

Review

Neocortex–Cerebellum Circuits for Cognitive Processing

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Although classically thought of as a motor circuit, the cerebellum is now understood to contribute to a wide variety of cognitive functions through its dense interconnections with the neocortex, the center of brain cognition. Recent investigations have shed light on the nature of cerebellar cognitive processing and information exchange with the neocortex. We review findings that demonstrate widespread reward-related cognitive input to the cerebellum, as well as new studies that have characterized the codependence of processing in the neocortex and cerebellum. Together, these data support a view of the neocortex–cerebellum circuit as a joint dynamic system both in classical sensorimotor contexts and reward-related, cognitive processing. These studies have also expanded classical theory on the computations performed by the cerebellar circuit.

Cerebellum and Cognitive Function

The cerebellum was traditionally thought to contribute mainly to motor coordination [1–4]. However, more precise behavioral assays and a finer-grained parcellation of cerebellar functional domains have suggested that a large part of the cerebellum likely contributes to primarily cognitive functions [5,6]. Evidence has implicated the cerebellum in cognitive abilities ranging from spatial reasoning to language and working memory [7–10], and in cognitive disorders as varied as autism and schizophrenia [11–14]. However, the neural representations of cognitive information within the cerebellum, and the exchange of that information with the rest of the brain, have remained little understood.

The most likely route for cerebellar contribution to cognition is via interactions with the neocortex. The cerebellum and cerebral cortex have jointly expanded over mammalian evolution, and together account for ~99% of neurons in the human brain [15–19]. Moreover, dense reciprocal pathways connect most regions of the cerebellum and nearly all the neocortex through recurrent communication loops [20–24]. Fully discerning the role of the cerebellum in brain function requires understanding both the types of cognitive signals that are processed in the cerebellum, as well as how the cerebellum and neocortex exchange such information.

Recent technical advances that allow collection of new classes of cerebellar physiology data have shed new light on both of these topics. Here, we review recent *in vivo* cerebellar physiology studies demonstrating that a widespread cognitive signal that is processed in the cerebellum is information related to the expectation of reward. We then discuss new investigations of the codependence of neural dynamics in the neocortex and the cerebellum. Finally, we outline several potential implications of these findings for theories of cerebellar contributions to brain function.

Cerebellar Signaling of Reward Expectation

The cerebellum receives input from two pathways. Cerebellar granule cells, which comprise most of the neurons in the mammalian brain [18], receive mossy fiber inputs that arise from throughout the brain and spinal cord via several brainstem and pontine nuclei [25–27]. Cerebellar Purkinje cells – the principal neurons of the cerebellar cortex and postsynaptic targets of granule cells – directly receive the other primary input to the cerebellum, the climbing fibers, which are axons of neurons in the inferior olive [26] (Figure 1A,B). Each Purkinje cell receives ~100 000 granule cell inputs but only a single climbing fiber input [28], which is thought to instruct the Purkinje cell as to which granule cell inputs are most important in a given behavioral context [29]. Purkinje cell axons innervate the cerebellar nuclei, which in turn transmit cerebellar output to diverse brain regions (Figure 1B). In addition, the cerebellum exhibits gross functional organization, with some cerebellar regions (notably

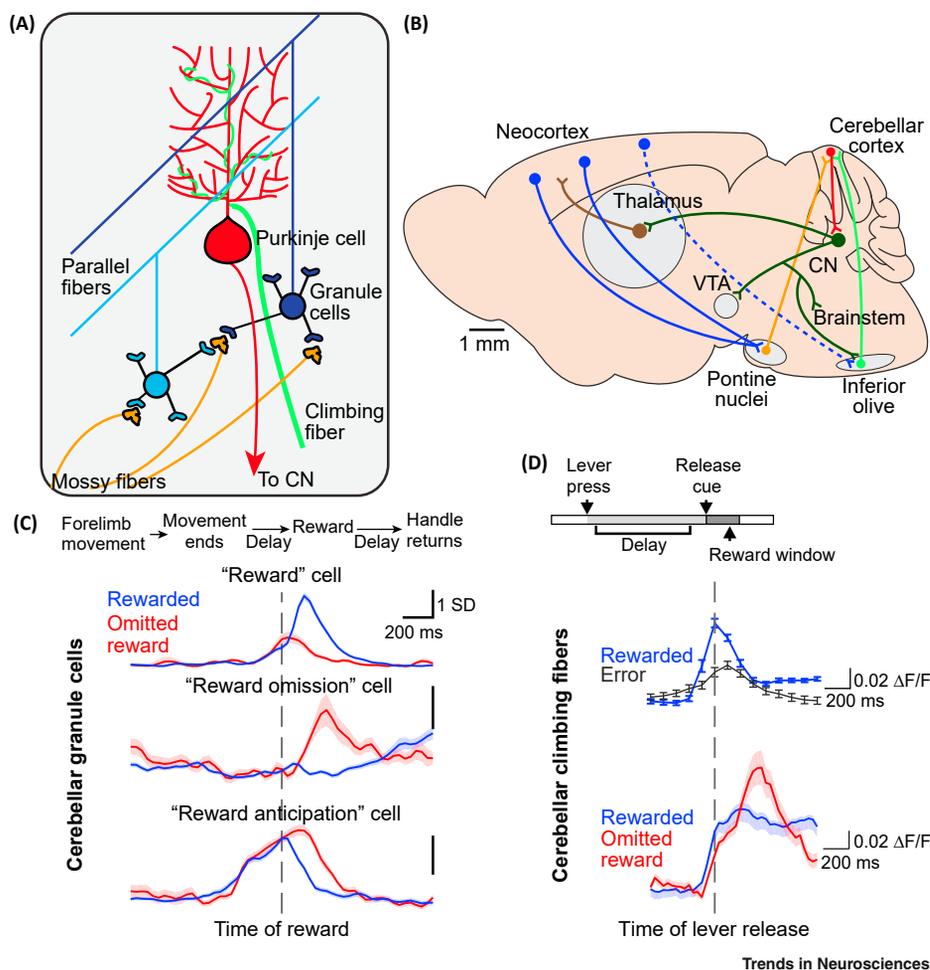
Highlights

Classic studies have mainly focused on sensorimotor information transmitted through the two cerebellar input pathways, granule cells and climbing fibers. Recent investigations indicate that the cerebellum receives diverse reward expectation-related information via granule cells, and reward prediction error signals via climbing fibers. The cerebellum may in turn reciprocally influence brain-wide reward circuitry via output pathways from the cerebellar nuclei.

Prevailing theories of cerebellar function posit that the granule cell layer generates a dimensionally expanded representation of its mossy fiber inputs. Recent observations in multiple contexts and species indicate that granule cells may perform a richer set of functions, including the faithful transmission of neocortical neuronal dynamics to the cerebellar circuit.

Similarly, classical views of climbing fibers as reporting movement errors have broadened to incorporate instructive signals that might drive more flexible and varied types of reinforcement learning.

Recent experiments also identified a critical role for cerebellar output in sustaining cortical preparative activity that underlies cognitive and working memory processes. Thus, the neocortex–cerebellum circuit can be conceptualized as a joint dynamic system performing both sensorimotor functions, as traditionally assigned to the cerebellum, and reward-related, cognitive processing.



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Figure 1. Cerebellar Circuits and Reward Signals.

(A) Cerebellar cortex microcircuit. Input arrives via the mossy fiber pathway from nuclei in the pons, medulla, and spinal cord, as well as via the climbing fiber pathway from the inferior olive. Each mossy fiber synapses onto ~50 granule cells, and each granule cell receives input from about four mossy fibers. Approximately 100,000 granule cell axons (parallel fibers) synapse onto each Purkinje cell, while each Purkinje cell receives input from only one climbing fiber. For simplicity, GABAergic interneurons in the cerebellar cortex are omitted from this schematic. Purkinje cells project axons to the cerebellar nuclei (CN), which also receive collaterals from both mossy fibers and climbing fibers (not shown). (B) Connections between the cerebellum and other brain regions. Nearly all subcortically-projecting layer 5 pyramidal neurons throughout the neocortex send an axon collateral to the pontine nuclei. The cerebellum receives mossy fibers from all pontine nuclei neurons (yellow), and climbing fibers from inferior olive neurons (green). The CN, targets of Purkinje cell axons, project to numerous targets including the cortex via the thalamus, the ventral tegmental area (VTA), and brainstem nuclei including the inferior olive. Broken line represents indirect input from the cortex to the inferior olive. (C) Reward expectation signaling in cerebellar granule cells. Top, mice executed a forelimb operant task for water reward during two-photon Ca^{2+} imaging [38]. Bottom, three example granule cell activity profiles. Traces show fluorescence aligned to reward delivery (broken vertical line) and averaged across either rewarded trials or trials on which reward was unexpectedly omitted. From top to bottom, these three cells were active preferentially during reward delivery, reward omission, or the delay while the mouse waited for the reward. Note that the reward anticipation cell remained active longer while the mouse continued waiting following unexpected reward omission, until the mouse gave up and ceased licking (licking not shown). SD, standard deviation used as unit for these z-scored traces. (D) Reward expectation signaling in cerebellar climbing fibers. Top, water-restricted mice executed a press-and-hold forelimb lever task for water reward during two-photon Ca^{2+} imaging of Purkinje cell dendrites [52], whose fluorescence reports climbing fiber activity, in lobule simplex of the

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lobules VI–VIII and the adjacent hemispheres) more closely linked both to the neocortex generally [30,31] and to more limbic neocortical regions in particular [32–34]. Thus, a key step toward understanding cerebellar contributions to the brain's cognitive processes is to decipher the types of cognitive information transmitted through both granule cells and climbing fibers. Furthermore, the differences between granule cell and climbing fiber cognitive representations are expected to affect subsequent computation, due to the differing roles of these inputs in the cerebellar circuit.

We discuss several recent studies, focused mainly near lobules VI, simplex, and crus 1, which indicate that a major class of cognitive information transmitted by both granule cells and climbing fibers relates to the expectation of reward. We then review findings that outline one pathway through which cerebellar output may impact reward processing in other brain circuits. As many forms of learning are reward-dependent, and as the cerebellum is believed to be an important learning center, these results bear critically on models of cerebellum-dependent learning.

Granule Cell Reward Signaling

Due to longstanding technical limitations, little has been known about granule cell activity in animals executing motivated behaviors. Thus, the nature of granule cell cognitive encoding had remained obscure. Two-photon Ca^{2+} imaging of granule cells [35–38], which likely primarily reports the occurrence of bursts of several action potentials *in vivo* [36], has recently provided a means to clear this technical hurdle. Via two-photon Ca^{2+} imaging of granule cells in mice performing operant and classical conditioning tasks, our group has found several common classes of reward-related granule cell activity profiles [38]. Some neurons responded preferentially following reward delivery, while others were activated after unexpected omission of an expected reward. A class of cells termed reward anticipation neurons became active selectively when the animal was awaiting an expected reward, but not following delivery of an unexpected reward (Figure 1C).

The prominence of these rich reward-related granule cell signals likely reflects the diverse, nonmotor mossy fiber input to lobules VI, simplex, and crus I of the cerebellum [32–34], and suggests that this information might be important for cerebellar cognitive processing. Classical cerebellar theory posits that Purkinje cells use the contextual information represented in their granule cell inputs to compute predictions of the future state of both the brain and the external world [39,40]. In this framework, granule cells might signal reward expectations because they carry salient predictive information about the future.

Climbing Fiber Reward Signaling

Granule cells are thought to convey internal and external contextual information to the cerebellum, whereas climbing fibers are thought to play a key role in cerebellar learning by instructing a Purkinje cell as to which of its granule cell inputs are most informative [41–43]. Climbing fiber spike bursts reliably elicit Purkinje cell complex spikes that can affect Purkinje cell plasticity processes [44]. Neighboring groups of Purkinje cells called microzones furthermore receive similarly coded climbing fibers that often spike synchronously due to gap junctional coupling in the inferior olive [45–48]. For regions of the cerebellum that contribute to brain cognitive functions, therefore, it is important to determine the nature of climbing fiber cognitive instructive signals. Anatomically, climbing fibers that carry cognitive information are likely driven in part by indirect input from the neocortex via several midbrain nuclei [49–51]. Several recent *in vivo* physiological studies during motivated behavior have shown that climbing fibers may carry prominent reward prediction error signals.

Heffley *et al.* studied mice executing an operant behavior while imaging Ca^{2+} activity in Purkinje cell dendrites of lobule simplex [52]. Ca^{2+} transients in Purkinje cell dendrites are known to reliably occur

cerebellum. Bottom, example climbing fiber activity. Climbing fibers became active preferentially at the time of the lever release on correctly-timed trials, which predicted subsequent reward, but not on error trials, which did not yield subsequent reward. On correctly timed trials on which the subsequent reward was unexpectedly omitted, a second climbing fiber response was elicited. $\Delta F/F$, percent change in fluorescence. (C) Reproduced, with permission, from [38], (D) reproduced, with permission, from [52].

during climbing-fiber-evoked complex spikes [53,54] (although Ca^{2+} transient magnitude is graded by both the climbing fiber spike burst size as well as other inputs to the Purkinje cell [55–57]). Mice obtained a water reward by holding a lever while waiting for a timed release cue. Climbing fibers exhibited enhanced activity during correctly executed movements that subsequently yielded reward (Figure 1D). This activity was absent in error trials, in which the mouse released the lever early. If the animal is aware of having made an error, and thus expects not to receive reward, the absence of a climbing fiber signal could be interpreted as a reward prediction signal. For a reward prediction signal, a reward-predicting event should also have the same value as an unpredicted reward, which the authors confirmed by demonstrating that unexpected rewards elicited climbing fiber signals similar to those during successful, reward-predicting forelimb movements. The same climbing fibers also responded a second time following omission of expected rewards, potentially signaling violation of the previous expectation (and in contrast to a signed reward prediction error signal [58]). These results suggest that climbing fiber activity in this task carries an unsigned reward-prediction error.

Kostadinov *et al.* also recorded lobule simplex climbing fiber activity in mice performing a cued, timed forelimb operant behavior, and found widespread activity during reward-predicting movement onset and to reward delivery itself, along with additional responses to omission of expected reward [59]. In addition, the authors found that some microzones became activate during reward, while others were suppressed, with larger changes evoked by unexpected rewards. Chronically monitoring these signals during training revealed that reward-delivery-evoked climbing fiber activity was gradually suppressed as animals learned the reward-predicting cue. Thus, along with the work of Heffley *et al.* [52], these studies identified climbing fiber activity related to animals' predictions about upcoming rewards.

Taking advantage of the greater behavioral repertoire of primates, Larry *et al.* electrophysiologically recorded climbing fiber activity in macaques executing an eye movement stimulus tracking task, in which the initial fixation cue signaled the magnitude of reward that would be delivered following successful trial completion [60]. The cue alone evoked increased climbing fiber activation selectively for large- but not small-reward trials. Because these responses to cue onset were temporally removed from both the eye movement itself and from reward delivery and consumption, they provide strong evidence that climbing fibers encoded the animal's learned association between cue identity and upcoming reward magnitude, rather than an extraneous sensorimotor variable. In contrast, climbing fiber activity did not depend on reward magnitude during reward delivery. This is in line with the interpretation of Heffley *et al.* [52] and Kostadinov *et al.* [59] that, once reward associations have been learned, climbing fibers report the reward-predictive stimuli rather than the subsequent reward itself, consistent with a reward prediction error.

Together, these results suggest a scenario in which, at least in the vermis and adjacent hemispheres of lobule VI, granule cells convey diverse information about the animal's experience and expectations of rewards, while the climbing fiber instructive signals convey reward prediction errors. Depending on how these signals interact, recipient Purkinje cells might thereby learn to perform a variety of reward-predictive computations. The functional impact of such putative computations would depend on the downstream brain circuits that receive the resulting cerebellar output.

Cerebellar Influence on Brain Reward Circuitry

The brain's classical reward circuitry consists of a number of prominent nodes, including dopamine neurons in the ventral tegmental area (VTA) [61], as well as two prominent projection targets of VTA dopamine neurons: the ventral striatum [62] and the prefrontal cortex [63]. While the specific origin of reward-related signals that reach the cerebellar cortex is not definitively known, they likely derive at least partly from the neocortex. The cerebellum may in turn reciprocally influence brain-wide reward circuitry via a number of output pathways from the cerebellar nuclei. These include: both the striatum [64] and the prefrontal cortex [65] via the thalamus; and via monosynaptic inputs to the VTA dopamine neurons [66,67].

Carta *et al.* studied the functional properties of the cerebellar nuclei to VTA projection [68]. Optogenetic stimulation of the cerebellar nuclei reliably evoked postsynaptic responses in both

dopaminergic and GABAergic VTA neurons. Moreover, the authors demonstrated that mice were motivated to self-stimulate their cerebellar nuclei-to-VTA projection, indicating that this pathway was reinforcing. Likewise, animals preferentially occupied the region of a chamber that was previously paired with cerebellar nuclei-to-VTA stimulation. In addition, suppressing cerebellar nuclei-to-VTA activity was sufficient to abolish the natural social preference of mice in a chambered box to explore the region that contains a conspecific. Finally, fiber photometry Ca^{2+} signals from cerebellar nuclei axons in the VTA increased during rewarding social exploration. When considered in combination with the previously discussed investigations of reward-related inputs to the cerebellum, this study demonstrates a pathway by which cerebellar reward processing could contribute to reward computations throughout the brain.

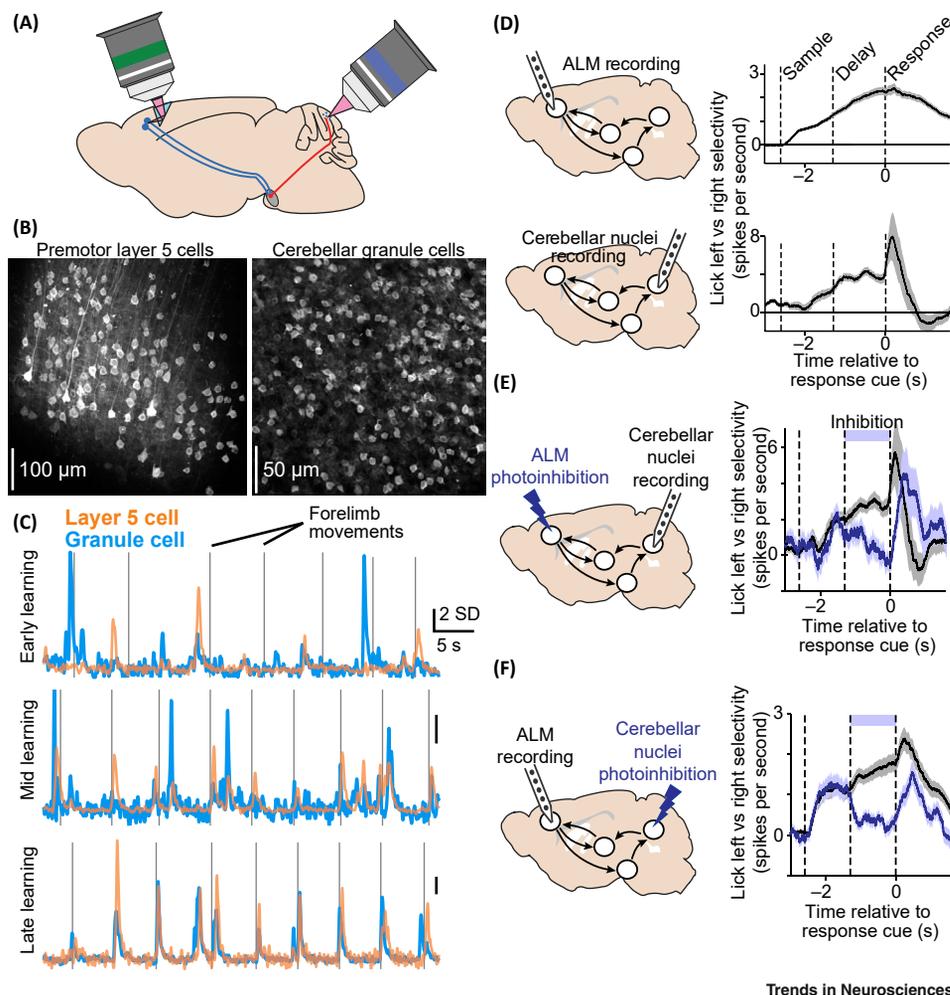
Cerebellar Interactions with the Neocortex

The mounting evidence described above for cerebellar processing of cognitive signals such as reward raises important questions about cerebellar interactions with the neocortex; the mammalian brain's central cognitive center and primary source of cerebellar input. Essentially all parts of the neocortex reciprocally communicate with the cerebellum via a highly conserved circuit. Specifically, nearly all subcortically projecting layer 5 pyramidal neurons send an axon collateral to the pontine nuclei, and the neurons of the pontine nuclei all project mossy fibers to the cerebellum [22,23,69–71]. Tracing using replication-deficient rabies virus showed that widespread corticocerebellar projections are disynaptic [72]. The cerebellar nuclei project back to the neocortex via the thalamus [20,65], although technical limitations have so far prevented definitively determining the extent of disynaptic cerebellar input to different cortical regions. In one recent study of this circuit, Proville *et al.* used optogenetic perturbations, tracing, and electrophysiological recordings to probe the properties of communication between the cerebellar hemispheres and both the motor and somatosensory cortices [73]. Cerebellar Purkinje cells and Golgi cells were found to exhibit polysynaptic responses to stimulation of both upstream primary motor and somatosensory cortices and, reciprocally, Purkinje cell stimulation triggered rebound excitation in downstream thalamic and motor cortical neurons. To fully decipher the behavioral role of corticocerebellar circuitry, it is critical to determine the types of behavioral information exchanged between these two structures, as well as the role of neocortical inputs in cerebellar computation and vice versa.

We next discuss several recent studies that have directly probed the interactions and codependence of neural activity between neocortex and cerebellum in animals executing skilled behaviors, and their evolution during learning.

Corticocerebellar Communication

Classical ideas concerning neocortex to cerebellum transmission were centered on the transformation of neuronal representations into sparser and more high-dimensional forms [42]. Wagner *et al.* performed simultaneous two-photon Ca^{2+} imaging of both layer 5 output neurons of the rostral forelimb area of the premotor cortex as well as downstream granule cells in the cerebellar cortex, while animals executed an alternating leftward and rightward forelimb movement sequence planning task [72] (Figure 2A,B). Surprisingly, premotor layer 5 pyramidal neurons and cerebellar granule cells contained highly similar types, proportions, and diversity of task-encoding neurons. Broadly, these included neurons whose activity was related to movement planning and execution, and those related to the delivery of rewards, selectively for either left or right trials. In addition, although only ~80 cells were simultaneously recorded in each brain region, it was common to observe layer 5–granule cell pairs with highly correlated activity across single trials (Figure 2C). This is unexpected because, according to classical theory, individual granule cells integrate and detect coincidences among their four inputs. By contrast, these results indicate that the activity of some granule cells may be dominated by just a single neocortically driven mossy fiber (see Figure 3A and theory section below). By leveraging the ability of two-photon imaging to track neuronal identities over weeks, it was further demonstrated that shared corticocerebellar dynamics emerged only gradually over the weeks-long learning process. Over time, layer 5–granule cell pairs that were initially dissimilar and only weakly task encoding converged onto similar and more restricted sets of task-encoding activity patterns.



Trends in Neurosciences

Figure 2. Neocortex–Cerebellum Communication.

(A) Schematic of strategy for simultaneous two-photon Ca^{2+} imaging of both premotor cortical layer 5 pyramidal neurons of the rostral forelimb area, and cerebellar granule cells, during a forelimb movement planning task. (B) Mean two-photon brain images of the premotor cortex and cerebellum showing detected layer 5 cells and granule cells highlighted in grayscale. (C) An example layer 5–granule cell pair that was tracked over several weeks of task learning. Traces show time-varying fluorescence magnitude. Over learning, this pair develops strongly correlated activity. SD, standard deviation used as unit for these z-scored traces. (A–C) Reproduced, with permission, from [72]. (D) Mice discriminated two-whisker stimuli and reported stimulus identity by licking left or right after an enforced delay period. Top, recordings from the anterior lateral motor area (ALM) during the task. ALM neurons develop stimulus selectivity during the sample period (between the left and middle broken lines) that persists through the delay period (between the middle and right broken lines) and into the response period. Bottom, recordings from the cerebellar output nuclei reveal a similar timeline of stimulus selectivity. (E, F) Cerebellar nuclei recordings during ALM photoinhibition (E) and ALM recordings during cerebellar nuclei photoinhibition (F) demonstrated that directional selectivity in either brain region requires intact signaling in the other region. (D, E) Reproduced, with permission, from [75].

Thus, rather than extensively transforming their cortical input, the granule cell layer contained a faithful recapitulation of cortical task encoding in expert animals.

These findings highlight the importance of better understanding of the pontine intermediary between neocortical output and cerebellar input. Guo *et al.* performed electrophysiological recordings of pontine

neurons during a cued reach-to-grasp food pellet task [74]. Pontine neurons – those determined via photoactivation to receive monosynaptic motor cortical input – encoded all aspects of the task, which they must transmit onward to cerebellar granule cells. Some motor cortical neurons were also reciprocally affected by pontine stimulation, likely via the ponto-cerebello-thalamo-cortical pathway. Such cortical neurons exhibited more preparatory activity than their untagged counterparts, consistent with the importance of preparatory corticocerebellar activity observed in other studies discussed here [72,75,76]. Taken together, these studies indicate that the full diversity of neocortical representations of behavior can be faithfully transmitted to cerebellar granule cell activity via the pontine nuclei.

Cerebellocortical Communication

In addition to the pathway from the cortex to the cerebellum via the pons, information returns from the cerebellar nuclei to the cortex via the thalamus. Gao *et al.* studied the relationship between activity of the cerebellar nuclei and that of the anterolateral motor cortex (ALM), while animals discriminated between two whisker stimuli and reported the results via leftward or rightward licking after an enforced delay [75]. Lesions and optogenetic perturbations of the medial (fastigial) cerebellar nucleus degraded task performance. Electrophysiological recording of spiking activity in either the ALM or the cerebellar nuclei demonstrated that neurons of both areas exhibited similar degrees of selectivity for each trial type, with widespread preparatory activity throughout both regions (Figure 2D). Photo-inhibition of ALM significantly reduced trial-type selectivity in the cerebellar nuclei and, similarly, optogenetic perturbation of the cerebellar nuclei abolished selectivity in ALM neurons (Figure 2E,F). This study thereby demonstrated a role for cerebellar output in sustaining neocortical preparatory activity, which is critical for task execution.

Chabrol *et al.* also recorded spiking activity in either the ALM, the lateral (dentate) cerebellar nucleus, or upstream Purkinje cells in the lateral cerebellar cortex (crus 1), in mice running on a virtual track to obtain water reward [76]. Neurons in all three regions primarily modulated their spiking activity near the time of reward delivery. Neurons in both the ALM and the cerebellar dentate nucleus similarly increased their activity in the runup to reward delivery. By contrast, Purkinje cell simple spiking was more likely to exhibit a preparatory decrease in activity, which would be expected to relieve the monosynaptic inhibition from Purkinje cells to dentate cells that disynaptically excite the ALM. Purkinje cell complex spiking was elevated just after reward, raising the possibility that decreased simple spiking in the runup to reward delivery was a learned consequence of reward-evoked complex spiking [77]. By activating Purkinje cells that inhibit the dentate nucleus prior to reward delivery, Chabrol *et al.* [76] suppressed most of the preparatory activity in the ALM with short latency.

This pair of studies [75,76] indicates a critical codependence of the neocortex and cerebellum in sustaining preparatory activity that is thought to underlie cognitive and working memory processes. Notably, Gao *et al.* [75] found that lesions of the fastigial nucleus but not the dentate nucleus degraded task performance, while some assays of Chabrol *et al.* [76] suggested that the dentate nucleus more directly drove frontal neocortical activity during their task. Differences between the studies in both the behavior and the specific neurophysiological assays used make direct comparisons difficult, but the discrepancies indicate that more investigation is needed to fully understand the differential functional contributions of specific corticocerebellar domains in different behavioral contexts. All three studies of corticocerebellar circuitry discussed here focused on overlapping regions of the premotor cortex [72,75,76]. The finding of abundant reward-related activity in the premotor cortex with parallel representations in granule cells makes it a likely candidate for cerebellar reward signaling discussed previously. Nevertheless, given the wide array of diverse neocortical regions that contribute to corticocerebellar circuitry, it will be important to investigate other corticocerebellar domains to fully characterize principles of corticocerebellar function.

Implications for Computational Theories of Cerebellar Function

The recent studies discussed above have raised interesting questions about classical theories of cerebellar function [41,42,78–80]; these theories have had a lasting influence in the field in the past decades.

Granule Cell Signaling beyond Dimensionality Expansion

In classical theory, the granule cell layer is hypothesized to generate a dimensionally expanded representation of its mossy fiber inputs (Figure 3A, top). This would be achieved via sparse input sampling, as each granule cell receives only four inputs (on average) that can arise from disparate sources [81], and a large expansion in cell number, as granule cells compose more than half of all neurons in the mammalian brain [82]. However, recent observations in multiple contexts and species [36–38,72,83,84] suggest that granule cells may perform a richer set of functions than only dimensionality expansion, and these functions may depend on behavioral context [85] and learning. For example, when animals are actively engaged or are executing learned tasks, substantial fractions of granule cells densely represent the behavior. Furthermore, Wagner *et al.* [72] explicitly compared the diversity and dimensionality of representation in neocortical output cells to those in downstream granule cells, and found a high degree of similarity. Lower dimensional representations that are consistent with task dimensionality – as reported in higher-order cortical areas [86,87] – coemerged in both cerebellum and cortex as mice gained task expertise. (It remains possible that if corticocerebellar dynamics were evaluated on faster timescales, results might differ from those reported by the slower kinetics of Ca²⁺ imaging [88].) These results may be consistent with re-examinations of classical theory that have suggested that dimensionality expansion is not always optimal, especially if the inputs are noisy [89,90]. Highly correlated layer 5–granule cell pairs suggest that, contextually, some granule cells may act as faithful relays of a single neocortically derived input (Figure 3A, bottom). This is because, given the low odds that four randomly selected inputs of diverse origins will share similar selectivity, preserving the strong selectivity present in the cortex likely requires that downstream granule cells preferentially transmit the activity of a single selective input. This may sacrifice some dimensionality expansion while boosting noise reduction, potentially facilitated by pontine integration mechanisms [74].

Recent studies have also demonstrated a large and unexpected role for learning in shaping granule cell representations [36,38,72]. While classical theory does not explicitly address learning-related changes in granule cell signaling, granule cells have often implicitly been thought to provide a massive and fixed basis set to uniquely represent all possible contexts (if each granule cell represents a highly specific and unique event, and the large number of granule cells spans all possible events). From this fixed basis, Purkinje cells could extract information relevant to a particular behavior via granule-cell-to-Purkinje cell synaptic plasticity. Instead, it seems that granule cells undergo learned representational changes that mirror and are likely inherited from those in the neocortex [72]. It is also possible that this reflects additional plasticity at the corticopontine or pontine–granule cell synapses [91]. One potential implication is that Purkinje cells may need to continually adjust the synaptic input weights from different granule cells, as the information conveyed by those granule cells changes during learning.

An important question is what function is served by the learned and relatively lower-dimensional granule cell representations that mimic those in cortical output. The cerebellocortical communication studies described above demonstrated the importance of cerebellar output for maintaining neocortical representations that drive behavior [75,76]. This hints at significant incorporation of cerebellar output neuron activity into the activity of cortical circuits. One possibility, therefore, is that such integration requires that certain features of cerebellar output neuronal dynamics are matched to those in neocortex. Recruiting a subset of granule cells primarily as relays (Figure 3A, bottom) [92] of neocortical dynamics might provide a way to shape cerebellar output returning to neocortex [72]. Importantly, such a scheme would not preclude other granule cells from performing classical sparse combinatorial coincidence detection (Figure 3A, top) [93,94]. Indeed, in these data, the majority of granule cells was apparently silent [72], which might indicate that these cells were subject to a high coincidence detection input threshold. This might hint at a parcellation of the granule cell ensemble, depending on which cells receive mossy fibers whose activity in a particular context is strong enough to relay through target granule cells (e.g., via gating mechanisms in the pontine nuclei). In such a scenario, global assessments of granule cell dimensionality may fail to capture the likely higher dimensionality of cells performing coincidence detection, while placing disproportionate emphasis on densely active, relay granule cells, which might serve a distinct function. It would therefore be

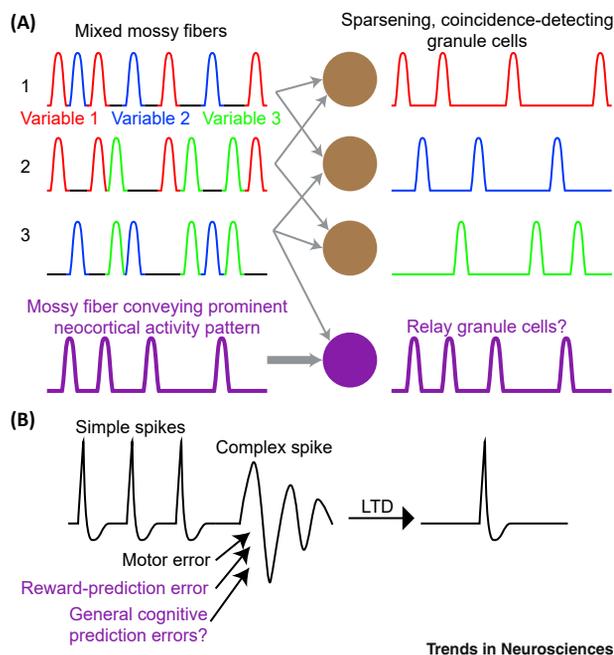


Figure 3. Computational Theories of Cerebellar Function.

(A) Top, in classical theory, granule cells threshold their approximately four inputs (here, granule cells 1, 2, and 3 will spike only if two inputs are simultaneously active), in order to perform coincidence detection. In this diagram, the activity of mossy fibers 1, 2, and 3 (left) are mixtures of underlying signals of interest (represented by differently colored activity events in red, blue, and green). Since the number of granule cells far exceeds the number of unique mossy fiber inputs, if each granule cell integrates and thresholds the activity of a unique combination of four randomly chosen mossy fibers, the resulting granule cell ensemble output will be sparse and high dimensional. This would allow individual granule cells to convey ‘unmixed’ forms of the colored signals of interest (right). This therefore allows Purkinje cells to discriminate between activity that appears very similar at the level of the mixed mossy fibers. Bottom (purple), during motivated behavior, some granule cells appear to be densely active in ways that faithfully recapitulate the selectivity and tuning of individual cortical signals, putatively relayed by a task-critical mossy fiber input. (B) Left, a Purkinje cell’s simple spikes are periodically interspersed with complex spikes from the climbing fiber input. In classical theory, complex spikes are triggered by motor errors, which indicate that the previous simple spiking was inappropriate, and thus produce long-term depression (LTD) at the Purkinje cell’s synaptic inputs from the set of parallel fibers that were active in the previous several hundred milliseconds (right). New evidence indicates that events that predict upcoming reward, in addition to a violation of that prediction via a reward omission, both can elicit complex spiking. This may be consistent with an unsigned reward prediction error signal, while opening the door to a potential range of other types of cognitive prediction error signals.

informative to determine how the granule cells that relay low-dimensional cortical representations affect downstream Purkinje cells, and in turn how these impact cerebellar output neuron dynamics.

Climbing Fiber Signaling beyond Movement Errors

In the Marr–Albus theory [41,42], and as confirmed by classic studies of various oculomotor tasks and reflexes [56,95–97], climbing fibers have long been proposed to signal mainly the occurrence of movement errors [98]. Because climbing fiber activity triggers plasticity at recently active parallel fiber inputs (i.e., during the preceding several hundred milliseconds) onto the same Purkinje neuron, it is thought that such error signaling helps to drive motor learning (Figure 3B, black). Studies recording during more complex volitional tasks, however, especially from cerebellar regions that receive denser neocortically derived input, have hinted at more complex and varied roles for climbing fiber input [99–102]. In addition, it has been observed that climbing fibers in one region signal errors correlated with changes in Purkinje cell simple spiking, while climbing fibers in another region during the same task

tonically signaled events through synchronized activity [102], potentially to directly affect ongoing motor output. Taken with the recent demonstrations of reward-expectation-related climbing fiber signaling described above [52,59,60], these data suggest more diverse functions than movement error signaling alone. Proposed extensions of classical climbing fiber theory suggest that climbing fibers may mediate more flexible and varied types of reinforcement learning [101]. For example, climbing fibers might signal reward prediction errors that are unsigned: that is, they can predictively signal unpredicted positive events such as upcoming reward magnitude, and reactively signal unpredicted negative events such as reward omission. In this case, they might drive more general learning of predictive internal models. Such a general learning mechanism might benefit from the recently demonstrated flexibility of the climbing-fiber-driven plasticity rules, both in timing [103], and potentially even in the magnitude or direction of plasticity that could vary depending on context [104].

Studies of climbing fiber activity over longer learning timescales raise a key distinction between adaptation and novel task acquisition. In adaptation, either a reflex or a previously trained volitional behavior is disrupted by a perturbation that requires altering a specific parameter of movement in order to bring the behavior back to its basal state [105–108]. During learning of novel volitional tasks, animals that are motivated to seek reward must simultaneously learn the task contingencies and update motor plans to produce more appropriate motor output. As a result, the variables signaled by climbing fibers gradually change or emerge over time [59] as upstream input sources in the forebrain undergo synaptic plasticity during task learning. In such contexts, the relevant error signals may not even be known *a priori*, nor indeed immediately available via preexisting climbing fiber inputs, without plastic circuit changes. One general strategy might involve monitoring reward outcomes, and the contexts, events, and behaviors that predict and yield reward (Figure 3B, magenta). These observations suggest that there is much to be discovered about how climbing fiber dynamics evolve with and depend on the learning of novel behavior-reward task contingencies, which may shed further light on the algorithms implemented by this remarkable learning machine [77,109].

Concluding Remarks and Future Perspectives

While recent research sheds new light on the physiology underlying cerebellar cognitive processing and interactions with the neocortex, major questions remain (see Outstanding Questions). Although studies indicate that reward signals are processed in the cerebellum, it is incompletely understood what the cerebellum computes using these signals, and little is known about what specific contributions these cerebellar computations make to processing in the rest of the brain. The relationship and interactions between granule cell and climbing fiber reward signals is another key open question. Moreover, how reward signals in the cerebellum are derived from the brain's canonical reward processing centers, and how in turn the cerebellum feeds back reward signals to these centers remain to be elucidated.

A close association has now been demonstrated between neocortical dynamics and those of cerebellar granule cells and output from the cerebellar nuclei. However, to decipher corticocerebellar functions, it will be critical to identify general and conserved principles of cerebellar contributions to processing throughout the neocortex. In motor contexts, the cerebellum seems to generate sensory predictions to guide movement [8,110]. In corticocerebellar circuits, therefore, the cerebellum may use present neocortical dynamics to predict future neocortical dynamics, and to make fine corrections as needed. For now, these ideas remain untested, and gaining this type of algorithmic understanding will require substantial technical and theoretical advancements.

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Outstanding Questions

The neocortical regions that interact with the cerebellum span the full diversity of cortical circuits, yet cerebellar circuitry is strikingly stereotyped. What is the basic, conserved computational contribution of cerebellar output to all neocortical function?

A massive reduction in cell number occurs between cerebellar granule cells and the final cerebellar output nuclei. How do the small number of cerebellar output nuclei cells contribute to processing throughout the neocortex?

What are the primary specific sources of reward-related input to granule-cell and climbing-fiber pathways? How do reward-related cerebellar computations affect downstream brain reward circuitry?

What kinds of learning-related plasticity are driven by climbing-fiber reward-related signals, and how do these affect Purkinje cell processing of granule-cell reward-related inputs?

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