warming and acidification. Rising sea temperatures can lead to coral bleaching events and coral death; acidification can reduce coral growth and also lead to their death. These stressors might also affect Trapeziid crabs, even if their host coral isn't killed. In experiments simulating future climate change, increased water temperature caused reductions in crab abundance and egg production, and caused crabs to expel their mates and other crustaceans that also help defend corals. The resulting decline in Trapeziid densities and defense of corals might further accelerate the demise of coral reefs, underscoring the urgent need for conservation efforts to protect corals and their inhabitants by dramatically reducing global carbon emissions.

Where can I find out more?

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Primer
The cerebellum

Megan R. Carey

The cerebellum, that stripey 'little brain', sits at the back of your head, under your visual cortex, and contains more than half of the neurons in your entire nervous system. The cerebellum is highly conserved across vertebrates, and its evolutionary expansion has tended to proceed in concert with expansion of cerebral cortex. The crystalline neuronal architecture of the cerebellar cortex was first described by Cajal a century ago, and its functional connectivity was elucidated in exquisite anatomical and physiological detail by the mid-20th century. The ability to clearly identify molecularly distinct cerebellar cell types that constitute discrete circuit elements is perhaps unparalleled among brain areas, even within the context of modern circuit neuroscience. Although traditionally thought of as primarily a motor structure, the cerebellum is highly interconnected with diverse brain areas and, as I will explain in this Primer, is well-poised to influence a wide range of motor and cognitive functions.

What does the cerebellum do? Part I: Movement

Some of the earliest descriptions of the effects of cerebellar damage were of World War 1 veterans who displayed visible deficits in coordinating movements across the body. Cerebellar dysfunction leads to a characteristic ataxia, or uncoordinated movement, across vertebrate species. Additionally, oculomotor disturbances, slurred speech, intention tremor, and balance difficulties can all reflect cerebellar dysfunction. Cerebellar neurons are particularly susceptible to the effects of ethanol, leading to the familiar phenomenon of alcohol-induced cerebellar dysfunction that presents as drunken incoordination.

In addition to its clear role in the coordination of movement, a crucial role for the cerebellum in learning has been revealed by many experiments in humans and animal models. This includes basic forms of associative learning like classical conditioning, as well as a form of motor learning known as motor adaptation. Motor adaptation is typically studied as a gradual shift in motor output in response to a consistently applied external perturbation (Figure 1). Motor adaptation occurs rapidly and can be thought of as a re-calibration of well-established movement commands. Movements that are consistently associated with an error are tuned or calibrated to alter the motor output, thereby avoiding future errors. This cerebellar calibration signal is largely unconscious, or 'implicit', and remarkably, it persists even when explicit strategies, like aiming or other forms of cognitive control, attempt to override it.

Motor learning experiments reveal the robust plasticity of motor systems, in that behaviors we perform hundreds or thousands of times a day can be substantially altered within just minutes of exposure to a consistent perturbation. However — of course! — the cerebellum did not evolve just so that we would be prepared when an experimenter handed us a pair of prism goggles. Rather, motor adaptation reveals one of the brain's most powerful solutions to the problem of rapid, effective control in the face of delayed feedback. To avoid having to wait for sensory feedback that an error has occurred, the cerebellum learns to predict likely errors, and uses those predictions to pre-emptively generate compensatory adjustments. The end result is that our movements are effortlessly accurate, in a wide variety of contexts, most of the time.

The cerebellum works together with many other brain areas to control movement; not all forms of motor control or learning are cerebellum-dependent. Instead, the cerebellum seems to be particularly important for forms of motor learning — and aspects of motor control — that require temporally-precise predictions. How could such predictive mechanisms be embedded within cerebellar circuits?

The cerebellar circuit

The cerebellum consists of an intricately foliated cortical sheet surrounding output nuclei, often aptly termed the 'deep' cerebellar nuclei.
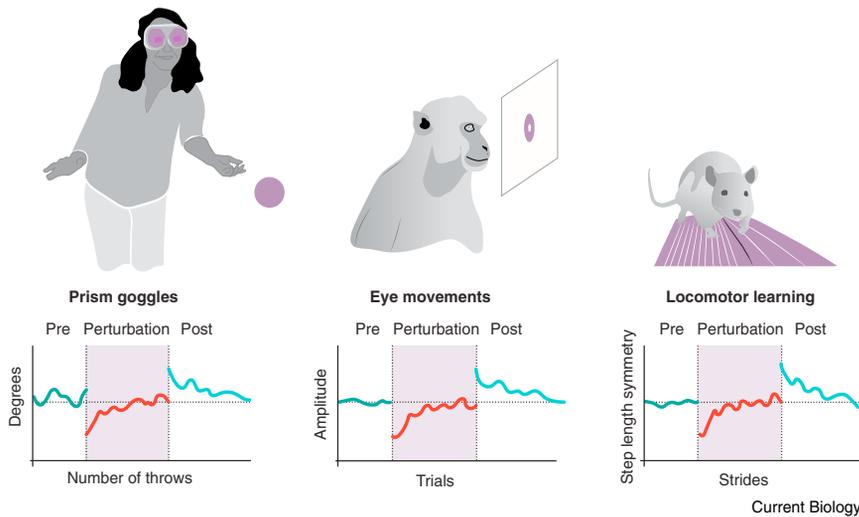
Figure 1. Examples of cerebellum-dependent motor learning.
The cerebellum is essential for motor adaptation, a form of implicit learning that proceeds in response to externally applied perturbations. Similar neural mechanisms are thought to support motor adaptation across a range of behaviors, from throwing/reaching movements (left), to eye movements (center), to locomotor symmetry (right). In all cases, consistently predictable distortions of visual and/or physical feedback trigger sensorimotor errors that lead to re-calibration of movement. When the perturbation is removed, movements exhibit oppositely directed aftereffects, which reveal the learned changes that have been stored in the brain. The cerebellar mechanisms underlying movement adaptation are thought to be critical for ensuring accurate and coordinated movements in a wide variety of dynamic contexts. (Figure by Gil Costa.)

The oft-lauded 'highly stereotyped circuit architecture' of the cerebellum refers mainly to the cerebellar cortex, in which molecularly identifiable neuronal cell types are not only connected to each other in highly specific ways, but are also organized into layers that are clearly visible, even to the naked eye.

The essentials of the canonical cerebellar cortical circuit were described by Cajal a century ago (Figure 2). Two anatomically and functionally distinct excitatory input pathways — mossy fibers and climbing fibers — project to both the cerebellar cortex and the cerebellar nuclei. In the cerebellar cortex, mossy fibers synapse onto tiny granule cells, the brain's most numerous cell type. Individual granule cells receive input from a handful of mossy fibers, and their axons ascend through the granule cell layer, past Purkinje cell bodies, into the molecular layer, where they bifurcate and become parallel fibers. Parallel fibers, as the name implies, run together in parallel, transverse beams, making en-passant synapses onto dendrites of Purkinje cells and inhibitory interneurons: stellate, basket, and Golgi cells.

Purkinje cells famously comprise the 'sole output of the cerebellar cortex'. They fire two distinct forms of action potentials — simple and complex spikes — with distinct electrophysiological signatures and anatomical sources. A single Purkinje cell receives excitatory synaptic inputs from tens of thousands of individual granule cells. These parallel fiber inputs are integrated with feed-forward inhibition from basket and stellate cells, as well as the cell's own intrinsic excitability, to trigger traditional, 'simple spike' action potentials. In contrast, each mature Purkinje cell typically receives input from just a single climbing fiber situated in the inferior olive, the axon of which, as the name implies, climbs the Purkinje cell dendritic tree, making hundreds of synaptic contacts. Each action potential in a presynaptic climbing fiber yields a dramatic postsynaptic 'complex spike' in the dendrites of its target Purkinje cells, consisting of multiple spikelets and a complex set of conductances that are associated with large increases in postsynaptic calcium.

The cerebellum's two excitatory input pathways are functionally, as well

as anatomically and physiologically, distinct. The mossy fiber-granule cell pathway carries a broad array of contextual signals — including information about all kinds of sensory inputs and ongoing movement commands — from diverse brain areas and broadcasts them widely across large swaths of the cerebellum. In contrast, climbing fibers fire at remarkably low rates of just a few spikes per second, and appear to be specialized for representing highly processed, temporally precise information about unexpected inputs.

The same basic modular circuit is repeated many times throughout the cerebellum; what changes across cerebellar regions is the nature of the inputs and outputs (Figure 3). It is tempting to think that such a beautifully organized circuit must be optimized for a particular set of computations. This notion is reinforced by the highly conserved nature of cerebellar circuitry across vertebrates, as well as the recognition that cerebellum-like structures have popped up repeatedly throughout evolution, featuring prominently, for example, in the electrosensory brainstems of fish and in the insect mushroom body.

The tantalizing combination of a well-described circuit architecture combined with clear functional significance led, in the second half of the 20th century, to a race to identify what those fundamental computations might be.

One computation to rule them all?
Once the circuit logic was worked out, the striking distinctiveness of the two excitatory input pathways to the cerebellum led quickly to the idea that such a circuit could serve as a powerful 'learning machine'. A strong hypothesis emerged: When a certain set of sensorimotor signals — conveyed by a set of cerebellar mossy fiber inputs — is predictive of an error (conveyed by the powerful climbing fiber), cerebellar output is adjusted to alter the motor command, thus avoiding future errors. Computational modeling has shown that plasticity of this type could be well-suited for generating the kind of temporally-precise predictions required for cerebellum-dependent learning and motor coordination.

The original instantiation of this hypothesis, often referred to as the Marr–Albus–Ito hypothesis, focused specifically on synaptic plasticity between parallel fibers and Purkinje cells. According to this model, errors encoded by climbing fiber inputs to Purkinje cells would, via complex spike-associated elevations of post-synaptic calcium, drive long-term depression of parallel fiber inputs to those same Purkinje cells. Such plasticity would decrease the strength of excitatory inputs to Purkinje cells that were consistently predictive of an error, thereby inhibiting the same incorrect movement from happening again. The sheer number of granule cells and their connectivity patterns would support the simultaneous storage of an enormous number of such predictions.

Soon thereafter, a second model emerged, known as the Miles and Lisberger hypothesis, which focused on plasticity in the cerebellar nuclei. This model recognized that sensorimotor events that elicit complex spikes often also drive changes in Purkinje cell simple spikes, which could themselves serve as instructive signals for plasticity between mossy fibers and cerebellar nucleus neurons. The end result, like in the Marr–Albus–Ito model, would be to adjust cerebellar output to improve future movements.

Early investigations focused on proving or disproving each of these apparently competing models. For years, much of the debate centered around the relative capacity of parallel fiber–Purkinje versus mossy fiber–nucleus neuron synapses to undergo plasticity. We now know that under the right conditions — exposure to suitable spatiotemporal activation patterns of their inputs — synapses throughout the cerebellum can exhibit plasticity.

But establishing which cerebellar circuit elements were plastic turned out not to be the biggest challenge. The hard part is linking specific changes in behavior directly to specific neural plasticity mechanisms, particularly within dynamic circuits during continuous behavior. Understanding exactly how and when various plasticity mechanisms are engaged to support specific aspects of
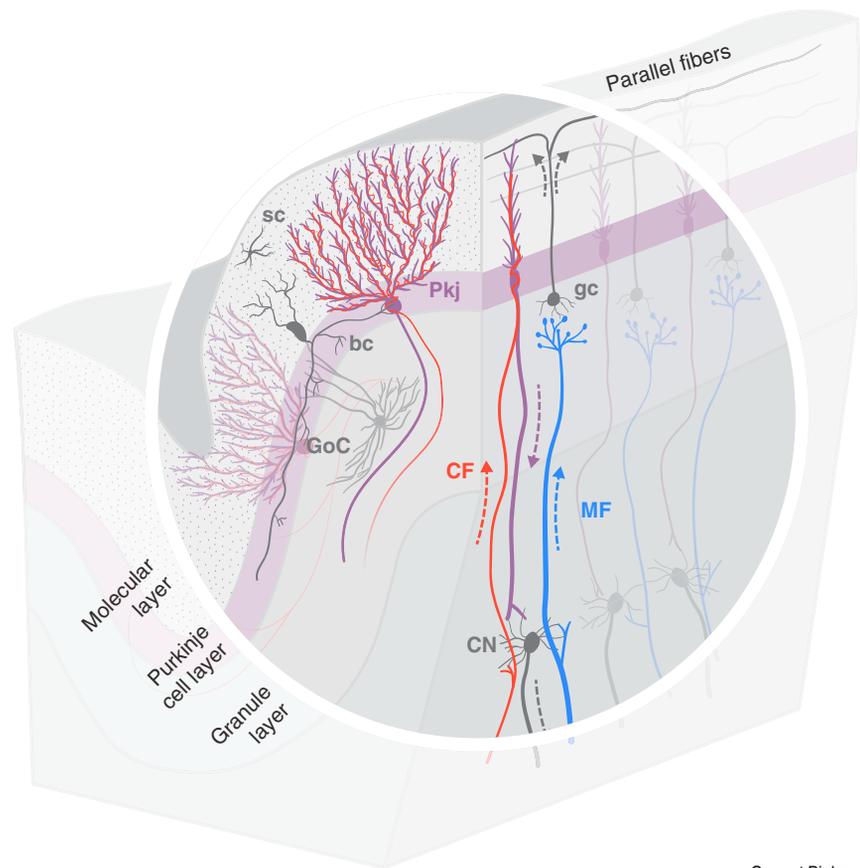
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**Figure 2. The canonical cerebellar cortical circuit.**
Diagram depicting the major layers and cell types of the cerebellum. Excitatory inputs are conveyed by mossy fibers (MF) and climbing fibers (CF), which both project to the cerebellar cortex and send collaterals to the cerebellar nuclei (CN), which represent the major outputs of the cerebellum. More than half the neurons in the vertebrate brain are cerebellar granule cells (gc), which receive MF inputs and in turn project onto Purkinje cells and inhibitory interneurons (stellate cells, sc; basket cells, bc; Golgi cells GoC) via parallel fiber axons. Purkinje cells have planar dendrites elaborated in the parasagittal plane and are the sole outputs of the cerebellar cortex, projecting to the cerebellar nuclei. (Figure by Gil Costa.)

behavioral learning is a challenge that will likely require technical advances — including direct measurements of plasticity and/or synaptic strength, as well as more specific circuit manipulations — before it can be resolved. Importantly, these problems are not unique to the cerebellum; the history of cerebellar neuroscience holds valuable lessons for the modern circuit neuroscientist.

The genetic tools that have made it possible to measure and manipulate neural activity selectively in genetically identifiable cell types throughout the brain are arguably at their most powerful in the cerebellum, where the cell types are not only identifiable, but their anatomical and physiological connectivity patterns

are well-described. Yet at the same time, attempts to link specific plasticity mechanisms to cerebellum-dependent learned behaviors with genetic circuit dissection have advanced our understanding while also, at times, complicating the full picture. This is due both to our incomplete knowledge of the consequences of our circuit manipulations, as well as the inevitable problem of the unknown compensatory mechanisms that they trigger in physiological systems.

Our understanding of learning on the behavioral level has also become more sophisticated, adding to the challenge. For instance, in most forms of cerebellum-dependent motor adaptation, learning takes place within minutes, and often does not exhibit
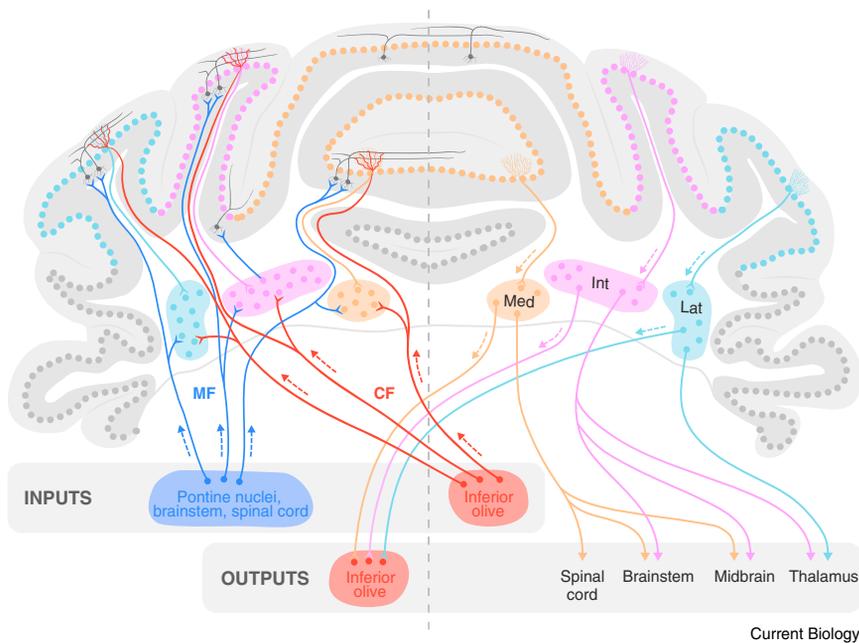
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Figure 3. Modular cerebellar circuitry supports a vast array of inputs and outputs for control of diverse brain functions.
A coronal view of the cerebellum and its major input (left) and output (right) pathways. Inputs and outputs are labelled and illustrated on the left and right, respectively. There is a broad medio-lateral functional organization, particularly in terms of outputs, delineated by the distinct projection patterns of the cerebellar nuclei (labelled here as Medial/Fastigial, Med; Interposed, Int; Lateral/Dentate, Lat. Additional output nuclei, including brainstem vestibular nuclei and the parabrachial nucleus, are not shown). (Figure by Rita Félix.)

savings (or faster re-learning) after extinction or washout. In contrast, the cerebellum-dependent acquisition of new learned behaviors, such as classical eyeblink conditioning, takes days to emerge, and does exhibit savings. These differences likely reflect variations in the relative contributions of distinct forms of neural plasticity in the cerebellar cortex, nuclei, and additional brain areas, which are likely to form a continuum across a range of real-world behaviors.

A general consensus is emerging that plasticity in the cerebellar cortex and nuclei most likely work together, probably with other forms of synaptic and non-synaptic plasticity, to support various aspects of behavioral learning and keep cerebellar circuit activity balanced under physiological conditions.

Not so simple after all
Although the core building blocks of the cerebellar circuit were already well described the better part of a century ago, our understanding of the full complexity and diversity of the cerebellar circuit continues to grow.

Some recent studies have identified connections between specific cerebellar cell types that were previously unknown to exist. Others have appreciated the molecular and physiological heterogeneity of Purkinje cells across different cerebellar zones. In particular, distinctive striped 'zebrin' bands exhibit differential gene expression patterns. Purkinje cells within versus outside these regions exhibit differences in baseline firing rates and in their propensity for induction of synaptic plasticity. Neuromodulatory inputs, including serotonergic, noradrenergic, and dopaminergic fibers, also vary across cerebellar regions.

Together, these differences could amount to distinct functional modules, optimized for particular aspects of neural computation. For now, however, the significance of the circuit heterogeneity across the cerebellum, and its relationship to potential functional heterogeneity, remains largely unknown.

What is abundantly clear is that there are substantive differences in the inputs and outputs interconnecting

various regions of the cerebellum to the rest of the brain. Generally there is a medio-lateral gradient (Figure 3), with more medial connections focused on postural control via spinal cord and brainstem, and more lateral regions exhibiting enriched connectivity with thalamus and ultimately cerebral cortex.

Within that broad functional organization, however, establishing specific roles for individual regions or modules of cerebellar cortex is more challenging. The challenges in part reflect the unusual geometry of the cerebellar cortex. Parallel fibers broadcast their signals in a transverse plane to thousands of Purkinje cells across millimeters of cerebellar cortex, while climbing fibers and inhibitory interneurons provide the opportunity for shared connectivity along an orthogonal, sagittal plane.

These overlapping maps yield a 'fractured somatotopy' that is apparent in electrophysiological studies, with individual body parts represented multiple times across different regions of the cerebellum. For motor control, these different regions may reflect a map of functional space, rather than body space — that is, separate representations for different kinds of movements effected by the same body parts, for example.

Recent, comprehensive mapping of cerebellar function with fMRI in humans has revealed complex patterns of functional segregation across the cerebellum. Remarkably, these functional subregions do not appear to follow obvious anatomical or topological divisions such as the boundaries between cerebellar lobules.

What does the cerebellum do? Part II: To cognition and beyond
Although motor symptoms are the most obvious hallmarks of cerebellar damage, and sensorimotor tasks continue to be the central focus of most laboratory studies of cerebellar function, it is becoming increasingly apparent that the cerebellum contributes to a range of non-motor functions. Evidence for this idea comes from the human clinical literature as well as from animal models.

Given the profound sensorimotor deficits that result from acute cerebellar damage, it can be challenging to isolate additional, non-motor effects. Ultimately, we ask patients and experimental subjects to report their subjective experiences through some kind of movement. Non-motor, cognitive impairments can often be masked by more immediately obvious motor control impairments. However, there is a growing appreciation for the fact that many cerebellar patients — especially those who experienced cerebellar injury early during development — can exhibit cognitive, linguistic, and affective symptoms far beyond sensorimotor difficulties.

It perhaps should not be surprising that the cerebellum is critical for certain aspects of cognitive function. The dramatic expansion of cerebral cortex in human evolution has been paralleled by comparable expansion of the lateral cerebellum, and the two are highly interconnected. Recent evidence suggests that cortico-cerebellar loops are important for higher-order motor functions, such as motor planning, as well as more cognitive functions like working memory. Notably, cerebellar outputs are conveyed not just to motor cortex, but also to areas, including frontal and pre-frontal cortices, that are implicated in higher cognition.

Recent work has revealed that a surprisingly rich set of signals are represented within the cerebellum itself. For example, until recently, the activity of cerebellar granule cells — a crucial cerebellar circuit element — was essentially a black box, due to the enormous technical challenge of recording electrophysiologically from these tiny neurons. The use of genetically encoded calcium indicators has exploded onto the scene. Early results suggest that granule cell encoding of sensorimotor and higher-order signals may be much richer and more complex than we previously thought. In particular, beyond encoding of purely sensorimotor signals, both granule cells and climbing fibers can convey information about rewards, and even reward prediction.

The role of the cerebellum in the generation of appropriate social behavior is of particular interest. Recent studies have implicated intact cerebellar function in the demonstration of typical social behavior in mice, and there is perhaps no other cognitive domain which requires more rapid, high dimensional predictive coding — exactly the computations for which the cerebellum appears to be optimized.

Perhaps related to this idea, autism spectrum disorders (ASD) have long been associated with structural abnormalities of the cerebellum, and neonatal cerebellar injury is one of the strongest risk factors for developing ASD. Moreover, ASD mouse models with genetic manipulations targeted specifically to the cerebellum have been shown to have specific deficits in cerebellar associative learning. Intriguingly, individuals with autism spectrum disorders also often have problems with motor control and coordination. It will be interesting to learn more about the extent of cerebellar involvement in the various aspects of behavior and cognition that are altered in ASD.

Conclusion and outlook

We are in the midst of an explosion in our understanding of cerebellar circuit function. Recent technological advances have enabled insights into cerebellar population activity on an unprecedented scale. At the same time, there is a renewed appreciation for its diversity of function, and anatomical and physiological variation across different cerebellar regions.

As it becomes more and more clear that the cerebellum is not a purely sensorimotor structure, we face the imminent challenge of first characterizing and then understanding its specific contributions to cognition and beyond. The rich history and continued progress of understanding how cerebellar computations support sensorimotor control and learning can hopefully provide a roadmap to guide future discoveries of how the conserved circuit architecture of the cerebellum contributes to more abstract brain functions.

DECLARATION OF INTERESTS

The author declares no competing interests.

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