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The Cerebellar Cortex

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Abstract

The cerebellar cortex is an important system for relating neural circuits and learning. Its promise has reflected the longstanding idea that it contains simple, repeated circuit modules with only a few cell types and a single plasticity mechanism that mediates learning according to classical Marr-Albus models. However, emerging data have revealed surprising diversity in neuron types, synaptic connections, and plasticity mechanisms, both locally and regionally within the cerebellar cortex. In light of these findings, it is not surprising that attempts to generate a holistic model of cerebellar learning across different behaviors have not been successful. While the cerebellum remains an ideal system for linking neuronal function with behavior, it is necessary to update the cerebellar circuit framework to achieve its great promise. In this review, we will highlight recent advances in our understanding of cerebellar-cortical cell types, synaptic connections, signaling mechanisms, and forms of plasticity that enrich cerebellar processing.

Keywords

Cerebellar interneurons; Purkinje cell; ephaptic signaling; climbing fiber; cerebellar circuit; motor learning

I. Introduction

The apparent simplicity and regularity of cerebellar circuit organization has played a key role in establishing it as a model system for linking neuronal activity with behavior and learning. The cerebellar cortex contains a central trisynaptic arc: primary input from mossy fibers (MFs) excites granule cells (GrCs), which in turn excite Purkinje cells (PC) that provide the sole output synapses of the cerebellar cortex (Figure 1A). In addition, local interneurons termed Golgi cells (GoCs) and molecular layer interneurons (MLIs) inhibit GrCs and PCs respectively, while climbing fibers (CFs) powerfully excite PCs. This striking ‘crystalline’ cellular architecture is repeated throughout the cerebellar cortex, and has inspired extensive theoretical work to explain how this circuit generates learning.

Cerebellar research has been largely guided by a conceptual framework referred to as the “Marr-Albus model” (Albus, 1971; Ito, 1972; Marr, 1969). This classical view has evolved over time, but is based on the premise that the cerebellar cortex utilizes a small number of

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cell types organized into repeated modules in order to 1) separate incoming sensorimotor information provided by MFs into unique GrC firing patterns, and 2) selectively modify GrC to PC connections to alter motor output. According to Marr-Albus models, the first goal is achieved in the GrC layer. Here, MFs from diverse sources synapse onto a much larger pool of GrCs (Raymond and Medina, 2018), and random input mixing and strong inhibition establishes sparse, decorrelated GrC activity patterns. Learning requires that GrCs uniquely represent each sensorimotor context carried by MFs. For example, in cerebellar-dependent associative learning tasks such as eyelid conditioning, GrCs carry information about the conditioned stimulus that predicts a noxious corneal airpuff (Steinmetz et al., 1989). GrCs must encode the conditioned stimulus with a unique population response to distinguish it from other stimuli. In the Marr-Albus model, sparse coding, in which very few GrCs (<5%) respond to any given stimulus, reduces overlap and aids in pattern separation. To achieve the second goal, hundreds of thousands of GrCs converge onto each PC. In turn, PCs generate predictive motor outputs that are refined when climbing fibers (CFs) instruct long-term synaptic depression (LTD) of GrC-to-PC synapses in response to motor errors.

It is increasingly clear, however, that the cerebellar cortex is far more complex than the simple framework envisioned by Marr-Albus models. Recent work has revealed considerable diversity in cell types (Figure 1B), regional circuit specializations, plasticity mechanisms and other physiological processes. At the same time, behaviors associated with cerebellar processing have expanded widely across both motor and nonmotor domains, challenging the idea of a homogenous cerebellar circuit function. The goal of this review is to highlight advances in our understanding of the cerebellar cortex, with a particular focus on new cell types and connections, to provide a more comprehensive framework for evaluating cerebellar computation.

Emerging Principles:

- The cerebellar cortex has far greater molecular, anatomical and functional diversity within ‘cell types’ than was previously appreciated.
- New connections and regional specializations have been identified that alter the previously accepted cerebellar circuit diagram.
- New synaptic and intrinsic plasticity mechanisms have been identified that could support learning.
- New roles have been identified for previously recognized cell types and synapses
- New modulatory mechanisms and population dynamics have been revealed that could flexibly alter behavior and learning

II. Granule Cell Layer

The granule cell layer utilizes multiple mechanisms to process incoming MF input. Current evidence suggests that this processing can generate GrC activity that deviates from the sparse levels predicted by Marr-Albus models (Giovannucci et al., 2017; Knogler et al., 2017; Lanore et al., 2021; Ozden et al., 2012; Sylvester et al., 2017) (Figure 2A), and has suggested new roles for GrC layer processing (Wagner and Luo, 2020). Here we will review

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what is known about the GrC layer, and highlight recent advances that update classical views of its role in cerebellar function.

A. Mossy Fibers

Mossy fibers are the major excitatory inputs to the cerebellar cortex. They are predominantly glutamatergic, but can also release other neurotransmitters such as acetylcholine (Fore et al., 2020). Numerous regions with different functional roles provide MF inputs (Sillitoe et al., 2012): the pontine nucleus and the tegmental pontine reticular nucleus are involved in vision, planning and executing movement; the spinal cord and cuneate provide proprioceptive signals; the vestibular nucleus and primary vestibular inputs are involved in balance, posture and the control of eye movement; the lateral reticular nucleus and red nucleus are involved in coordinating movement, and the cerebellar nuclei (CbN, also sometimes referred to as deep cerebellar nuclei, or DCN) that can provide feedback corollary discharge signals to enhance associative learning (Gao et al., 2016; Houck and Person, 2014). Remarkably, these diverse sources all give rise to MFs within the granular layer that have the same basic ultrastructure (Billings et al., 2014; Eccles et al., 1967). MF boutons are large, contain multiple active zones, and make synapses with many tens of GrCs. Each MF bouton and its GrC dendritic targets are ensheathed by glia within specialized structures known as glomeruli. MFs also activate GoCs, UBCs, and candelabrum cells (Kanichay and Silver, 2008; Mugnaini et al., 2011; Osorno et al., 2021).

The glomerular organization confers specialized signaling properties. Within a glomerulus, neurotransmitters can pool, accumulate and persist to activate receptors on many cells. For example, single vesicle fusion at a MF active zone causes rapid stochastic excitation of target GrCs, and the collective release of many vesicles leads to glutamate pooling and reliable excitation of multiple GrCs (DiGregorio et al., 2002). Neurotransmitter pooling also allows MFs to suppress release from GoCs, and GoCs to inhibit release from MFs (Mitchell and Silver, 2000a, b), thereby allowing transmitters from different sources to provide both positive and negative feedback to GrCs.

MFs are specialized to favor fast and reliable excitatory synaptic transmission that may contribute to the dense GrC responses that have recently been observed *in vivo*. MFs have ultrafast action potentials, tight coupling of calcium channels to vesicle release, rapid exocytosis, an extremely large readily-releasable vesicle pool, rapid endocytosis and vesicle replenishment to sustain transmission, and fast AMPA receptors that recover rapidly from desensitization (Delvendahl and Hallermann, 2016; Hallermann et al., 2010; Ritzau-Jost et al., 2014; Saviane and Silver, 2006; Xu-Friedman and Regehr, 2003). Single MF action potentials can be translated to postsynaptic spikes when GrC inhibition is low (Chadderton et al., 2004). However, this powerful transmission is counteracted by synaptic inhibition onto GrCs that can impose a requirement for either multiple MFs (Jorntell and Ekerot, 2006) or bursting in single MFs (Rancz et al., 2007) to drive GrC spiking.

MFs originating from different sources can synapse onto a single GrC (Huang et al., 2013). Different MF pathways vary in their initial synaptic strength and short-term dynamics, which range from strong depression to pronounced facilitation. Consequently, the same presynaptic firing pattern in different types of MFs evokes GrC responses with distinct

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temporal dynamics, allowing decorrelation in the time domain (Chabrol et al., 2015) (Figure 2B). The logic of MF input mixing is only beginning to be elucidated (Shuster et al., 2021), and is a key challenge in our understanding of GrC layer computation. Together, input mixing and input diversity can provide a rich repertoire of signal transformations that decorrelates incoming inputs and enhances pattern separation.

B. Granule cells

GrCs have a small soma with an average of four short dendrites (Eccles et al., 1967). They have a high input resistance, making them sensitive to small changes in synaptic conductance. While classical models assume that GrCs are homogenous, recent studies suggest that there are three molecularly separable GrC subtypes located preferentially in different cerebellar regions (Kozareva et al., 2021). In addition, GrCs within a given region are not uniform (Straub et al., 2020). Thus, while their functional differences are not known, it seems likely that GrCs are specialized to differentially contribute to processing across regions, and their local differences may help decorrelate MF inputs.

Transgenic animals have provided a means to assess the contribution of the GrC layer to cerebellar-dependent behaviors. For example, suppressing the output of the GrC layer by eliminating P-type calcium channels in most GrCs impairs motor learning without affecting overall motor performance (Galliano et al., 2013). However, manipulations with temporal and regional specificity will be necessary for more detailed analysis of granule cell layer computation.

C. Golgi Cells

GoCs have profuse axons within the GrC layer that can span several millimeters to inhibit thousands of GrCs by releasing GABA, and in some cases glycine. GoCs inhibit GrCs via two distinct types of $GABA_A$ receptors: low affinity α_1 subunit-containing receptors that mediate inhibitory postsynaptic currents (IPSCs) lasting several milliseconds, and high-affinity, non-desensitizing $\alpha_6\delta$ subunit-containing $GABA_A$ receptors that mediate a very slow tonic current on a timescale of seconds (Brickley et al., 1996; Rossi and Hamann, 1998)(Figure 2C). This inhibition can elevate the threshold for GrC spiking in response to MF input (Brickley et al., 1996; Chadderton et al., 2004).

GoCs fire spontaneously at around 5Hz and continuously release GABA to tonically inhibit GrCs. GoCs provide highly variable phasic and tonic inhibition to different GrCs (Crowley et al., 2009) (Figure 2C). Such diversity may arise from differences in the number of GoC inputs per glomerulus (Jakab and Hamori, 1988), the number of dendrites per GrC (Palay and Chan-Palay, 1974), the diversity of GoC subtypes (Geurts et al., 2001; Kozareva et al., 2021; Neki et al., 1996; Simat et al., 2007), and differences in GABA receptor expression (Wall, 2002). In addition, the magnitude of GrC tonic inhibition is regulated by bidirectional neuromodulation of GoC firing rates (Fleming and Hull, 2019; Fore et al., 2020), dynamic regulation of GoC firing via intrinsic plasticity (Hull et al., 2013), and by altering the sensitivity of δ-containing $GABA_A$ receptors (Rudolph et al., 2020). These many ways of regulating tonic GrC inhibition provide a means of increasing processing flexibility within the GrC input layer.

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GoCs are excited by MFs to evoke feedforward inhibition, and by GrCs to evoke feedback inhibition. The role of GoC feedforward inhibition is currently unclear, as it is weaker and is more temporally variable than other feedforward circuits (Duguid et al., 2015; Kanichay and Silver, 2008; Pouille and Scanziani, 2001). GoCs are also excited by many GrCs, which likely contributes to their broad stimulus tuning, and may generate feedback inhibition that is proportional to the average ongoing GrC population activity. In other systems, such broadly tuned feedback inhibition can enhance dynamic range and sharpen tuning, but it is not known if this is the case for GrCs, where tuning can be remarkably precise and may be determined primarily by subthreshold MF input (Chen et al., 2017).

There are several intriguing aspects of GoC signaling that should be considered in evaluating their role in cerebellar processing. First, GoCs are gap-junction coupled to each other, primarily on dendrites in the molecular layer, allowing them to share synaptic input from the parallel fibers (Vervaeke et al., 2012). Second, GoC cells inhibit other GoCs (Hull and Regehr, 2012), which may enrich the diversity of GoC responses and spiking in their target GrCs. Third, there are two different subtypes of GoCs based on the differential gene expression, including Gjd2 that encodes connexin 36 (Kozareva et al., 2021). And finally, in a departure from feedforward models of cerebellar processing, both glutamatergic and glycinergic/GABAergic neurons of the CbN project back to GoCs (Ankri et al., 2015; Batini et al., 1989; Houck and Person, 2015). The inhibitory projections extensively innervate a subpopulation of exclusively GABAergic GoCs with distinctive firing properties (Ankri et al., 2015). This raises the possibility that inhibitory CbN feedback could ultimately decrease GrC inhibition, and promote the flow of signals within targeted regions of the cerebellar cortex.

We are only beginning to understand how GoCs contribute to cerebellar processing. Tonic inhibition can increase the signal-to-noise of sensory responses by reducing spontaneous GrC spiking (Duguid et al., 2012), and regulate the gain of GrC spiking to extend the dynamic range over which GrCs can read out MF input (Mitchell and Silver, 2003). This may help GrCs linearly encode vestibular inputs over a wide range (Arenz et al., 2008). There are also many poorly understood aspects of GoC signaling, including the behavioral importance of GoC inhibition. It has long been hypothesized that inhibition from GoCs is necessary for pattern separation, and hence specificity of cerebellar associative learning, but this has yet to be tested. Further, selective deletion of the δ-subunit of $GABA_A$ receptors in GrCs strongly attenuates tonic inhibition and increases GrC excitability, but surprisingly does not impair motor performance or motor learning, instead only influencing nonmotor behaviors (Rudolph et al., 2020). This suggests that the cerebellum may utilize extensive compensatory mechanisms to overcome chronic reductions of inhibitory tone, and that restricting GrC layer excitability is an essential feature of cerebellar processing.

D. Unipolar Brush Cells

Unipolar brush cells (UBCs) are excitatory interneurons in the GrC layer that can transform brief MF inputs into long-lasting changes in firing, and are important for temporal processing (Mugnaini et al., 2011). UBCs are typically excited by a single MF or by

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another UBC. In turn, they excite several hundred GrCs, and other UBCs, enabling GrC layer responses that greatly outlast MF inputs (Mugnaini et al., 2011).

UBCs have traditionally been divided into ON and OFF subtypes based on their response to MF inputs, but there is growing evidence that UBCs have a continuum of properties (Figure 2D). In traditional OFF-UBCs, a MF burst suppresses firing for hundreds of milliseconds by activating inhibitory group II metabotropic glutamate receptors (mGluR2/3) coupled to inwardly rectifying potassium channels (Borges-Merjane and Trussell, 2015; Knoflach and Kemp, 1998; Russo et al., 2008). In traditional ON-UBCs, MF activation increases firing primarily due to a prolonged glutamate signal and long-lasting AMPA receptor activation (Kinney et al., 1997; Rossi et al., 1995; van Dorp and De Zeeuw, 2014; Zampini et al., 2016). However, in many UBCs, metabotropic glutamate receptors also dominate excitatory responses (mGluR1 coupled to TRPC3). snRNAseq experiments revealed inversely correlated expression gradients in the mGluR1 and mGluR2/3 signaling pathways in UBCs, and electrophysiological studies found that MF bursts evoke continuously varying responses in different UBCs (Guo et al., 2020; Kozareva et al., 2021). In this way, graded molecular variations across components of metabotropic signaling pathways generates a diverse continuum of cell-intrinsic synaptic responses that is suited for temporal learning over multiple timescales.

There is a high degree of specificity in the MF (Balmer and Trussell, 2019) and inhibitory connections made onto different types of UBCs. Inhibition by both GoCs and PCs shapes UBC responses, and the contributions of different neurotransmitters and receptors are specialized for different types of UBCs (Dugue et al., 2005; Guo et al., 2021; Kim et al., 2012). This complexity and specificity of connections is a enriches the diversity of GrC population responses, and is a departure from the traditional view that global synaptic inhibition regulates the GrC layer.

Most studies of UBCs have focused on vestibular regions, where UBCs transform sinusoidally modulated inputs into responses with different phase shifts and amplitudes (Guo et al., 2020; Zampini et al., 2016). As a result, GrCs fire with diverse phases that are useful for cerebellar learning. mGluR2-mediated outward currents generate phase inversion, and phase delays reflect slow AMPAR recovery from desensitization. Although there are pronounced regional differences in UBC densities, they are present in all regions of the cerebellar cortex. Because a single UBC can influence many GrCs, even a low density of UBCs will likely play an important role in regions outside of the vestibulocerebellum.

III. The Molecular Layer

Following integration and processing in the GrC layer, information is conveyed to the molecular layer via GrC axons. These axons have an ascending branch that then bifurcates to give rise to parallel fibers, so named for their dense parallel arrangement along the mediolateral axis of the cerebellar cortex. Here, GrCs release glutamate via *en passant* synapses on both their ascending axon and parallel fibers onto the dendrites of PCs, MLIs, GoCs, and at least some types of PC layer interneurons (PLIs) (Figure 3A). In addition, each PC receives a single CF fiber input. Studies of the molecular layer have centered on

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CF-instructed plasticity, but recent studies suggest additional complexity and processing in this layer.

A. Molecular Layer Interneurons

Molecular layer interneurons are the most abundant inhibitory interneurons in the cerebellar cortex. They are spontaneously active (~ 10 Hz), and their dendrites and axons are confined to the parasagittal plane (orthogonal to the parallel fibers). MLIs are directly and powerfully excited by GrC parallel fibers, and are excited by a spillover of glutamate from CF to PC synapses (Jorntell and Ekerot, 2003; Szapiro and Barbour, 2007). MLIs in turn inhibit other MLIs and PCs, and some MLIs are inhibited by PCs (Witter et al., 2016). Interestingly, MLIs do not inhibit GoCs despite their close proximity (Hull and Regehr, 2012).

MLIs have previously been subdivided into stellate cells and basket cells based on their position and morphology. Stellate cells are located in the distal two thirds of the molecular layer, and make conventional inhibitory synapses onto both MLIs and PCs. Basket cells are located in the inner third of the molecular layer, and in additional to conventional synapses, they form specialized pinceau structures on the initial segment of PCs that inhibit PC firing through extremely rapid ephaptic signals (Blot and Barbour, 2014).

snRNAseq studies have identified two molecularly distinct types of MLIs, MLI1 and MLI2, that surprisingly do not correspond to stellate cells and basket cells (Kozareva et al., 2021) (Figure 3B, *left*). These subtypes are intermingled throughout the molecular layer, and their morphologies of both depend upon their layer position. For both types of MLIs, neurons located in the top two thirds of the molecular layer look like stellate cells, while those in the inner third of the molecular layer look superficially like basket cells, extending axons to the PC layer (although MLI1s in the inner third of the molecular layer have a more clearly defined pinceau). MLI1 and MLI2 neurons are physiologically distinct. MLI1s have higher rates of spontaneous activity, are less sensitive to depolarization, and are electrically coupled, whereas MLI2s are not electrically coupled. MLI1s also exhibit considerable molecular diversity that is dependent upon distance from the PC layer, with *Grm8* (mGluR8) and other genes expressed at much higher levels in MLI1s near the PC layer (Figure 3B, *right*). It is not clear whether MLI1s are two discrete subtypes (MLI1_1 and MLI1_2), or a single population with continuously varying properties.

New insights are emerging regarding the contribution of MLIs to behavior. Measurements of MLI activity with genetically encoded calcium indicators have revealed large coordinated changes in MLI activity that correlate with movement rate (Gaffield and Christie, 2017). In addition, MLIs can regulate the magnitude and extent of CF-evoked calcium signals by regulating the excitability of PC dendrites, thereby controlling GrC to PC synaptic plasticity and possibly motor learning (Rowan et al., 2018). Moreover, a conditional genetics approach based on birth date has allowed selective suppression of either stellate cell or basket cell synapses (Brown et al., 2019), and revealed that suppression of stellate cell synapses increases simple spike regularity, while suppression of basket cell synapses increases simple spike frequency.

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Currently, the roles of molecularly defined MLI subtypes are not known, and it cannot be assumed that the inputs and outputs of MLI1 and MLI2 are the same. Thus, clarification of their connectivity could provide important insight into their function. Because previous *in vivo* studies were performed prior to the identification of MLI1 and MLI2 subtypes, it will be important to determine whether there are differences in the activity of these populations, or in their influences on postsynaptic targets and behavior.

B. Climbing Fibers

Neurons in the inferior olive give rise to glutamatergic CFs that form extensive synaptic contacts onto PC dendrites, and each PC receives a single CF input. CFs powerfully depolarize PCs, activating voltage-activated calcium channels to produce both a dendrite-wide regenerative calcium spike and a brief flurry of sodium-based simple spikes in the soma and axon. This distinctive combined response is known as a “complex spike”. CF activation instructs long-term depression (LTD) of GrC to PC synapses (Ito, 1989). However, recent work suggests that CFs have additional roles.

Even though CFs do not directly contact MLIs or GoCs, glutamate released from CF to PC synapses spills out to excite nearby MLIs and GoCs (Nietz et al., 2017; Szapiro and Barbour, 2007) (Figure 3C). When CFs excite nearby MLIs, they can generate feedforward inhibition of more distant MLIs (Coddington et al., 2013). Hence, CF spillover can lead to both inhibition and disinhibition of nearby PCs (Arlt and Hausser, 2020). Similarly ,CF spillover can activate both excitatory and inhibitory glutamate receptors on GoCs (Nietz et al., 2017), and can therefore have a complex influence on processing in the GrC layer.

At present, the role of such CF activity in behavior and learning remains unclear. While considerable evidence supports a role for CFs in signaling supervised learning according to Marr-Albus models, recent evidence also suggests a broader role CFs, which may include forms for reinforcement learning for some behaviors (Hull, 2020). Hence, it will be important to understand the relationship between the different cellular plasticity and signaling mechanisms mediated by CFs and their diverse roles in behavior and learning.

IV. The Purkinje Cell Layer

Once viewed as containing only a homogenous pool of PC somata, the PC layer has undergone perhaps the largest revision in the cerebellar cortex in terms of identified cell types and connections. Here we will review this newfound complexity, highlighting the importance of previously underappreciated interneurons and recurrent synapses.

A. Purkinje cell layer interneurons

Interneurons whose cell bodies are located in or near the PC layer are known collectively as Purkinje layer interneurons (PLIs). Previous studies suggested a subdivision of PLIs into three types: Lugaro cells, globular cells and candelabrum cells (Figure 3A). However, the properties of PLIs have been incompletely characterized, and these subdivisions should be considered tentative. Consequently, their functional roles remain obscure, and they are not included in most models of the cerebellar cortex.

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Lugaro cells are GABAergic/glycinegic PLIs with a characteristic fusiform soma that are inhibited by PCs, that locally inhibit GoCs and MLIs, and that send long-range axons to distant targets in the cerebellar cortex (Laine and Axelrad, 1996; Miyazaki et al., 2020; Palay and Chan-Palay, 1974; Sahin and Hockfield, 1990; Simat et al., 2007). Globular cells are glycinegic cells located near or below the PC layer that are inhibited by PCs (Hirono et al., 2012; Laine and Axelrad, 2002). Finally, there are candelabrum cells, which were identified in 1994 based solely on their distinctive light-level morphology (Laine and Axelrad, 1994). Until recently, candelabrum cells were the most enigmatic neuron of the cerebellar cortex.

Molecular characterization of the adult cerebellar cortex using snRNAseq has provided important insights by identifying three types of PLIs that may correspond to Lugaro cells, globular cells and candelabrum cells (Kozareva et al., 2021). These three types of PLIs are present in all regions of the cerebellar cortex, and together the PLIs are more numerous than GoCs.

Molecular characterization, identification of a transgenic mouse that labels candelabrum cells, electrophysiological recordings, and serial EM reconstructions have led to a major clarification of candelabrum cells within the cerebellar cortical circuitry (Osorno et al., 2021). These data revealed that MFs and GrCs excite candelabrum cells, and that PCs inhibit them. Candelabrum cells in turn primarily inhibit MLIs, leading to disinhibition of PCs (Figure 3E). The ability of candelabrum cells to weigh inputs to the cerebellar cortex (MFs), outputs from the cortex (PCs), and activity within the cortex (GrCs) to ultimately regulate PC excitability indicates their function is distinct from that of MLIs and GoCs.

Based on their prevalence, ubiquitous distribution, and unique circuit properties, PLIs must be considered important interneurons of the cerebellar cortex that need to be more fully characterized and then incorporated into circuit models to gain a full understanding of cerebellar processing.

B. Purkinje Cells

Purkinje cells fire spontaneous action potentials at high frequency (~20-100 Hz), and utilize a great many voltage and calcium-activated channels to generate diverse firing patterns. Despite this capacity for generating complex, nonlinear responses, there is a linear relationship between the number of active GrC inputs and the firing rate of the target PC (Walter and Khodakhah, 2009). It is possible, however, that when enough GrC inputs are activated, non-linearities can be generated by local dendritic spiking accompanied by a burst of simple spikes and subsequent pauses in firing (Zang and De Schutter, 2021).

PCs are organized into approximately 200 μm wide parasagittal ‘microzones’ that are thought to constitute discrete processing modules, and that can exhibit differential activity patterns during behavior (Heffley et al., 2018; Kostadinov et al., 2019; Tsutsumi et al., 2019). Microzones are innervated by CFs from discrete subdivisions of the inferior olive, and make specific contacts within the subregions of the cerebellar nuclei (Apps et al., 2018). Thus, microzones establish functional loops between the cerebellar cortex, CbN and IO.

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PCs also have diverse molecular and physiological properties that correlate with microzonal organization. Molecular specialization is apparent in the differential expression pattern of Aldolase C (Aldoc, or “zebrin II”) that gives rise to the parasagittal zebrin stripes of the cerebellar cortex (Hawkes and Gravel, 1991). Aldoc− PCs express more TRPC3, fire at higher frequencies (Zhou et al., 2014), are more vulnerable to excitotoxity (Slemmer et al., 2007), express different glutamate transporters and are more susceptible to LTD (Wadiche and Jahr, 2005), and project to more rostrodorsal regions of the cerebellar nuclei (Fujita et al., 2014; Sugihara and Shinoda, 2007). This likely accounts for differential effects on cerebellar behaviors in PC-specific TRPC3 KO mice, in which eyelid conditioning is defective (in Aldoc− regions) and eye movement adaptation is unaffected (Aldoc + region) (Wu et al., 2019). RNA_{seq} data indicate that PCs can be further subdivided into seven Aldoc+ and two Aldoc− subtypes that are differentially distributed within the cerebellar cortex (Kozareva et al., 2021), thought how these different PC subtypes are functionally specialized is not known.

Importantly, PCs do not simply convey output from the cerebellar cortex, as they have extensive axonal collaterals confined to a parasagittal plane that feed back to influence processing within the cerebellar cortex (Witter et al., 2016). PCs strongly inhibit other PCs, candelabrum cells, Lugaro cells, globular cells, some MLIs, GrCs in some regions and a subset of UBCs (Guo et al., 2021; Guo et al., 2016; Hirono et al., 2012; Orduz and Llano, 2007; Witter et al., 2016). PC collateral feedback could have several functional roles. In very young animals, collaterals propagate patterned waves of PC spiking that participate in the developmental refinement of downstream circuits (Watt et al., 2009). In adults, PC feedback could be a gain control mechanism that allows elevated PC output to suppress elements within the cerebellar cortex to maintain cerebellar cortical activity within an optimal range. PC feedback could also control the timing of firing of many elements of the cerebellar cortex (de Solages et al., 2008; Witter et al., 2016), though additional studies are needed to test such predictions.

VI. Mechanisms and Principles of Cerebellar Circuit Processing

In this section we highlight new advances and non-classical mechanisms of neuronal signaling likely to play a major role in cerebellar circuit processing.

A. Ephaptic Signaling

Ephaptic signaling has recently been shown to powerfully influence PC firing (Figure 3C-D). This form of signaling occurs when current flow across the neuronal membrane generates extracellular signals large enough to alter the firing of neighboring neurons (Anastassiou and Koch, 2015). Ephaptic signaling regulates PC firing in three ways: First, basket cell axons regulate sodium channels in PC axons (Figure 3D). Basket cells have a characteristic presynaptic specialization known as a pinceau that surrounds the proximal axon of PCs and lacks chemical synapses (Iwakura et al., 2012). When an action potential invades a pinceau, it opens potassium channels that produce a depolarizing extracellular signal. In turn, this extracellular depolarization almost instantly inhibits the activation of voltage-activated sodium channels in the axon of its associated PC (Blot and Barbour, 2014).

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Second, ephaptic coupling also occurs between PCs (Figure 3D). When an action potential in a PC opens sodium channels in its own initial segment, it generates a hyperpolarizing extracellular signal that activates sodium channels in the axons of neighboring PCs to rapidly initiate spiking (Han et al., 2018). Thus, while opposite in effect, ephaptic signals from both basket cells and other PCs directly influence the site of PC action potential generation by locally regulating voltage-activated sodium channels.

PC firing is also regulated by a third form ephaptic signaling. CF synapses evoke a large intracellular depolarization of a PC dendrite that is accompanied by an extracellular hyperpolarization (Figure 3C). This extracellular hyperpolarization locally excites neighboring PC dendrites, but these dendrites lack the high density of sodium channels present in the axon. However, the extracellular hyperpolarization is sufficiently large and widespread that it also passively hyperpolarizes the somas and initial segments of nearby PCs to inhibit firing. This generates the surprising property that a powerful excitatory synapse almost instantly inhibits firing in neighboring PCs (Han et al., 2020).

Ephaptic signaling has several functional consequences in the cerebellum. Ephaptic inhibition provided by basket cells is almost a millisecond faster than chemical inhibition (Blot and Barbour, 2014). Consequently, direct GrC synaptic excitation and disynaptic MLI ephaptic inhibition of PCs occur roughly simultaneously, perhaps allowing GrCs to produce a net inhibition of PC spiking. In addition, ephaptic coupling between PCs could promote synchronous PC firing that is very rapid, with the firing of neighboring PCs having a dip at 0 latency and a peak at ±0.6 ms latency (Han et al., 2018). This mechanism may contribute to very fast PC layer oscillations observed *in vivo* (~200 Hz)(de Solages et al., 2008). In contrast, CF-mediated ephaptic inhibition of nearby PCs may briefly pause their firing (Han et al., 2020). Unfortunately, in contrast to other types of signaling that can be manipulated either pharmacologically or molecularly, it is not possible to selectively manipulate ephaptic signaling, making it challenging to directly determine its role in behavior and learning.

B. Spontaneous firing

Unlike most cortical areas, the cerebellar cortex contains many cell-types that fire action potentials spontaneously, including PCs, GoCs, and MLIs. The biophysical basis of such pacemaking has been well described for most cerebellar neurons (Hausser et al., 2004; Khaliq et al., 2003; Raman and Bean, 1999). For PCs, the unusually high rate of spontaneous firing (~20-100 Hz) comes at considerable energetic cost that likely makes them susceptible to cell death. This suggests that high spontaneous firing rates must have computational advantages. One possibility is that this property allows changes in PC firing to rapidly and bidirectionally influence the firing of CbN neurons. Multiple disorders ranging from ataxias to Autism Spectrum Disorders have been linked to inappropriate firing rates in PCs, further indicating that PC outputs must be finely calibrated to maintain normal cerebellar function (De Zeeuw et al., 2011; Tsai et al., 2012). It has also been suggested that changes in the precision of PC firing independent of changes in the spike rate can lead to cerebellar disfunction (Walter et al., 2006), although how this affects firing in the CbN sufficiently to disrupt cerebellar function is not understood.

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C. Population Synchrony

There is considerable evidence that the cerebellar cortex can utilize a rate code for PC signaling to downstream CbN neurons to control behavior (Chen et al., 2016; Herzfeld et al., 2015; Payne et al., 2019). However, recent findings also suggest a role for temporal coding mediated by synchronous firing within different neuronal populations (Person and Raman, 2012). Accordingly, emerging evidence has suggested that there are multiple circuit mechanisms that allow certain classes of cerebellar neurons to synchronize their spiking.

i. Mechanisms of Cerebellar synchrony—In addition to ephaptic signaling discussed above, gap junctions are thought to play a key role synchronizing neuronal firing, with IO neurons (the source of CFs) and subpopulations of GoCs and MLI1s all expressing connexin 36. These gap junctions pass an attenuated and filtered action potential consisting of a small depolarization followed by a prominent slow AHP (Condorelli et al., 1998; Dugue et al., 2009; Llinas et al., 1974; Sotelo et al., 1974; van Welie et al., 2016; Vervaeke et al., 2010). This combined, passive sequence of depolarization followed hyperpolarization can act much like a traditional synaptic feedforward inhibitory circuit to enforce integration time windows and contribute to population synchrony (Hoehne et al., 2020).

Gap junction coupling of GoC dendrites (Vervaeke et al., 2012) has been shown to synchronize their firing and produce low frequency oscillations (5-30 Hz) in the GrC layer during periods of quiet wakefulness (Dugue et al., 2009). While the behavioral role of GrC layer oscillations remains unclear, they may support timing computations in the GrC layer by establishing narrow time windows for GrC spiking, and help bind activity in the cerebellum and neocortex during periods of motor preparation or passive expectancy (Courtemanche and Lamarre, 2005; O'Connor et al., 2002). GoC gap junctions are also thought to diversify their responses to allow both broad, relatively homogenous population activity on the timescale of seconds, as well as more heterogeneous, task specific activity on faster time scales (Gurnani and Silver, 2021).

Gap junctions can also synchronize MLI firing (Mann-Metzer and Yarom, 1999), such that the firing of two MLIs is correlated with a dip at 0 ms and peak firing offset by 1.7 ms (Han et al., 2018). MLI dendrites are confined to a parasagittal plane, and the extent of electrical coupling is strongest in MLI1s near the PC layer (Alcami and Marty, 2013; Kozareva et al., 2021). This suggests that electrical coupling could synchronize MLI1 basket cell firing within parasagittal planes (Hoehne et al., 2020), and may synchronize PC firing within parasagittal planes (Wise et al., 2010). Calcium imaging data suggests that MLI activity is correlated during movement (Gaffield and Christie, 2017), but this has not been addressed with high-temporal measurements (such as electrophysiology), and the role of electrical coupling is not known.

Electrical coupling can also promote synchronous firing of neighboring IO neurons with a precision of several milliseconds by synchronizing subthreshold membrane potential oscillations (Leznik and Llinas, 2005; Llinas and Yarom, 1986; Long et al., 2002). This results in synchronous CF activation during behaviors (Blenkinsop and Lang, 2006). While the role of such synchrony is debated, it has been hypothesized that it coordinates the pauses

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that follow complex spikes in many PCs, and can regulate CF-dependent associative learning (Kitazawa and Wolpert, 2005).

Synaptic inhibition can also promote synchronous firing. Feedforward inhibitory synapses can regulate spike timing by restricting the integration time window of their targets (Pouille and Scanziani, 2001). Such effects have been demonstrated in the cerebellum for feedforward connections from MLIs to PCs (Mittmann et al., 2005), where GrC inputs are integrated in a brief window due to feedforward MLI inhibition. Recurrent inhibition can also promote synchrony. In particular, recurrent inhibitory connections between PCs (Witter et al., 2016), between MLIs (Palay and Chan-Palay, 1974) and between GoCs (Hull and Regehr, 2012) could help promote population synchrony (Bartos et al., 2007).

ii. Synchrony and Cerebellar Output—Synchrony of PC firing that arises from recurrent inhibition, ephaptic signaling, and shared excitatory inputs, can have important consequences for cerebellar output. *In vitro* studies have shown that for synapses between PCs and the excitatory projection neurons of the CbN, a combination of convergence (Person and Raman, 2011), ultrafast IPSC kinetics (Najac and Raman, 2015), CbN intrinsic properties (Najac and Raman, 2015), and presynaptic neurotransmitter release properties (Turecek et al., 2016, 2017) allow synchronous PC firing to entrain CbN neuron spiking. Synchronous spiking among even a modest percentage (~ 10%) of the many PC inputs that converge onto a single CbN neuron can transiently reduce synaptic inhibition, both entraining and elevating CbN spiking (Person and Raman, 2011). *In vivo*, there is considerable evidence that PCs can achieve millisecond synchrony (Person and Raman, 2012), and indications that synchronous PC firing can entrain CbN firing (Brown and Raman, 2018; Sarnaik and Raman, 2018).

Although most attention has focused on synchronous PC firing, brief synchronous suppression of PC firing is also a highly effective means of promoting firing in the CbN (Han et al., 2020). This has been shown *in vitro* with dynamic clamp and *in vivo* by optogenetically suppressing PC firing for several milliseconds. Remarkably, brief suppression of a fraction of PCs converging onto a CbN neuron can lead to large, short latency (~ 1 ms), precise (~ 2 ms) increases in the firing of CbN neurons (10% PC suppression more than doubles CbN neuron firing). Synchronized suppression of PC firing could occur during synchronized CF-induced pauses, when a CF suppresses firing of nearby PCs, or when MLIs inhibiting many PCs.

Many aspects of cerebellar synchrony are also not understood. For example, it is unclear how PCs transition to and from states of broad population synchrony, allowing them to differentially influence their CbN neuron targets. It is also unclear how rate codes and population synchrony may differentially contribute to downstream processing and behavior (Hong et al., 2016).

D. Distributed Sites of Long-Term Plasticity

According to Marr-Albus models, and essentially all models of cerebellar function, cerebellar learning is achieved by modifying GrC to PC synapses (Albus, 1971; Ito, 1972; Marr, 1969). Most attention has focused on postsynaptic long-term depression (LTD) of

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GrC to PC synapses that are activate immediately prior to CF activation (Ekerot and Kano, 1985; Ito et al., 1982; Sakurai, 1987). However, GrC-PC LTD is not always required for learning, because chronic impairment of GrC to PC LTD (Schonewille et al., 2011), or a lack of CF activity (Kimpo et al., 2014) do not disrupt some forms of cerebellum-dependent learning. Thus, other types of long-term plasticity must be able to mediate some types of cerebellar learning. Importantly, this does not mean that the central role of synapse-specific plasticity of GrC to PC synapses needs to be abandoned. GrC to PC synapses exhibit multiple mechanisms of long-term plasticity, including presynaptic LTP (Salin et al., 1996) and LTD (Hoxha et al., 2016), and postsynaptic LTP (Belmeguenai and Hansel, 2005). Thus, the observation that some forms of cerebellar dependent leaning do not rely on postsynaptic LTD is still compatible with plasticity of the GrC to PC synapses being central to cerebellar-dependent learning.

There are also many other forms of long-term plasticity in the cerebellum (Figure 4). These can be broadly categorized into long-term synaptic plasticity, and long-term changes in excitability (Figure 4A). LTD and LTP are both present at MF to GrC synapses (D'Angelo et al., 1999; D'Errico et al., 2009; Gall et al., 2005), MF and GrC to GoCs synapses (Locatelli et al., 2021; Robberechts et al., 2010), MLIs (Jorntell and Ekerot, 2003; Liu and Cull-Candy, 2000; Rancillac and Crepel, 2004; Soler-Llavina and Sabatini, 2006), and output synapses onto either CbN neurons (Aizenman et al., 1998; Pugh and Raman, 2006) or vestibular nucleus neurons (McElvain et al., 2010). Moreover, intrinsic plasticity mechanisms can also modify the firing and excitability of GoCs (Hull et al., 2013), MLIs (Alexander and Bowie, 2021), PCs (Belmeguenai et al., 2010), GrCs (Armano et al., 2000), CbN neurons (Aizenman and Linden, 2000) and vestibular nucleus neurons (Nelson et al., 2003). There are also likely to be intrinsic and synaptic plasticity for recently identified cell types and their connections (Figure 4B).

Importantly, numerous mechanisms can regulate the induction of long-term plasticity. The ability of CFs to induce GrC-to-PC LTD is regulated by MLI inhibition of PCs (Gaffield et al., 2018; Rowan et al., 2018), by presynaptic CF inhibition (Carey and Regehr, 2009), and by CF-LTD (Hansel and Linden, 2000). There is also evidence that the timing rules for LTD induction are highly precise and regionally dependent (Suvrathan et al., 2016), although it is not known how the signaling mechanisms that underlie LTD produce such temporal precision. CF input is also not binary, and CF burst firing can prolong the duration of complex spikes (number of spikelets) (De Gruijl et al., 2012; Lang et al., 2014), and enhance the postsynaptic calcium signal in PC dendrites (Gaffield et al., 2019; Roh et al., 2020), consistent with the observation that the number of spikelets in a complex spike correlates with learning on a single trial basis (Yang and Lisberger, 2014). Finally, behavioral context likely regulates plasticity and learning (Albergaria et al., 2018; Lawrenson et al., 2016), likely by mechanisms such as neuromodulation that can alter transmission and plasticity (Carey and Regehr, 2009; Dieudonne and Dumoulin, 2000; Fleming and Hull, 2019; Fore et al., 2020; Prestori et al., 2013).

With so many sites and forms of plasticity in the cerebellar cortex, it is hard to believe that CF-gated postsynaptic GrC to PC LTD mediates all cerebellar learning. However, it is equally difficult to imagine that all plasticity mechanisms play a direct role in cerebellar

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learning. The anatomical arrangement of MFs, GrCs, and PCs strongly implicate GrC to PC synapses as crucial sites of plasticity and learning. Thus, a key requirement for understanding cerebellar learning will be to determine how other forms of plasticity may complement the plasticity of GrC to PC synapses. For example, decreasing GrC to PC synaptic strength cannot inhibit PC firing, so regulation of MLI synapses and/or firing must also be involved in learning. It will also be necessary to assess other roles of plasticity, apart from a direct contribution to learning. For example, some forms of plasticity likely fine tune the cerebellar circuity during development, or according to behavioral context to optimize circuit function.

VII. Conclusions

Together, these recently described cell types, circuit connections, plasticity and signaling mechanisms, and other features of the cerebellar cortex not previously incorporated in classical Marr-Albus models vastly enrich our understanding of how this structure processes information. Newfound complexities, such as subtypes of MLIs and PLIs that are ubiquitously present, must be integrated into the canonical circuit. In addition, while the cerebellar cortex consists of repeated modules of the same basic circuit, it has also exhibits strong local and regional differences that allow specialized processing and learning. These new discoveries require major revisions of cerebellar circuit models. With such revisions, the cerebellum will remain an ideal system to relate neural circuit function and plasticity with behavior and learning. Such efforts will enable a more complete understanding of cerebellar function, and inform how it can contribute to behaviors ranging from motor control to social and cognitive tasks.

Future Issues

Recent advances have shown that the previous view of the cerebellar cortex was an oversimplification, but newly discovered features have not yet been incorporated into a new model of the cerebellar cortex.

1. What are the functional roles of newly discovered cell types and subtypes of the cerebellar cortex?
2. What is the logic of mossy fiber input to granule cells?
3. How does granule cell layer inhibition differentially contribute across behaviors and learning paradigms?
4. How do the molecular specializations within microzones tailor them for unique cerebellar computations?
5. What is the role of PC synchrony in behavior and learning, and how do PCs transition into and out synchrony?
6. How do different forms of ephaptic signaling contribute to behavior and learning?
7. How do diverse forms of plasticity combine to enable different forms of cerebellar learning?

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Terms and definitions

MF	Mossy fiber
CF	Climbing fiber
GrC	Granule cell
UBC	Unipolar brush cell
GoC	Golgi cell
CC	Candelabrum cell
LC	Lugaro cell
GlC	Globular cell
MLI	Molecular layer interneuron
MLI1	MLI type 1
MLI2	MLI type 2
PC	Purkinje cell
CbN	Cerebellar Nuclei

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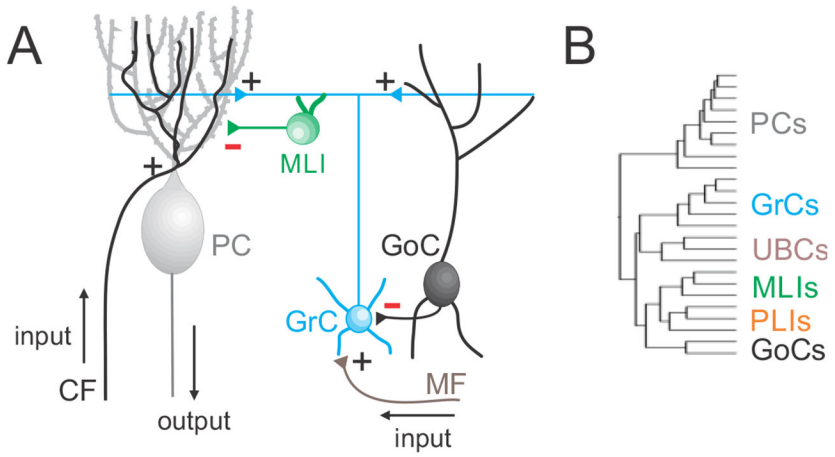

Figure 1. Basic circuitry and cell types of the cerebellar cortex.

A. Simplified circuit of the cerebellar cortex. **B.** Dendrogram of the neurons based on RNAseq data reveals additional types and subtypes of neurons in the cerebellar cortex (Kozareva et al., 2021). Abbreviations: climbing fiber (CF), mossy fiber (MF), granule cell (GrC), Golgi cell (GoC), molecular layer interneuron (MLI), Purkinje cell (PC), unipolar brush cells (UBCs), and Purkinje layer interneurons (PLIs).

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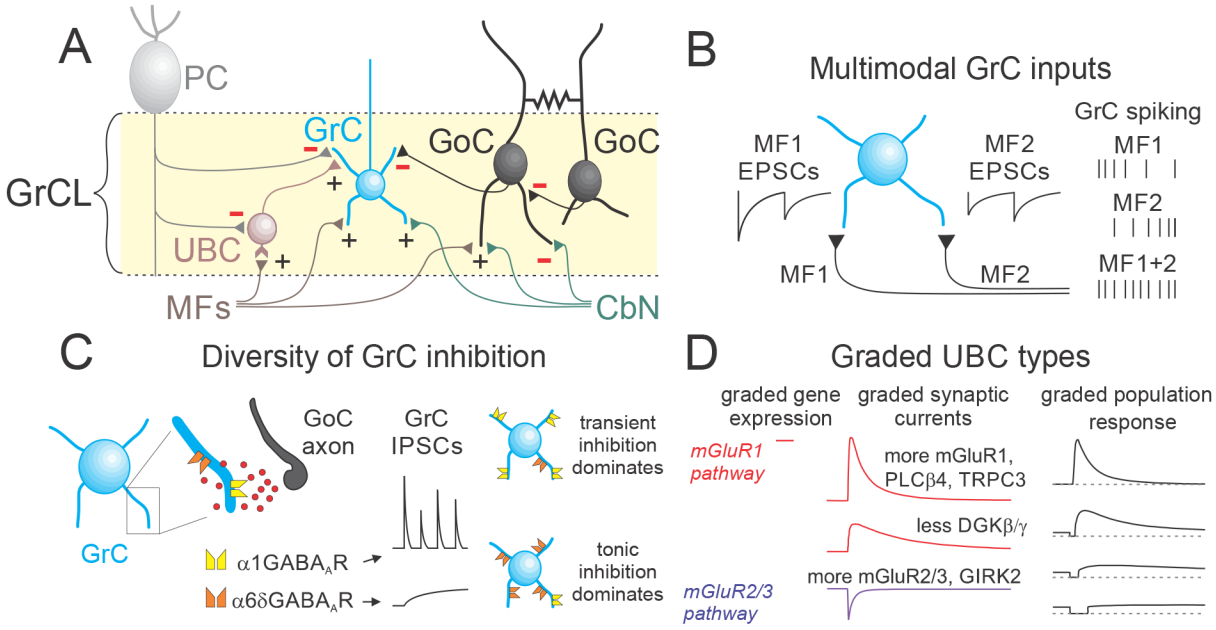

Figure 2. Circuit specializations of the input layer of the cerebellar cortex.

A. There are additional cell types and connections in the GrC layer that are neglected in simplified models of the cerebellar cortex: inhibitory feedback from the CbN, UBCs, gap junction coupling between GoCs, and PC feedback to GrCs and UBCs. **B.** MFs have disparate properties that evoke spiking in GrCs with diverse temporal properties (Chabrol et al., 2015). In this example MF1 has a high initial probability of release and depresses, whereas MF2 has a low initial probability of release and facilitates. GrC spiking evoked by activation of MF1 alone, MF2 alone and coactivation of MF1 and MF2. **C.** Specialized $GABA_A$ receptors in GrCs mediate inhibition with a conventional fast component (α1 subunit containing). and a slow tonic component (α6δ subunit containing). **D.** Cerebellar UBCs express elements of the mGluR1 excitatory pathway and the mGluR2 inhibitory pathway in inverse gradients to generate a continuum of temporal responses.

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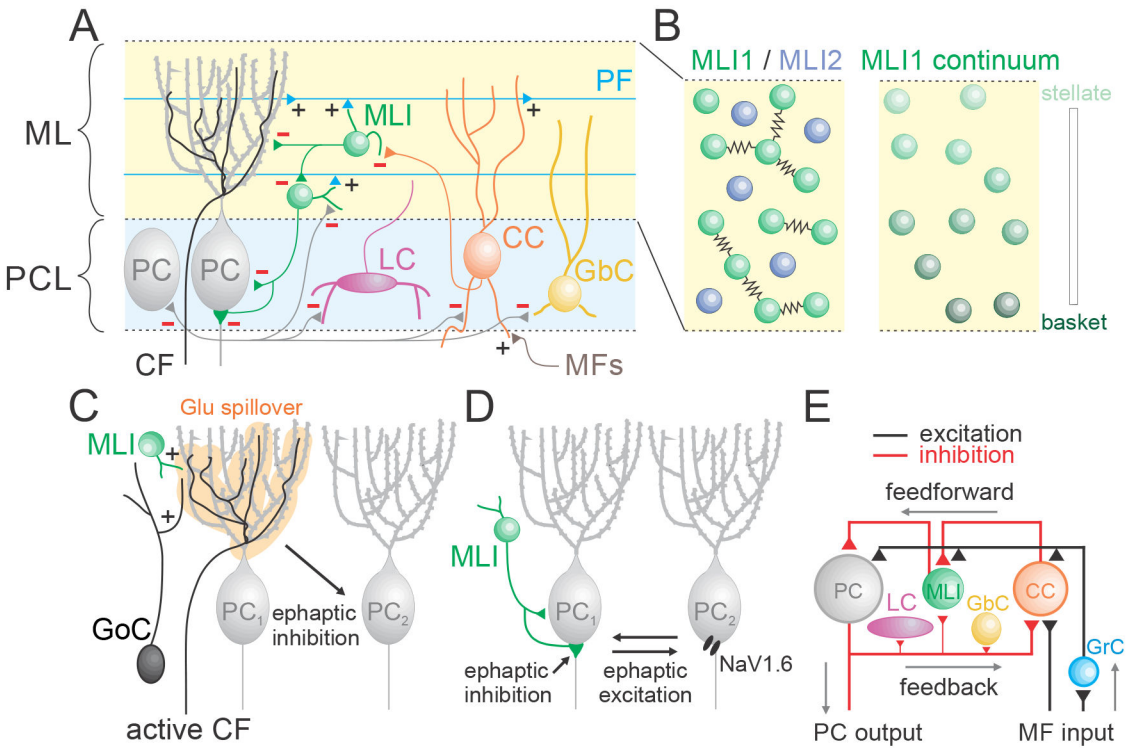

Figure 3. Additional circuit elements and signaling mechanisms in the molecular layer (ML) and the PC layer (PCL).

A. Schematic showing additional cell types and connections between cells that are not considered in the simplified circuit of the cerebellar cortex (Figure 1). Abbreviations for types of PLIs: Lugaro cell (LC), candelabrum cell (CC), and globular cell (GbC). Known inhibitory (−) and excitatory (+) synapses are shown. **B.** (left) An expanded view of the ML showing intermingled molecularly and functionally distinct subtypes of MLIs. MLI1s are gap junction coupled with each other, but MLI2s are not (right). The MLI1 population displays a molecular and anatomical gradient of properties. **C.** CFs, in addition to powerfully and directly exciting PCs, produce a glutamate signal that spills over to excite MLIs and GoCs. CFs also generate extracellular ephaptic signals that suppress firing in neighboring PCs. **D.** Extracellular ephaptic signals allow MLIs to rapidly inhibit and PCs to rapidly excite neighboring signals. **E.** PLIs are usually disregarded in considering the circuitry of the cerebellar cortex. PCs powerfully inhibit LCs, GbCs and CCs, and CCs primarily inhibit MLIs leading to disinhibition of PCs.

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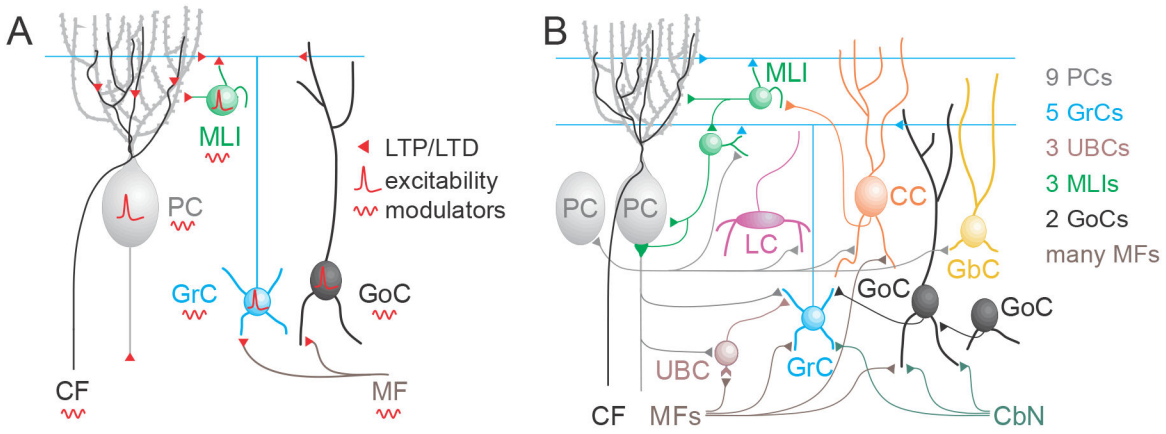

Figure 4. Cell types, synapses, circuitry and sites of plasticity.

A. Known sites of plasticity in the cerebellar cortex, showing synapses that undergo LTP and LTD, cell types where excitability and spontaneous activity can be altered, and sites that are known targets of modulators. **B.** Updated circuit showing the cells and known connections of the cerebellar cortex that could all undergo plasticity. The number of known subtypes of cells are indicted in the inset.