The diversity of the nature of input and output signals in the cerebellum suggests a diversity of function

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Highlights

- The local cerebellar circuit is constant and well described across a range of motor behaviors
- The nature of mossy and climbing fiber inputs, as well as the function of the output can vary widely across tasks, and even within a motor domain.
- This diversity makes the idea that the cerebellum performs a single computational function unlikely.
- New results suggest that different cerebellar modules play different roles within a single motor behavior.

Abstract [100-120]

Cerebellar research has been guided by the idea that it subserves a single computational function - the "universal cerebellar transform" - across different tasks. This idea is motivated by the uniform cerebellar circuit and our understanding of how it supports simple motor learning tasks. In this review we examine findings for three motor domains (eyeblink conditioning, saccades, and reaching arm movements) that highlight inconsistencies in the nature of input and output signals across tasks, and show that the cerebellum may even contribute in multiple different ways to a single task, challenging this classical view. Even though this review cannot offer a coherent picture of cerebellar function across tasks, we stress the importance of considering the possibility that the cerebellar circuit subserves multiple computational, rather than one universal, function.

Acknowledgement

Introduction

While the cerebellum appears to be involved in a multitude of tasks [1], it has a relatively invariant local neural circuitry, which is well preserved across different functional regions and different species. This has given rise to the idea that the cerebellar circuit subserves a single computational function across tasks - the universal cerebellar transform [2]. In this review, we will critically examine this idea across three different motor domains.

At the circuit-level, cerebellar information processing is well understood. More than 50 years ago Marr, Albus and Ito [3–5] formulated a hypothesis of circuit-level function that, at least in its main tenets, has stood the test of time. Glancing over many physiological details (Fig. 1), the cerebellum transforms a mossy fiber input (X) into Purkinje cell activity (W) that then modulates activity in the cerebellar nuclei, which ultimately conveys the cerebellar output (Y). The main idea is that the circuit of cerebellum is uniquely suited to learn complex functions $Y=F(X)$, based on a relatively sparse teaching signal - the climbing fiber input from the inferior olive (Z) [5–7].

The circuit has a number of special features that endow it with a special capacity to learn. First, the mossy fiber input is distributed on a simply astounding number of granule cells, each of which integrates 4-5 mossy fiber inputs in a nonlinear manner [8]. This arrangement may give the cerebellum the ability to learn very high-dimensional functions of the input [5,9]. This massively expanded input signal is then relayed to the large Purkinje cells, which receives >175,000 inputs via parallel fibers. Each Purkinje cell also receives typically one climbing fiber which provides a powerful plasticity-inducing input to the Purkinje cell. The climbing fiber input (Z) tunes the transformation of the mossy fiber input into Purkinje cell activity ($W=G(X)$), leading to the reduction in the simple-spike firing rates of Purkinje cells (W), hence indirectly modulating the input-output relationship ($Y=F(x)$). Through long-term depression, Purkinje cells can learn to lower their simple-spike (SS) firing rate in anticipation of the climbing-fiber input in a temporal precisely tuned manner [10,11]. This reduction in SS rate leads to a disinhibition of the targeted deep cerebellar nuclei (DCN) cells, which also receive direct input from the mossy fibers. The output of the DCN goes to a multitude of targeted downstream structures, for example brainstem motor nuclei or the thalamus. Additionally, each DCN circuit also sends inhibitory input to the IO cells that send climbing fibers to the associated Purkinje cells. In this way, the circuit learns to predict climbing fiber input based on a high-dimensional input signal - and automatically cancels this teaching signal when its occurrence was predicted.

The highly consistent nature of this circuitry has given rise to the idea that the cerebellum, when working with other brain structures to solve a specific task, also performs a unique common function, the so-called "universal cerebellar transform" [2,12]. One of the most influential formulations of this idea is that it implements a forward model [13–16]. Here the main idea is that the output of the cerebellum is used as a sensory prediction, which then can be used to be compared to the incoming sensory signal. The discrepancy between the two signals is then fed back to the system as an error signal via climbing fibers (Fig. 2). Alternatively, the cerebellar output may serve as a motor command, i.e. the cerebellum may constitute an inverse model [17–19]. Other hypotheses have highlighted timing [20–22] or prediction as a general principle [23–27].

Even though our understanding of the local cerebellar circuitry is advancing every year, it has been extremely difficult to test these domain general ideas of how this system works when it is put into the context of the brain-wide system to control a behavior. We will argue that the main reason for this failure is to appreciate the diversity of the nature of input-output mappings that the cerebellum performs. We will summarize the results of electrophysiological studies in relatively simple motor behaviors, which show that the nature of the mossy fiber input signal (X), of the teaching signal (Z), and the function of the output can vary dramatically across different tasks. Furthermore, we summarize recent evidence that the cerebellar circuit may fulfill different functions at multiple stages of even a single task. We argue that it is important to understand this multitude of functions, rather than assuming a-priori that all processes can be neatly summarized as subserving a single computational principle.

Main text

Eyeblink conditioning

Pavlovian eyeblink conditioning is likely one of the simplest and most well-understood examples of cerebellar associative learning. In this paradigm, an air puff (the unconditioned stimulus) is delivered to the eye, eliciting a protective closure of the eyelid (the unconditioned response). By pairing the unconditioned stimulus systematically with an auditory, visual or tactile stimulus (the conditioned stimulus), the animal learns to anticipate the air puff and begins to close the eye in anticipation (the conditioned response).

The learned response is highly cerebellar dependent [28], and is generated by the specific deep cerebellar sub-nucleus [the rostral anterior interpositus nucleus, 29], which in turn receive input from Purkinje cells in lobule HVI of the mouse cerebellum. This cerebellar system exerts direct control over the eyelid. For instance, Heiney et al. [28] reported that optogenetic suppression of Purkinje cells firing led to eyelid movements whose duration and magnitude could be finely controlled with very short latency. Climbing fibers in these areas carry information about the teaching signal, the unexpected occurrence of the air puff. After a pairing of the conditioned and unconditioned stimuli, Purkinje cells lower their SS firing rate in anticipation of the air puff [30], disinhibiting the DCN cells, leading to the closure of the eye.

The inhibitory connection between the DCN and the inferior olive also suppresses the climbing fiber activity related to the air puff. Thus, cerebellar Purkinje cells learn to predict their error signal and cancel it out. This mechanism also explains why the climbing fiber activity is suppressed when the air puff is omitted. Thus, the climbing fiber provides a signed error [31] signal that is sufficient for both the acquisition of the eyeblink response, as well as for its extinction [32]. In sum, the function of the cerebellum in eyeblink condition can be summarized as a system that acquires a temporal tuned prediction of an error-signal (**Z**), based on an input (**X**). The output (**Y**) is compared to the sensory inflow to determine a signed error signal, that is, it serves as a forward model prediction. Additionally, the output is used to drive the actual motor behavior [33], a function that would be more consummate with that of an inverse model.

A number of new results, however, suggest that this classical view may not capture all cerebellar functions within this simple paradigm. First, the nature of the error signal itself appears to undergo plastic changes as learning proceeds. In the untrained animal the climbing fibers (**Z**) to the relevant areas signal the unexpected air puff. However, after conditioning, the same climbing fiber increases its firing probability right after the occurrence of the conditioned stimulus (e.g. light) [31]. The shift of complex spikes from the time of the unconditioned air puff to the conditioned stimulus is reminiscent of dopaminergic neurons in the ventral tegmental area [34] underlying temporal difference learning. This suggests that the system first is trained to predict the air puff and issue an appropriate defensive motor command. In later phases, the circuit may now be trained to predict the predictive stimulus itself. Complicating the issue is that the climbing fiber response does not only signal a signed prediction error, but to some degree also encodes the novelty of a sensory stimulus [31], suggesting possibly multiple functions for this single circuit.

Finally, the circuitry described above is only one of the cerebellar circuits that is involved in eyeblink conditioning. Directly adjacent, one can find a different population of Purkinje cells [35] whose climbing fibers do not signal the air puff. Nonetheless, these Purkinje cells exhibit a learned modulation of their SS firing rate in the eyeblink conditioning task. In contrast to Purkinje cells in the classical circuit, which decrease their firing, this population increases their firing rate in a way that is correlated with eyelid position [35]. Furthermore, there is clear evidence [35] that learning in the classical circuit is necessary to drive the behavior in the second module, possibly transmitted by direct projections from the deep cerebellar to granule cells.

Based on these results, Ohmae et al. [35] argue that, rather than the cerebellum performing a unitary function in a specific task (Fig. 3a), multiple cerebellar units may be linked in a spiral-like arrangement (Fig. 3b). Following this idea, the output of one cortico-cerebellar circuit provides the input to the next. The paper also raises the intriguing idea that these circuits may communicate directly with each other (dashed line).

Saccades

Saccades are rapid and short eye movements that redirect the gaze to a new location. In the oculomotor vermis, which is implicated in the control of saccadic eye movements, mossy fibers (**X**) carry directional information about the upcoming saccade, with the directional specificity appearing around 10-20ms before saccade onset [36,37]. This activity closely resembles the output of the superior colliculus [38] and therefore resembles an efference copy signal. In the oculomotor vermis, the population response of a large group of Purkinje cells (**W**) provides precise information about saccade onset and offset [39] and about the eye velocity during the ongoing saccade [40] with a 20ms time lead. In addition, the direction of the error at the end of a saccade and the amplitude of this error (**Z**) can be computed from, respectively, the probability and duration of complex spikes [41]. Consistent with the idea of a teaching signal, the presence of a complex spike at the end of a saccade influences eye velocity during the next trial [42] but only for Purkinje cells whose complex spike exhibits a directional preference consistent with the experienced error [41]. Together, these results can be understood in terms of the classical view

that the cerebellum provides a forward model of eye kinematics that is then used to brake the eye movement.

Yet, other results depart from this view and suggest that there is a diversity of signals present at all levels. First, in contrast to the classical view that complex spikes carry an error signal that is used to drive the recalibration of saccadic eye movements, complex spikes do not represent motor errors in a consistent way. For instance, while the probability of a complex spike decreases during gain-up saccade adaptation in parallel with the decrease in error [43], the probability of complex spikes increases over the course of learning in gain down adaptation [44]. Furthermore, in other saccadic paradigms, complex spikes detected after trial onset appear to also carry information unrelated to retinal errors or to upcoming movement kinematics, such as information about the time of the target jump or the upcoming required behavior in partially overlapping populations of Purkinje cells [45]. Similarly, adjacent populations of Purkinje cells appear to contribute differently to saccadic eye movements [46]. These populations are defined by the input that they receive via climbing fibers: either sensory prediction error signals or information about upcoming movement. These populations also affect upcoming movements in different ways [46]. Finally, next to the classical inhibitory pathway between the output of the cerebellum and the inferior olive, there also exists an excitatory pathway from the deep cerebellar nuclei to the inferior olive, which is involved in the fine control of saccades [47]. This diversity in the anatomy suggests that the climbing fibers can play different roles for the control of saccades and that different circuits contribute to these rapid eye movements. Together, these results suggest that the diversity of information carried by the climbing fibers (saccade kinematics, motor errors, trial structure) is at odds with the idea that the cerebellum only serves as a forward model of eye kinematics. Rather, the results are more consistent with the idea that saccadic eye movements are controlled via a series of interactions between the cortex and the cerebellum (Fig. 3b).

Arm movements

Input (**X**), output (**Y**) and teaching signals (**Z**) have also been identified for reaching arm movements (e.g. moving the hand from one location to another) and resemble to some degree what has been described in the context of saccadic eye movements. During arm movements, mossy fiber input (**X**) carries an efference copy of motor commands linked to specific joints [48]. This efference copy reflects activity in motor and premotor areas [49]. The output of the cerebellar cortex (**W**) as measured by simple spike activity of Purkinje cells, is correlated with future arm movement position and velocity in a range of manual tasks [50–56] with a lead of a few tens of milliseconds. Purkinje cells often exhibit directional tuning before movement onset [49,57], which correlates with muscle activity with a lead time of 0 to 100ms [58]. The correlation of simple spike activity of Purkinje cells with arm kinematic, but not with arm dynamics [59] is consistent with the forward model hypothesis.

Consistent with the idea of a sensory prediction error (**Z**), the probability of climbing fiber activity decreases during motor learning in parallel to the reduction of error during the task [43]. In simple upper limb movements, complex spikes encode information about motor errors at

different times within the trial [60]. The amount of information encoded peaks at the end of movement [50], consistent with the idea that it provides a teaching signal for a forward model that predicts the outcome of an arm movement.

Yet, as for eyeblink conditioning and saccadic eye movements, the input (**X**), output (**Y**) and teaching signals (**Z**) carry much more information than what is hypothesized by the classical view. For instance, mossy fiber input is much richer than a mere efference copy as it also carries information about sensory feedback [48, see also 61] and even a copy of neocortical activity and not only of motor commands [62]. Similarly, SS activity seems to represent more than the future state of the arm - it is also influenced by arm dynamics [63], inconsistent with the role of a forward model of arm kinematics. Furthermore, SS activity is much more diverse than what would be expected if the cerebellum subserved a single function during the control of reaching. Beyond movement kinematics, SS discharge also reflects events like target appearance [60,64] or onset of target motion when animals are reaching to a moving target [65].

Similarly, climbing fiber activity (Z) during arm movements also represents a diversity of signals. During reaching arm movements, climbing fiber activity represents motor errors, target appearance, and movement onset [50,60,64]. During manual tracking, it represents the error between the hand cursor and the target [66–68], movement direction and distance [69], and future position, velocity or acceleration of the limb [67,68]. Finally, in reward tasks where animals have to perform arm movements (lever press or turning a wheel) to obtain a water reward, climbing fiber discharge has been found to be time-locked to task events that were predictive of reward outcomes [70] and is modulated by reward delivery and omission, and reward expectation [71]. These results and others from eyeblink conditioning [31] and licking behavior [72,73] confirm the large diversity in the nature of the signals that are represented by climbing fiber activity, including reward signals [74,75].

Conclusions

Across three apparently simple motor behaviors, we have demonstrated that there is a wide variety in the nature of cerebellar input and output signals. For instance, mossy fiber input (**X**) carries in some cases a copy of the motor commands, but can also signal other relevant sensory stimuli or context. The climbing fiber input (**Z**) can be often characterized as an error signal, but also sometimes simply signal expected stimuli or even reward signals [70,74]. Simple spike discharge (**W**) relates to upcoming velocity of the eye, the eyelid and the arm consistent with state estimation but can also directly influence motor output [33,76]. The output of the cerebellar circuit (**Y**) can sometimes be interpreted as sensory prediction, but often also is used directly to drive motor behaviors.

What are the consequences of this diversity if we want to generalize neurophysiological findings from motor behaviors to cognitive functions of the cerebellum in the human? First, we cannot rely on a single description of the cerebellar function (for example as a forward model). Rather, each cerebellar circuit needs to be carefully described in terms of the information present in the mossy fiber input (**X**), the nature of the climbing fiber input (**Z**), and the effects of cerebellar

output (**Y**) on downstream targets. Secondly, we need to consider the possibility that the nature of the input changes dynamically through learning - shifting the very learning objective for each cerebellar circuit. Finally, it is very likely that each behavior in questions is supported by a number of cerebellar modules, each of which may perform a different function [35,46,77]. These modules may be linked with each other in a spiral-like arrangement (Fig. 3b), each one providing input to the next.

These insights clearly complicate the development of a single theory of the functional role of the cerebellum, and this review will be disappointing to many readers as it fails to provide any significant steps towards this goal. Nonetheless, we believe it is important to illustrate the diversity of signals and functions in the cerebellar circuit even in apparently simple motor behaviors. It appears to us imperative to understand cerebellar function in its diversity, rather than to assume a-priori that it can be summarized neatly with a single computational operation.
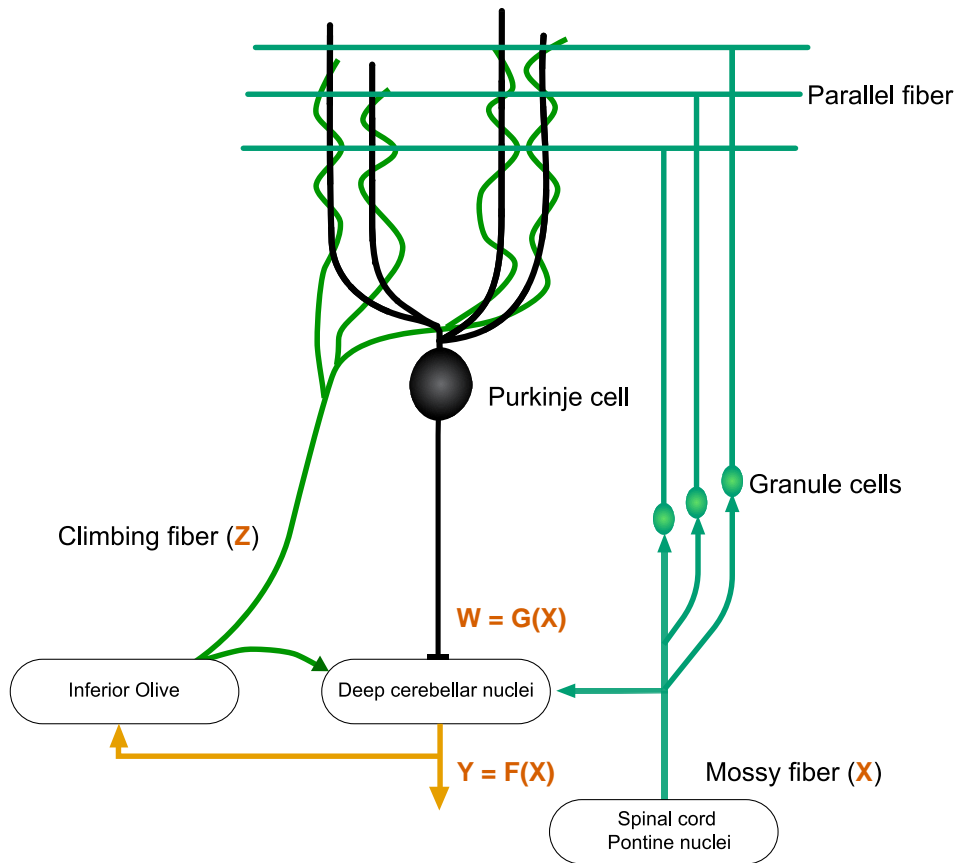
Figure 1. The basic cerebellar circuit. The input signal is carried by mossy fibers and relayed by granule cells via parallel fibers, which leads to a massive expansion of information (green part of the diagram). Each parallel fibers synapses on the dendrites of several Purkinje cells (only one is represented in black). Purkinje cells fire at a relatively high frequency and directly inhibit neurons in the deep cerebellar nuclei, with 50-100 Purkinje cells projecting on a single neuron. In addition to parallel fibers, each Purkinje cell also receives input from a single climbing fiber (blue) originating from neurons in the inferior olive. The climbing fiber activity results in a complex spike. Complex spikes are considered to be a teaching signal that leads to changes at the parallel fibers-Purkinje cell synapses. The nature of the teaching signal determines the function of the cerebellar module. Deep cerebellar neurons also receive a copy of the signal carried by the mossy fibers and by the climbing fibers, both through excitatory synapses. This architecture is present throughout cerebellar regions with little variations.
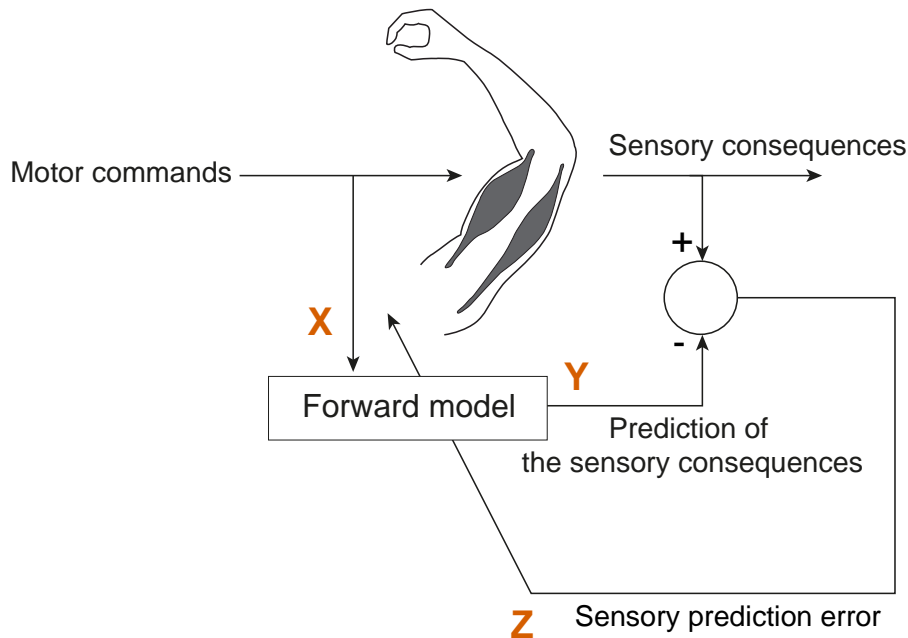
Figure 2. A forward model for motor control [13]. The forward model takes an efference copy of the motor commands as input (**X**) and the motor commands is then used by the cerebellum to compute the change in state (output **Y**, e.g. position/velocity of the arm, which will determine the predicted sensory consequences). In this scenario, the sensory prediction error (**Z**, the difference between the predicted and actual sensory consequences of the motor commands) ensures that the output of the forward model remains accurate and can reliably predict incoming sensory information.
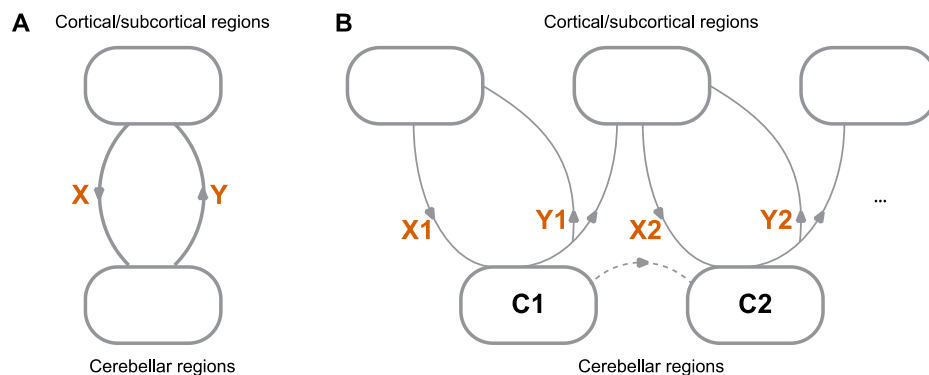

Figure 3. Two different ways in which the cerebellum can contribute to a behavior. Following the classical view (**A**), a single cerebellar circuit is connected in a closed-loop arrangement with a single cortical or subcortical area [78]. In contrast, the modern view suggests that multiple cerebellar circuits may contribute to a single task through a spiral-like arrangement (**B**). Cerebellar circuit C1 provides input to a downstream cortical / subcortical area, which in turn projects to a second cerebellar circuit (C2). Even direct connections between cerebellar circuits (dashed line) may exist [35].

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Heiney SA, Wojaczynski GJ, Medina JF: Action-based organization of a cerebellar module specialized for predictive control of multiple body parts. Neuron 2021, 109:2981-2994.e5.
This paper convincingly shows that a particular population of neurons from a deep cerebellar nucleus helps control and coordinate eyelid, neck and forelimb in order to protect the eye from an airpuff. This suggests that the output of the cerebellar circuit does not only provide predictions about movement kinematics.

Markanday A, Inoue J, Dicke PW, Thier P: Cerebellar complex spikes multiplex complementary behavioral information. PLOS Biol 2021, 19:e3001400.
This paper illustrates the richness of the information contained in the teaching signal (**Z**) carried by the climbing fibers. This goes beyond the classical view that climbing fibers carry error information.

Calame DJ, Becker MI, Person AL: Cerebellar associative learning underlies skilled reach adaptation. Nat Neurosci 2023, doi:10.1038/s41593-023-01347-y.
This paper found coding of reaching movement kinematics in a specific Purkinje population kinematic coding. Optogenetic stimulation of mossy fiber input (**X**) can perturb the accuracy of reaching movement but repeated stimulation leads to plasticity in the cerebellar circuitry. This paper suggests that both eyeblink conditioning and motor adaptation are instances of associative learning.

Gaffield MA, Sauerbrei BA, Christie JM: Cerebellum encodes and influences the initiation, performance, and termination of discontinuous movements in mice. eLife 2022, 11:e71464.
This paper suggests that a population of Purkinje cells from the mouse cerebellum can serve different functions depending on the context (anticipatory licking for upcoming water reward or reactive licking to delivered water reward).

Zhu J, Hasanbegović H, Liu LD, Gao Z, Li N: Activity map of a cortico-cerebellar loop underlying motor planning. Nat Neurosci 2023, doi:10.1038/s41593-023-01453-x.
This paper investigates the interaction between the anterior lateral motor cortex and the cerebellum in the mouse. In contrast to the popular view that each area of the cortex is connected reciprocally with one area of the cerebellum, they showed that there is only partial overlap of the cerebellar regions that receive input and provide output to the anterior lateral motor cortex, and that these regions have different functions.