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Current Opinion in
Neurobiology

Recent data on the cerebellum require new models and theories

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Abstract

The cerebellum has been a popular topic for theoretical studies because its structure was thought to be simple. Since David Marr and James Albus related its function to motor skill learning and proposed the Marr-Albus cerebellar learning model, this theory has guided and inspired cerebellar research. In this review, we summarize the theoretical progress that has been made within this framework of error-based supervised learning. We discuss the experimental progress that demonstrates more complicated molecular and cellular mechanisms in the cerebellum as well as new cell types and recurrent connections. We also cover its involvement in diverse non-motor functions and evidence of other forms of learning. Finally, we highlight the need to explain these new experimental findings into an integrated cerebellar model that can unify its diverse computational functions.

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Current Opinion in Neurobiology 2023, **82:**102765

This review comes from a themed issue on **Motor circuits in action 2023**

Edited by **Dawn Blitz** and **Sten Grillner**

For complete overview of the section, please refer the article collection - Motor circuits in action 2023

Available online 15 August 2023

https://doi.org/10.1016/j.conb.2023.102765

Keywords

Supervised learning, Marr-Albus model, Cognition, Reward, Purkinje neuron, Long-term depression, Long-term potentiation, Recurrent connection, Credit assignment.

Introduction

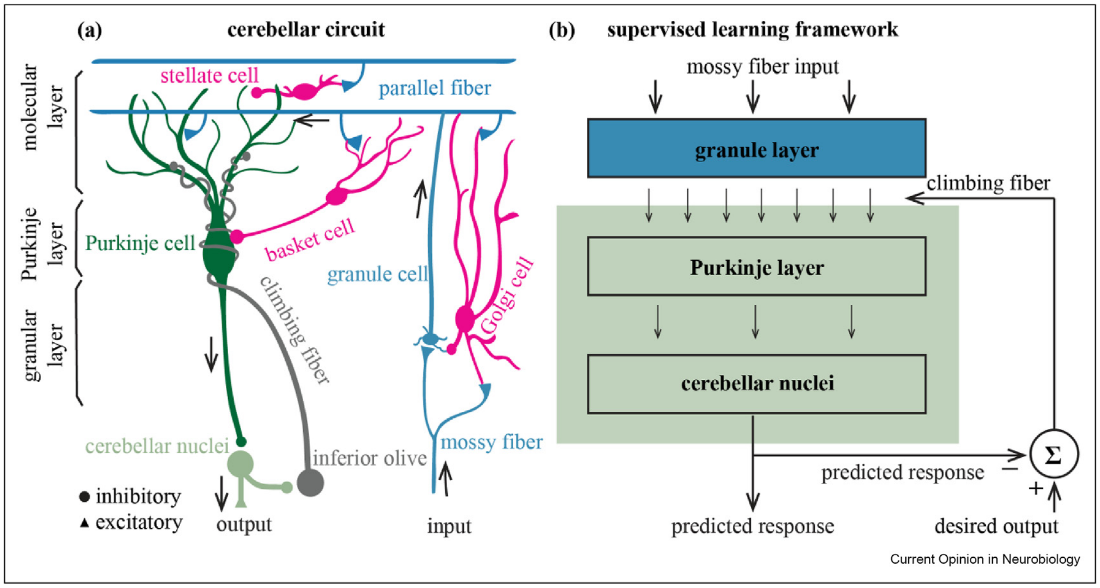
Any information processing system can be analyzed at three levels, computational, algorithmic, and implementation [1]. The cerebellum was assumed to have a relatively simple structure, containing a handful of cell types whose properties are well characterized. More importantly, the cerebellar circuitry is relatively uniform across the cerebellar cortex. Consequently, the cerebellum was proposed to use a common input—output transformation algorithm, although it needs to process inputs and send outputs from/to many different brain areas. Based on clinical findings, this was thought to be a motor coordination role. The importance of the cerebellum was indirectly demonstrated in a recent detailed model of the motor control of arm reaching that lacks a cerebellum and is therefore ataxic [2].

Next came the suggestion that the cerebellum performs motor learning, as in the classical Marr-Albus theory [3,4]. Sensory-motor information enters the cerebellum through mossy fibers and is then preprocessed by granule cells, whose axons, called parallel fibers, activate Purkinje neurons in a feedforward manner. As the sole output of the cerebellar cortex, Purkinje neurons compute the preprocessed sensory-motor information, make predictions of upcoming movements, and then distribute responses to other regions by the cerebellar nuclei. If the motor response doesn't match the desired output, inferior olive neurons in the brainstem will send error signals to instruct the cerebellum to learn (Figure 1). The error detection is performed outside of the olivocerebellar circuit.

The theory of error-based supervised learning has driven cerebellar research for many years. A considerable amount of experimental data support supervised learning, especially for simple tasks such as eyelid conditioning [5]. However, accumulating data have emerged that may falsify the Marr-Albus theory, including other types of learning involved in non-motor functions.

In this paper, we first review the theoretical progress that has been recently made within the framework of supervised learning. Then, we summarize new evidence that prompts us to reconsider the process of cerebellar supervised learning. Finally, we discuss several unsolved theoretical questions that require a new cerebellar theory to unify its diverse learning paradigms and computational functions.

Figure 1



The cerebellar structure interpreted as a supervised learning framework.
(**a**) the main cell types and neuronal connections in the cerebellum. Input to cerebellar cortex is excitatory, but output to the nuclei and inferior olive is inhibitory. (**b**) the error-based supervised learning framework based on the cerebellar structure (modified from Ref. [6]). In each block (or layer), local computations occur. For example, mossy fiber→Golgi cell→granule cell can regulate granule cell spike activities. Granule cell layer performs input preprocessing; Purkinje neurons and molecular layer interneurons perform input–output transformation; climbing fibers send error signals for learning.

Cerebellar models for supervised learning

Information preprocessing

Sensory-motor information is preprocessed by the cerebellar input layer. According to Marr-Albus [3,4], the granule cell layer is perfect for separating overlapping patterns conveyed by mossy fibers because of the divergent architecture from mossy fibers to granule cells (mossy fiber: granule cell = 1: 30). Granule cells account for more than half of the brain cells and each of them only receive ∼4 mossy fiber inputs (in the range of 2–7, sparse connection [7,8]). In theoretical studies, granule cells were thought to use an ultra-sparse coding strategy (<5% of granule cells activated within a relative time window [3,4,9]) to achieve efficient learning. Two inhibitory pathways, mossy fiber→Golgi cell→granule cell and granule cell→Golgi cell→granule cell, can both contribute to depressing granule cell spike activities (sparse coding).

To understand how different factors contribute to pattern separation, Cayco-Gajic et al. constructed models of the cerebellar input layer with spatially correlated input patterns and evaluated the separation performance using a perceptron classifier (mimicking a Purkinje neuron) on input and output patterns [8]. Their results suggest that the sparse connections, rather than sparse granule cell spike activities, determine pattern separation efficiency. These findings agree with another theoretical study showing that the sparse connection between granule cells and mossy fibers is optimized for associative learning [7]. Experimental data have emerged to support the pattern separation theory in the granule cell layer [10**]. However, whether granule cells use ultra-sparse coding has become controversial. While sparse coding can contribute to pattern separation performance [9], it suffers from a lower capacity for generalization [9,11]. In contrast, several recent calcium imaging experiments suggest quite dense activation of granule cells in zebrafish and mice during movements or in response to sensory stimuli [12–14]. These experiments analyzed fluorescence signals instead of detected spikes and results may therefore have been contaminated by the slow kinetics of the calcium indicators.

The divergent architecture of the granule cell layer can also increase the coding space by generating temporal basis sets [6,15,16], which may be a way to learn timed responses correctly. In addition to the divergent architecture, other factors, such as the divergent short-term plasticity at mossy fiber→granule cell synapses, may sculpt the temporal neural dynamics [17*].

Information transformation

In the next stage, preprocessed information is fed into Purkinje neurons, which act as the decoders and the sole output of the cerebellar cortex. Although Purkinje neurons have very elaborate dendrites, they were thought to function like a simple perceptron for many years [8,17*]. They have been reported to use linear simple spike rates to encode synaptic inputs in slices [18] and *in vivo* [19,20], despite the presence of many ion channels distributed on the dendrite. Opposing data suggests more complex, multiplexed coding. In monkeys, saccadic eye movement velocities are encoded by Purkinje neuron spike rates, but the onset of eye movements is encoded by the initiation of simple spike pauses [21]. In a follow-up study, identification of population spike dynamics using manifolds in both mossy fibers and Purkinje neurons showed that Purkinje neuron output amplifies the variability of the mossy fiber input [22*]. Other recent studies confirm the importance of simple spike variability, e.g. simple spikes encode reach kinematics on a reach-by-reach basis in mice [23]. These findings imply that averaging Purkinje neuron spike responses, as is done in many experimental studies, may remove significant parts of the encoded signal. It also suggests that the cerebellum can predict dynamical deviations from its learned model, which may be important for fast adaptation.

To simulate possible origins of the multiplexed coding and motivated by experiments showing that sensory stimulation triggers clustered parallel fiber input in mice [24], we simulated the response of Purkinje neurons to clustered input using a well-validated multi-compartmental model [25**]. For weak input, Purkinje neuron dendritic responses linearly increase with synaptic input. However, when granule cells are densely activated, local dendritic calcium spikes occur, which cause a burst of somatic spikes and a subsequent pause. This study provides a neuronal mechanism explaining the transitions between spike rate and pause coding observed in experiments [21]. Recent data support the occurrence of parallel fiber dendritic spikes *in vivo* [26], which is enhanced by dense activation of granule cells [12–14].

Whether Purkinje neurons also use simple spike synchrony to encode information remains a matter of debate [27–30]. The phase response curve is a neuronal property that measures the efficiency of a weak stimulus in shifting the next spike. In Purkinje neurons, firing rate-dependent phase response curves bridge the strategies of rate- and timing-coding [31]. In a recurrently inhibitory network model [32**], that mimics axonal collaterals between neighboring Purkinje neurons [33], this neuronal property causes high-frequency oscillations as observed *in vivo* [34] and enables correlated spikes only between neurons with increased firing rates. The dependence of loose synchrony on firing rate allows for rapid formation and dissolution of assemblies that can strongly inhibit nuclear neurons [28]. Another mechanism to increase spike-to-spike synchrony between Purkinje neurons is ephaptic coupling [27].

Cerebellar learning

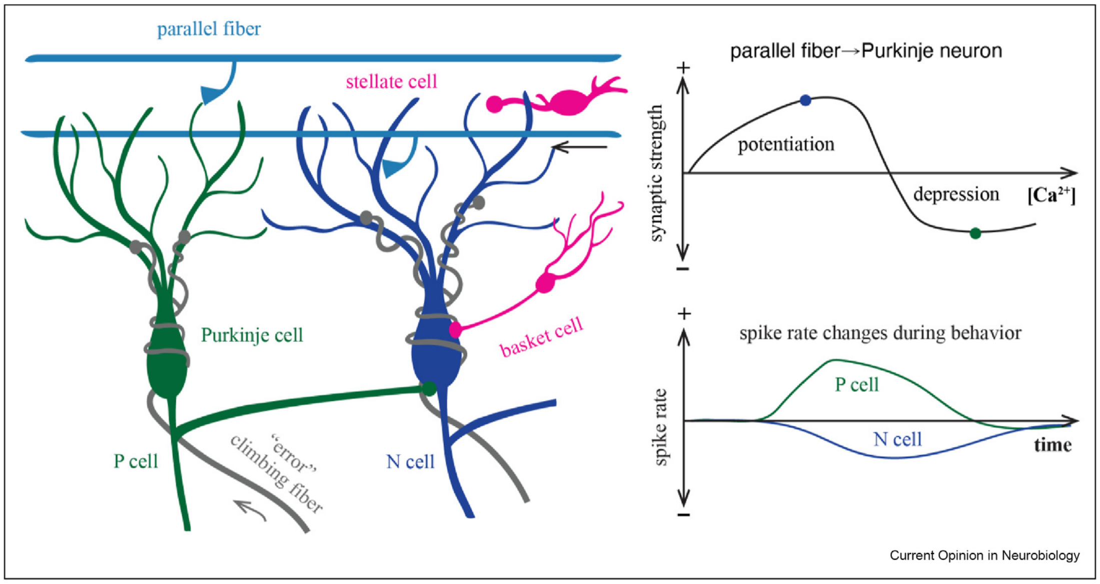
According to the Marr-Albus theory, the primary site of learning is located at parallel fiber→Purkinje neuron synapses [3,4]. When the predicted response does not match the desired output, climbing fiber synapses made by inferior olive neurons will trigger a complex spike in the Purkinje neuron that causes cerebellar learning through long-term depression (LTD) of parallel fiber synapses [35]. Considerable evidence suggests the role of parallel fiber LTD in behavioral learning, especially in simple behaviors like eyelid conditioning [5]. However, parallel fiber synaptic plasticity depends on the concentration of calcium at the synapse, with LTD at high concentrations and long-term potentiation (LTP) at low concentrations [36,37].

The Marr-Albus theory of supervised learning faces several challenges. The first is the change of synaptic weights in one direction only. This makes sense in simple pattern recognition learning by perceptrons but is less suitable for learning complex motor control. An experimental data-based theoretical study proposed a plausible mechanism for variable weight changes by identical error signals [38,39] (Figure 2). Purkinje neurons can modulate the spatial range and the magnitude of climbing fiber dendritic responses because of the high expression of Kv4 channels in the distal dendrites. Molecular layer interneuron inhibition suppresses climbing fiber dendritic responses and modulates learning rules at the parallel fiber synapse [40]. Purkinje neurons with low firing rates are more likely to have regionalized and lower calcium concentration elevations, possibly causing the large variety of dendritic responses observed in voltage imaging experiments [41]. Purkinje neuron ensembles encoding behavioral properties use bidirectional spike rate changes [19,20,30]. The learning speed is expected to improve if parallel fibers can undergo LTP instead of LTD in weakly active Purkinje cells.

A more challenging problem is the spatial credit assignment problem [42]. Briefly, how does the strict anatomical subdivision of climbing fiber projections into microzones [43,44] allow for mapping a sensory error signal to the right motor regions? For example, during bicycle driving a vestibular error signal may need to affect arm movements. Marr-Albus assume that parallel fibers can provide the necessary context, but, considering the large number of possible combinations needed, it is unclear whether classic cerebellar anatomy supports the full credit assignment range.

A similar issue exists in time: the temporal credit assignment problem. Depending on connectivity delays, error signals arrive at different times. However, timing-dependent plasticity of parallel fiber synapses may partially solve this problem [45].

Figure 2



Variable weight changes induced by climbing fiber signals.
The ensemble that encodes behavioral properties consists of Purkinje neurons with positive (P cell) and negative (N cell) changes of their simple spike rates, the latter can be caused by molecular inhibitory neurons or inhibitory axonal collaterals. Climbing fiber-evoked dendritic calcium influx differs between these two cells, with high calcium concentrations in P cells causing LTD and low calcium concentrations in N cells causing LTP [38].

Cerebellum beyond the Marr-Albus model

Over the last several years, new cell types have been identified in the cerebellar cortex [46,47]. The cerebellar circuitry is more complex than the often modeled simple feedforward circuitry [48]. Multiple recurrent feedback loops exist within the cerebellum [47,49–51]. Both the input and output layer of the cerebellum show structured connectivity, rather than a random network connectivity as assumed in past theoretical studies [52**,53]. Each neuronal type consists of populations with varying molecular, electrophysiological, and synaptic properties [15,17*,54]. Synaptic learning is not limited to parallel fiber synapses as it has been observed at many other synaptic connections. Cerebellar learning may rely on orchestrating synaptic and intrinsic plasticity at different anatomical sites and time scales [47,49,55*,56].

There is substantial evidence to suggest that the cerebellum has roles beyond motor control and its presumed supervised learning. Studies have demonstrated its involvement in cognitive processes, such as attention and language, as well as social ability, decision-making, working memory, vocal learning, and innate freezing behavior [57–62]. These behaviors may rely on other learning paradigms, including reinforcement learning and unsupervised learning. For instance, for decision-making [60], it may be more logical to maximize the reward than to have a "desired" output and this may also be supported by cerebellar projections to reward-encoding brain regions [58]. Similarly, unsupervised learning may be involved in innate freezing behavior and early motor learning.

In addition to its diverse functions, recent experimental data have extended our understanding of the signals entering the cerebellum. Granule cells do not code only sensory-motor information but also convey information about reward expectations in a densely activated manner [14,63]. Different groups of granule cells selectively respond to reward delivery, unexpected reward omission, and reward anticipation. Studies have shown that molecular interneurons in the vermis respond differentially to odorants in go/no-go tasks, and their responses can switch when valence is reversed [64*]. Another surprising finding is that climbing fiber-evoked complex spikes can reflect actions or events that predict upcoming rewards [65–67]. These findings suggest that the cerebellum is also involved in reward-based reinforcement learning. As expected in a degenerate brain [68], the cerebellum may therefore combine multiple forms of learning.

Conclusions and future challenges

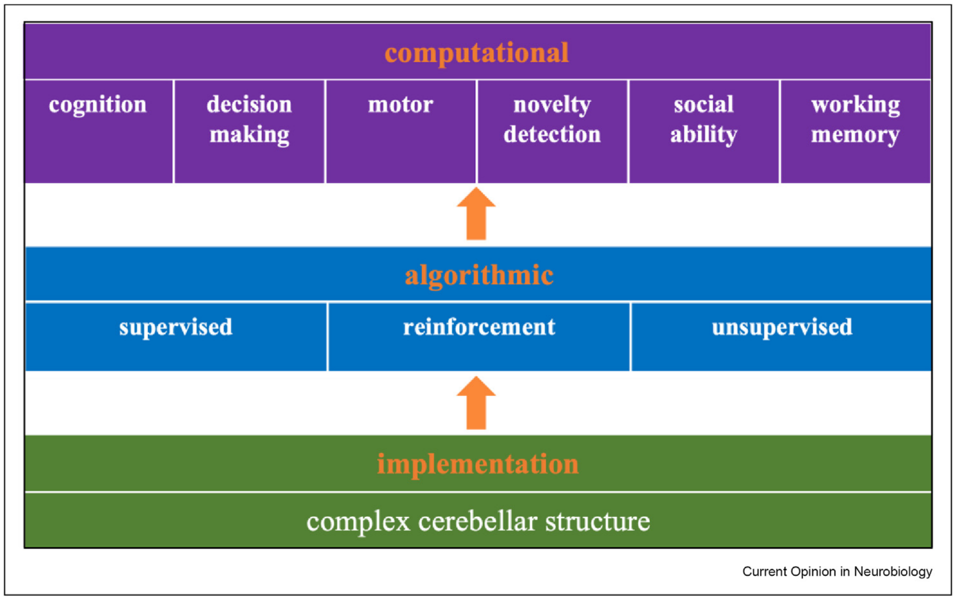
Theoretical models have been successful in stimulating and inspiring cerebellar research. The Marr-Albus theory successfully predicted the synaptic plasticity at parallel fiber synapses [35] and the expansion of coding space in the granule cell layer [10**] (experimental data only emerged 50 years later). Within the supervised learning framework, we keep progressing on information preprocessing, information transformation, and neuronal strategies for overcoming the credit assignment problems during cerebellar learning.

However, theoretical modeling has not kept up with experimental progress in recent years, especially regarding the diverse functions of the cerebellum. We propose several theoretical challenges that need to be solved in the future.

1. The impact of recurrent loops within the cerebellum on cerebellar learning remains largely unexplored in modeling. How do these new loops and local computations affect the computational capacity of the cerebellum in terms of coding space expansion, input—output transformation, and learning? Can they help with the spatial credit assignment problem?
2. Although multisite plasticity seems promising to improve learning efficiency, there is a chance of interference between multiple sites. Additionally, what is the relationship between single-trial learning and long-term memory [69,70]? In general, experiments have not distinguished cerebellar adaptation, for example biking under varying environmental conditions, well from cerebellar motor learning, like learning to ride a bike.
3. Granule cells can expand the coding space and learn representations of stimuli or actions that predict upcoming rewards. How can granule cell-conveyed reward signals be integrated into the cerebellar learning framework? Do granule cells in a particular region selectively receive one type of input information, or can they process both types of information at different stages of learning and be gated by other mechanisms?
4. Climbing fibers convey both error signals and reward signals. Two relevant questions need to be addressed: Why does the cerebellum use both granule cells and climbing fibers to convey reward signals? How do these two input pathways complement each other to increase learning efficiency [71]?
5. The most urgent task may be to compile recent experimental progress into a new cerebellar theory that can integrate different computational tasks using different learning paradigms (Figure 3). This new theory will help us better understand how the cerebellum works under normal and diseased conditions [58,72—74] and may advance the development of general artificial intelligence. Note that a theoretical study exploring its function in language processing has emerged [75].

Overall, we propose that the powerful computations and the multifunctionality of the cerebellum may rely on the orchestration of the aforementioned molecular, neuronal, and structural factors. Oversimplified computational rules and learning algorithms in a classical “skeleton” cerebellar circuitry may demonstrate the cerebellar

Figure 3



A new cerebellar theory is needed to integrate diverse computational functions.
In a top-down order, at the computational level, the cerebellum is involved in different computational tasks; at the algorithmic level, different learning paradigms may be required; at the implementation level, the cerebellum has a relatively uniform structure but it is more complex than initially thought.

learning process for simple behaviors that are well-mapped between errors and desired output [76], but may not be sufficient to integrate different learning rules for more complex computational functions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgement

Y.Z. thanks Dr. Eve Marder's generous support for this review when Y.Z. worked in her lab and the NIH Grants R35 NS097343 and R01MH046742. EDS is supported by the Okinawa Institute of Science and Technology Graduate University.

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