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Perspective

Reward signals in the cerebellum: Origins, targets, and functional implications

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SUMMARY

The cerebellum has long been proposed to play a role in cognitive function, although this has remained controversial. This idea has received renewed support with the recent discovery that signals associated with reward can be observed in the cerebellar circuitry, particularly in goal-directed learning tasks involving an interplay between the cerebellar cortex, basal ganglia, and cerebral cortex. Remarkably, a wide range of reward contingencies—including reward expectation, delivery, size, and omission—can be encoded by specific circuit elements in a manner that reflects the microzonal organization of the cerebellar cortex. The facts that reward signals have been observed in both the mossy fiber and climbing fiber input pathways to the cerebellar cortex and that their convergence may trigger plasticity in Purkinje cells suggest that these interactions may be crucial for the role of the cerebellar cortex in learned behavior. These findings strengthen the emerging consensus that the cerebellum plays a pivotal role in shaping cognitive processing and suggest that the cerebellum may combine both supervised learning and reinforcement learning to optimize goal-directed action. We make specific predictions about how cerebellar circuits can work in concert with the basal ganglia to guide different stages of learning.

INTRODUCTION

The canonical reward circuitry of the brain comprises multiple brain regions, most notably midbrain dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc)—where most neurons respond to delivery of external rewards (Engelhard et al., 2019; Schultz, 1998). These neurons influence goal-directed decision-making and behavior through their projections to the striatum and frontal cortex (Björklund and Dunnett, 2007; Cox and Witten, 2019; Ott and Nieder, 2019). The signals in dopaminergic neurons are thought to encode subjective value that can be used to select and reinforce actions (Schultz et al., 1997; Yokel and Wise, 1975). Activity in these dopaminergic neurons is generally considered in the context of temporal difference learning (Sutton, 1988) and consists of responses that encode reward prediction, delivery, and omission, underpinning the consensus that these reward signals are the main locus of reinforcement learning in the brain (Bayer and Glimcher, 2005; Doya, 2000; Schultz et al., 1997). More recent experiments using tools from experimental economics have led to suggestions that the dopaminergic reward signal encodes economic utility (Schultz et al., 2017).

Recently, several studies have demonstrated that reward delivery during both operant and associative behavioral tasks drives widespread activation in cerebellar neurons in a manner that exhibits hallmarks of reward-related activity in the dopaminergic circuitry (Heffley and Hull, 2019; Heffley et al., 2018; Kostadinov et al., 2019; Larry et al., 2019; Wagner et al., 2017), building on earlier work suggesting that the cerebellum is involved in reward-related behaviors (Berns et al., 2001; Ramnani et al., 2004; Tanaka et al., 2004; Thoma et al., 2008). These physiological findings have been complemented by recently discovered anatomical pathways showing that the cerebellum is poised to influence and be influenced by reward circuitry through its reciprocal connectivity with the VTA and SNc (Carta et al., 2019; Fallon et al., 1984; Pisano et al., 2021; Watabe-Uchida et al., 2012) as well as the striatum (Bostan and Strick, 2018; Chen et al., 2014; Hoshi et al., 2005; Ichinohe et al., 2000) and neocortex (Chabrol et al., 2019; Gao et al., 2018; Kelly and Strick, 2003; Pisano et al., 2021; Wagner et al., 2019; Wagner and Luo, 2020). A key first step for understanding the interactions between these systems is to examine where in the cerebellar circuit specific reward contingencies are represented and to define the similarities and differences in encoding of reward-related information across these different brain regions.

Overview of the cerebellar circuitry

The cerebellum is innervated by two distinct sources of glutamatergic input: mossy fiber inputs arising from the spinal cord, brainstem, and pontine nuclei and climbing fiber inputs originating in the inferior olivary nucleus (Figure 1A). These input pathways converge in the cerebellar cortex within Purkinje cells and have traditionally been thought to carry complementary information streams (Albus, 1971; Marr, 1969). Mossy fiber inputs, which are routed to Purkinje cells via the parallel fiber axons of

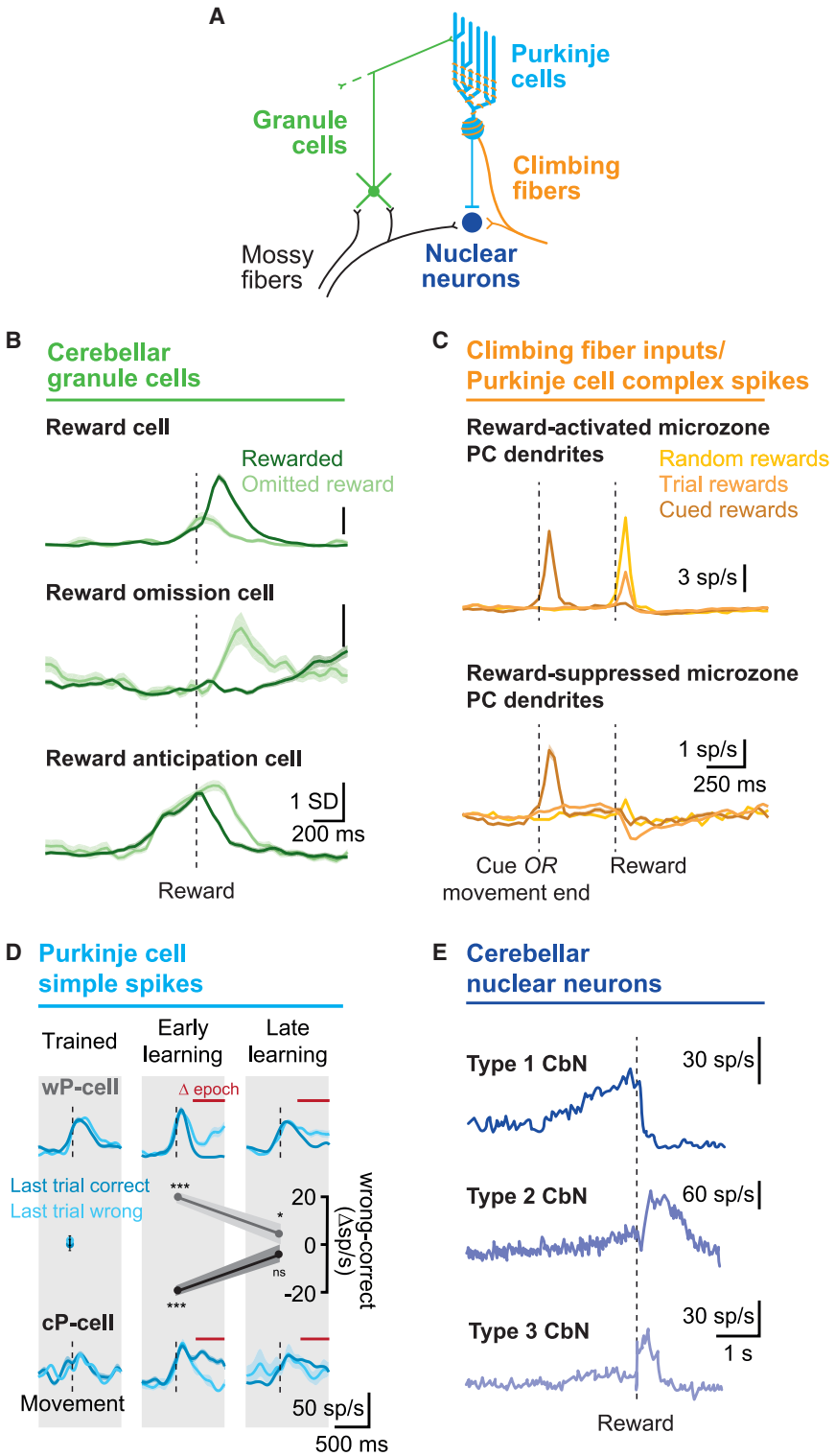

Figure 1. Reward signals in specific locations in cerebellar circuits

(A) Schematic of the canonical cerebellar microcircuit. Excitatory input arrives via two sources: the mossy fiber pathway from nuclei in the pons, brainstem, and spinal cord and via the climbing fiber pathway originating in the inferior olivary nucleus. Mossy fiber inputs activate granule cells in the cerebellar cortex, which then send parallel fiber axons that excite Purkinje cells, which also receive excitatory input from a single climbing fiber. Purkinje cells form the sole output of the cerebellar cortex, sending inhibitory projections to the cerebellar nuclei, which also receive excitatory inputs from collaterals of both mossy fibers and climbing fibers. Inhibitory interneurons are omitted from this schematic for simplicity.

(B) Reward signals in cerebellar granule cells recorded using two-photon calcium imaging as mice executed a forelimb operant task for water reward. Trial-averaged fluorescence activity of three example granule cells is aligned to reward delivery time on rewarded trials or trials on which reward was unexpectedly omitted. Individual granule cells exhibit delivery, omission, and anticipation signals (modified from Wagner et al., 2017).

(C) Reward signals in climbing fiber input to Purkinje cells measured using two-photon calcium imaging of Purkinje cell (PC) dendrites as mice performed a visuomotor integration task for operate rewards and received interleaved random and tone-cued rewards. Trial-averaged dendritic event rates, which faithfully report climbing fiber input and complex spiking, in response to random, operant, and cued rewards in PCs classified as reward-activated and reward-suppressed based on their response to operant reward delivery. Predictability exerts a suppressive effect on reward responses (modified from Kostadinov et al., 2019).

(D) Reward signals in Purkinje cell simple spikes in monkeys performing a visuomotor association task. Neurons could be classified based on whether their activity was higher after incorrect outcomes (wrong-reporting Purkinje cells; wP-cells) or after correct outcomes (correct-reporting Purkinje cells; cP-cells) during learning of novel visuomotor associations. Differences in firing rate occurred during "delta epochs" (denoted by red dashes) and were not present at the end of a learning block (trained), instead emerging transiently during the learning of new associations (modified from (Sendhilnathan et al., 2020).

(E) Reward signals in cerebellar nuclear neurons in mice running down a virtual corridor to a reward location. Cerebellar nuclear neurons (CbNs) exhibited three types of responses: type 1 cells increased their firing as animals approached the reward location and decreased their firing upon reward delivery, type 2 cells exhibited increased firing before and after reward delivery, and type 3 cells were activated only after reward delivery (modified from Chabrol et al., 2019).

granule cells, are thought to carry contextual sensory, motor, and internal state signals that form a temporal basis for learning in Purkinje cells. Meanwhile, climbing fibers, which synapse directly onto Purkinje cells, are thought to carry instructive signals that inform Purkinje cells about which mossy fiber inputs are important (and which are not) (Albus, 1971; Marr, 1969). Coincident activation of climbing fiber and parallel fiber inputs triggers long-term depression of parallel fiber synapses (Ito and Kano, 1982). Moreover, plasticity at this synapse is timing-dependent (Safo and Regehr, 2008; Suvrathan et al., 2016;

Wang et al., 2000) and bidirectional, since parallel fiber synapses that are active independent of climbing fiber inputs undergo long-term potentiation (Boyden and Raymond, 2003; Coesmans et al., 2004; Gao et al., 2012; Jörntell and Hansel, 2006; Salin et al., 1996). Climbing fiber inputs trigger complex spikes in Purkinje cells and are traditionally thought to convey predictive timing and sensorimotor error signals that improve motor performance (Kawato et al., 1987; Medina, 2011; Wolpert et al., 1998). These inputs organize the cerebellum into microzones, groups of neighboring Purkinje cells about 100–200 μm wide. These microzones form functional and anatomical modules that coordinate activity, drive plasticity, and, ultimately, control cerebellar output via the cerebellar nuclei (Apps and Garwicz, 2005; Cerminara et al., 2015; De Zeeuw, 2021; Herzfeld et al., 2015; Michikawa et al., 2021; Person and Raman, 2011). This is due to the unique anatomical organization of climbing fiber projections and functional properties of inferior olive neurons, the sole origin of the climbing fibers (Apps and Garwicz, 2005; Sugihara and Shinoda, 2004). Olivary neurons form gap junction-coupled networks that exhibit coherent subthreshold oscillations (Llinas et al., 1974; Mathy et al., 2009; Van Der Giessen et al., 2008). Coupled groups of olivary neurons, which innervate neighboring Purkinje cells, fire action potentials synchronously, in turn triggering synchronous complex spikes in their target Purkinje cells. Thus, groups of Purkinje cells organized into microzones experience climbing fiber plasticity coherently and coordinate cerebellar output and learning via synchronous output to neurons of the cerebellar nuclei (Tsutsumi et al., 2020; Van Der Giessen et al., 2008). Because a given external input activates some groups of climbing fibers while suppressing others, different microzones may preferentially experience long-term depression (i.e., be downbound) or potentiation (i.e., be upbound) during learning in a particular behavioral context, allowing for flexible and synergistic learning (De Zeeuw, 2021).

Thus, the cerebellar cortex features one of the most beautifully ordered functional architectures of any circuit in the brain, which has now been well established and is intensively studied for decades (Eccles et al., 1967; De Zeeuw et al., 2021)—inspiring many theories of learning based primarily on performance error signals conveyed by the climbing fiber pathway. It was therefore quite unexpected and disruptive to suddenly find reward signals throughout the cerebellum, delivered to specific elements of the cerebellar circuitry by activity in the mossy fibers and climbing fibers (Heffley and Hull, 2019; Heffley et al., 2018; Kostadinov et al., 2019; Larry et al., 2019; Wagner et al., 2017, 2019). Next, we will describe the evidence for reward signals in these distinct pathways.

Reward signals in the mossy fiber-granule cell pathway

Cerebellar granule cells are the most numerous neuronal cell type, comprising approximately half of all neurons in the brain. However, they are also very small and exceptionally difficult to record from using electrophysiological approaches, which has, until recently, prohibited studies of their function *in vivo* during behavior (but see Powell et al., 2015). To overcome this hurdle, several recent studies have used two-photon imaging of calcium signals in granule cells (Giovannucci et al., 2017; Wagner et al., 2017, 2019), which likely reflect action potential bursts, to measure population activity in granule cells in awake behaving mice.

In a landmark study, Wagner and colleagues used this approach to observe prominent reward-related signals in granule cell populations across cerebellar lobules VI, simplex, and Crus I during both operant and classical conditioning behavior (Wagner et al., 2017). They reported that subsets of granule cells (1) are activated by reward delivery, (2) encode reward predictively (active between motor action and reward and sensory cue and reward), and (3) can signal a lack of expected reward (Figure 1B). By tracking populations across training, they also showed that granule cells undergo important learning-dependent changes. Although movement-related signals remained relatively constant across learning, reward-prediction and reward-omission signals were both substantially enhanced over the course of learning. Thus, the mossy fiber-granule cell pathway can convey both sensorimotor context as well as reward-related signals to Purkinje cells during complex behavior. More recently, the same group used dual two-photon imaging of neocortical output neurons and granule cells to study the interplay between movement and reward-related information in the corticocerebellar loop. Interestingly, they showed that reward-related signals are conditional—there are granule cells that are specifically tuned to combinations of actions (left and right arm movements) and reward (Wagner et al., 2019). Thus, granule cells may be capable of parcellating behavior and binding specific sensorimotor features to upcoming reward, providing an even richer set of parameters for Purkinje cell microzones to learn. These learned pattern combinations could then be routed out to various extracerebellar targets via specific modules, binding specific motor synergies to rewarding outcomes (De Zeeuw, 2021; Heiney et al., 2021).

Reward signals in the climbing fiber pathway

Several recent studies have probed the organization and functional properties of predictive and feedback climbing fiber signals, showing that they transcend pure sensorimotor associations and can signal learned predictions about reward. Two groups used two-photon imaging of calcium signals in Purkinje cell dendrites, which reflect complex spikes driven by climbing fiber input (Gaffield et al., 2019; Kitamura and Hausser, 2011; Tsutsumi et al., 2015), to reveal how these inputs convey and evaluate the outcome of predictions about upcoming rewards (Heffley et al., 2018; Kostadinov et al., 2019). Using an operant forelimb task in which mice were trained to release a lever in response to a visual cue to receive reward, Heffley and colleagues showed that climbing fiber inputs in lobule simplex are activated more strongly by correct (rewarded) lever releases in response to the visual cue than incorrect or spontaneous lever releases (Heffley et al., 2018). In a complementary study, Kostadinov and colleagues used a visually guided sensorimotor integration task in which mice obtain operant rewards for performing accurate steering wheel movements that translate a virtual object to a target location to study the diversity of climbing fiber signals conveyed to distinct microzones in lobule simplex (Kostadinov et al., 2019) (Figure 1C). By delaying reward delivery relative to the animals' movements, this study was able to distinguish signals related to sensorimotor modulation from predictive and

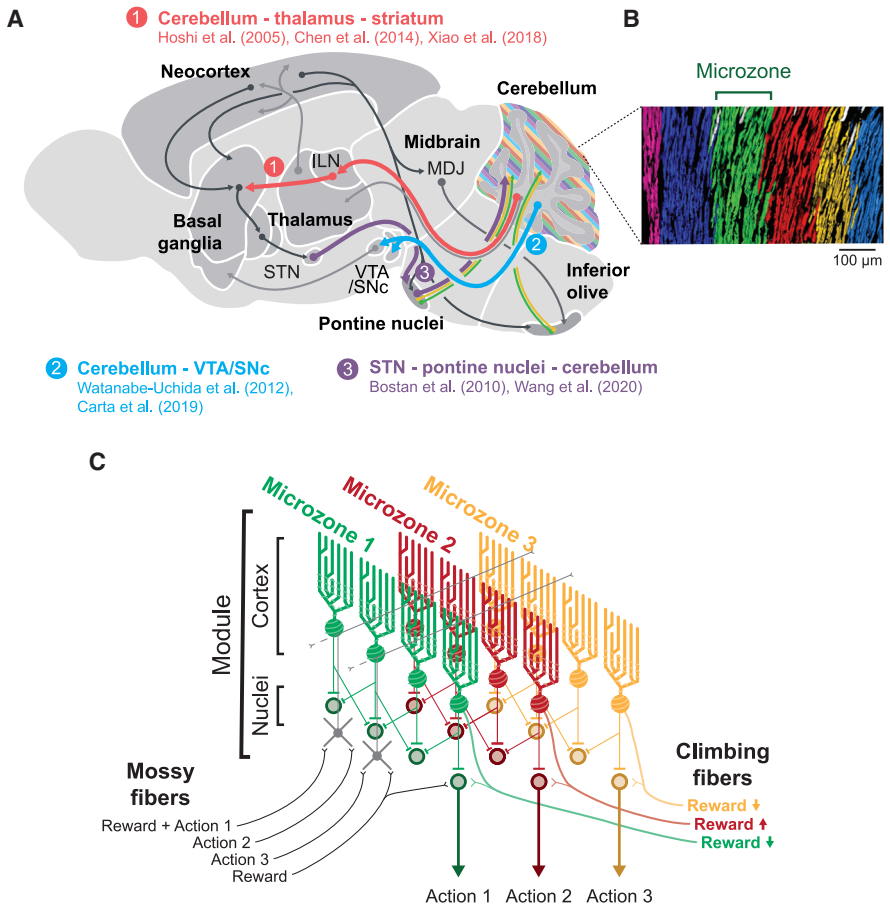

Figure 2. Anatomical connections between cerebellar circuits and reward-related areas

(A) Summary of the major brain-wide anatomical connections that could be engaged in cerebellar reward signaling, most notably the reciprocal interactions between the cerebellum and basal ganglia circuits, and the cerebellocortico-thalamic loops (see Bostan and Strick, 2018). Recently identified connections are highlighted.

(B) Example image of cerebellar Purkinje cells sorted by microzone identity based on recording of spontaneous activity. These microzones comprise the computational units of cerebellar cortical computation (modified from Kostadinov et al., 2019).

(C) Schematic of cerebellar modules that form the full computational subunits of the cerebellum and may engage in distinct loops with various reward-related structures. Sensorimotor and reward context are conveyed to multiple modules via the mossy fiber pathway, and reward-related teaching signals are conveyed to individual microzones by reward-activated and reward-suppressed climbing fiber inputs. Ultimately, predictive control of behavior is achieved through combinatorial activation and suppression of action-specific output from the cerebellar nuclei.

reactive reward-related activity. Importantly, this study found that reward signals are organized into crisply defined microzones of Purkinje cells (Figure 2B) that could signal reward delivery bidirectionally: some microzones were activated, whereas others were suppressed by reward. Furthermore, reward-suppressed microzones were also more likely to signal expected rewards predictively in the delay between the end of the animals' movement and the upcoming reward. The microzonal structure of reward signaling suggested an organizing principle for how the cerebellar circuitry mediates reward signaling: specific action contexts that are predictive of rewards, carried by the mossy fiber-granule cell pathway, may be learned flexibly through activation and suppression of Purkinje cell microzones and transmitted to the rest of the brain through modular action map outputs via the cerebellar nuclei (Figure 2C).

Both studies also probed how violations of animals' reward-related expectations were represented by climbing fiber inputs: delivering unexpected rewards evoked climbing fiber responses in many Purkinje cells, and this reward-related activation was significantly stronger than that present during operant behavior (when the reward was predictable). Conversely, omitting expected reward on operant task trials evoked secondary error-like responses when animals realized that an expected reward was not present (Heffley et al., 2018; Kostadinov et al., 2019). Thus, the same climbing fiber populations can signal both the expectation of an upcoming reward and a violation of a learned, reward-related expectation.

Several groups have also documented reward-related climbing fiber signals by measuring complex spiking in Purkinje cells using electrophysiology. Using a smooth pursuit tracking task in monkeys in which the visual cue predicted reward size, Larry et al. showed that climbing fibers in the cerebellar flocculus can signal upcoming reward size (Larry et al., 2019). Although these authors did not observe complex spike modulation at the time of

reward delivery, their recordings were performed in trained animals where rewards would be expected and climbing fiber signals may therefore be suppressed (Heffley and Hull, 2019; Kostadinov et al., 2019), possibly through direct inhibitory feedback from the cerebellum to the inferior olive (Kim et al., 2020). Using a visuomotor association learning task in monkeys and recording from Purkinje cells in Crus I and II, Sendhilnathan et al. showed that when reward-related task timing is predictable, climbing fiber inputs signal these events predictively (Sendhilnathan et al., 2021). Finally, Chabrol et al. also recorded Purkinje cell activity in Crus I in mice running on a treadmill to a reward location in a virtual track and found that reward delivery triggered robust "fat spikes," which likely reflect dendritic events in Purkinje cells associated with climbing fiber input (Chabrol et al., 2019; Davie et al., 2008). An important next step toward elucidating how these reward-related climbing fiber inputs contribute to behavior is to understand how these signals are modified over the course of learning.

Climbing fiber reward signals may be used for learning

By interleaving tone-cued rewards into their behavioral paradigm while imaging across learning, Kostadinov et al. were able to demonstrate that predictive reward signals in lobule simplex emerge over the course of training and that responses to cued, anticipated (i.e., fully predictable) rewards are almost completely suppressed (Kostadinov et al., 2019). Furthermore, in a subsequent study that used a visual Pavlovian conditioning paradigm instead of their previous operant motor task and also recorded in both naive and trained animals, Heffley et al. demonstrated that climbing fiber inputs to Purkinje cells in multiple lobules in the cerebellar hemispheres can encode reward-predictive sensory cues (Heffley and Hull, 2019). Climbing fiber inputs learned to convey these reward-predictive cues in addition to other sensory responses that were already present in naive animals. Specifically, in lobules simplex and Crus II, where climbing fibers did not exhibit visual responses in naive animals, responses to the reward-predicting visual cue emerged with learning. However, in Crus I, where climbing fibers already exhibited visual sensory responses in naive animals, the learned reward-predictive response was present in addition to the baseline visual response.

Thus, climbing fiber inputs, which are classically viewed as the cerebellum's teachers, are themselves subject to reward-related learning. Predictive reward signals emerge as animals learn which sensory and motor task parameters lead to reward, and reward responses are suppressed when rewards are predictable. These are both hallmark features of a temporal difference reinforcement learning signal (Sutton, 1988) and are similar to reward-related activity in midbrain dopaminergic neurons (Schultz, 1998; Schultz et al., 1997). Interestingly, the acquisition of such predictive signals may not be limited only to appetitive stimuli; cerebellar responses during delayed eye-blink conditioning also exhibit signatures of temporal difference learning including predictive activation and a signed prediction error (Giovannucci et al., 2017; Ohmae and Medina, 2015; ten Brinke et al., 2015; Ten Brinke et al., 2017). Reward-related feedback climbing fiber signals are, on the other hand, dissimilar from dopaminergic neurons (and climbing fiber signals during eye-blink conditioning). These signals universally report reward omission through activation and are therefore more consistent with an unsigned prediction error signal. If these reward prediction error signals reflect activity in the dopaminergic circuitry, they must be rectified on their way to reaching the inferior olive or they are instead driven by other reward-related circuits, such as the locus coeruleus (Rouhani and Niv, 2021; Sara, 2009). Alternatively, these cerebellar reward signals may represent the violation of a sensory expectation of about the physical presence of the reward, which are detected without the aid of specific reward circuitry. This may explain why reward omission signals are present in some cerebellar modules but not others (De Zeeuw, 2021; Kostadinov et al., 2019).

Cerebellar output mediated by the Purkinje cells ultimately relies on the interplay of information from the mossy fiber-granule cell and climbing fiber pathways. Thus, it is crucial to understand how these input streams are integrated in Purkinje cells. In the following section, we discuss several recent studies that have used electrophysiological methods, which provide sufficient temporal resolution to measure these signals simultaneously, to define the relationship between reward-related simple spikes (modulated by the mossy fiber-granule cell pathway) and complex spikes (driven by climbing fiber inputs).

How do reward signals in different pathways converge in Purkinje cells?

Mossy fiber and climbing fiber inputs conveying functionally similar information converge in individual microzones (Apps and Garwicz, 2005; Brown and Bower, 2001). Given that reward signals have been observed in both mossy fiber (granule cell) and climbing fiber pathways, it is therefore likely that these two streams of reward signaling will converge in individual Purkinje cells, via interactions between parallel fiber and climbing fiber inputs. Crucially, coincident activation of these inputs has been shown to lead to long-term depression at the parallel fiber synapse, whereas activation of parallel fibers by themselves leads to long-term potentiation (Boyden and Raymond, 2003; Coesmans et al., 2004; Gao et al., 2012; Ito and Kano, 1982; Jörntell and Hansel, 2006; Salin et al., 1996). These forms of plasticity have long been postulated to be the locus of memory storage during motor learning (Albus, 1971; Marr, 1969). This has been supported by a large body of work showing that climbing fiber inputs to Purkinje cells during learning exert bidirectional modulation of coincident parallel fiber inputs (Gilbert and Thach, 1977; Herzfeld et al., 2018; Medina and Lisberger, 2008), leading to reciprocal task coding by complex and simple spikes within individual neurons (Badura et al., 2013; Gilbert and Thach, 1977; Stone and Lisberger, 1990). A key to placing cerebellar reward signals within the context of known cerebellar functions is, therefore, to define how complex and simple spikes represent reward in individual Purkinje neurons. Several recent studies have used electrophysiological methods to compare reward-related activity in complex and simple spikes in the same cells.

To this end, Larry and colleagues recorded from the floccular complex of monkeys performing a visual pursuit that contained a cue period during which reward size was signaled (by cue color) and followed by a smooth pursuit period allowed them to directly assess the relationship between reward-related and movement-

related simple and complex spike firing in the same Purkinje cells. Although simple and complex spike signals were anticorrelated during the pursuit period of each trial, these signals were not consistently reciprocal during the reward cue period (Larry et al., 2019). The simple spike rates of Purkinje cells during the pursuit phase did vary slightly in trials with different cues (and therefore different reward sizes), but motor kinematics were sufficient to explain these differences (Lixenberg et al., 2020). Thus, in this behavioral paradigm, complex spike but not simple spike activity may play a central role in encoding reward value in trained animals.

The question of how these two Purkinje cell firing modes encode information during learning has been addressed by a recent set of studies by Sendhilnathan and colleagues. Using a visuomotor association learning task in monkeys and recording lobules Crus I and II, these authors demonstrated that the simple spike rates of Purkinje cells encode a reinforcement error signal during the learning of new visuomotor associations, reporting the outcome of the animal's most recent decision in short periods that they termed "delta epochs" (Figure 1D). Although each neuron's selectivity for previously correct or incorrect trials differed only in these short epochs, Purkinje cells as a population tiled the whole duration from one decision to the next. Thus, this population activity maintained a working memory of the last trial's outcome that could be used to guide the subsequent decision. This delta epoch encoding was transient (the differences in firing disappeared after the new visuomotor associations were learned) and did not depend on the particular movement kinematics or sensory cue that was presented. Surprisingly, the timing of simple spike delta epochs in individual Purkinje cells was not systematically related to the timing of complex spike firing in these neurons, which often occurred in response to reward-predictive cues and actions (Sendhilnathan et al., 2020).

These studies suggest that predictive complex spikes may engage the cerebellum differently than canonical error-related feedback complex spikes. An intriguing possibility is that these predictive climbing fiber inputs may serve as a "perturbation" signal that opens up the cerebellar circuitry for further plasticity based on upcoming sensory or motor events, as proposed in a recent study by Bouvier and colleagues (Bouvier et al., 2018). It remains unclear whether these "perturbation" complex spikes would exhibit any specific biophysical signature that allows them to exert different actions, but this is an open possibility when considering the exquisite calcium sensitivity of plasticity at the parallel fiber to Purkinje cell synapses (Coesmans et al., 2004; Jörntell and Hansel, 2006; Rowan et al., 2018; Wang et al., 2000) as well as the diversity of climbing fiber-mediated dendritic calcium signals and complex spike durations observed in Purkinje cells under a variety of task conditions (Mathy et al., 2009; Najafi et al., 2014; Ten Brinke et al., 2019; Yang and Lisberger, 2014). These predictive climbing fiber inputs may not only serve a function in the cerebellum itself. They may also serve as a precise timing signal in distally connected brain regions, including the basal ganglia, that important behavioral events are about to occur (Howe and Dombeck, 2016; Nashef et al., 2018; Simpson et al., 1996; Tsutsumi et al., 2020). More broadly, this priming signal for upcoming salient events would be consistent with the Pearce-Hall model of learning (Pearce and Hall, 1980).

Where do cerebellar reward signals come from, and where do they go?

Understanding the functional significance of cerebellar reward signals crucially depends on knowledge of their origin. Are the cerebellar reward pathways simply sent copies of reward signals processed by the classical midbrain reward centers in the VTA/SNc, or are there distinct reward signals computed elsewhere that govern cerebellar reward signaling? These two alternatives are not mutually exclusive, and the extensive reciprocal interconnections between the cerebellum and other brain structures that have been discovered over the past 15 years (Caligiore et al., 2017; Strick et al., 2009) suggest that there may be numerous convergent and parallel systems that influence cerebellar reward signals (Figure 2A).

Afferent inputs to the inferior olive from the forebrain arise from a variety of sources including direct projections from neocortex as well as signals relayed via the mesodiencephalic junction (De Zeeuw et al., 1998; Garden et al., 2017; Ten Brinke et al., 2019; Wang et al., 2021). A specific connection between the VTA and the inferior olive has also been suggested based on anterograde tracing studies (Fallon et al., 1984), which could provide the basis for reward signals mediated by the climbing fiber pathway. For the mossy fiber-granule cell pathway, there is currently no evidence for a direct projection from midbrain dopaminergic neurons to the circuits that form the mossy fibers. However, the subthalamic nucleus, a major source of excitation within in the basal ganglia, projects directly to the pontine nuclei (Bostan et al., 2010), providing a pathway for basal ganglia circuits to deliver reward-related information to the cerebellar cortex via the mossy fibers. Furthermore, most neocortical regions project disynaptically to the cerebellum via the basilar pons (Huang et al., 2013; Wagner et al., 2019). In particular, the prefrontal cortex (PFC), a region known to be engaged in control of goal-directed behavior via dopaminergic reciprocal pathways with the striatum, features strong reciprocal interconnectivity with the cerebellum (Middleton and Strick, 2001).

Cerebellar output via the deep cerebellar nuclei has also been shown to engage with reward circuits throughout the brain. Populations of neurons in the cerebellar nuclei can exhibit both reward-predictive ramping as well as directly encoding reward delivery (Chabrol et al., 2019) (Figure 1E), and these neurons have been shown to send a monosynaptic excitatory projection directly to dopaminergic neurons in the VTA (Carta et al., 2019; Pisano et al., 2021; Watabe-Uchida et al., 2012). Importantly, activation of this pathway can modulate reward-driven behavior and is engaged in cerebellar-dependent social interaction tasks (Carta et al., 2019), providing a causal link between cerebellar output and reward signaling. The deep cerebellar nuclei also engage with other elements of the basal ganglia: the dentate nucleus (DN) has a disynaptic connection with an input stage of basal ganglia processing, the striatum (Hoshi et al., 2005; Ichinohe et al., 2000). Cerebellar output also influences cortical reward circuits via the dense reciprocal connectivity with the prefrontal cortex (Kelly and Strick, 2003; Middleton and Strick, 1994, 2001), via thalamic relays. These long-range connections have been shown to be critical for the maintenance of preparatory signals in premotor regions of neocortex (Chabrol et al., 2019; Gao et al., 2018; Li and Mrsic-Flogel, 2020) and have the

ability to drive heterosynaptic plasticity of corticostriatal synapses in the basal ganglia (Chen et al., 2014).

In summary, there is evidence both for direct connections between cerebellar circuits and midbrain dopaminergic neurons (Carta et al., 2019; Fallon et al., 1984; Watabe-Uchida et al., 2012), the canonical reward-processing neurons of the brain, as well as indirect connections via the basal ganglia and cortical reward-processing circuits. Importantly, the connections with the basal ganglia and with the neocortex are via multiple reciprocal nested loops, providing multiple opportunities for mutual interaction. These pathways therefore provide opportunities for the reward system to directly influence cerebellar function, as well as for higher-level processing to manipulate reward signals before transmission to the cerebellum. Furthermore, cerebellar output can itself influence dopaminergic neuron activity (Carta et al., 2019), which in turn will affect basal ganglia and cortical reward processing. Finally, it is possible that some aspects of reward-related activity in the cerebellum exist as reverberating activity within the cerebellum itself (Gao et al., 2016; Khilkevich et al., 2018; Kim et al., 1998). Further anatomical and physiological experiments, in particular using optogenetic and chemogenetic activation and silencing approaches, are needed to identify the direct and indirect anatomical pathways that contribute causally to cerebellar reward signals.

Interpreting cerebellar reward signals in the context of models of learning

It has long been suggested that the basal ganglia and cerebellum play complementary roles in learning and are specialized for different types of learning. Specifically, it has been proposed that basal ganglia are responsible for reinforcement learning, and the cerebellum is responsible for supervised learning (Doya, 2000). In this classical framework, dopaminergic reward prediction errors teach the striatum which actions will maximize reward and thus should be selected, whereas the sensory prediction error mediated by the climbing fiber system teaches the cerebellar cortex how to modify motor commands in order to execute the action correctly, thus implementing forward and inverse models for motor control (Kawato et al., 1987; Wolpert and Miall, 1996; Wolpert et al., 1998). The strongest evidence for this view of cerebellar function comes from interrogation of the oculomotor system, where studies of visual reflex, smooth pursuit, and saccade adaptation have collectively extracted a common set of principles (De Zeeuw, 2021; De Zeeuw et al., 2021; Lisberger, 2009). The recent findings that reward-based learning can drive and modify signals in the cerebellum represents a major departure from the classical function attributed to this brain region (Medina, 2019). Specifically, the reward signals observed in cerebellar cortex are similar to reward prediction error signals in the dopaminergic neurons in the VTA and SNc (Schultz et al., 1997).

However, the cerebellar reward signals do not represent an identical copy of dopaminergic reward signals broadcast throughout the brain. Table 1 compares reward contingencies in the dopaminergic system with the reward signals recently observed in different elements of the circuitry of the cerebellar cortex. Although there is significant overlap between reward contingencies in the dopaminergic system and cerebellar reward signals, there are also important differences. For example, although the majority of midbrain dopaminergic neurons signal unexpected rewards with an increase in firing (Mirenowicz and Schultz, 1994; Schultz, 1998; Schultz et al., 1997; but see Menegas et al., 2018), climbing fiber inputs to some microzones are activated by reward, whereas inputs to other microzones are suppressed by reward (Kostadinov et al., 2019). Moreover, dopaminergic neurons signal negative reward predictions with a decrease in their firing—i.e., a signed reward-prediction error—whereas climbing fibers signal violations in reward expectation with an increase in firing, regardless of whether the quality of reward was better or worse than expected—i.e., an unsigned prediction error, a feature more similar to reward signals observed in various other brain regions including the locus coeruleus (Rouhani and Niv, 2021) and anterior cingulate cortex (Hayden et al., 2011). Thus, further work is required to examine exactly how close the parallels are between reward signals in the dopaminergic system and the cerebellum, ideally by recording from both circuits in the same behavioral tasks. Finally, given that even in the dopaminergic reward system there exists diversity in reward signals depending on projection target (Cox and Witten, 2019; Menegas et al., 2018; Parker et al., 2016; Tsutsui-Kimura et al., 2020) and that dopaminergic neurons can also encode sensory events and movement (Engelhard et al., 2019), future work will require a careful dissection of how sensory, motor, and reward contingencies are represented at each stage in the cerebellar circuit, as well as across different cerebellar lobules.

Taken together, these recent findings suggest that the cerebellum utilizes both performance-based (supervised) learning strategies—implemented via the climbing fiber pathway (Medina and Lisberger, 2008; Popa et al., 2016; Raymond and Lisberger, 1998)—as well as reward-based (reinforcement) learning strategies that are classically implemented by the dopaminergic system in the basal ganglia (Schultz, 1998). These findings challenge the traditional view that the cerebellum and basal ganglia use distinct learning strategies to guide learning (Doya, 2000) and raises several key questions. First, why does the cerebellum use two complementary strategies for learning and how are these strategies differentially engaged across behavioral tasks? Second, why are there parallel pathways for reinforcement learning in the basal ganglia and cerebellum?

Recent studies in humans performing reach adaptation tasks suggest an answer to both questions, namely that there is a dynamic interplay between reward-based learning and performance-based learning. Reach adaptation can be driven by both reward-based feedback as well as sensory error-based feedback (Izawa and Shadmehr, 2011; Therrien et al., 2016), but learning through these different mechanisms exhibits distinct features. Subjects with cerebellar damage trained on a reaching adaptation task exhibit an inability to retain the learned motor behavior when they had acquired this new skill through an error-based learning regime. However, these same subjects show substantial retention (savings) of the learned movement when they learned it under a reinforcement learning regime (Therrien et al., 2016). Conversely, control subjects trained under conditions of added sensory noise (meant to mimic the effects of cerebellar damage) exhibit slower learning, even under a

Table 1. Comparison of reward contingencies in midbrain dopaminergic neurons and cerebellar circuit elements

	Reward delivery	Reward omission	Reward anticipation	Reward size
Midbrain dopaminergic neurons	• Strong when unexpected • Weak when expected (Mirenowicz and Schultz, 1994)	• Signed prediction error (i.e., omission and delivery responses have opposite signs) (Schultz et al., 1997)	• Transient responses to reward-predictive cues (Ljungberg et al., 1992; Schultz et al., 1997) • Continuous response as reward predictions are updated (Howe et al., 2013; Kim et al., 2020)	• Strong responses to cues predicting larger rewards (Tobler and Schultz, 2005) • Monotonic increase with increased reward size (Eshel et al., 2015; Tobler et al., 2005)
Cerebellar granule cells	• Subset of neurons across multiple lobules activated by reward delivery (Wagner et al., 2017, 2019; Shuster et al., 2021) • Delivery response modulated by expectation (Wagner et al., 2017)	• Only evidence for activation by reward omission (Wagner et al., 2017) • Some evidence for signed reward prediction error (Wagner et al., 2017)	• Little to no evidence for transient activation by reward-predictive cues • Strong evidence for continuous (ramping) response during anticipation (Wagner et al., 2017)	• *Unknown*
Purkinje cell complex spikes	• Bidirectional activation and suppression depending on microzone • Strong modulation when unexpected, weak modulation when expected (Heffley et al., 2018; Heffley and Hull, 2019; Kostadinov et al., 2019)	• Unsigned prediction error—omission responses always result in activation (Heffley et al., 2018; Kostadinov et al., 2019)	• Transient response to reward-predictive cues (Heffley and Hull, 2019; Kostadinov et al., 2019) • Continuous response as reward predictions are updated (Kostadinov et al., 2019)	• Stronger response to cues predicting larger rewards (Larry et al., 2019) • *Responses to different uncued reward sizes is unknown*
Purkinje cell simple spikes	• Mixture of activation and suppression (Chabrol et al., 2019) • *Influence of expectation on delivery is unknown*	• *Unknown*	• Mixture of ramping activation and suppression, with suppression more common (Chabrol et al., 2019) • History-dependent encoding of reward state of previous task trial (Sendhilnathan et al., 2021)	• Small increase in activation to large reward-predictive cues that is explained by altered movements (Lixenberg et al., 2020) • *Responses to different uncued reward sizes is unknown*
Cerebellar nuclear neurons	• Mixture of activation and suppression (Gao et al., 2018; Chabrol et al., 2019) • *Influence of expectation on delivery is unknown*	• *Unknown*	• Predominately ramping activation (Chabrol et al., 2019)	• *Unknown*

Summary of available data comparing how different elements of the cerebellar circuit represent rewards, and how these signals compare with those in midbrain dopaminergic neurons. We also highlight where the corresponding data is currently unknown in cerebellar circuits. Key references are given (for further references see main text).

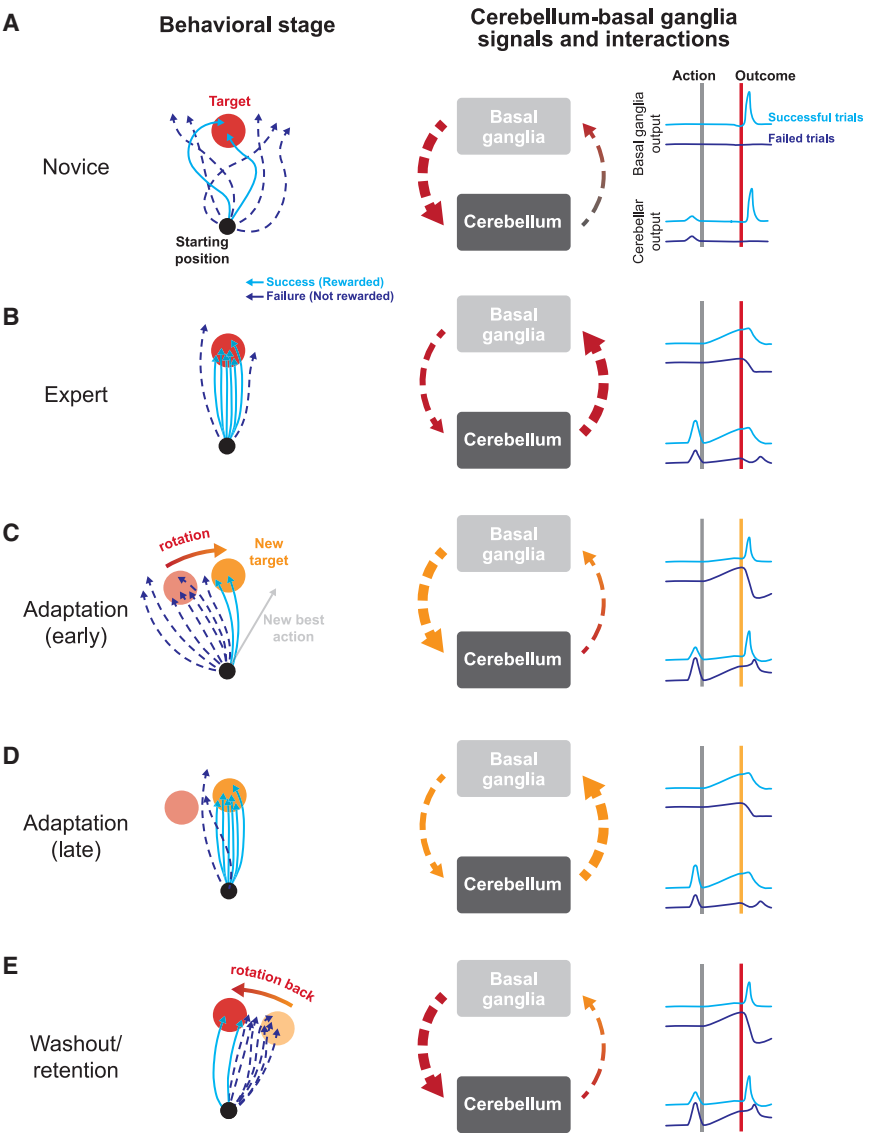

Figure 3. Proposed cerebellum-basal ganglia interactions during different stages of learning

A speculative framework for exploring how performance-based and reward-based mechanisms implemented by the basal ganglia and cerebellum may collaborate to drive learning.

(A) Left: As novice subjects learn to perform a new task (e.g., reach-learning tasks toward a target reward location, in which movement and sensory feedback can be decoupled) where correct outcomes are not known *a priori*, variable actions (reach trajectories, curved lines) are usually not rewarded (dark blue) but occasionally result in rewarded outcomes (light blue). Right: During this early stage of learning, signals from the basal ganglia (top traces) may teach the cerebellum (bottom traces) about task contingencies, allowing it to associate particular actions (encoded by specific modules) with upcoming rewards, generating predictive action maps.

(B) Left: In well-trained experts, most trials are executed accurately and rewarded. Right: Accurate activity in cerebellar modules that predict rewarded actions may assist the basal ganglia in anticipating future rewards, allowing it to reinforce specific actions that will lead to rewards.

(C) Left: When sensorimotor perturbations are applied in trained subjects, they increase movement variability in order to gain rewards through exploration. Right: Previously rewarded actions no longer lead to successful outcomes, leading to negative prediction errors in the basal ganglia and cerebellum. New sensorimotor coupling is learned based on occasional reward, updating the cerebellar internal model.

(D) Left: Following successful adaptation, subjects learn new sensorimotor contingencies but retain bias for original actions. Right: The cerebellum learns new sensorimotor mapping and delivers accurate action-predictive signals to the basal ganglia, aiding in the anticipation of future rewards and reinforcement of new appropriate actions.

(E) Left: Once adaptation learning has taken place, adapted sensorimotor mapping is transiently maintained. Right: Rewards obtained through original sensorimotor mapping are represented as novel rewards and evoke positive reward prediction errors in the basal ganglia, helping the cerebellum to restore original sensorimotor mapping.

reinforcement learning regime (Therrien et al., 2018). Moreover, when reward-based feedback is sparse, control subjects increase movement variability in order to explore if new actions can produce rewards, whereas patients with basal ganglia dysfunction fail to perform this type of exploration (Pekny et al., 2015). Thus, reward-related information in cerebellar circuits may be used to identify and refine sensorimotor patterns that maximize successful outcomes, whereas information sent to the basal ganglia from the cerebellum may serve to identify precisely which actions are most worthy of reinforcement. Our knowledge of the anatomical pathways connecting the cerebellum and basal ganglia can help to explain how this bidirectional learning strategy may be implemented: cerebellar modulation of the deep nuclear neurons that relay the temporal difference error (Ohmae and Medina, 2015) to midbrain dopaminergic neurons (Carta et al., 2019) and basal ganglia (Chen et al., 2014) provides a pathway for the cerebellum to influence reinforcement learning. Viral tracing studies in nonhuman primates indicate that cerebellar connections with the basal ganglia are topographically organized; hence, sensorimotor, cognitive, and limbic subregions in these brain areas are preferentially connected (Bostan and Strick, 2018). Thus, cerebellar modules with distinct action maps are likely to influence basal ganglia regions with similar functions. This indicates that the cerebellum may work in concert with the basal ganglia in selecting the action that is most likely to lead to the largest rewards. This may provide a novel substrate for the view that economic utility can be reflected in a system's motor outputs (Shadmehr et al., 2019). Finally, combining error-based and reward-based learning in the climbing fiber system may be a necessary consequence of learning in multiple stages. For learned or well-parameterized tasks, the relevant error signals are known and easily

implemented. Indeed, in conditions where reliable sensory error signals are available, such as when trained animals occasional miss the target of a reaching movement, error-based learning predominates over reward-based learning (Izawa and Shadmehr, 2011). In contrast, when learning complex new tasks, the appropriate error signals are initially unknown and may change depending on task contingencies (Wagner et al., 2019), in which case estimating future success using reward-based learning may provide the best strategy.

We can thus speculate about the potential interactions between the cerebellum and basal ganglia during real-world learning situations where both reward-based and error-based mechanisms are engaged. In this framework, summarized in Figure 3, during the earliest stages of learning, before-task outcomes can be readily assessed using sensory feedback, the reward system may aid the cerebellum in the construction of accurate models that map successes and failures onto sensory predictions (Figure 3A). It achieves this by sending a copy of the reward signals (triggered by successful outcomes) in the dopaminergic neurons to the cerebellar circuits to inform the cerebellum about the value of a particular motor action, driving learning in specific action modules that resulted in rewarded outcomes. As the subject becomes an expert in the task, the cerebellum learns accurate sensorimotor mapping by updating and refining an internal model to incorporate the value of a particular action, specifically in cerebellar modules that are involved in performing this action. In other words, the cerebellum learns to extend an internal model from accurately predicting the sensory consequences of motor actions to also predicting the values of these actions. The cerebellar internal model could then in turn convey confident predictive signals for these specific actions to the basal ganglia, aiding in their reinforcement (Figure 3B). In subjects with cerebellar damage, these accurate estimates of sensorimotor mapping may be difficult to generate, leading to slow or inappropriate learning (Therrien et al., 2018). Now, if sensorimotor contingencies are changed in expertly trained subjects, movement variability is increased as reward rates drop, a process that depends on proper basal ganglia function (Pekny et al., 2015). This increased variability results in occasional rewards that reinforce these new actions and allow the basal ganglia to alert the cerebellum that it should once again update the internal model (Figure 3C). As these new sensorimotor contingencies are learned, the cerebellum generates new robust action-predictive signals, and rewards obtained in this new contingency become predictable (Figure 3D). Finally, if the original sensorimotor contingencies are then restored, the adapted behavior is transiently maintained in healthy subjects (Figure 3E). In patients with cerebellar damage, retention of new contingencies is only ensured if they were learned through a reward-based mechanism (Therrien et al., 2016).

Reward signals as a substrate for the role of the cerebellum in cognition

The wider implications of the discovery of cerebellar reward-related signaling are that the cerebellum is involved in regulating a far greater range of behaviors than simply motor control. This suggestion taps into a deep vein of cerebellar research suggesting that this structure might be involved in cognitive processing (Ito, 2008; Leiner et al., 1991, 1993; Middleton and Strick, 2000; Schmahmann, 1991; Sokolov et al., 2017). Indeed, internal models of mental activities were initially postulated by Ito as an analogy to internal models for motor control (Ito, 2008). The suggestion that the cerebellum may support a range of cognitive behaviors is supported by the recently identified anatomical pathways described above (Figure 2A), which place the cerebellum not only at the nexus between the motor and sensory systems but also with dense reciprocal connectivity with all regions of the cerebral cortex, as well as the basal ganglia (Caligiore et al., 2017; Chabrol et al., 2019; Gao et al., 2018; Middleton and Strick, 2000; Strick et al., 2009). Further support is provided by the fact that disruption of cerebellar activity, connectivity, and development causes deficits in a variety of social and cognitive behaviors (Badura et al., 2018; Carta et al., 2019; Deverett et al., 2018; Stoodley et al., 2017; Tsai et al., 2012). The recent findings that cerebellar reward signals may contribute to reinforcement learning suggest that the cerebellum may help to select the most valuable action and, in concert, ensure the correct execution of that action for a wide range of behaviors. The new spotlight on cerebellar reward signaling may therefore lead to fresh insights into learning mechanisms mediated by many brain areas.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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