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Cerebellar Function

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Introduction

The cerebellum is a large subcortical brain structure that influences movement, sensation, and cognitive behaviors through interactions with the cerebral cortex and brainstem. Cerebellar damage does not abolish these behaviors, but instead reduces their accuracy and flexibility. It has been hypothesized that the cerebellum contributes to its various functions by providing predictions about future sensory and motor states, and by implementing a fast error-driven learning process, which calibrates well-trained behaviors to environmental changes.

Cell types and physiology

The cerebellum consists of a highly folded cortical sheet surrounding white matter and deep cerebellar nuclei. A remarkable feature of the cerebellum is its three-layered cortex, which is homogenous in both cell type and arrangement (Fig. 1a).

[INSERT FIG 1 HERE]

The main source of input to the cerebellum is provided by mossy fibers, which transmit information from the neocortex via the pontine nuclei, from brainstem structures including the vestibular and reticular nuclei, or directly from the spinal cord via the spino-cerebellar tracts. Mossy fibers synapse on granule cells (Fig. 1b), which account for over half of the neurons in the human brain (Azevedo et al., 2009). Granule cells send axons into the molecular layer where they branch into parallel fibers and form excitatory synapses onto Purkinje cells. Purkinje cells have flat but elaborate dendritic trees, branching orthogonally to the direction of the parallel fibers. In this way, each Purkinje cell can receive input from ~174,000 granule cells. At rest, Purkinje cells fire action potentials, known as simple spikes, at a rate of 40-70Hz. Climbing fibers provide more sparse input to the cerebellum. Each Purkinje cell receives input from a single climbing fiber, while each climbing fiber branches to innervate ~ 10 Purkinje cells. Climbing fibers cause Purkinje cells to fire powerful action potentials with complex waveforms, termed complex spikes, at the low rate of 1-4 Hz.

Purkinje cells inhibit cells in the deep cerebellar nuclei, which provide the cerebellum's only output. Pauses in the firing of specific sets of Purkinje cells release inhibition of the deep cerebellar nuclei cells, which in turn emit an excitatory burst of action potentials. The largest of these nuclei, the dentate nucleus, receives input from the lateral hemispheres of the cerebellar cortex and projects via thalamus back to contralateral premotor, prefrontal, and parietal neocortical regions. More medially, the

interposed (emboliform and globose) nuclei receive input from intermediate cerebellar cortex (paravermis) and project to the spinal chord via red nucleus and to primary motor cortex via thalamus. The most medial nucleus, the fastigial nucleus, receives input from the midline areas of cerebellar cortex (vermis) and projects to neocortex and brainstem targets, influencing descending vestibulo- and reticulo-spinal pathways.

Functional anatomy

The cerebral cortex can be parcellated into different regions based on their cytoarchitectonic organization. In contrast, the neural circuit of the cerebellar cortex is remarkably invariant. Even though, the human cerebellum contains many distinct functional modules. In the medial-lateral direction it consists of a set of parasaggital compartments which can be revealed by labeling the expression of Aldolase C or Zebrin (Sugihara & Shinoda, 2004). In the anterior-posterior direction, a series of horizontally running fissures divide the cerebellum into a set of lobules (Fig. 2), labeled I-X based on Olof Larsell's careful comparative work (Larsell & Jansen, 1972).

[INSERT FIG 2 HERE]

Lobules I-V form the anterior cerebellum, and are mainly concerned with motor control. Lobules IV and V have reciprocal connections with primary motor cortex (Kelly & Strick, 2003) and a reliable somatotopic organization (Grodd, Hulsmann, Lotze, Wildgruber, & Erb, 2001). The feet are represented in superior and medial aspects of lobule IV, and the arm and hand in the hemispheric part of lobule V. The latter also contains representations of single finger movements (Wiestler, McGonigle, & Diedrichsen, 2011). Upper-limb representations are strongly lateralized. Hand movements activate the ipsilateral anterior lobe almost exclusively. The representation of oro-facial movements extends from lobule V into the neighboring lobule VI.

Complex limb movements preferentially activate lobule VI (Schlerf, Verstynen, Ivry, & Spencer, 2010). In contrast to lobule V, lobule VI generally shows bilateral activation for unilateral hand movements. This suggests that it acts in concert with cortical secondary motor areas such as premotor and supplementary motor area. Indeed, functional connectivity studies show high correlations between activity in lobule VI and activity in the contralateral premotor cortex (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011). Language tasks, including verb generation, also activate right lobule VI (and Crus I of lobule VII, see below), even when motor output-related activity is controlled for. Left lobule VI may be associated with spatial tasks (Stoodley & Schmahmann, 2009). The

vermis of lobules VI and VII controls eye movements and is known as the oculomotor vermis (Prsa & Thier, 2011).

Lobule VII is the largest lobule of the human cerebellum, accounting for roughly half the cerebellar gray matter volume (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009). It is subdivided into lobule VIIa (consisting of Crus I and II) and lobule VIIb. In the monkey, the hemispheres of Crus II have reciprocal connections with Brodman area 46, (Kelly & Strick, 2003), and human functional connectivity data indicate that lobule VII participates in at least 3 sub-networks including dorso-lateral prefrontal, inferior parietal and lateral temporal areas (Buckner et al., 2011). Functionally, various language, working memory and executive function tasks activate lobule VII (Stoodley & Schmahmann, 2009).

Lobules VIIIa and VIIIb are part of a second motor cortical–cerebellar loop (Kelly & Strick, 2003). As with the anterior motor representation, these lobules have a convergent representation of movement and sensory information from the whole body. While there is discernable somatotopy in these regions, it is weaker than that in the anterior lobe.

The hemispheres of lobule IX connects to the anterior cingulate and pre-cuneus (Buckner et al., 2011). The vermal aspect of lobule IX appears to be involved in the regulation of the autonomic nervous system, for example in cardiovascular control. Finally, the relatively small lobule X (flocculus + nodulus) is involved in vestibular functions and eye movement control.

Together, the cerebellar cortex comprises a patchwork of areas, each with its own pattern of connectivity and functional specialization. The information-processing role that each cerebellar region fulfills within its respective loop remains unclear. However, given the homogenous functional architecture of the cerebellar cortex, many researchers agree that a single computational function should characterize the role of the cerebellum across motor and non-motor domains (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Schmahmann, 2004). However, what constitutes this "universal cerebellar transform," is a much-debated matter.

Clinical aspects

Neurological diseases, tumors, malformations, and stroke can all damage the cerebellum. Loss of movement coordination or "ataxia" is the most common and obvious deficit. Because the cerebellum projects to contralateral neocortical areas, right

cerebellar damage affects right-sided movements. Recovery of motor function often occurs, but is generally worse if deep cerebellar nuclei are affected. In a recent study, children and adults recovered better from surgical tumor removal when deep cerebellar nuclei were spared (Konczak, Schoch, Dimitrova, Gizewski, & Timmann, 2005).

Although ataxia is often used to describe specific deficits, e.g., arm ataxia during reaching, gait ataxia during walking, it is a global term that refers to specific features of dyscoordination. For example, during ataxic reaching movements, hand paths are highly curved and tend to be quite variable from reach to reach (Fig. 3a). An underlying inability to account for complex limb mechanics may cause this abnormal curvature (Bastian, Martin, Keating, & Thach, 1996). Consistent with this idea, patients show greater deficits when they reach quickly and move many joints or body parts simultaneously. Patients compensate by moving more slowly and breaking movements down into simpler components, a phenomenon originally described by Gordon Holmes as decomposition of movement (Holmes, 1939).

One common element of ataxia is dysmetria, poor control over the extent of movement. People with cerebellar damage often overshoot (hypermetria) or undershoot (hypometria) targets. As a result, their movements show oscillations when approaching the target, a phenomenon known as intention tremor. Intention tremor likely represents a series of corrective movements, and may stem from use of time-delayed sensory feedback (see below). Consistent with this idea, intention tremor is reduced or absent when patients point to a target with their eyes closed, reducing visually guided corrections (Day, Thompson, Harding, & Marsden, 1998).

Walking ataxia has been described as an irregular, somewhat drunken looking gait pattern, involving widened stance, irregular steps, and oscillations in trunk control. Interestingly, it is not necessarily due to leg control deficits—patients often can make normal isolated leg motions yet still show profound walking ataxia (Morton & Bastian, 2003). This suggests that cerebellar influence over walking is distinct from that over voluntary control of isolated leg movements, with the former involving midline, and the latter intermediate and lateral structures.

There are clear oculomotor deficits associated with cerebellar damage, depending upon the region involved. Dysmetria of saccadic eye movements occurs with damage to the oculomotor vermis or the fastigial nucleus. Nystagmus, an involuntary eye movement consisting of slow drift and fast resetting phases, often occurs after cerebellar damage.

Abnormalities in the gain of the vestibule-ocular reflex also occur following cerebellar damage, particularly when lobule X is damaged.

Recent work suggests that cerebellar damage may impair somatosensory function, but only in the context of active movement. Cerebellar patients show normal proprioceptive acuity when a limb is passively moved (Maschke, Gomez, Tuite, & Konczak, 2003), but exhibit clear deficits in force perception under active conditions (Bhanpuri, Okamura, & Bastian, 2012).

In contrast to the pronounced disturbances of sensory-motor function, the consequences of cerebellar damage on cognitive processes are much less obvious. This is puzzling, as much of the cerebellum projects to and receives input from frontal, parietal and temporal regions of neocortex, and because cognitive tasks often activate the cerebellum in fMRI experiments. Cognitive deficits have been reported in tests of language, executive function, emotion, and attention after cerebellar damage (Ivry et al., 2002; Schmahmann, 1997). Yet, there is considerable variation between studies, with patients performing normally in one study but not another. A review by Timmann and Daum (2010) suggests that cognitive deficits are most pronounced in people with acute lesions. Thus, variability may be due longer term neocortical compensations for cerebellar loss. However, cognitive deficits may be more robust and long lasting when cerebellar damage is acquired in childhood. Thus, cognitive deficits arising from cerebellar damage are difficult to characterize. What is clear is that cerebellar loss affects motor function more robustly than cognitive function—due perhaps to the fact that neocortical regions for movement control compensate less for cerebellar loss than do those involved in cognitive processes.

Cerebellum as a predictive device for motor control

A central theory about the cerebellum is that it serves as a predictive forward model for motor control (Miall, Weir, Wolpert, & Stein, 1993; Wolpert, Miall, & Kawato, 1998). Forward models are used in engineering to establish stable control in systems with sensory and motor delays. Consider the diagram in Fig. 3b. A controller (i.e., motor cortex) computes motor commands based on the goal and an estimate of the body's current state (i.e., position, velocity). Motor commands are sent to the muscles, causing them to contract and move the body. Sensory feedback about these changes is then used to update the state estimate, closing the feedback loop. However, there is one important problem with such control architecture. Given both motor (~30ms) and sensory (~30-70ms) delays, a feedback controller may become unstable during fast movements: the

controller may command a reaching movement to stop when sensory feedback indicates that the hand approaches its target. However, by that time the hand may have overshot the target, and antagonist muscle activity for decelerating will arrive too late. The same problem applies to movement corrections. Thus, closed-loop control of a device with considerable sensory delay can cause dysmetria and endpoint oscillations, similar to the ataxia exhibited in cerebellar disease. One solution many patients choose to correct this problem is to move more slowly, meaning that sensory feedback has time to catch up with the actual state of the limb.

[INSERT FIGURE 3 HERE]

Fast movement execution requires a different approach. The engineering solution is to employ a predictive device, which uses a copy of the motor command (efference copy) to predict the future state of a limb. This prediction is then integrated (accounting for sensory delays) with actual sensory feedback (Miall et al., 1993). Replacing real sensory feedback with a prediction about limb state allows for smooth and stable real-time control.

The similarity between symptoms of ataxia and a control system using delayed feedback is compelling, and argues that the cerebellum may serve as a forward model in motor control. Early evidence for this idea comes from experiments in which a monkey must hold a handle at a specific position and counteract unexpected perturbations (Hore & Flament, 1988). Normally when perturbed (Fig. 3c, 0ms), the monkey quickly returns the handle to the specified position. When cerebellar input to motor cortex is disrupted by cooling the dentate nucleus, the arm initially overshoots and then oscillates around the hold position (solid line, upper panel). This is not due to poor control of the agonist muscle that initially corrects the movement. Even during dentate cooling, the initial activity in primary motor cortex neurons appeared normal when a given muscle (triceps) acted as the agonist (Fig. 3c, gray box, middle panel). Rather, oscillations were caused by delayed timing of the antagonist (breaking) muscle that *terminates the corrective response*: When the triceps acted as an antagonist, dentate cooling delayed the predictive response (Fig. 3c, gray box, bottom panel). This suggests that the intact cerebellum plays a role in advancing responses of primary motor cortex, changing it from reactive to predictive control.

The role of prediction in motor control is especially evident in tasks requiring coordination between multiple joints or limbs, as in the fast isolated elbow movements used when whipping eggs. Although the task does not require shoulder movement, the

monoarticular muscles around the shoulder joint activate to counteract the torques induced to shoulder by the elbow joint's acceleration. Cerebellar damage impairs active compensation for interaction torques during voluntary elbow movements, causing considerable shoulder instability (Bastian et al., 1996). Interestingly, this predictive control even occurs during fast feedback responses, in which the motor system modulates shoulder-muscle responding, based on induced motion to the elbow joint (Kurtzer, Pruszynski, & Scott, 2008). Such mechanisms can be understood as the consequence of a forward model, in which motor commands to correct elbow joint position after perturbation allow predictive corrections of shoulder perturbations. Indeed, long-latency reflexes are modulated by intersegmental information 20-30ms after the onset of an initial response (Pruszynski et al., 2011). After cerebellar damage, coordinative feedback responses are still present, but are additionally delayed by 10ms and reduced in size (Kurtzer et al., 2013). These changes may account for the observation that movement deficits in cerebellar patients become exaggerated during multi- versus single-joint movements (Bastian et al., 1996).

Another example of prediction in motor control is the so-called "waiter task", in which someone supports a loaded tray with one hand, and then removes the load using the other hand. Healthy individuals reduce the EMG of the load-bearing muscles, 50ms before any load change occurs (Hugon, Massion, & Wiesendanger, 1982). This predictive behavior effectively minimizes possible destabilization effects that might occur when the tray is removed. Indeed, when the load is lifted by an external agent (even a predictable agent), no anticipatory response occurs and the tray shows a small upward displacement, requiring feedback mechanisms to re-stabilize the system. Cerebellar damage causes this anticipatory response to be poorly calibrated in both size and onset (Diedrichsen, Verstynen, Lehman, & Ivry, 2005).

While these findings provide evidence that the cerebellum acts as a predictive device in motor control, they also show that the cerebellum is not the sole source of predictions. In cerebellar damage, predictive responses are often ill timed and inappropriately scaled, but nonetheless clearly present. Thus, other brain structures can also generate well-learned predictions. Thus, rather than being the exclusive site of a predictive forward model, the cerebellum may control the exact timing (Ivry et al., 2002) of forward models stored elsewhere, or adapt these to changes in task dynamics. Consistent with latter idea, cerebellar patients do not adjust their anticipatory responses in the waiter task after a catch trial (Diedrichsen, Verstynen, et al., 2005).

Cerebellum and error-based learning

The problems experienced by patients with cerebellar pathology in using predictive mechanisms points to a second major domain of cerebellar function: adaptation or error-based learning. Error-based learning in this context refers to the modification of behaviors based on performance errors. This definition excludes learning based on reward prediction errors, i.e., sensory feedback signaling only the relative success or failure of a movement (Schultz, Dayan, & Montague, 1997). Instead, error-based learning is driven by discrepancies between actual and predicted movement outcomes (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). Importantly, prediction errors signal not only *that* a movement has failed, but exactly *how* it has failed. One defining feature of error-based learning is that it utilizes a single prediction error to change behavior in the desired direction on the next attempt.

[INSERT FIG. 4 HERE]

Take the example of throwing darts at a dartboard: In a typical context, there is a match between where a person is looking and where they aim the movement. However, if you wear laterally displacing prism glasses that shift visual world, the dart will miss the target (Fig. 4a). Thus, the initial error is equal to the perturbation. Error-based learning will partially correct the next throw in the opposite direction to the shift induced by the prisms. For this to happen, an error-based learning system needs to translate the perceived error direction into a desired motor command change. To avoid instabilities due to overcorrection, the motor system usually correct for much less than 100% of the error, meaning that it takes repeated throws to fully adapt to prism glasses. After adaptation, removal of the glasses reveals an aftereffect: the throws show the opposite error and then re-adapt to the original calibration. Such aftereffects are unavoidable, arising even when participants know that the perturbation has been removed. These aftereffects are considered to signal genuine error-based learning as opposed to conscious or strategic action re-planning (Mazzoni & Krakauer, 2006).

Error-based learning is even observed when perturbations are inconsistent and random across trials (Fig. 4b). Each induced error leads to a measureable small adjustment on the next trial (Thoroughman & Shadmehr, 2000), demonstrating that the error-based mechanism adjust for single performance errors, even when participants know that all perturbations are random (Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005). Thus, error-based learning is continuously engaged to correct for small environment changes or performance fluctuations, keeping well-trained motor behaviors calibrated.

Over the last 15 years, substantial evidence has accumulated pointing to a critical role for the cerebellum in error-based learning. An early demonstration comes from prism adaptation during dart throwing (Martin, Keating, Goodkin, Bastian, & Thach, 1996). Patients with focal cerebellar lesions did not adjust throwing movements to displacement prisms despite repeated unsuccessful throws. Importantly, after removing the glasses, the patients did not show the aftereffects that are found in healthy participants. Thus, cerebellar damage appeared to disrupt error-based learning at a basic level.

Since this initial report, deficits across a range of adaptation tasks have been reported in cerebellar patients. In force field adaptation tasks, a robotic device is used to introduce perturbations when people make point-to-point reaching movements (Fig. 4c). Error-based learning leads to adjustments in the forces generated by the arm, attenuating the effects of the perturbing forces. To probe this form of anticipatory control, the robotic device is switched off on "catch trials", revealing large and robust aftereffects. Cerebellar patients are highly impaired in this learning task, evidenced by increased errors and reduced aftereffects (Maschke, Gomez, Ebner, & Konczak, 2004; Smith & Shadmehr, 2005). Similar deficits in adaptation have been reported during split-belt treadmill walking (Morton & Bastian, 2006) and reaching under novel visuo-motor transformations (Tseng et al., 2007). The latter paper also shows that observing unexpected movement outcomes, rather than correcting unsuccessful movements, is the likely source of the error signal. Finally, cerebellar damage impairs adaptation of outward saccadic eye movements, although adaptation of inward saccadic eye movements appears to be intact (Golla et al., 2008). However, this is likely due to uncompensated central fatigue, rather than error-driven adaptive processes (Prsa & Thier, 2011).

Cellular mechanisms of cerebellar learning

The idea that the cerebellum implements error-based learning is especially attractive, because we have a relatively detailed picture of how behavioral learning phenomena may relate to the underlying cellular mechanisms.

Marr (1969) and Albus (1971) proposed an influential computational model of error-based learning within the cerebellar neuronal circuit (Fig. 1). They suggested that the mossy fiber-parallel fiber system carries information about the motor command (an efference copy) and the current state of the system to Purkinje cells. The climbing fibers, which emanate from the inferior olive, transmit error signals that induce learning via

complex spike activity (CS). Consistent with this hypothesis, climbing fibers discharge during unexpected sensory events, such as the slip of a retinal image, or a misreach (for a review, see De Zeeuw et al., 1998). The resulting CS in the Purkinje cell triggers an influx of Ca++, inducing long-term depression. This process is specific to the parallel fiber-Purkinje synapses that were active 100-200ms before climbing fiber input (Wang, Denk, & Hausser, 2000). Consequently, the arrival of a similar pattern of parallel fiber input causes a reduced simple spike (SS) firing rate in Purkinje cells, releasing deep cerebellar nuclei from inhibition.

[INSERT FIG. 5 HERE]

This model has been supported in studies of arm control (Gilbert & Thach, 1977), eye-blink conditioning (Thompson, 2005) and adaptation of the vestibulo-ocular reflex (Lisberger, 1988). Recent work by Medina and Lisberger (2008) provides a particularly elegant demonstration. In their task, a monkey was rewarded for visually tracking a moving target. At 0ms, a target appeared and moved downward; at 250ms, it deviated from the path, moving slightly to the right (Fig. 5a). Purkinje cells in flocculus (the hemispheric part of lobule X) showed SS activity related to eye-movement pursuit direction. Fig. 5b shows a cell that increases its activity for downward movement, but decreases activity for rightward movements. The sudden deviation of the target from the downward trajectory induces a slip of the retinal image and a CS (gray triangle). On the next trial, the cell showed a lower SS rate. Importantly, this SS decrease preceded the CS and hence the moment of directional change. Thus, the Purkinje cell is predicting the error. The decrease in firing rate related to an anticipatory rightward movement of the eye and increased tracking performance accuracy. To prevent SS firing rates from decreasing indefinitely, this system also requires a counteracting (i.e., potentiating) learning mechanism. This can be seen in the potentiating effect of trials in which CS activity does not change from baseline (Fig. 5c). These results provide strong evidence in support of the Marr and Albus' hypothesis that the climbing fiber provides an error signal. However, the results also point to the operation of other learning mechanisms within the cerebellar circuitry.

Concluding remarks and open questions

Many open questions about cerebellar function remain. Although the Marr–Albus model of cerebellar learning provides an elegant account of many experimental findings, there is also substantial evidence opposing this theory. For example, the low-frequency CS activity (1-5Hz) may not be high enough to provide the temporal resolution necessary

for error-based adaptation of finely controlled motor behaviors (Horn, Pong, & Gibson, 2004; but see, Kitazawa, Kimura, & Yin, 1998). Furthermore, during saccade adaptation the pattern of CS activity increases with learning, consistent with a role in adaptive output production, rather than decreasing as would be predicted if it encoded an error signal (Catz, Dicke, & Thier, 2005; but see Soetedjo, Kojima, & Fuchs, 2008).

On a systems level, it remains unclear whether the cerebellum implements predictive forward models, or whether it merely adapts forward models stored elsewhere. Clearly, some well-learned predictive motor mechanisms are preserved in cerebellar patients. Furthermore, recent evidence using transcranial direct current stimulation (tDCS) (Galea, Vazquez, Pasricha, Orban de Xivry, & Celnik, 2011) suggests that the cerebellum may produce short-term modifications of forward models, whereas the neocortex may store longer-lasting motor memories.

At the whole-brain level, it has become clear that the cerebellum is not simply a motor control device, but has functional involvement in a wide array of mental abilities. How the cerebellum contributes to these non-motor functions remains unclear . We hope that the next generation will fulfill the dream of a universal theory that explains cerebellar function from cellular to behavioral levels, as envisioned by David Marr more than 40 years ago.

Figures

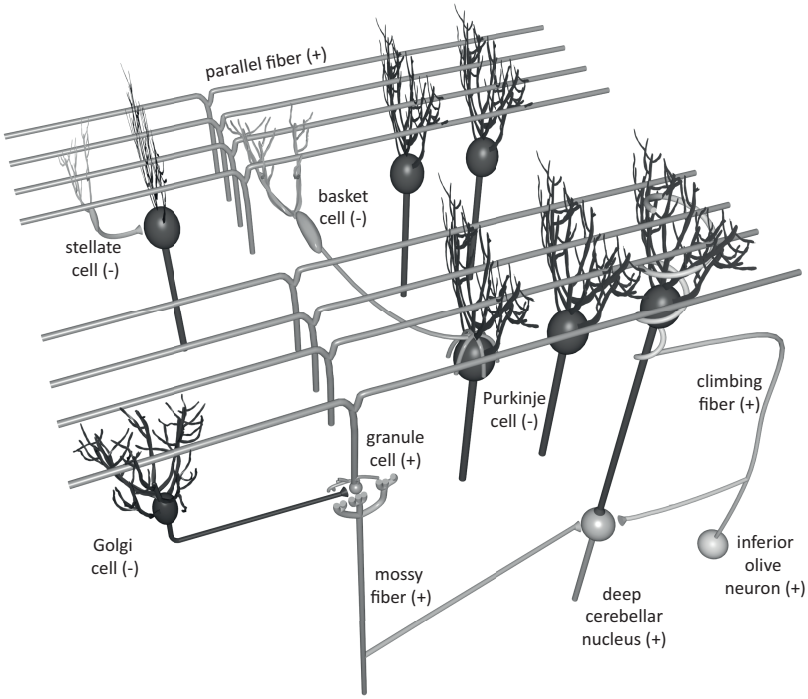

Figure 1. Main anatomical layout of the cerebellar cortex, displaying major cell types and connections. The sign indicates whether the cell gives rise to excitatory (+) or inhibitory (-) connections.

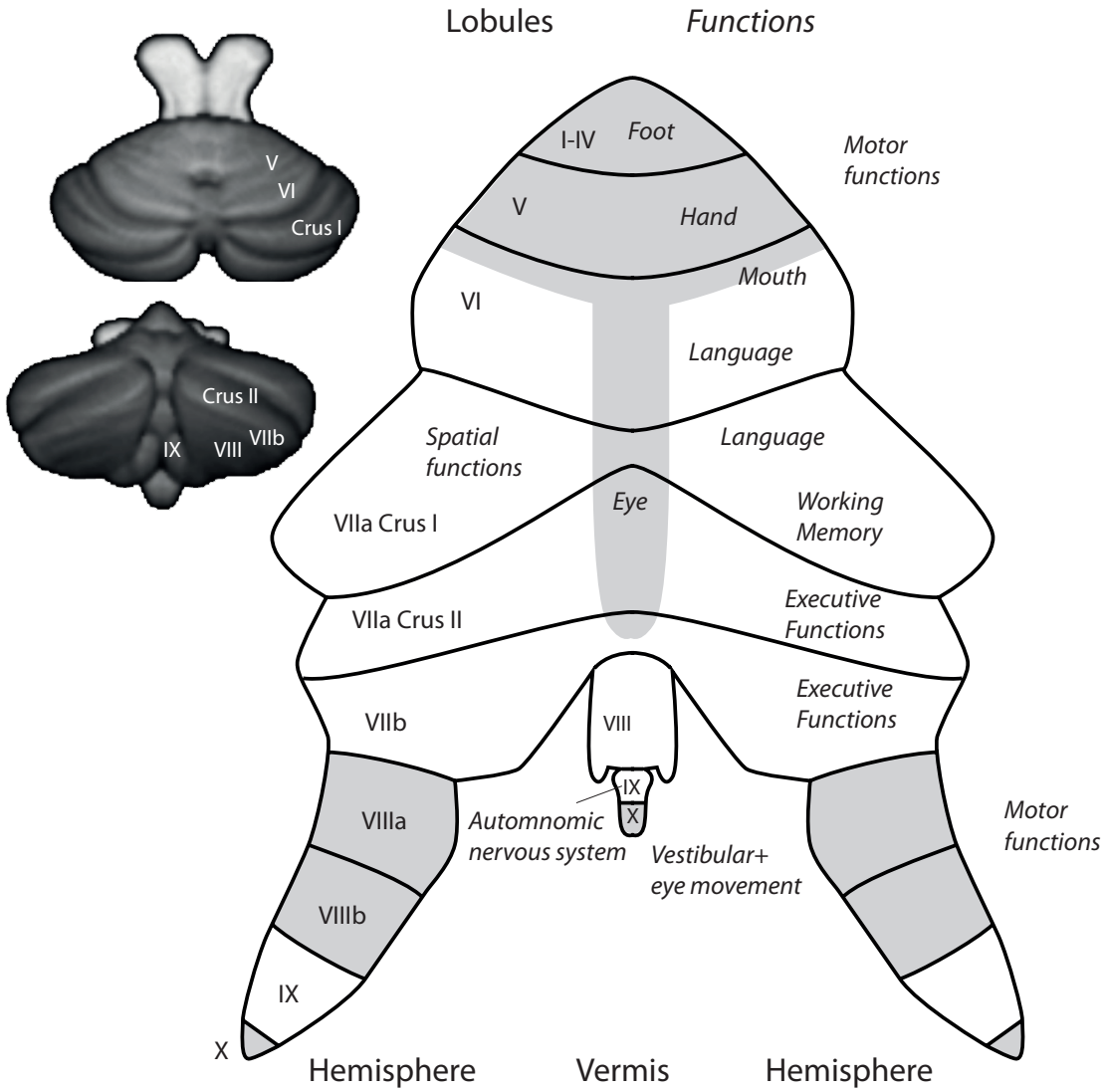

Figure 2. Functional anatomy of the human cerebellum shown on a flattened representation of the cerebellar cortex (based on Van Essen, 2002). Lobule surface area is roughly proportional to real size. The upper inset shows dorsal and ventral views of a cerebellar 3d-reconstruction. Roman numerals indicate lobules following Larsell's notation, italics indicate likely involvement in behavioral functions. Gray shading indicates sensory-motor involvement and connectivity to motor regions.

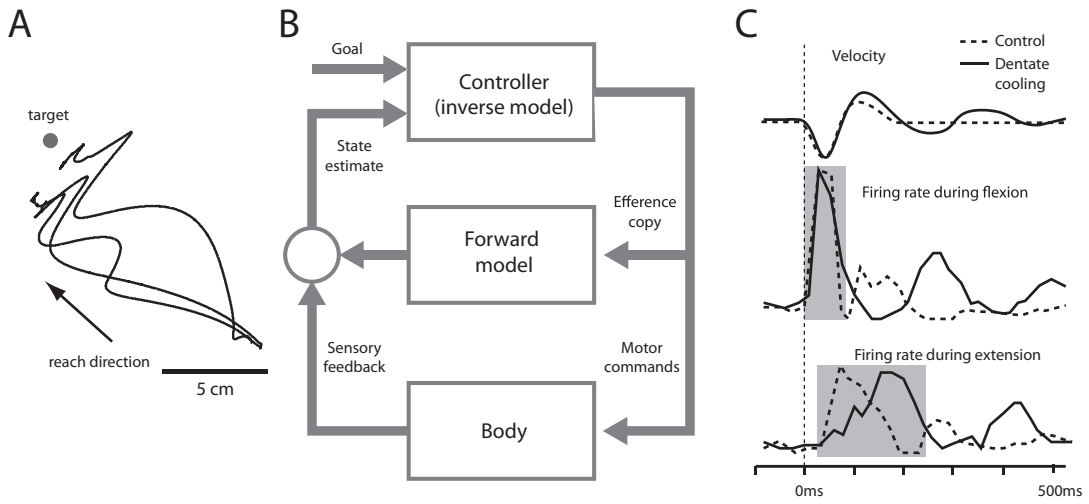

Figure 3. The cerebellum as a predictive forward model. (**A**) Hand paths made by a cerebellar patient reaching towards a target. Note features of ataxia including dysmetria and endpoint oscillations. (**B**) A controller generates a motor command based on a behavioral goal and an estimate of the body's state. It sends an efference copyof the command to the forward model (cerebellum), which predicts the command's influence on body state, thereby avoiding problem's associated with delayed sensory feedback. (**C**) Velocity and firing rate of a motor cortical neuron during typical movement (control; dashed line) and when cerebellar input is blocked through dentate cooling (solid line). Data redrawn from Hore and Flament (1988).

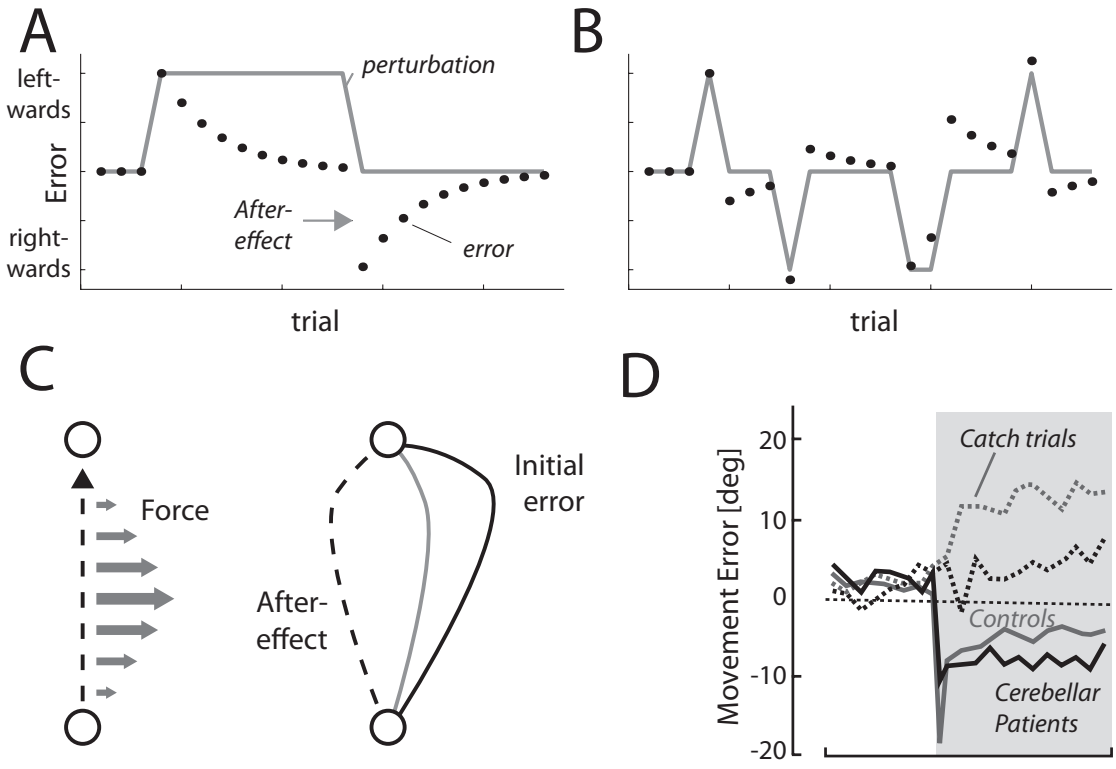

Figure 4. The role of cerebellum in error-based learning. (**A**) Traditional adaptation experiment in which a perturbation suddenly occurs, leading to an exponential learning curve. Upon perturbation removal, an aftereffect is observed. (**B**) A key feature of error-based learning is that it occurs even during random perturbations, which induce small, but measurable changes in behavior. (**C**) During a force-field reaching task, a robotic device exerts a force perpendicular to the direction of movement. After an initial error, the movement adapts, resuming a nearly straight trajectory (gray line). When the force is suddenly removed, an aftereffect in the opposite direction occurs. (**D**) Deficit of cerebellar patients in adapting to force fields. The force field is switched on (gray box), causing a large initial error. Healthy individuals show increasing after-effects on trials with no force field, but patients with cerebellar degeneration do not (Smith & Shadmehr, 2005).

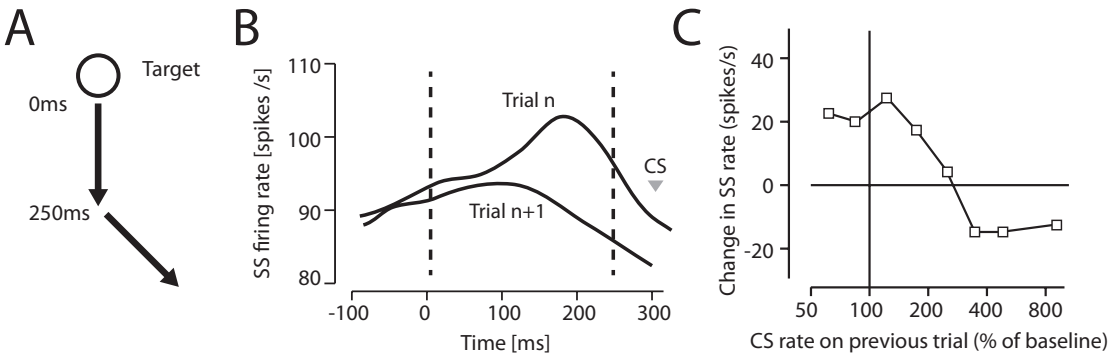

Figure 5. Cellular mechanisms underlying cerebellar learning. (**A**) In the task, a monkey fixated a moving target that changed direction 250ms after movement onset. (**B**) Trial-to-trial change in the SS rate of a Purkinje cell. The gray triangle shows the occurrence of a complex spike (CS) on trial n. (**C**) Relationship between CS-probability and change in SS rate. Based on Medina and Lisberger (2008).

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