its dysregulation. The roles of parallel fiber–PC plasticity in behavior are further explored in Sect. 5.3.1.

3.4.2 Zebrin II and Synaptic Plasticity

LTD is thought to be the predominant form of parallel fiber–PC plasticity in regions of cortex containing Z– PCs because of their relatively high baseline firing rate, while for Z+ PCs their lower firing rate predisposes them to LTP (De Zeeuw and Ten Brinke 2015; De Zeeuw 2021). Zebrin II colocalizes with EAAT4, a transporter that limits the duration of action of glutamate at the synapse, and this reduction of glutamate prevents LTD by reducing activation of metabotropic glutamate receptors. Consistent with this transmitter regulation, studies in rat cerebellar slices, in which parallel fiber stimulation was paired with PC depolarization, induced LTD of parallel fiber inputs to Z– PCs (in lobule III), but under the same conditions did not elicit plasticity at parallel fiber inputs to Z+ PCs (in lobule X; Wadiche and Jahr 2005). EAAT4 is also likely to influence other cerebellar cortical signaling, as it regulates glutamate spillover from climbing fibers to MLIs (Malhotra et al. 2021). Such findings therefore strongly suggest that the same synaptic transmission and plasticity rules are not likely to apply to the cerebellum as a whole.

3.4.3 Plasticity at Cerebellar Nuclei Synapses

Studies in mice in vitro have shown that LTP can be induced at the mossy fiber–CN synapse by high-frequency stimulation of mossy fibers combined with hyperpolarization of the postsynaptic CN neuron, which in turn leads to rebound firing (Person and Raman 2010; Pugh and Raman 2006). By contrast, LTD can be induced at the same synapse via high-frequency stimulation either with or without depolarization of the postsynaptic CN neuron (Zhang and Linden 2006). LTP (Ouardouz and Sastry 2000) and LTD (Morishita and Sastry 1996) can also be induced at PC inputs to CN neurons. Indeed, one study has shown that a particular burst protocol can

induce both LTP and LTD at PC synapses onto CN neurons in rat cerebellar slices, depending upon the level of postsynaptic excitation (Aizenman et al. 1998). The direction of plasticity (LTP versus LTD) depends on the state of the postsynaptic CN neuron, which suggests that the level of inhibition from PCs (and potentially local interneurons) regulates plasticity of excitatory synapses to CN neurons. Such an arrangement could be a homeostatic mechanism to maintain synaptic strength within an operational range.

As both LTP and LTD can occur at various nodes within the cerebellar circuitry, this creates a high level of complexity that goes beyond the classical view of LTD at the parallel fiber–PC synapse being the key mechanism of cerebellar synaptic plasticity (for more detail, see Sect. 5.3.1). The balance of increases and decreases in plasticity, which lead to changes in cerebellar output, depends upon the timing of synaptic inputs, the state of excitability of the neurons, and the cerebellar region of interest. Little is known about how different forms of plasticity interact with one another to influence cerebellar information processing.

4 Systems Physiology

4.1 Somatotopic Organization

Central to cerebellar function, particularly for its contributions to motor control, is how the cerebellum receives sensory inputs from the body and sense organs. The first systematic report of a somatotopic organization in the cerebellum was by Snider and Stowell (1944) who recorded, in the anesthetized cat and monkey, field potentials on the cerebellar surface evoked by peripheral tactile stimulation, and observed responses in discrete regions of the cerebellar cortex that were organized in a similar pattern in both species—one map in the anterior lobe and two more in the posterior lobe of the cerebellum. A similar somatotopic organization has subsequently been described in a range of other species, notably the rat (Atkins and Apps 1997; Jörntell et al. 2000), and fine-resolution mapping has shown that this somatotopy corresponds to cerebellar cortical zones (Sect. 2.2.1). More recently, non-invasive functional magnetic resonance imaging (fMRI) has shown, albeit at a coarser level of spatial resolution, that the same general somatotopic arrangement is also present in the human cerebellum (Fig. 4, Grodd et al. 2001; Ashida et al. 2019; Boillat et al. 2020).

A basic somatotopy also exists within the CN, and therefore in the cerebellar output. For example, in cats and monkeys the fore- and hindlimbs are represented in posterior and anterior regions, respectively, of the anterior interpositus (van Kan et al. 1993; Garwicz and Ekerot 1994), while in dentate both face and eyes are represented (van Kan et al. 1993). However, in other CN regions a somatotopy is not evident. For example, in the posterior interpositus in monkeys there is no clear separation between representation of the fore- and hindlimbs (van Kan et al. 1993).

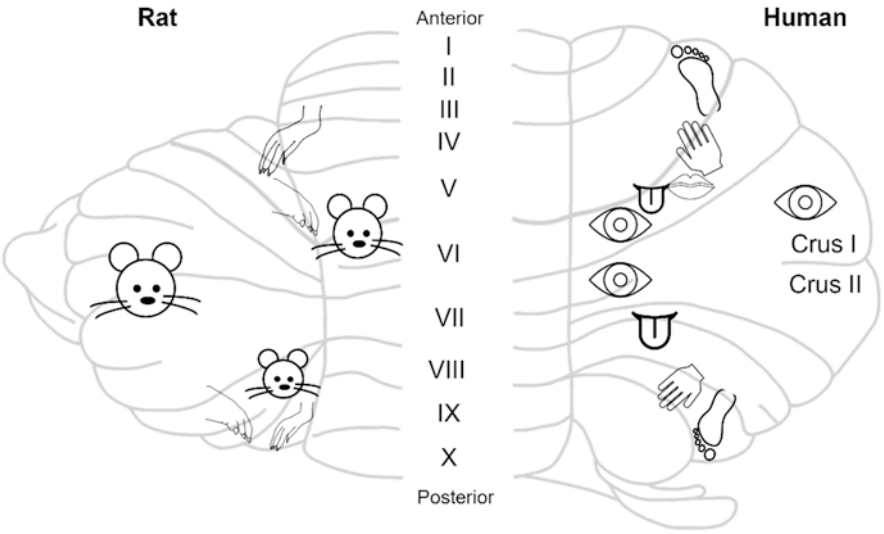

Fig. 4 Somatotopic organization in a dorsal view of the rat and human cerebellar cortex. Left shows approximate locations of representations of the hindlimb, forelimb, and face in the rat based on works by Atkins and Apps et al. (1997), Jörntell et al. (2000), and Bosman et al. (2010), determined by electrophysiological responses to peripheral stimulation. Right shows approximate representations of the foot/toes, hand/digits, tongue, eyes, and lips as described by Boillat et al. (2020) and Grodd et al. (2001), determined using fMRI in participants voluntarily moving specified body parts

The somatotopy within the CN has been studied in most detail in the anterior interpositus in the cat and a finer map of the ipsilateral forelimb is present that relates to the olivo-cortico-nuclear projections of the paravermal C1, C3, and Y modules (Garwicz and Ekerot 1994). Ekerot et al. (1995) found that microstimulation of these different CN regions in cat elicited different patterns of multi-segmental ipsilateral forelimb movement. This suggests that, at least for paravermal regions, the cerebellar control of movements is organized in a modular framework. Consistent with this possibility, recent research in mice has shown that a small area in the rostral part of the anterior interpositus controls motor synergies that protect the eye during eyeblink conditioning by coordinating the eyelid, neck, and forelimb muscles, and that individual CN neurons encode information related to all these effectors (Heiney et al. 2021). This provides support to the general concept that cerebellar maps are related more to actions of different body parts rather than being strictly somatosensory (Apps and Garwicz 2005).

As outlined above (Sect. 2.2.2), anatomical studies have provided evidence that mossy fibers generally align with the climbing fiber organization in the cerebellum. However, detailed electrophysiological mapping of multiunit granule cell activity driven by mossy fiber inputs in anesthetized rats has also revealed a “fractured somatotopy” of tactile responses whereby different body parts are represented in a patchy mosaic pattern in the hemispheres of the cerebellar cortex (Shambes et al. 1978; Kassel et al. 1984; Apps and Hawkes 2009). The apparent discrepancy

between a fractured and a more systematic somatotopic arrangement could be the result of several possibilities including regional differences in cerebellar physiology (paravermal versus hemispheral cortex), and the extent to which local granule cells have their main influence on overlying PCs or on PCs in other regions of cortex via their parallel fibers. Further studies are required to investigate these and other possibilities.

In summary, the somatotopic organization of inputs to and outputs from the cerebellum suggests that the physiological organization of cerebellar connectivity is highly conserved across species, and that output of different cerebellar regions is likely to subserve control of coordinated movements that may involve a combination of different body parts. However, the way CN interact with the rest of the central nervous system to coordinate complex movements remains poorly understood.

4.2 Physiologically Defined Olivocerebellar Pathways

Electrophysiological studies have revealed a complex array of spino-olivocerebellar pathways (SOCPs, Fig. 5) that transmit information from skin, muscle, and joints to the inferior olive, which in turn forward this information to the cerebellum via climbing fibers (Oscarsson 1980; Ito 1984). Transmission in SOCPs can be recorded as evoked climbing fiber field potentials in the cerebellum, and combined electrophysiological mapping and anatomical tract tracing experiments have shown that cerebellar cortical zones defined by their SOCP input and those defined anatomically by their olivo-cortico-nuclear connectivity are largely congruent (e.g., Trott and Armstrong 1987a, b; Trott and Apps 1991, 1993; Edge et al. 2003).

A similar arrangement occurs for descending inputs from the cerebral cortex, which collectively are termed cerebro-olivocerebellar pathways (COCPs, Fig. 5). COCPs originate in many regions of the cerebral cortex and project to the inferior olive via the mesodiencephalic junction (Wang et al. 2022). COCPs also conform to the zonal organization of the cerebellum; they converge on the same olivary regions that supply climbing fibers to the cortical zones defined by the SOCPs (Andersson and Nyquist 1983). For example, stimulation of the ipsilateral forelimb and the somatotopically corresponding region of the contralateral motor cortex results in convergent cerebellar climbing fiber responses in the forelimb-receiving part of the C1 zone in the rat (Ackerley et al. 2006).

The source of climbing fibers, the inferior olive, receives a variety of sensory and motor inputs from regions including the trigeminal nuclei, dorsal column nuclei, red nuclei, cerebral cortex (via the mesodiencaphalic junction, as described above), CN, and spinal cord (De Gruijl et al. 2013). This convergence of inputs, together with the fact that COCPs conform to the zonal organization of the olivocerebellar system, reinforces the close relationship between ascending and descending pathways to the cerebellum and highlights the potential role of the inferior olive as a comparator of these two sources of information (Oscarsson 1980; for further discussion, see Sect. 6).

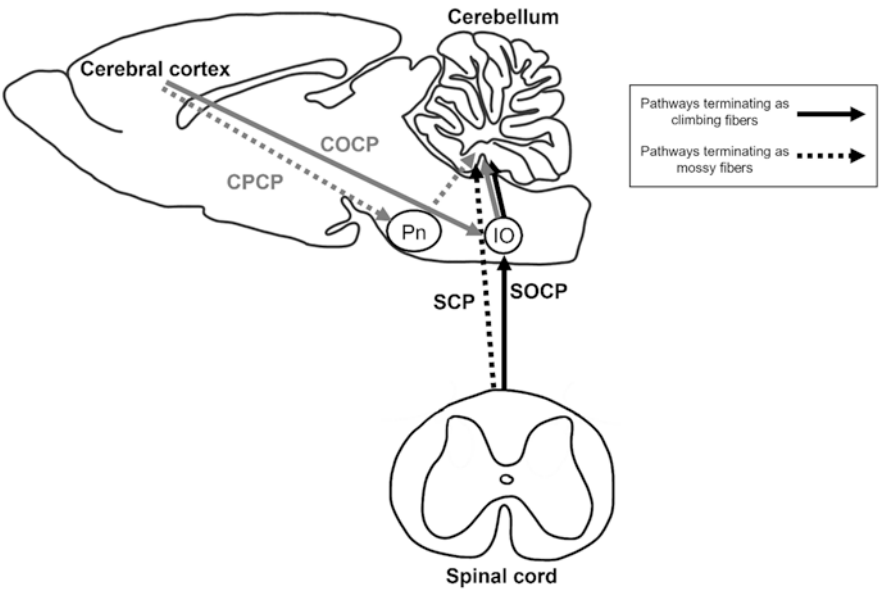

Fig. 5 Simplified diagram of cerebellar input pathways as depicted on a rat brain and spinal cord. Spino-olivocerebellar pathways (SOCPs) carry information from the spinal cord to the inferior olive (IO), which send climbing fiber inputs to the cerebellum. These ascending pathways include both direct spino-olivary projections and indirect pathways via various brainstem relays including the dorsal column nuclei. Cerebro-olivocerebellar pathways (COCPs) also provide climbing fiber input to the cerebellum via the inferior olive but originate in the cerebral cortex and include descending pathways that relay in a range of brainstem nuclei including the midbrain tectum. Mossy fibers include both direct and indirect projections from the spinal cord (spinocerebellar pathway, SCP), and indirect projections from the cerebro-pontocerebellar pathway (CPCP)

The flow of information via SOCPs and COCPs is modulated during active movements. In particular, a series of studies in awake behaving cats has shown that separate modulatory drives act on the climbing fiber pathways that target the paravermal zones (Apps et al. 1990, 1995, 1997; Lidierth and Apps 1990; Apps and Lee 1999; Pardoe et al. 2004). For example, low-intensity electrical stimulation of the ipsilateral superficial radial nerve in cats evokes SOCP-mediated field potentials in the cerebellar cortex, which vary systematically in size throughout the step cycle. By comparison to rest, responses recorded in the C2 zone were usually smallest (implying reduced SOCP transmission) in the swing phase of the step cycle in the ipsilateral forelimb (Apps et al. 1990). In contrast, in the neighboring C1 zone, the smallest responses consistently occurred during the stance phase in the ipsilateral forelimb (Lidierth and Apps 1990). Such differences suggest functional variations between zones, and it is thought that the gating of sensory inputs serves to prevent the transmission of self-generated, predictable signals in a task-dependent manner (Lawrenson et al. 2016).

4.3 Spinocerebellar Mossy Fibers

Cerebellar mossy fibers arise via multiple pathways including spinocerebellar, cuneocerebellar, reticulocerebellar, and cortico-pontocerebellar tracts (Fig. 5). Spinocerebellar pathways provide proprioceptive information from skin, muscle, and joints to the cerebellum (Bloedel and Burton 1970; Snyder et al. 1978), but may encode information about movement of a body region, e.g., a whole limb rather than individual joints or muscles (Bosco and Poppele 2001). The importance of these pathways is emphasized by the fact that they include some of the fastest conducting axons in the central nervous system, with degeneration of spinocerebellar tracts resulting in profound disorders to movement control, characterized by Friedreich's ataxia.

4.4 Cerebro-Cerebellar Pathways

The cerebellum receives substantial inputs from the cerebral cortex mainly via pontine nuclei (cerebro-pontocerebellar pathways; Fig. 5) and the inferior olive (COCPs). The cerebellum also sends projections to the cerebral cortex, predominantly via the thalamus, and these reciprocal cerebro-cerebellar connections likely contribute to the variety of cerebellar functions that extend beyond the motor domain (Strick et al. 2009). Recent evidence for reciprocal cerebro-cerebellar interactions has found, for example, that neurons in the CN display preparatory ramping activity related to planning future movement when holding a short-term memory, or anticipating a reward, as is known to occur in the frontal cortex (Gao et al. 2018; Chabrol et al. 2019). Inactivating the cerebellar fastigial nuclei (Gao et al. 2018) or lateral nuclei (Chabrol et al. 2019) disrupts preparatory activity in the frontal cortex, and inactivating the frontal cortex abolishes preparatory activity in the CN. Such findings therefore point to cerebro-cerebellar communication being important for anticipating and planning future actions.

An increasing number of studies have studied neural oscillations in cerebro-cerebellar circuits. Oscillations are rhythmic patterns of synchronous neural activity that can occur within local circuits and also between distant brain regions. They are thought to be important for input selection, plasticity, and communication between brain regions (Buzsáki and Draguhn 2004; Fries 2015). In the cerebellum oscillations occur at a wide range of frequencies (De Zeeuw et al. 2008), although their functional significance remains far from being clear. However, during whisking in rats, inactivation of the rat cerebellum disrupts coherent neural oscillations between the sensory and motor cortices (Popa et al. 2013). This raises the interesting possibility that the cerebellum may modulate cerebral processing by coordinating communication between cerebral regions. Clearly, however, much remains to be done to gain a full understanding of the functional significance of oscillatory activity within cerebro-cerebellar circuits.

5 Behavioral Physiology

5.1 Limb Control

5.1.1 Locomotion

The cerebellum is involved in the control of locomotion, and accordingly cerebellar damage can result in ataxia (Morton and Bastian 2004). Studies of cerebellar neuronal activity during locomotion, mainly in cats during treadmill or horizontal ladder walking, have found that PCs discharge simple spikes rhythmically in a manner that is time locked to the step cycle. Typically, PCs have one period of increased simple spike discharge per step, but some may have two or three peaks (Armstrong and Edgley 1984b), and the timing of discharge differs between cerebellar cortical regions.

In the vermal B zone in decerebrate cats, Udo et al. (1981) reported two profiles of PC simple spike discharge—one population of PCs had a peak of activity in the late swing or early stance phase of the step cycle of the ipsilateral forelimb, and a second population had two peaks: one during late swing, the other during late stance/early swing. The pattern of activity during late swing may relate to the preparation of limb touchdown, consistent with vermal regions of the cerebellum being involved in maintenance of stance and balance (Morton and Bastian 2004). Moreover, while the pattern of complex spike activity in B zone PCs in awake cats occurs without any clear relationship to the step cycle, an increase in probability occurs following a perturbation, as has been shown following an unexpected rung drop during horizontal ladder walking (Andersson and Armstrong 1987). This suggests that climbing fibers can signal unexpected events or "errors" during a predictable movement (see Sect. 5.3.1).

In the neighboring C1 zone in the paravermis, the peak of simple spike activity consistently occurs during the swing phase of the ipsilateral forelimb (Armstrong and Edgley 1984b). Activity of neurons in the anterior interpositus, which receive projections from C1 zone PCs, follows the same pattern of activity (Armstrong and Edgley 1984a, b). This suggests that, instead of shaping CN activity through inhibition, PCs may instead dampen excitatory drive to CN neurons in this case (for other ways in which PCs may influence CN activity, see Sect. 3.2). Simple spike activity of PCs in the paravermal C2 and C3 zones occurs slightly later in the step cycle, with peak activity at the transition between the stance and swing phases (Edgley and Lidierth 1988). Differences are also present across the mediolateral width of the C2 zone (Edgley and Lidierth 1988). This suggests that, rather than a systematic shift in the patterns of activity between cortical zones, there is a mediolateral gradient, with more medially located PCs in the paravermis discharging earlier in the step cycle.

In keeping with this trend, PCs in the hemispheral D zones tend to have peak activity in the swing phase of the step cycle of the ipsilateral forelimb while walking on a horizontal circular ladder (Marple-Horvat and Criado 1999). The same is also

the case for dentate nuclear cells. Thus, in agreement with Armstrong and Edgley (1984b), the pattern of modulation of nuclear activity parallels that of the overlying PCs from which the cells receive inhibitory input (Marple-Horvat and Criado 1999). Approximately 45% of lateral cerebellar neurons (cortical and nuclear) were found to be responsive to visual cues, over two-thirds of which also showed rhythmic modulation in relation to the step cycle (Marple-Horvat et al. 1998). Taken together this suggests that D zone activity may be related to visually guided coordination of eye and body movements (Marple-Horvat and Criado 1999), consistent with control of whole body movements discussed above (Sect. 4.1).

Studies in rats freely traversing a track confirm that PC activity in lobules V and VI of the vermis is rhythmic during locomotion, and in addition that the patterns of modulation become variable due to other behavioral factors such as speed and acceleration (Sauerbrei Britton et al. 2015). Rhythmic patterns of cerebellar activity are therefore present during locomotion with a forced rhythm or stepping distance, as is the case with treadmill and ladder walking described above, and that which is self-initiated.

5.1.2 Reaching

Cerebellar disorders can result in deficits in reaching and grasping movements (Nowak et al. 2013; Zackowski et al. 2002). Cerebellar neurons, particularly those in paravermal regions, encode various components of single and multi-joint limb movements involved in reaching but the patterns of activity are quite mixed. For example, in monkeys performing arm and hand-based targeting tasks, activity of PCs is often modulated in relation to movement velocity, but may also correlate with position or acceleration, and can be tuned to preferred direction(s) (Hewitt et al. 2011; Marple-Horvat and Stein 1987; Fortier et al. 1989). The change in activity usually precedes movements, and an increase in PC discharge is most common with bursts of simple spikes positively correlated with limb muscle activity, although a proportion of PCs also show decreases in activity (Holdefer and Miller 2009). Generally speaking, individual PCs therefore display quite variable patterns of activity during even stereotypical movements such as reach-to-grasp. The reason for this variability is unclear but may in part be due to sampling PCs from different cerebellar zones (as is the case for studies of locomotion). Further investigations are needed in which PCs are studied in relation to cerebellar cortical modules and their microzonal subunits in order to gain a full understanding of cerebellar information processing.

Activity of CN neurons can also precede reaching movements and correlate with velocity, position, and acceleration, as well as have a preferred direction (Marple-Horvat and Stein 1987). A large proportion of interpositus neurons in the monkey increase their activity preferentially during a reach-to-grasp movement but only when the movement included grasping (van Kan et al. 1994). This suggests that the interpositus may be important in the control of grasping an object but not necessarily in the control of directing the limb to grasp the object. In contrast, a more recent

study in mice performing a forelimb reaching task found that the activity of interpositus neurons was modulated near the endpoint of a reach and was therefore likely related to limb deceleration to enhance accuracy (Becker and Person 2019). Besides possible species differences, subpopulations of neurons within the cerebellar nuclei (potentially relating to the output of different cerebellar modules) may encode different aspects of complex, multi-joint limb movements, including activation or inactivation of relevant effector muscles.

Other cerebellar regions may also encode reaching-relevant information. For example, PCs in the D2 zone of the lateral cat cerebellum encode visual information related to a predictable moving target, and this activity continues even in the temporary absence of the target, consistent with PCs encoding a feedforward prediction (internal model) of the expected movement (Cerminara et al. 2009). The role of the cerebellum as a feedforward controller is further discussed in Sect. 6.

5.2 Eye Movements

The posteromedial cerebellum, flocculus, and paraflocculus are involved in the optimization of eye movements, including saccades and smooth pursuit, via vestibular nuclear inputs to oculomotor neurons. As such, saccade dysmetria and nystagmus are often observed in cerebellar patients (Moscovich et al. 2015). Caudal fastigial nucleus neurons in the monkey discharge a burst of action potentials for almost every saccade, and the timing of these bursts suggests this signal is related to the start of contraversive saccades and the end of ipsiversive saccades—perhaps relating to acceleration and deceleration respectively (Fuchs et al. 1993; Robinson and Fuchs 2001). Caudal fastigial activity precedes smooth pursuit onset, and floccular PCs burst after the onset of movement so may be involved in maintaining smooth pursuit (Robinson and Fuchs 2001). In accordance with its control of eye movements, one classical example of cerebellar learning is the vestibulo-ocular reflex (VOR), which is further described in Sect. 5.3.2.

5.3 Associative Learning

Early theories of cerebellar learning by Marr (1969) proposed that climbing fibers provide an "error" signal to the cerebellum to induce learning or refinement of movements, and were extended by Albus (1971) to suggest that this involved depression of parallel fiber–PC synapses. Ito and Kano (1982) showed that parallel fiber activation in conjunction with climbing fiber activation was able to induce LTD at this synapse in the cerebellum, using electrical stimulation in decerebrate rabbits, providing early evidence of cerebellar synaptic plasticity and the role of climbing fibers in cerebellar learning. It is now known that the interval between mossy fiber and climbing fiber signals, which induces plasticity, varies across cerebellar regions

(ranging from ~0 to 150 milliseconds), accounting for the range of feedback delays relevant to the behavioral functions of each region (Suvrathan et al. 2016).

Associative learning in the cerebellum can be demonstrated by Pavlovian classical conditioning, where a previously neutral conditioned stimulus (CS) elicits a behavioral response after repeated presentations with an unconditioned stimulus (US). The US is thought to be signaled to the cerebellum via the inferior olive by climbing fibers, while the CS is conveyed by mossy fibers via the pontine nuclei (Steinmetz et al. 1989). These two pathways converge in the cerebellum, in both the cerebellar cortex and CN, and the sites of anatomical convergence are thought to underlie learning of the association between the two inputs. In line with the roles of the cerebellum in eye movements, two of the most widely studied forms of learning involve the eye—eyeblink conditioning and the VOR.

5.3.1 Eyeblink Conditioning

Eyeblink conditioning is perhaps the best studied form of cerebellar learning. An air puff to the eye (US) is repeatedly paired with a CS, such as a tone, so that after learning the CS alone induces an eyeblink response. The underlying circuitry has been shown in a range of species to depend upon discrete cerebellar microzones in hemispheric lobule VI with cortico-nuclear projections to anterior interpositus. This cerebellar nuclear region, in turn, has projections to the facial nucleus via the red nucleus (Yeo et al. 1984, 1985a, b; Ten Brinke et al. 2019).

Studies of eyeblink conditioning have provided evidence of a clear link between changes in patterns of neural activity and learnt behavior. Presentation of a novel tone or light stimulus (equivalent to a CS) alone may evoke climbing fiber activity; however, this response reduces with repeated presentations as saliency decreases (Ohmae and Medina 2015). During CS–US pairings in early acquisition of eyeblink conditioning, however, the US (air puff) evokes a climbing fiber response that drives learning of the conditioned eyelid response in response to the CS; in later stages of learning, the eyelid closure is initiated after the CS in anticipation of the air puff (Sears and Steinmetz 1991; Medina et al. 2002). Once the conditioned response is acquired, climbing fibers fire in response to the predictive stimulus (CS) (Ohmae and Medina 2015). Conditioned eyelid closure is associated with simple spike suppression in PCs, which results in disinhibition of CN neurons (Johansson et al. 2014; Hesslow and Ivarsson 1994; Rasmussen et al. 2008). Increased activity of CN neurons during expression of the conditioned response subsequently inhibits climbing fiber activity driven by the US in the inferior olive, due to increased inhibition via nucleo-olivary projections (Medina et al. 2002; Rasmussen et al. 2008). During extinction learning, the CS is repeatedly presented without the US so it is learned that the expression of the defensive response is no longer required (Jirenhed et al. 2007). Climbing fiber inhibition resulting from the conditioned response (increased CN inhibition of the inferior olive) in the absence of the US is thought to be an important teaching signal for extinction (Ohmae and Medina 2015).

Long-term synaptic plasticity at parallel fiber to PC synapses is thought to underlie eyeblink conditioning, resulting in the suppression of PC firing as described

above. Paired stimulation of parallel fibers and climbing fibers, corresponding to the CS and US respectively, has been shown to induce LTD at parallel fiber–PC synapses, and interfering with metabotropic glutamate receptors and protein kinase C pathways involved in parallel fiber–PC LTD has been shown to inhibit synaptic plasticity and learning of the conditioned eyeblink response (Aiba et al. 1994; Koekkoek et al. 2003). However, Schonewille et al. (2011) found no significant impairment in eyeblink conditioning when a later step in the LTD pathway, AMPA receptor internalization, was blocked in three types of mutant mice. The authors argued that impairments produced by manipulating earlier steps in the LTD pathway may be related to cellular processes other than LTD. A subsequent study by Yamaguchi et al. (2016) using two of these mutant mouse models found that while conventional protocols did not induce LTD in these mice, LTD could be induced in vitro using intensified stimulation protocols, for example pairs of parallel fiber stimulations combined with PC depolarization at 1 Hz for 3 minutes (as opposed to a single parallel fiber and climbing fiber stimulus at 1 Hz for 5 minutes). Compensatory mechanisms may therefore be at play in mice with disrupted LTD mechanisms, although further experiments are required to investigate how any of these protocols relate to physiological LTD in vivo. In summary, despite the attractiveness of LTD at the parallel fiber–PC synapse being the cellular mechanism underpinning cerebellar contributions to motor learning, evidence remains lacking to show conclusively that this is the case.

5.3.2 Vestibulo-Ocular Reflex

The VOR is a gaze stabilizing reflex that produces eye movements opposing the direction of head movements. In an experimental setting, VOR can be manipulated by moving the head and visual inputs in the same or opposite directions at varying speeds and amplitudes, with eye movements adapting to each novel configuration to re-stabilize vision. The flocculus and ventral paraflocculus of the cerebellum receive visual error signals, which converge with vestibular and eye movement information (Frens et al. 2001; Noda 1986). Simple spike modulation of PCs in these regions correlates with head and eye position, and VOR adaptation drives changes in modulation of PC activity (De Zeeuw et al. 1995; De Zeeuw and Ten Brinke 2015). These PCs inhibit the vestibular nuclei, which project to oculomotor nuclei to control muscles of the eyes.

Genetically modified mice lacking protein phosphatase 2B, which is involved in parallel fiber–PC LTP and modifying the intrinsic excitability of PCs, show VOR adaptation deficits (Schonewille et al. 2010). Mice deficient in parallel fiber–PC LTD are still able to show VOR adaptations (Schonewille et al. 2011), suggesting that under such experimental conditions LTP may be the most important form of plasticity for this type of learning. However, this may not be true for all forms of VOR adaptation (for example, opposite gain modulation), with multiple forms of plasticity likely to contribute under physiological conditions when all signaling pathways are intact (Boyden et al. 2004; Kimpo et al. 2014).

5.3.3 Higher-Order Learning

Associative learning principles may also apply to higher-order forms of learning in which the cerebellum is involved—in particular, reward-based learning, as the cerebellum has been shown to encode several aspects of reward. For example, granule cells in mice encode expectation of reward (Wagner et al. 2017) and climbing fibers signal reward prediction in the lateral cerebellum (lobule simplex, Crus I and II) during learning (Heffley and Hull 2019). Climbing fibers can also signal reward delivery and omission, which map onto different cerebellar cortical microzones—reward delivery causes activation in a subset of microzones within lobules V and VI and suppression in others, whereas reward omission activates both sets of microzones (Kostadinov et al. 2020).

The reward omission signal conveyed by the climbing fiber system may be an "error" signal that occurs when the outcome is unexpected, in accordance with error-based theories of climbing fiber function (e.g., Zang and De Schutter 2019) and classical theories of cerebellar-dependent motor learning (Marr 1969). Supporting this idea, climbing fiber responses to predictable rewards are suppressed during learning (Kostadinov et al. 2020), and the phenomenon may be generalized to the cerebellar mossy fiber–granule cell–parallel fiber system because reward-related error signals in PC simple spike responses diminish as monkeys learn a reward-association task (Sendhilnathan et al. 2020).

During trial-and-error-based visuomotor association learning, PC simple spikes encode the outcome of the monkey's most recent decision throughout the subsequent trial, updating with each trial and decreasing with improved performance (Sendhilnathan et al. 2020). Cognitive learning in the cerebellum could therefore be driven by similar mechanisms as error-based motor learning, with learning in both motor and cognitive domains involving testing predictions against actual outcomes. However, this may not be true for all types of behavior given that climbing fibers do not always signal error, as explored in the next section.

5.3.4 Climbing Fibers and Learning

Providing an error signal may not be the universal function of climbing fiber inputs to the cerebellum, since varying patterns of PC complex spike activity during learning have been observed. For example, complex spikes in the posterior vermis of the monkey occur randomly before saccadic adaptation, yet a distinct response profile emerges (with an increase or decrease in probability of occurrence depending on direction of adaptation) during the adaptation process that may act to stabilize the learned behavior (Catz et al. 2005); the opposite might be expected if the complex spikes signaled error, as error signals would decrease with learning. In reward-driven behaviors, which require a cognitive component, complex spikes have been shown to signal reward prediction and thus may guide cerebellar learning in a feedforward, predictive manner (Heffley and Hull 2019).

Complex spike responses may adapt to respond preferentially to salient sensory cues over less behaviorally relevant cues (Bina et al. 2021). For example, complex spikes can adapt to occur in response to a tactile reward-related cue rather than a neutral auditory cue, which in turn promotes potentiation of simple spike responses to the salient cue (Bina et al. 2021). Climbing fibers, and resulting complex spikes, therefore can drive learning, but this may occur in different ways depending upon the type of behavior, the region of the cerebellum, and the larger brain networks involved. Simple spikes themselves may also signal error in motor behaviors as well as movement kinematics (Popa et al. 2012), providing an alternative route through which error-based learning may occur.

As outlined above (Sect. 3.1), climbing fibers have long been thought to carry an "all or nothing" signal (Eccles et al. 1966), but more recent work suggests that information may also be conveyed in the waveform of individual complex spikes (Burroughs et al. 2017; Zang and De Schutter 2019). For example, the amplitude of PC calcium signals triggered by climbing fiber synapses in mice is enhanced when there is a sensory event, which may drive plasticity (Najafi et al. 2014). Also, during learning of smooth eye pursuit movements in the monkey, longer climbing fiber bursts lead to longer-duration complex spikes (and by inference a larger number of spikelets) that promote plasticity and enhance learning (Yang and Lisberger 2014). Similarly, the number of spikelets in a complex spike (Fig. 3) has been shown to increase following acquisition of delay eyeblink conditioning in mice (Titley et al. 2020). Thus, the relationship between complex spikes and learning extends beyond an all or none action potential type event and is likely to contribute to the diversity of climbing fiber function in learning. Clearly this is a subject that merits further study, particularly in light of the systematic differences in complex spike waveform related to synchrony (Sect. 3.1) and also to zebrin topography (Sect. 3.4).

6 The Cerebellum as a Feedforward Controller

In terms of motor control, the cerebellum is thought to generate internal models (feedforward predictions) about the sensory outcomes of intended movements and update these using movement-related sensory feedback (Fig. 6). The sensory prediction error generated can then guide movements online, account for sensory reafference occurring from self-generated movement, and guide motor learning (Popa and Ebner 2019). The fact that loops such as cortico-nucleo-olivary circuits and reciprocal connectivity with regions of the cerebral cortex are at the heart of cerebellar connectivity makes it well suited as a feedforward controller. Recently described inhibitory projections from the interpositus nucleus to sensory-related areas in the brainstem (Sect. 3.2) add extra feedback loops that could in theory modulate predictions of actions and sensory reafference (Judd et al. 2021).

There is an increasing body of evidence to support the cerebellar feedforward prediction model, whereby a forecast of the consequences of an action is made before the action is completed (e.g., Miall and Wolpert 1996; Miall et al. 1998;

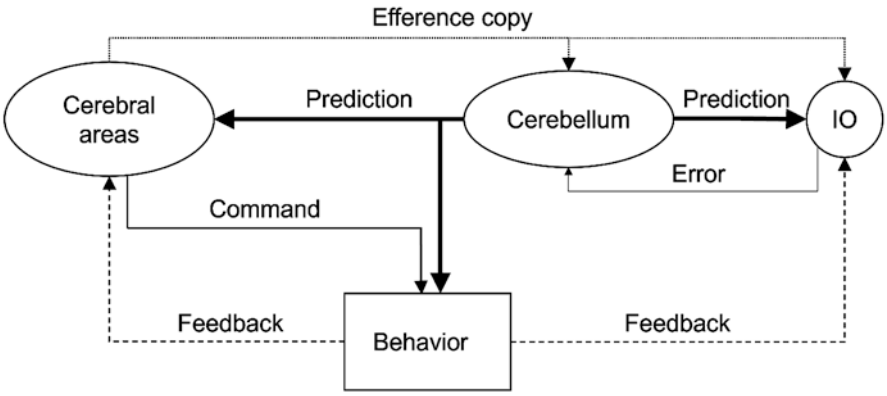

Fig. 6 A simplified schematic of circuits showing how the cerebellum acts as a prediction machine. Motor and non-motor actions such as goal-directed movements and problem solving occur following commands from cerebral areas (e.g., motor and prefrontal cortices, respectively) via connections to effector systems, such as the spinal cord for motor commands and association areas of the cerebral cortex for cognitive commands (behavior). An efference copy of these commands is sent to the cerebellum, via the pontine nuclei, and to the inferior olive (IO). Following behavior, feedback is delivered to the cerebellum via the IO and also to cerebral areas, and the IO compares cerebellar predictions to feedback to generate an error signal. The cerebellum compares the intended action (efference copy) and IO error signal to update its prediction. The prediction generated by the cerebellum allows online corrections of behavior through cerebellar connections to effector systems and updates the command in cerebral areas via the thalamus

Kitazawa et al. 1998; Cerminara et al. 2009; Ishikawa et al. 2016). In a recent example, recordings from a monkey during step tracking movements of the wrist found that activity in the dentate nucleus could predict the firing rate of mossy fibers, suggesting that the cerebellum is able to predict upcoming sensory inputs (Tanaka et al. 2019). There is also evidence from human subjects with cerebellar degeneration, who show impaired adaptive abilities during reaching and speech production compared to controls, suggesting problems with feedforward processing but not with compensatory responses, indicating that feedback systems are still intact (Parrell et al. 2021).

An extension of the internal model theory is to consider the cerebellum more generally as a "prediction machine" (Ramnani et al. 2000; Hull 2020). This expands cerebellar involvement in relatively simple circuits underpinning specific forms of motor learning, for example eyeblink conditioning, to more complex neocortical prediction paradigms involving interactions between multiple brain regions (Fig. 6). The reciprocal connections of the cerebellum with a multitude of brain structures provide the anatomical substrate to be involved in sensory, motor, and cognitive processes (Welniarz et al. 2021). It is therefore perhaps unsurprising that PCs are able to encode predictive and feedback signals of both movement and task performance, the latter associated with cognitive involvement (Popa and Ebner 2019). Such findings suggest that cognitive processing contributes to cerebellar-mediated learning by providing information about whether or not an action was successful

(Popa and Ebner 2019), just as reward signals can reinforce accuracy of goal-directed movements as described in Sect. 5.3.3.

7 Summary

The cerebellum is traditionally thought of as a brain structure with a highly regular cytoarchitecture, concerned primarily with motor control. However, we now know that there are additional complexities to cerebellar circuits, including recurrent loops both within the cerebellum and between the cerebellum and other brain regions, as well as systematic anatomical and physiological differences between cerebellar regions that likely relate to regional specialization of function. Nevertheless, a feature that may be common to all cerebellar circuits is the computation of differences between expected and actual outcomes of behavior, in all its different forms—enabling the cerebellum to regulate a wide variety of motor and non-motor functions via general principles applied to different brain networks. A key challenge for future research is to understand how the physiology of the cerebellum enables it to function as a universal prediction machine.

References

Ackerley R, Pardoe J, Apps R. A novel site of synaptic relay for climbing fibre pathways relaying signals from the motor cortex to the cerebellar cortical C1 zone. J Physiol. 2006;576(Pt 2):503–18. https://doi.org/10.1113/jphysiol.2006.114215.

Aiba A, Kano M, Chen C, Stanton ME, Fox GD, Herrup K, Zwingman TA, Tonegawa S. Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. Cell. 1994;79(2):377–88.

Aizenman CD, Linden DJ. Regulation of the rebound depolarization and spontaneous firing patterns of deep nuclear neurons in slices of rat cerebellum. J Neurophysiol. 1999;82(4):1697–709.

Aizenman CD, Manis PB, Linden DJ. Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. Neuron. 1998;21(4):827–35. https://doi.org/10.1016/s0896-6273(00)80598-x.

Albus JS. A theory of cerebellar function. Math Biosci. 1971;10(1–2):25–61.

Alvina K, Walter JT, Kohn A, Ellis-Davies G, Khodakhah K. Questioning the role of rebound firing in the cerebellum. Nat Neurosci. 2008;11(11):1256–8. https://doi.org/10.1038/nn.2195.

Andersson G, Armstrong DM. Complex spikes in Purkinje cells in the lateral vermis (b zone) of the cat cerebellum during locomotion. J Physiol. 1987;385:107–34. https://doi.org/10.1113/jphysiol.1987.sp016487.

Andersson G, Nyquist J. Origin and sagittal termination areas of cerebro-cerebellar climbing fibre paths in the cat. J Physiol. 1983;337:257–85. https://doi.org/10.1113/jphysiol.1983.sp014623.

Andersson G, Oscarsson O. Climbing fiber microzones in cerebellar vermis and their projection to different groups of cells in the lateral vestibular nucleus. Exp Brain Res. 1978;32(4):565–79. https://doi.org/10.1007/bf00239553.

Ankri L, Husson Z, Pietrajtis K, Proville R, Lena C, Yarom Y, Dieudonne S, Uusisaari MY. A novel inhibitory nucleo-cortical circuit controls cerebellar Golgi cell activity. elife. 2015;4:26. https://doi.org/10.7554/eLife.06262.

Apps R, Garwicz M. Anatomical and physiological foundations of cerebellar information processing. Nat Rev Neurosci. 2005;6(4):297–311. https://doi.org/10.1038/nrn1646.

Apps R, Hawkes R. Cerebellar cortical organization: a one-map hypothesis. Nat Rev Neurosci. 2009;10(9):670–81. https://doi.org/10.1038/nrn2698.

Apps R, Lee S. Gating of transmission in climbing fibre paths to cerebellar cortical C1 and C3 zones in the rostral paramedian lobule during locomotion in the cat. J Physiol. 1999;516(Pt 3):875–83. https://doi.org/10.1111/j.1469-7793.1999.0875u.x.

Apps R, Lidierth M, Armstrong DM. Locomotion-related variations in excitability of spino-olivocerebellar paths to cat cerebellar cortical c2 zone. J Physiol. 1990;424:487–512. https://doi.org/10.1113/jphysiol.1990.sp018079.

Apps R, Hartell NA, Armstrong DM. Step phase-related excitability changes in spino-olivocerebellar paths to the c1 and c3 zones in cat cerebellum. J Physiol. 1995;483(Pt 3):687–702. https://doi.org/10.1113/jphysiol.1995.sp020614.

Apps R, Atkins MJ, Garwicz M. Gating of cutaneous input to cerebellar climbing fibres during a reaching task in the cat. J Physiol Lond. 1997;502(1):203–14. https://doi.org/10.1111/j.1469-7793.1997.203bl.x.

Arenz A, Silver RA, Schaefer AT, Margrie TW. The contribution of single synapses to sensory representation in vivo. Science. 2008;321(5891):977–80. https://doi.org/10.1126/science.1158391.

Arenz A, Bracey EF, Margrie TW. Sensory representations in cerebellar granule cells. Curr Opin Neurobiol. 2009;19(4):445–51. https://doi.org/10.1016/j.conb.2009.07.003.

Armstrong DM, Edgley SA. Discharges of nucleus interpositus neurones during locomotion in the cat. J Physiol. 1984a;351:411–32. https://doi.org/10.1113/jphysiol.1984.sp015253.

Armstrong DM, Edgley SA. Discharges of Purkinje cells in the paravermal part of the cerebellar anterior lobe during locomotion in the cat. J Physiol. 1984b;352:403–24. https://doi.org/10.1113/jphysiol.1984.sp015300.

Armstrong DM, Rawson JA. Activity patterns of cerebellar cortical neurones and climbing fibre afferents in the awake cat. J Physiol Lond. 1979;289(APR):425–48.

Ashida R, Cerminara NL, Edwards RJ, Apps R, Brooks JCW. Sensorimotor, language, and working memory representation within the human cerebellum. Hum Brain Mapp. 2019;40(16):4732–47. https://doi.org/10.1002/hbm.24733.

Ashizawa T, Xia G. Ataxia. Continuum (Minneap Minn). 2016;22(4 Movement Disorders):1208–26. https://doi.org/10.1212/con.0000000000000362.

Atkins MJ, Apps R. Somatotopical organisation within the climbing fibre projection to the paramedian lobule and copula pyramidis of the rat cerebellum. J Comp Neurol. 1997;389(2):249–63.

Bagnall MW, Zingg B, Sakatos A, Moghadam SH, Zeilhofer HU, du Lac S. Glycinergic projection neurons of the cerebellum. J Neurosci. 2009;29(32):10104–10. https://doi.org/10.1523/jneurosci.2087-09.2009.

Becker MI, Person AL. Cerebellar control of reach kinematics for endpoint precision. Neuron. 2019;103(2):335–348.e335. https://doi.org/10.1016/j.neuron.2019.05.007.

Beekhof GC, Gornati SV, Canto CB, Libster AM, Schonewille M, De Zeeuw CI, Hoebeek FE. Activity of cerebellar nuclei neurons correlates with ZebrinII identity of their Purkinje cell afferents. Cell. 2021;10(10):2686. https://doi.org/10.3390/cells10102686.

Bengtsson F, Ekerot CF, Jorntell H. In vivo analysis of inhibitory synaptic inputs and rebounds in deep cerebellar nuclear neurons. PLoS One. 2011;6(4):12. https://doi.org/10.1371/journal.pone.0018822.

Bina L, Romano V, Hoogland TM, Bosman LWJ, De Zeeuw CI. Purkinje cells translate subjective salience into readiness to act and choice performance. Cell Rep. 2021;37(11):110116. https://doi.org/10.1016/j.celrep.2021.110116.

Binda F, Dorgans K, Reibel S, Sakimura K, Kano M, Poulain B, Isope P. Inhibition promotes long-term potentiation at cerebellar excitatory synapses. Sci Rep. 2016;6:12. https://doi.org/10.1038/srep33561.

Blenkinsop TA, Lang EJ. Synaptic action of the olivocerebellar system on cerebellar nuclear spike activity. J Neurosci. 2011;31(41):14708. https://doi.org/10.1523/jneurosci.3323-11.2011.

Bloedel JR, Burton JE. Electrophysiological evidence for a mossy fiber input to the cerebellar cortex activated indirectly by collaterals of spinocerebellar pathways. J Neurophysiol. 1970;33(2):308–19. https://doi.org/10.1152/jn.1970.33.2.308.

Boillat Y, Bazin PL, van der Zwaag W. Whole-body somatotopic maps in the cerebellum revealed with 7T fMRI. NeuroImage. 2020;211:116624. https://doi.org/10.1016/j.neuroimage.2020.116624.

Bosco G, Poppele RE. Proprioception from a spinocerebellar perspective. Physiol Rev. 2001;81(2):539–68. https://doi.org/10.1152/physrev.2001.81.2.539.

Bosman LW, Koekkoek SK, Shapiro J, Rijken BF, Zandstra F, van der Ende B, Owens CB, Potters JW, de Gruijl JR, Ruigrok TJ, De Zeeuw CI. Encoding of whisker input by cerebellar Purkinje cells. J Physiol. 2010;588(Pt 19):3757–83. https://doi.org/10.1113/jphysiol.2010.195180.

Boyden ES, Katoh A, Raymond JL. Cerebellum-dependent learning: the role of multiple plasticity mechanisms. Annu Rev Neurosci. 2004;27:581–609. https://doi.org/10.1146/annurev.neuro.27.070203.144238.

Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol. 2001;63(6):637–72. https://doi.org/10.1016/s0301-0082(00)00039-3.

Brown AM, Arancillo M, Lin T, Catt DR, Zhou J, Lackey EP, Stay TL, Zuo Z, White JJ, Sillitoe RV. Molecular layer interneurons shape the spike activity of cerebellar Purkinje cells. Sci Rep. 2019;9(1):1742. https://doi.org/10.1038/s41598-018-38264-1.

Burroughs A, Wise AK, Xiao J, Houghton C, Tang T, Suh CY, Lang EJ, Apps R, Cerminara NL. The dynamic relationship between cerebellar Purkinje cell simple spikes and the spikelet number of complex spikes. J Physiol. 2017;595(1):283–99. https://doi.org/10.1113/jp272259.

Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science. 2004;304(5679):1926–9. https://doi.org/10.1126/science.1099745.

Campbell NC, Hesslow G. The secondary spikes of climbing fiber responses recorded from Purkinje cell somata in cat cerebellum. J Physiol Lond. 1986;377:207–24.

Catz N, Dicke PW, Thier P. Cerebellar complex spike firing is suitable to induce as well as to stabilize motor learning. Curr Biol. 2005;15(24):2179–89. https://doi.org/10.1016/j.cub.2005.11.037.

Cerminara NL, Apps R. Behavioural significance of cerebellar modules. Cerebellum. 2011;10(3):484–94. https://doi.org/10.1007/s12311-010-0209-2.

Cerminara NL, Apps R, Marple-Horvat DE. An internal model of a moving visual target in the lateral cerebellum. J Physiol Lond. 2009;587(2):429–42. https://doi.org/10.1113/jphysiol.2008.163337.

Chabrol FP, Arenz A, Wiechert MT, Margrie TW, DiGregorio DA. Synaptic diversity enables temporal coding of coincident multisensory inputs in single neurons. Nat Neurosci. 2015;18(5):718–27. https://doi.org/10.1038/nn.3974.

Chabrol FP, Blot A, Mrsic-Flogel TD. Cerebellar contribution to preparatory activity in motor neocortex. Neuron. 2019;103(3):506–519.e504. https://doi.org/10.1016/j.neuron.2019.05.022.

Chaumont J, Guyon N, Valera AM, Dugue GP, Popa D, Marcaggi P, Gautheron V, Reibel-Foisset S, Dieudonne S, Stephan A, Barrot M, Cassel JC, Dupont JL, Doussau F, Poulain B, Selimi F, Lena C, Isope P. Clusters of cerebellar Purkinje cells control their afferent climbing fiber discharge. Proc Natl Acad Sci U S A. 2013;110(40):16223–8. https://doi.org/10.1073/pnas.1302310110.

Courtemanche R, Robinson JC, Aponte DI. Linking oscillations in cerebellar circuits. Front Neural Circuits. 2013;7:125. https://doi.org/10.3389/fncir.2013.00125.

D'Angelo E. The critical role of Golgi cells in regulating spatio-temporal integration and plasticity at the cerebellum input stage. Front Neurosci. 2008;2(1):35–46. https://doi.org/10.3389/neuro.01.008.2008.

D'Angelo E. Physiology of the cerebellum. Handb Clin Neurol. 2018;154:85–108. https://doi.org/10.1016/b978-0-444-63956-1.00006-0.

De Gruijl JR, Bosman LWJ, De Zeeuw CI, De Jeu MTG. Inferior olive: all ins and outs. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, editors. Handbook of the cerebellum and cerebellar disorders. Dordrecht: Springer Netherlands; 2013. p. 1013–58. https://doi.org/10.1007/978-94-007-1333-8_43.

De Zeeuw CI. Bidirectional learning in upbound and downbound microzones of the cerebellum. Nat Rev Neurosci. 2021;22(2):92–110. https://doi.org/10.1038/s41583-020-00392-x.
De Zeeuw CI, Hoogland TM. Reappraisal of Bergmann glial cells as modulators of cerebellar circuit function. Front Cell Neurosci. 2015;9:246. https://doi.org/10.3389/fncel.2015.00246.
De Zeeuw CI, Ten Brinke MM. Motor learning and the cerebellum. Cold Spring Harb Perspect Biol. 2015;7(9):19. https://doi.org/10.1101/cshperspect.a021683.
De Zeeuw CI, Wylie DR, Stahl JS, Simpson JI. Phase relations of Purkinje cells in the rabbit flocculus during compensatory eye movements. J Neurophysiol. 1995;74(5):2051–64. https://doi.org/10.1152/jn.1995.74.5.2051.
De Zeeuw CI, Hoebeek FE, Schonewille M. Causes and consequences of oscillations in the cerebellar cortex. Neuron. 2008;58(5):655–8. https://doi.org/10.1016/j.neuron.2008.05.019.
DiGregorio DA, Nusser Z, Silver RA. Spillover of glutamate onto synaptic AMPA receptors enhances fast transmission at a cerebellar synapse. Neuron. 2002;35(3):521–33. https://doi.org/10.1016/s0896-6273(02)00787-0.
Dugué GP, Brunel N, Hakim V, Schwartz E, Chat M, Lévesque M, Courtemanche R, Léna C, Dieudonné S. Electrical coupling mediates tunable low-frequency oscillations and resonance in the cerebellar Golgi cell network. Neuron. 2009;61(1):126–39. https://doi.org/10.1016/j.neuron.2008.11.028.
Eccles JC, Llinas R, Sasaki K. The excitatory synaptic action of climbing fibres on Purkinje cells of the cerebellum. J Physiol Lond. 1966;182(2):268–96.
Eccles JC, Ito M, Szentágothai J. The cerebellum as a neuronal machine. 1st ed. Berlin, Heidelberg: Springer; 1967. https://doi.org/10.1007/978-3-662-13147-3.
Edge AL, Marple-Horvat DE, Apps R. Lateral cerebellum: functional localization within crus I and correspondence to cortical zones. Eur J Neurosci. 2003;18(6):1468–85. https://doi.org/10.1046/j.1460-9568.2003.02873.x.
Edgley SA, Lidierth M. Step-related discharges of Purkinje cells in the paravermal cortex of the cerebellar anterior lobe in the cat. J Physiol. 1988;401:399–415. https://doi.org/10.1113/jphysiol.1988.sp017169.
Ekerot CF, Garwicz M, Schouenborg J. Topography and nociceptive receptive fields of climbing fibres projecting to the cerebellar anterior lobe in the cat. J Physiol. 1991;441:257–74. https://doi.org/10.1113/jphysiol.1991.sp018750.
Ekerot CF, Jorntell H, Garwicz M. Functional relation between corticonuclear input and movements evoked on microstimulation in cerebellar nucleus interpositus anterior in the cat. Exp Brain Res. 1995;106(3):365–76.
Fortier PA, Kalaska JF, Smith AM. Cerebellar neuronal activity related to whole-arm reaching movements in the monkey. J Neurophysiol. 1989;62(1):198–211. https://doi.org/10.1152/jn.1989.62.1.198.
Frens MA, Mathoera AL, van der Steen J. Floccular complex spike response to transparent retinal slip. Neuron. 2001;30(3):795–801. https://doi.org/10.1016/s0896-6273(01)00321-x.
Fries P. Rhythms for cognition: communication through coherence. Neuron. 2015;88(1):220–35. https://doi.org/10.1016/j.neuron.2015.09.034.
Fuchs AF, Robinson FR, Straube A. Role of the caudal fastigial nucleus in saccade generation. I. Neuronal discharge pattern. J Neurophysiol. 1993;70(5):1723–40. https://doi.org/10.1152/jn.1993.70.5.1723.
Gao ZY, van Beugen BJ, De Zeeuw CI. Distributed synergistic plasticity and cerebellar learning. Nat Rev Neurosci. 2012;13(9):619–35. https://doi.org/10.1038/nrn3312.
Gao ZY, Proietti-Onori M, Lin ZM, ten Brinke MM, Boele HJ, Potters JW, Ruigrok TJH, Hoebeek FE, De Zeeuw CI. Excitatory cerebellar nucleocortical circuit provides internal amplification during associative conditioning. Neuron. 2016;89(3):645–57. https://doi.org/10.1016/j.neuron.2016.01.008.
Gao Z, Davis C, Thomas AM, Economo MN, Abrego AM, Svoboda K, De Zeeuw CI, Li N. A cortico-cerebellar loop for motor planning. Nature. 2018;563(7729):113–6. https://doi.org/10.1038/s41586-018-0633-x.

Garwicz M. Spinal reflexes provide motor error signals to cerebellar modules–relevance for motor coordination. Brain Res Brain Res Rev. 2002;40(1–3):152–65. https://doi.org/10.1016/s0165-0173(02)00198-4.

Garwicz M, Ekerot CF. Topographical organization of the cerebellar cortical projection to nucleus interpositus anterior in the cat. J Physiol. 1994;474(2):245–60. https://doi.org/10.1113/jphysiol.1994.sp020017.

Giovannucci A, Badura A, Deverett B, Najafi F, Pereira TD, Gao Z, Ozden I, Kloth AD, Pnevmatikakis E, Paninski L, De Zeeuw CI, Medina JF, Wang SSH. Cerebellar granule cells acquire a widespread predictive feedback signal during motor learning. Nat Neurosci. 2017;20(5):727–34. https://doi.org/10.1038/nn.4531.

Graham DJ, Wylie DR. Zebrin-immunopositive and -immunonegative stripe pairs represent functional units in the pigeon vestibulocerebellum. J Neurosci. 2012;32(37):12769–79. https://doi.org/10.1523/jneurosci.0197-12.2012.

Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum Brain Mapp. 2001;13(2):55–73. https://doi.org/10.1002/hbm.1025.

Guo C, Witter L, Rudolph S, Elliott HL, Ennis KA, Regehr WG. Purkinje cells directly inhibit granule cells in specialized regions of the cerebellar cortex. Neuron. 2016;91(6):1330–41. https://doi.org/10.1016/j.neuron.2016.08.011.

Guo C, Rudolph S, Neuwirth ME, Regehr WG. Purkinje cell outputs selectively inhibit a subset of unipolar brush cells in the input layer of the cerebellar cortex. elife. 2021;10:e68802. https://doi.org/10.7554/eLife.68802.

Han KS, Chen CH, Khan MM, Guo C, Regehr WG. Climbing fiber synapses rapidly and transiently inhibit neighboring Purkinje cells via ephaptic coupling. Nat Neurosci. 2020;23(11):1399–409. https://doi.org/10.1038/s41593-020-0701-z.

Hausser M, Clark BA. Tonic synaptic inhibition modulates neuronal output pattern and spatiotemporal synaptic integration. Neuron. 1997;19(3):665–78. https://doi.org/10.1016/s0896-6273(00)80379-7.

Heffley W, Hull C. Classical conditioning drives learned reward prediction signals in climbing fibers across the lateral cerebellum. elife. 2019;8:21. https://doi.org/10.7554/eLife.46764.

Heiney SA, Wojaczynski GJ, Medina JF. Action-based organization of a cerebellar module specialized for predictive control of multiple body parts. Neuron. 2021;109(18):2981–2994. e2985. https://doi.org/10.1016/j.neuron.2021.08.017.

Herculano-Houzel S. Coordinated scaling of cortical and cerebellar numbers of neurons. Front Neuroanat. 2010;4:8. https://doi.org/10.3389/fnana.2010.00012.

Herrero L, Pardoe J, Apps R. Pontine and lateral reticular projections to the c1 zone in lobulus simplex and paramedian lobule of the rat cerebellar cortex. Cerebellum. 2002;1(3):185–99. https://doi.org/10.1080/14734220260418411.

Herrero L, Pardoe J, Cerminara NL, Apps R. Spatial localization and projection densities of brainstem mossy fibre afferents to the forelimb C1 zone of the rat cerebellum. Eur J Neurosci. 2012;35(4):539–49. https://doi.org/10.1111/j.1460-9568.2011.07977.x.

Hesslow G, Ivarsson M. Suppression of cerebellar Purkinje cells during conditioned responses in ferrets. Neuroreport. 1994;5(5):649–52. https://doi.org/10.1097/00001756-199401000-00030.

Hewitt AL, Popa LS, Pasalar S, Hendrix CM, Ebner TJ. Representation of limb kinematics in Purkinje cell simple spike discharge is conserved across multiple tasks. J Neurophysiol. 2011;106(5):2232–47. https://doi.org/10.1152/jn.00886.2010.

Hoebeek FE, Witter L, Ruigrok TJH, De Zeeuw CI. Differential olivo-cerebellar cortical control of rebound activity in the cerebellar nuclei. Proc Natl Acad Sci. 2010;107(18):8410–5. https://doi.org/10.1073/pnas.0907118107.

Holdefer RN, Miller LE. Dynamic correspondence between Purkinje cell discharge and forelimb muscle activity during reaching. Brain Res. 2009;1295:67–75. https://doi.org/10.1016/j.brainres.2009.07.085.

Hoogland TM, De Gruijl JR, Witter L, Canto CB, De Zeeuw CI. Role of synchronous activation of cerebellar Purkinje cell ensembles in multi-joint movement control. Curr Biol. 2015;25(9):1157–65. https://doi.org/10.1016/j.cub.2015.03.009.

Horn KM, Pong M, Gibson AR. Functional relations of cerebellar modules of the cat. J Neurosci. 2010;30(28):9411–23. https://doi.org/10.1523/jneurosci.0440-10.2010.

Houck BD, Person AL. Cerebellar loops: a review of the Nucleocortical pathway. Cerebellum. 2014;13(3):378–85. https://doi.org/10.1007/s12311-013-0543-2.

Houck BD, Person AL. Cerebellar premotor output neurons collateralize to innervate the cerebellar cortex. J Comp Neurol. 2015;523(15):2254–71. https://doi.org/10.1002/cne.23787.

Hoxha E, Tempia F, Lippiello P, Miniaci MC. Modulation, plasticity and pathophysiology of the parallel fiber-Purkinje cell synapse. Front Synaptic Neurosci. 2016;8:35. https://doi.org/10.3389/fnsyn.2016.00035.

Hull C. Prediction signals in the cerebellum: beyond supervised motor learning. elife. 2020;9:e54073. https://doi.org/10.7554/eLife.54073.

Husson Z, Rousseau CV, Broll I, Zeilhofer HU, Dieudonne S. Differential GABAergic and glycinergic inputs of inhibitory interneurons and Purkinje cells to principal cells of the cerebellar nuclei. J Neurosci. 2014;34(28):9418–31. https://doi.org/10.1523/jneurosci.0401-14.2014.

Ishikawa T, Tomatsu S, Izawa J, Kakei S. The cerebro-cerebellum: could it be loci of forward models? Neurosci Res. 2016;104:72–9. https://doi.org/10.1016/j.neures.2015.12.003.

Isope P, Barbour B. Properties of unitary granule cell-->Purkinje cell synapses in adult rat cerebellar slices. J Neurosci. 2002;22(22):9668–78. https://doi.org/10.1523/jneurosci.22-22-09668.2002.

Ito M. The cerebellum and neural control. New York: Raven Press; 1984.

Ito M. Cerebellar circuitry as a neuronal machine. Prog Neurobiol. 2006;78(3–5):272–303. https://doi.org/10.1016/j.pneurobio.2006.02.006.

Ito M, Kano M. Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. Neurosci Lett. 1982;33(3):253–8. https://doi.org/10.1016/0304-3940(82)90380-9.

Ito M, Sakurai M, Tongroach P. Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells. J Physiol. 1982;324:113–34. https://doi.org/10.1113/jphysiol.1982.sp014103.

Jaarsma D, Ruigrok TJH, Caffe R, Cozzari C, Levey AI, Mugnaini E, Voogd J. Cholinergic innervation and receptors in the cerebellum. Cereb Struct Control. 1997;114:67–96.

Jelitai M, Puggioni P, Ishikawa T, Rinaldi A, Duguid I. Dendritic excitation–inhibition balance shapes cerebellar output during motor behaviour. Nat Commun. 2016;7(1):13722. https://doi.org/10.1038/ncomms13722.

Jirenhed DA, Bengtsson F, Hesslow G. Acquisition, extinction, and reacquisition of a cerebellar cortical memory trace. J Neurosci. 2007;27(10):2493–502. https://doi.org/10.1523/jneurosci.4202-06.2007.

Jirenhed D-A, Bengtsson F, Jörntell H. Parallel fiber and climbing fiber responses in rat cerebellar cortical neurons in vivo. Front Syst Neurosci. 2013;7:16. https://doi.org/10.3389/fnsys.2013.00016.

Johansson F, Jirenhed DA, Rasmussen A, Zucca R, Hesslow G. Memory trace and timing mechanism localized to cerebellar Purkinje cells. Proc Natl Acad Sci U S A. 2014;111(41):14930–4. https://doi.org/10.1073/pnas.1415371111.

Jörntell H. Cerebellar physiology: links between microcircuitry properties and sensorimotor functions. J Physiol. 2017;595(1):11–27. https://doi.org/10.1113/jp272769.

Jörntell H, Ekerot CF. Properties of somatosensory synaptic integration in cerebellar granule cells in vivo. J Neurosci. 2006;26(45):11786–97. https://doi.org/10.1523/jneurosci.2939-06.2006.

Jörntell H, Ekerot C, Garwicz M, Luo XL. Functional organization of climbing fibre projection to the cerebellar anterior lobe of the rat. J Physiol. 2000;522(Pt 2):297–309. https://doi.org/10.1111/j.1469-7793.2000.00297.x.

Judd EN, Lewis SM, Person AL. Diverse inhibitory projections from the cerebellar interposed nucleus. elife. 2021;10:e66231. https://doi.org/10.7554/eLife.66231.

Kassel J, Shambes GM, Welker W. Fractured cutaneous projections to the granule cell layer of the posterior cerebellar hemisphere of the domestic cat. J Comp Neurol. 1984;225(3):458–68. https://doi.org/10.1002/cne.902250311.

Kimpo RR, Rinaldi JM, Kim CK, Payne HL, Raymond JL. Gating of neural error signals during motor learning. elife. 2014;3:e02076. https://doi.org/10.7554/eLife.02076.

Kitazawa S, Kimura T, Yin PB. Cerebellar complex spikes encode both destinations and errors in arm movements. Nature. 1998;392(6675):494–7. https://doi.org/10.1038/33141.

Koekkoek SKE, Hulscher HC, Dortland BR, Hensbroek RA, Elgersma Y, Ruigrok TJH, De Zeeuw CI. Cerebellar LTD and learning-dependent timing of conditioned eyelid responses. Science. 2003;301(5640):1736–9. https://doi.org/10.1126/science.1088383.

Kostadinov D, Beau M, Blanco-Pozo M, Hausser M. Predictive and reactive reward signals conveyed by climbing fiber inputs to cerebellar Purkinje cells (vol 45, pg 897, 2019). Nat Neurosci. 2020;23(3):468. https://doi.org/10.1038/s41593-020-0594-x.

Lainé J, Axelrad H. The candelabrum cell: a new interneuron in the cerebellar cortex. J Comp Neurol. 1994;339(2):159–73. https://doi.org/10.1002/cne.903390202.

Lainé J, Axelrad H. Extending the cerebellar Lugaro cell class. Neuroscience. 2002;115(2):363–74. https://doi.org/10.1016/s0306-4522(02)00421-9.

Lang EJ, Tang T, Suh CY, Xiao J, Kotsurovskyy Y, Blenkinsop TA, Marshall SP, Sugihara I. Modulation of Purkinje cell complex spike waveform by synchrony levels in the olivocerebellar system. Front Syst Neurosci. 2014;8:210. https://doi.org/10.3389/fnsys.2014.00210.

Lawrenson CL, Watson TC, Apps R. Transmission of predictable sensory signals to the cerebellum via climbing fiber pathways is gated during exploratory behavior. J Neurosci. 2016;36(30):7841–51. https://doi.org/10.1523/jneurosci.0439-16.2016.

Lev-Ram V, Wong ST, Storm DR, Tsien RY. A new form of cerebellar long-term potentiation is postsynaptic and depends on nitric oxide but not cAMP. Proc Natl Acad Sci U S A. 2002;99(12):8389–93. https://doi.org/10.1073/pnas.122206399.

Leznik E, Llinás R. Role of gap junctions in synchronized neuronal oscillations in the inferior olive. J Neurophysiol. 2005;94(4):2447–56. https://doi.org/10.1152/jn.00353.2005.

Lidierth M, Apps R. Gating in the spino-olivocerebellar pathways to the c1 zone of the cerebellar cortex during locomotion in the cat. J Physiol. 1990;430:453–69. https://doi.org/10.1113/jphysiol.1990.sp018301.

Lippiello P, Hoxha E, Volpicelli F, Lo Duca G, Tempia F, Miniaci MC. Noradrenergic modulation of the parallel fiber-Purkinje cell synapse in mouse cerebellum. Neuropharmacology. 2015;89:33–42. https://doi.org/10.1016/j.neuropharm.2014.08.016.

Llinás R, Leznik E, Makarenko VI. On the amazing olivocerebellar system. Ann N Y Acad Sci. 2002;978:258–72. https://doi.org/10.1111/j.1749-6632.2002.tb07573.x.

Llinas RR, Walton KD, Lang EJ. Cerebellum. In: Shepherd GM, editor. The synaptic organization of the brain. 5th ed. New York: Oxford University Press; 2004.

Lu H, Yang B, Jaeger D. Cerebellar nuclei neurons show only small excitatory responses to optogenetic olivary stimulation in transgenic mice: in vivo and in vitro studies. Front Neural Circuits. 2016;10:10. https://doi.org/10.3389/fncir.2016.00021.

Malhotra S, Banumurthy G, Pennock RL, Vaden JH, Sugihara I, Overstreet-Wadiche L, Wadiche JI. Climbing fiber-mediated spillover transmission to interneurons is regulated by EAAT4. J Neurosci. 2021;41(39):8126–33. https://doi.org/10.1523/jneurosci.0616-21.2021.

Mann-Metzer P, Yarom Y. Electrotonic coupling interacts with intrinsic properties to generate synchronized activity in cerebellar networks of inhibitory interneurons. J Neurosci. 1999;19(9):3298–306. https://doi.org/10.1523/jneurosci.19-09-03298.1999.

Mapelli L, Pagani M, Garrido JA, D'Angelo E. Integrated plasticity at inhibitory and excitatory synapses in the cerebellar circuit. Front Cell Neurosci. 2015;9:17. https://doi.org/10.3389/fncel.2015.00169.

Marple-Horvat DE, Criado JM. Rhythmic neuronal activity in the lateral cerebellum of the cat during visually guided stepping. J Physiol. 1999;518(Pt 2):595–603. https://doi.org/10.1111/j.1469-7793.1999.0595p.x.

Marple-Horvat DE, Stein JF. Cerebellar neuronal activity related to arm movements in trained rhesus monkeys. J Physiol. 1987;394:351–66. https://doi.org/10.1113/jphysiol.1987.sp016874.
Marple-Horvat DE, Criado JM, Armstrong DM. Neuronal activity in the lateral cerebellum of the cat related to visual stimuli at rest, visually guided step modification, and saccadic eye movements. J Physiol. 1998;506(Pt 2):489–514. https://doi.org/10.1111/j.1469-7793.1998.489bw.x.
Marr D. A theory of cerebellar cortex. J Physiol. 1969;202(2):437–70. https://doi.org/10.1113/jphysiol.1969.sp008820.
Medina JF, Nores WL, Mauk MD. Inhibition of climbing fibres is a signal for the extinction of conditioned eyelid responses. Nature. 2002;416(6878):330–3. https://doi.org/10.1038/416330a.
Miall RC, Wolpert DM. Forward models for physiological motor control. Neural Netw. 1996;9(8):1265–79. https://doi.org/10.1016/S0893-6080(96)00035-4.
Miall RC, Keating JG, Malkmus M, Thach WT. Simple spike activity predicts occurrence of complex spikes in cerebellar Purkinje cells. Nat Neurosci. 1998;1(1):13–5. https://doi.org/10.1038/212.
Middleton FA, Strick PL. The cerebellum: an overview. Trends Neurosci. 1998;21(9):367–9. https://doi.org/10.1016/s0166-2236(98)01330-7.
Morishita W, Sastry BR. Postsynaptic mechanisms underlying long-term depression of GABAergic transmission in neurons of the deep cerebellar nuclei. J Neurophysiol. 1996;76(1):59–68.
Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. Neuroscientist. 2004;10(3):247–59. https://doi.org/10.1177/1073858404263517.
Moscovich M, Okun MS, Favilla C, Figueroa KP, Pulst SM, Perlman S, Wilmot G, Gomez C, Schmahmann J, Paulson H, Shakkottai V, Ying S, Zesiewicz T, Kuo SH, Mazzoni P, Bushara K, Xia G, Ashizawa T, Subramony SH. Clinical evaluation of eye movements in spinocerebellar ataxias: a prospective multicenter study. J Neuroophthalmol. 2015;35(1):16–21. https://doi.org/10.1097/WNO.0000000000000167.
Mugnaini E, Sekerkova G, Martina M. The unipolar brush cell: a remarkable neuron finally receiving deserved attention. Brain Res Rev. 2011;66(1–2):220–45. https://doi.org/10.1016/j.brainresrev.2010.10.001.
Najafi F, Giovannucci A, Wang SS, Medina JF. Sensory-driven enhancement of calcium signals in individual Purkinje cell dendrites of awake mice. Cell Rep. 2014;6(5):792–8. https://doi.org/10.1016/j.celrep.2014.02.001.
Noda H. Mossy fibres sending retinal-slip, eye, and head velocity signals to the flocculus of the monkey. J Physiol. 1986;379:39–60. https://doi.org/10.1113/jphysiol.1986.sp016240.
Nowak DA, Timmann D, Hermsdörfer J. Deficits of grasping in cerebellar disorders. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, editors. Handbook of the cerebellum and cerebellar disorders. Dordrecht: Springer Netherlands; 2013. p. 1657–67. https://doi.org/10.1007/978-94-007-1333-8_73.
Ohmae S, Medina JF. Climbing fibers encode a temporal-difference prediction error during cerebellar learning in mice. Nat Neurosci. 2015;18(12):1798–803. https://doi.org/10.1038/nn.4167.
Oostland M, van Hooft JA. The role of serotonin in cerebellar development. Neuroscience. 2013;248:201–12. https://doi.org/10.1016/j.neuroscience.2013.05.029.
Oscarsson O. Functional organisation of the olivary projection to the cerebellar anterior lobe. In: Courville J, de Montigny C, Lamarre Y, editors. The inferior olivary nucleus. New York: Raven Press; 1980. p. 279–90.
Ouardouz M, Sastry BR. Mechanisms underlying LTP of inhibitory synaptic transmission in the deep cerebellar nuclei. J Neurophysiol. 2000;84(3):1414–21.
Özcan OO, Wang X, Binda F, Dorgans K, De Zeeuw CI, Gao Z, Aertsen A, Kumar A, Isope P. Differential coding strategies in glutamatergic and GABAergic neurons in the medial cerebellar nucleus. J Neurosci. 2020;40(1):159–70. https://doi.org/10.1523/jneurosci.0806-19.2019.
Pardoe J, Edgley SA, Drew T, Apps R. Changes in excitability of ascending and descending inputs to cerebellar climbing fibers during locomotion. J Neurosci. 2004;24(11):2656–66. https://doi.org/10.1523/jneurosci.1659-03.2004.

Parrell B, Kim HE, Breska A, Saxena A, Ivry RB. Differential effects of cerebellar degeneration on feedforward versus feedback control across speech and reaching movements. J Neurosci. 2021;41:8779. https://doi.org/10.1523/jneurosci.0739-21.2021.

Paukert M, Huang YH, Tanaka K, Rothstein JD, Bergles DE. Zones of enhanced glutamate release from climbing fibers in the mammalian cerebellum. J Neurosci. 2010;30(21):7290. https://doi.org/10.1523/jneurosci.5118-09.2010.

Person AL, Raman IM. Deactivation of L-type Ca current by inhibition controls LTP at excitatory synapses in the cerebellar nuclei. Neuron. 2010;66(4):550–9. https://doi.org/10.1016/j.neuron.2010.04.024.

Person AL, Raman IM. Purkinje neuron synchrony elicits time-locked spiking in the cerebellar nuclei. Nature. 2012a;481(7382):502. https://doi.org/10.1038/nature10732.

Person AL, Raman IM. Synchrony and neural coding in cerebellar circuits. Front Neural Circuits. 2012b;6:15. https://doi.org/10.3389/fncir.2012.00097.

Pijpers A, Apps R, Pardoe J, Voogd J, Ruigrok TJH. Precise spatial relationships between mossy fibers and climbing fibers in rat cerebellar cortical zones. J Neurosci. 2006;26(46):12067–80. https://doi.org/10.1523/jneurosci.2905-06.2006.

Popa LS, Ebner TJ. Cerebellum, predictions and errors. Front Cell Neurosci. 2019;12:524. https://doi.org/10.3389/fncel.2018.00524.

Popa LS, Hewitt AL, Ebner TJ. Predictive and feedback performance errors are signaled in the simple spike discharge of individual Purkinje cells. J Neurosci. 2012;32(44):15345–58. https://doi.org/10.1523/jneurosci.2151-12.2012.

Popa D, Spolidoro M, Proville RD, Guyon N, Belliveau L, Léna C. Functional role of the cerebellum in gamma-band synchronization of the sensory and motor cortices. J Neurosci. 2013;33(15):6552–6. https://doi.org/10.1523/jneurosci.5521-12.2013.

Pugh JR, Raman IM. Potentiation of mossy fiber EPSCs in the cerebellar nuclei by NMDA receptor activation followed by postinhibitory rebound current. Neuron. 2006;51(1):113–23. https://doi.org/10.1016/j.neuron.2006.05.021.

Ramnani N, Toni I, Josephs O, Ashburner J, Passingham RE. Learning- and expectation-related changes in the human brain during motor learning. J Neurophysiol. 2000;84(6):3026–35. https://doi.org/10.1152/jn.2000.84.6.3026.

Rancz EA, Ishikawa T, Duguid I, Chadderton P, Mahon S, Häusser M. High-fidelity transmission of sensory information by single cerebellar mossy fibre boutons. Nature. 2007;450(7173):1245–8. https://doi.org/10.1038/nature05995.

Rasmussen A, Jirenhed DA, Hesslow G. Simple and complex spike firing patterns in Purkinje cells during classical conditioning. Cerebellum. 2008;7(4):563–6. https://doi.org/10.1007/s12311-008-0068-2.

Rieubland S, Roth A, Häusser M. Structured connectivity in cerebellar inhibitory networks. Neuron. 2014;81(4):913–29. https://doi.org/10.1016/j.neuron.2013.12.029.

Robinson FR, Fuchs AF. The role of the cerebellum in voluntary eye movements. Annu Rev Neurosci. 2001;24:981–1004. https://doi.org/10.1146/annurev.neuro.24.1.981.

Salin PA, Malenka RC, Nicoll RA. Cyclic AMP mediates a presynaptic form of LTP at cerebellar parallel fiber synapses. Neuron. 1996;16(4):797–803. https://doi.org/10.1016/s0896-6273(00)80099-9.

Sauerbrei Britton A, Lubenov Evgueniy V, Siapas Athanassios G. Structured variability in Purkinje cell activity during locomotion. Neuron. 2015;87(4):840–52. https://doi.org/10.1016/j.neuron.2015.08.003.

Schonewille M, Belmeguenai A, Koekkoek SK, Houtman SH, Boele HJ, van Beugen BJ, Gao Z, Badura A, Ohtsuki G, Amerika WE, Hosy E, Hoebeek FE, Elgersma Y, Hansel C, De Zeeuw CI. Purkinje cell-specific knockout of the protein phosphatase PP2B impairs potentiation and cerebellar motor learning. Neuron. 2010;67(4):618–28. https://doi.org/10.1016/j.neuron.2010.07.009.

Schonewille M, Gao ZY, Boele HJ, Veloz MFV, Amerika WE, Simek AAM, De Jeu MT, Steinberg JP, Takamiya K, Hoebeek FE, Linden DJ, Huganir RL, De Zeeuw CI. Reevaluating the role of LTD in cerebellar motor learning. Neuron. 2011;70(1):43–50. https://doi.org/10.1016/j.neuron.2011.02.044.

Schweighofer N, Doya K, Kuroda S. Cerebellar aminergic neuromodulation: towards a functional understanding. Brain Res Rev. 2004;44(2–3):103–16. https://doi.org/10.1016/j.brainresrev.2003.10.004.

Sears LL, Steinmetz JE. Dorsal accessory inferior olive activity diminishes during acquisition of the rabbit classically conditioned eyelid response. Brain Res. 1991;545(1–2):114–22. https://doi.org/10.1016/0006-8993(91)91276-7.

Sendhilnathan N, Semework M, Goldberg ME, Ipata AE. Neural correlates of reinforcement learning in mid-lateral cerebellum. Neuron. 2020;106(1):188–198.e185. https://doi.org/10.1016/j.neuron.2019.12.032.

Shambes GM, Gibson JM, Welker W. Fractured somatotopy in granule cell tactile areas of rat cerebellar hemispheres revealed by micromapping. Brain Behav Evol. 1978;15(2):94–140. https://doi.org/10.1159/000123774.

Shinoda Y, Sugiuchi Y, Futami T, Izawa R. Axon collaterals of mossy fibers from the pontine nucleus in the cerebellar dentate nucleus. J Neurophysiol. 1992;67(3):547–60. https://doi.org/10.1152/jn.1992.67.3.547.

Snider RS, Stowell A. Receiving areas of the tactile, auditory, and visual systems in the cerebellum. J Neurophysiol. 1944;7(6):331–57. https://doi.org/10.1152/jn.1944.7.6.331.

Snyder RL, Faull RL, Mehler WR. A comparative study of the neurons of origin of the spinocerebellar afferents in the rat, cat and squirrel monkey based on the retrograde transport of horseradish peroxidase. J Comp Neurol. 1978;181(4):833–52. https://doi.org/10.1002/cne.901810409.

Steinmetz JE, Lavond DG, Thompson RF. Classical-conditioning in rabbits using pontine nucleus stimulation as a conditioned-stimulus and inferior olive stimulation as an unconditioned stimulus. Synapse. 1989;3(3):225–33. https://doi.org/10.1002/syn.890030308.

Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. Annu Rev Neurosci Palo Alto. 2009;32:413–34. https://doi.org/10.1146/annurev.neuro.31.060407.125606.

Sugihara I. Compartmentalization of the deep cerebellar nuclei based on afferent projections and aldolase C expression. Cerebellum. 2011;10(3):449–63. https://doi.org/10.1007/s12311-010-0226-1.

Sugihara I, Wu HS, Shinoda Y. Morphology of single olivocerebellar axons labeled with biotinylated dextran amine in the rat. J Comp Neurol. 1999;414(2):131–48.

Suvrathan A, Payne HL, Raymond JL. Timing rules for synaptic plasticity matched to behavioral function. Neuron. 2016;92(5):959–67. https://doi.org/10.1016/j.neuron.2016.10.022.

Szapiro G, Barbour B. Multiple climbing fibers signal to molecular layer interneurons exclusively via glutamate spillover. Nat Neurosci. 2007;10(6):735–42. https://doi.org/10.1038/nn1907.

Tanaka H, Ishikawa T, Kakei S. Neural evidence of the cerebellum as a state predictor. Cerebellum. 2019;18(3):349–71. https://doi.org/10.1007/s12311-018-0996-4.

Tang T, Suh CY, Blenkinsop TA, Lang EJ. Synchrony is key: complex spike inhibition of the deep cerebellar nuclei. Cerebellum. 2016;15(1):10–3. https://doi.org/10.1007/s12311-015-0743-z.

Tang T, Xiao J, Suh CY, Burroughs A, Cerminara NL, Jia L, Marshall SP, Wise AK, Apps R, Sugihara I, Lang EJ. Heterogeneity of Purkinje cell simple spike-complex spike interactions: zebrin- and non-zebrin-related variations. J Physiol. 2017;595(15):5341–57. https://doi.org/10.1113/jp274252.

Tang T, Blenkinsop TA, Lang EJ. Complex spike synchrony dependent modulation of rat deep cerebellar nuclear activity. elife. 2019;8:e40101. https://doi.org/10.7554/eLife.40101.

Ten Brinke MM, Boele HJ, De Zeeuw CI. Conditioned climbing fiber responses in cerebellar cortex and nuclei. Neurosci Lett. 2019;688:26–36. https://doi.org/10.1016/j.neulet.2018.04.035.

Thach WT. Somatosensory receptive fields of single units in cat cerebellar cortex. J Neurophysiol. 1967;30(4):675.

Titley HK, Watkins GV, Lin C, Weiss C, McCarthy M, Disterhoft JF, Hansel C. Intrinsic excitability increase in cerebellar Purkinje cells after delay eye-blink conditioning in mice. J Neurosci. 2020;40(10):2038–46. https://doi.org/10.1523/jneurosci.2259-19.2019.

Trott JR, Apps R. Lateral and medial sub-divisions within the olivocerebellar zones of the paravermal cortex in lobule Vb/c of the cat anterior lobe. Exp Brain Res. 1991;87(1):126–40. https://doi.org/10.1007/bf00228514.

Trott JR, Apps R. Zonal organization within the projection from the inferior olive to the rostral paramedian lobule of the cat cerebellum. Eur J Neurosci. 1993;5(2):162–73. https://doi.org/10.1111/j.1460-9568.1993.tb00482.x.

Trott JR, Armstrong DM. The cerebellar corticonuclear projection from lobule Vb/c of the cat anterior lobe: a combined electrophysiological and autoradiographic study. I. Projections from the intermediate region. Exp Brain Res. 1987a;66(2):318–38. https://doi.org/10.1007/bf00243308.

Trott JR, Armstrong DM. The cerebellar corticonuclear projection from lobule Vb/c of the cat anterior lobe: a combined electrophysiological and autoradiographic study. II. Projections from the vermis. Exp Brain Res. 1987b;68(2):339–54. https://doi.org/10.1007/bf00248800.

Trott JR, Apps R, Armstrong DM. Zonal organization of cortico-nuclear and nucleo-cortical projections of the paramedian lobule of the cat cerebellum. 1. The C-1 zone. Exp Brain Res. 1998a;118(3):298–315. https://doi.org/10.1007/s002210050285.

Trott JR, Apps R, Armstrong DM. Zonal organization of cortico-nuclear and nucleo-cortical projections of the paramedian lobule of the cat cerebellum. 2. The C-2 zone. Exp Brain Res. 1998b;118(3):316–30. https://doi.org/10.1007/s002210050286.

Udo M, Matsukawa K, Kamei H, Minoda K, Oda Y. Simple and complex spike activities of Purkinje cells during locomotion in the cerebellar vermal zones of decerebrate cats. Exp Brain Res. 1981;41(3–4):292–300. https://doi.org/10.1007/bf00238886.

Uusisaari M, Knopfel T. Functional classification of neurons in the mouse lateral cerebellar nuclei. Cerebellum. 2011;10(4):637–46. https://doi.org/10.1007/s12311-010-0240-3.

Uusisaari MY, Knopfel T. Diversity of neuronal elements and circuitry in the cerebellar nuclei. Cerebellum. 2012;11(2):420–1. https://doi.org/10.1007/s12311-011-0350-6.

Valera AM, Binda F, Pawlowski SA, Dupont JL, Casella JF, Rothstein JD, Poulain B, Isope P. Stereotyped spatial patterns of functional synaptic connectivity in the cerebellar cortex. elife. 2016;5:22. https://doi.org/10.7554/eLife.09862.

van Kan PL, Houk JC, Gibson AR. Output organization of intermediate cerebellum of the monkey. J Neurophysiol. 1993;69(1):57–73. https://doi.org/10.1152/jn.1993.69.1.57.

van Kan PL, Horn KM, Gibson AR. The importance of hand use to discharge of interpositus neurones of the monkey. J Physiol. 1994;480(Pt 1):171–90. https://doi.org/10.1113/jphysiol.1994.sp020351.

Voogd J. Comparative aspects of the structure and fibre connexions of the mammalian cerebellum. Prog Brain Res. 1967;25:94–134. https://doi.org/10.1016/s0079-6123(08)60963-2.

Voogd J, Glickstein M. The anatomy of the cerebellum. Trends Neurosci. 1998;21(9):370–5. https://doi.org/10.1016/s0166-2236(98)01318-6.

Voogd J, Pardoe J, Ruigrok TJ, Apps R. The distribution of climbing and mossy fiber collateral branches from the copula pyramidis and the paramedian lobule: congruence of climbing fiber cortical zones and the pattern of zebrin banding within the rat cerebellum. J Neurosci. 2003;23(11):4645–56. https://doi.org/10.1523/jneurosci.23-11-04645.2003.

Wadiche JI, Jahr CE. Patterned expression of Purkinje cell glutamate transporters controls synaptic plasticity. Nat Neurosci. 2005;8(10):1329–34. https://doi.org/10.1038/nn1539.

Wagner MJ, Kim TH, Savall J, Schnitzer MJ, Luo L. Cerebellar granule cells encode the expectation of reward. Nature. 2017;544(7648):96–100. https://doi.org/10.1038/nature21726.

Wang X, Novello M, Gao Z, Ruigrok TJH, De Zeeuw CI. Input and output organization of the mesodiencephalic junction for cerebro-cerebellar communication. J Neurosci Res. 2022;100(2):620–37. https://doi.org/10.1002/jnr.24993.

Welniarz Q, Worbe Y, Gallea C. The forward model: a unifying theory for the role of the cerebellum in motor control and sense of agency. Front Syst Neurosci. 2021;15:644059. https://doi.org/10.3389/fnsys.2021.644059.

Wise AK, Cerminara NL, Marple-Horvat DE, Apps R. Mechanisms of synchronous activity in cerebellar Purkinje cells. J Physiol Lond. 2010;588(13):2373–90. https://doi.org/10.1113/jphysiol.2010.189704.

Witter L, Canto CB, Hoogland TM, de Gruijl JR, De Zeeuw CI. Strength and timing of motor responses mediated by rebound firing in the cerebellar nuclei after Purkinje cell activation. Front Neural Circuits. 2013;7:14. https://doi.org/10.3389/fncir.2013.00133.

Witter L, Rudolph S, Pressler RT, Lahlaf SI, Regehr WG. Purkinje cell collaterals enable output signals from the cerebellar cortex to feed back to Purkinje cells and interneurons. Neuron. 2016;91(2):312–9. https://doi.org/10.1016/j.neuron.2016.05.037.

Wolpert DM, Miall RC, Kawato M. Internal models in the cerebellum. Trends Cogn Sci. 1998;2(9):338–47. https://doi.org/10.1016/S1364-6613(98)01221-2.

Wu HS, Sugihara I, Shinoda Y. Projection patterns of single mossy fibers originating from the lateral reticular nucleus in the rat cerebellar cortex and nuclei. J Comp Neurol. 1999;411(1):97–118. https://doi.org/10.1002/(sici)1096-9861(19990816)411:1<97::aid-cne8>3.0.co;2-o.

Wu B, Blot FG, Wong AB, Osório C, Adolfs Y, Pasterkamp RJ, Hartmann J, Becker EB, Boele HJ, De Zeeuw CI, Schonewille M. TRPC3 is a major contributor to functional heterogeneity of cerebellar Purkinje cells. elife. 2019;8:e45590. https://doi.org/10.7554/eLife.45590.

Xiao J, Cerminara NL, Kotsurovskyy Y, Aoki H, Burroughs A, Wise AK, Luo Y, Marshall SP, Sugihara I, Apps R, Lang EJ. Systematic regional variations in Purkinje cell spiking patterns. PLoS One. 2014;9(8):e105633. https://doi.org/10.1371/journal.pone.0105633.

Yamaguchi K, Itohara S, Ito M. Reassessment of long-term depression in cerebellar Purkinje cells in mice carrying mutated GluA2 C terminus. Proc Natl Acad Sci U S A. 2016;113(36):10192–7. https://doi.org/10.1073/pnas.1609957113.

Yang Y, Lisberger SG. Purkinje-cell plasticity and cerebellar motor learning are graded by complex-spike duration. Nature. 2014;510(7506):529–32. https://doi.org/10.1038/nature13282.

Yeo CH, Hardiman MJ, Glickstein M. Discrete lesions of the cerebellar cortex abolish the classically conditioned nictitating membrane response of the rabbit. Behav Brain Res. 1984;13(3):261–6. https://doi.org/10.1016/0166-4328(84)90168-2.

Yeo CH, Hardiman MJ, Glickstein M. Classical conditioning of the nictitating membrane response of the rabbit. I. Lesions of the cerebellar nuclei. Exp Brain Res. 1985a;60(1):87–98. https://doi.org/10.1007/bf00237022.

Yeo CH, Hardiman MJ, Glickstein M. Classical conditioning of the nictitating membrane response of the rabbit. II. Lesions of the cerebellar cortex. Exp Brain Res. 1985b;60(1):99–113. https://doi.org/10.1007/bf00237023.

Zackowski KM, Thach WT, Bastian AJ. Cerebellar subjects show impaired coupling of reach and grasp movements. Exp Brain Res. 2002;146(4):511–22. https://doi.org/10.1007/s00221-002-1191-9.

Zang Y, De Schutter E. Climbing fibers provide graded error signals in cerebellar learning. Front Syst Neurosci. 2019;13:46. https://doi.org/10.3389/fnsys.2019.00046.

Zhang W, Linden DJ. Long-term depression at the mossy fiber-deep cerebellar nucleus synapse. J Neurosci. 2006;26(26):6935–44. https://doi.org/10.1523/jneurosci.0784-06.2006.

Zhou HB, Lin ZM, Voges K, Ju CH, Gao ZY, Bosman LWJ, Ruigrok TJ, Hoebeek FE, De Zeeuw CI, Schonewille M. Cerebellar modules operate at different frequencies. elife. 2014;3:47. https://doi.org/10.7554/eLife.02536.