

The Cerebellum: A Neuronal Learning Machine?

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Comparison of two seemingly quite different behaviors yields a surprisingly consistent picture of the role of the cerebellum in motor learning. Behavioral and physiological data about classical conditioning of the eyelid response and motor learning in the vestibulo-ocular reflex suggest that (i) plasticity is distributed between the cerebellar cortex and the deep cerebellar nuclei; (ii) the cerebellar cortex plays a special role in learning the timing of movement; and (iii) the cerebellar cortex guides learning in the deep nuclei, which may allow learning to be transferred from the cortex to the deep nuclei. Because many of the similarities in the data from the two systems typify general features of cerebellar organization, the cerebellar mechanisms of learning in these two systems may represent principles that apply to many motor systems.

The work of Brindley, Marr, Albus, and Ito (1, 2) made the idea that the cerebellum is a primary site of motor learning into one of the most appealing hypotheses of cerebellar function. Their general hypothesis has been supported by lesion, electrical stimulation, and recording studies in a variety of movement systems (3–5). However, the exact function of the cerebellum in movement and its specific role in learning have remained controversial.

To determine whether and how the cerebellum participates in motor learning, it is necessary to establish cause-and-effect relations between learning of motor responses and changes in the responses of cerebellar and extracerebellar neurons. Much progress toward this goal has been made for two forms of motor learning that require an intact cerebellum: classical conditioning of the eyelid response and motor learning in the vestibulo-ocular reflex (VOR). Here, on the basis of physiological and behavioral data from these two movement systems, we outline a set of unifying principles of cerebellum-dependent learning.

Basic Cerebellar Circuitry

The anatomy and physiology of the cerebellum are remarkably regular over different cerebellar regions and are highly conserved across species. These facts suggest that the cerebellum performs the same general computation for many different motor (and perhaps nonmotor) tasks. Because the anatomy and physiology of the cerebellum are so central to

thought about sites of plasticity and mechanisms of motor learning, we begin with a brief review of cerebellar organization (6).

The entire cerebellum shares a common architecture (Fig. 1). The two major anatomical compartments of the cerebellum are the cortex and the deep nuclei. Purkinje cells, the only outputs from the cerebellar cortex, project through inhibitory connections to the deep cerebellar nuclei, which provide the outputs to other brain regions. Inputs are transmitted to the cerebellum over climbing fibers and mossy fibers, two pathways with fundamentally different physiology and anatomy.

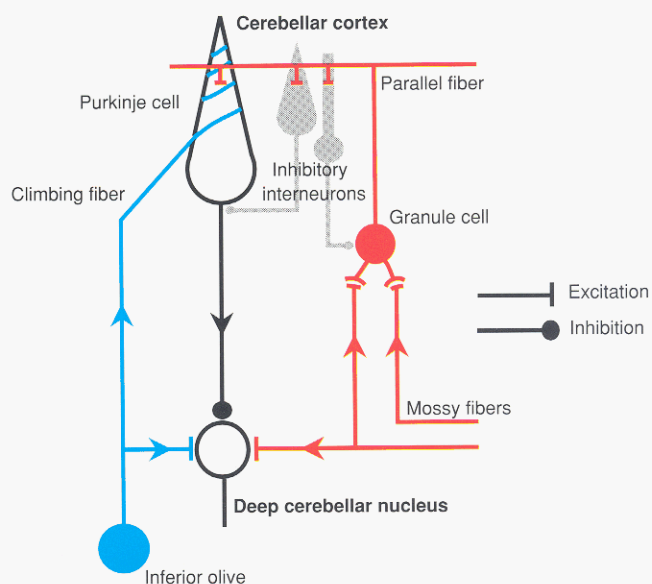
The climbing-fiber input to the cerebellum arises from the inferior olivary nuclei. In the cerebellar cortex, each Purkinje cell receives monosynaptic inputs from just one climbing fiber, and each climbing fiber projects to about 10 Purkinje cells. The climbing fibers cause Purkinje cells to emit complex spikes, which occur at rates of just one or a few per second. The infrequent

occurrence of the complex spikes is not compatible with traditional rate codes for information transfer and has led to the suggestion that climbing fibers are involved in guiding motor learning and in keeping time for movement coordination (1, 2, 5, 7).

The mossy-fiber inputs arise from a variety of brainstem nuclei as well as from the spinal cord, and they influence Purkinje cell firing through a web of interneurons in the cerebellar cortex. Mossy fibers synapse on granule cells, which in turn form parallel fibers and make excitatory contacts on numerous Purkinje cells as well as on inhibitory interneurons. The inhibitory interneurons synapse on Purkinje cells and also provide inhibitory feedback to the granule cells. Because of the massive convergence and divergence in the connections from granule cells and inhibitory interneurons onto Purkinje cells, the mossy fibers affect Purkinje cell firing through pathways that offer many opportunities for both spatial and temporal integration. In contrast to the complex spikes caused by the climbing-fiber inputs to Purkinje cells, the simple spikes driven by the mossy-fiber inputs fire at rates as high as 100 per second and probably use a frequency code to transmit information.

The best recognized actions of climbing fibers and mossy fibers are their inputs to the cerebellar cortex, but axon collaterals from both inputs also project to the deep cerebellar nuclei. Thus, the cerebellum contains parallel pathways for afferent information, one through the cerebellar cor-

Fig. 1. Schematic of the basic cerebellar circuit, which is iterated throughout the structure. A mossy fiber → granule cell → parallel fiber input (red), an inferior olive → climbing fiber input (blue), and some, but not all, of the intricate connections of the inhibitory interneurons (gray) are shown.



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tex and one directly through the deep nuclei. The signals transmitted through the deep nuclei and the signals transmitted through the cerebellar cortex are transformed by different intervening neural networks, which likely perform different computations and mediate different functions.

Common Behavioral Properties of Eyelid Conditioning and Motor Learning in the VOR

In classical conditioning of the eyelid response (4, 8), a puff of air serves as a reinforcing or unconditioned stimulus (US) that evokes a reflex eyelid response, which consists of retraction of the eyeball and closure of the nictitating membrane and the eyelids. If the US is paired repeatedly with an initially neutral conditioned stimulus (CS) such as a tone, then a response to the CS gradually develops until the CS evokes a reliable, learned eyelid response even in the absence of the US. A second form of cerebellum-dependent learning is motor learning in the VOR (3). When it is working well, the VOR causes an eye rotation opposite in direction to each head turn and of an appropriate amplitude to keep visual images from slipping across the retina. If the VOR fails to stabilize visual images, it is adjusted by motor learning. For example, if a person puts on spectacles that double the size of the visual scene, the VOR is suddenly rendered too small. Each head turn is associated with the motion of retinal images, and this association causes a gradual increase in the size of the VOR until visual images again are stable during head turns.

Behaviorally, conditioning of the eyelid response and motor learning in the VOR share the property that the temporal conjunction of two stimuli causes learning. The conjunction allows the prediction that one stimulus (tone or head turn) will be followed by another stimulus (air puff or image motion). The nervous system reacts to this predictive information by learning a new response to the tone or head turn that enables the organism to avoid the air puff or image motion. In eyelid conditioning, there is the acquisition of a new behavioral response (a blink) to a previously neutral CS; successful conditioning prevents subsequent air puffs from reaching the cornea. In the VOR, there is always a response to the vestibular stimulus and learning causes a change in the size of that response; successful learning reduces the amount of image motion during subsequent head turns. If we consider the change in the VOR evoked by a given head turn as the learned response, then the two systems have parallel behavioral properties. The head turn and the tone have parallel functions as the stimuli that

elicit the learned response, and the image motion and the air puff have parallel functions as the instructional or teaching stimuli. Although it may stretch the operational definition to discuss learning in the VOR as a form of classical conditioning, the vestibular stimulus can be thought of as a CS and the visual image motion stimulus as a US.

Similarity of Neural Circuits for VOR and Eyelid Response

Figure 2 shows the parallels between the neural circuits for motor learning in the VOR and conditioning of the eyelid response.

1) The basic motor pathways for each of the conditioned behaviors are in extracerebellar structures: in the red nucleus and other brainstem nuclei for eyelid conditioning, and in neurons in the vestibular nuclei [vestibular relay neurons (VRNs)] and other brainstem nuclei for the VOR. Subjects with cerebellar lesions can still blink and make smooth eye movements, even though they have substantial deficits in eyelid conditioning and learning in the VOR (9–13).

2) The sensory inputs that are subject to conditioning—vestibular inputs for the VOR, auditory inputs for the eyelid response—project in parallel to the deep cerebellar nucleus and the cerebellar cortex in each system. For eyelid conditioning, the anterior lobe is a relevant region of the cerebellar cortex, and the anterior interpositus nucleus (AIN) is the deep cerebellar nucleus involved (12, 14–17). For the VOR, the relevant part of the cerebellar cortex is the floccular complex (flocculus and ventral paraflocculus), which projects

directly to the vestibular nucleus (18); the floccular target neurons (FTNs) in the vestibular nucleus form the deep cerebellar nucleus for the VOR (19).

3) In each behavior, the two signals that must be paired to cause conditioning converge both in the cerebellar cortex and in the deep cerebellar nucleus. For the eyelid response, the tone CS is transmitted over mossy fibers from the auditory portion of the dorsolateral pontine nucleus; the somatosensory US is conveyed to both sites by mossy fibers, climbing fibers, and their collaterals to the deep cerebellar nuclei (12, 20–22). For the VOR, the vestibular stimulus is transmitted over mossy fibers from brainstem vestibular neurons, and the visual stimulus is transmitted by both mossy fibers and climbing fibers (23, 24). Thus, the functionally homologous sensory stimuli for the two systems have parallels in the pathways that transmit them to the cerebellum.

One feature of the circuit for the VOR that has not yet been reported in the eyelid conditioning system is feedback of an efference copy signal from the motor system to the cerebellar cortex. Signals related to eye velocity have been recorded in the floccular complex (23, 25), and models suggest that this signal is important in the VOR both before and after learning (26). The otherwise similar organization of the two systems and the general finding of this feature in other parts of the cerebellum (27) suggest that this difference in current knowledge may represent a gap in the data for the eyelid conditioning system rather than a difference in anatomy.

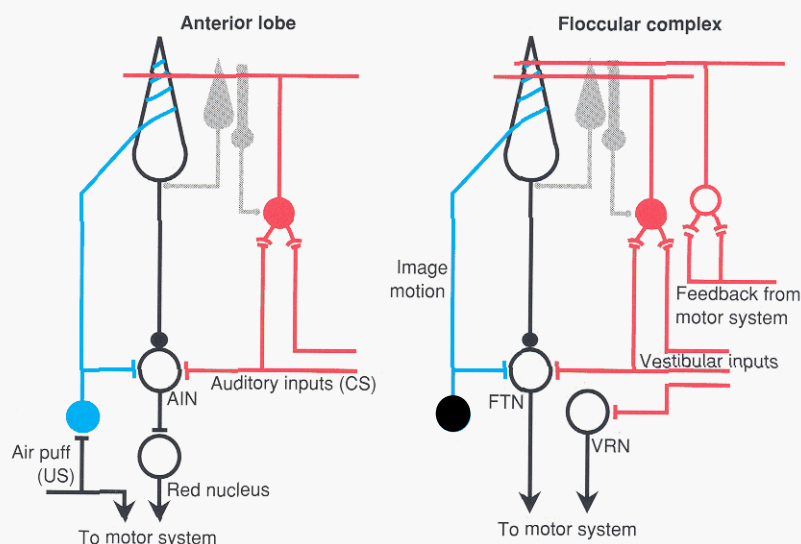


Fig. 2. Simplified circuit diagrams illustrating similarities of the neural pathways that mediate classical conditioning of the eyelid response (left) and motor learning in the VOR (right). The transmission of the air-puff US for eyelid conditioning and the image motion error signal for VOR learning over mossy-fiber pathways are discussed in the text but not shown here. AIN, anterior interpositus nucleus; FTN, floccular target neuron; VRN, vestibular relay neuron; color code as in Fig. 1.

Distributed Memory in the Cerebellar Cortex and the Deep Cerebellar Nuclei

Ablation experiments have provided evidence that the cerebellum is important for motor learning, both in eyelid conditioning and in the VOR. For the eyelid response, ablation of the AIN abolishes learned eyelid responses to the tone CS without preventing the reflex eyelid responses caused by the US alone (11–13, 28–30). For the VOR, lesions of the vestibular nucleus cause profound deficits in the overall behavior, although it is likely that a selective loss of the learned component of the response would occur if it were possible to ablate the FTNs selectively while sparing the other VRNs in the vestibular nucleus (31).

More compelling evidence that the cerebellum is important for eyelid conditioning comes from two sets of experiments that bracketed the sites of learning downstream from the mossy fibers and climbing fibers and upstream from the red nucleus, which is a target of the AIN. One set of experiments

showed that the CS and US could be replaced by stimulation of mossy fibers and climbing fibers, respectively, which suggested a site of learning downstream of the input pathways to the cerebellum (20). In the second set of experiments, the CS and US were delivered together during a series of daily conditioning sessions in which the red nucleus was inactivated reversibly. Even though the expression of conditioned eyelid responses was blocked during training, learning still occurred, as indicated by the expression of conditioned responses in the first trials after the inactivation was removed (32). Because learning occurred with the red nucleus inactivated, the site of learning must be upstream from the red nucleus, presumably in the cerebellum.

The results of these experiments indicate that the cerebellum is likely a site of memory storage for motor learning, but they do not resolve the relative importance of the cerebellar cortex and the deep cerebellar nucleus. Preliminary answers to this question have come from the results of additional ablation experiments. Reversible

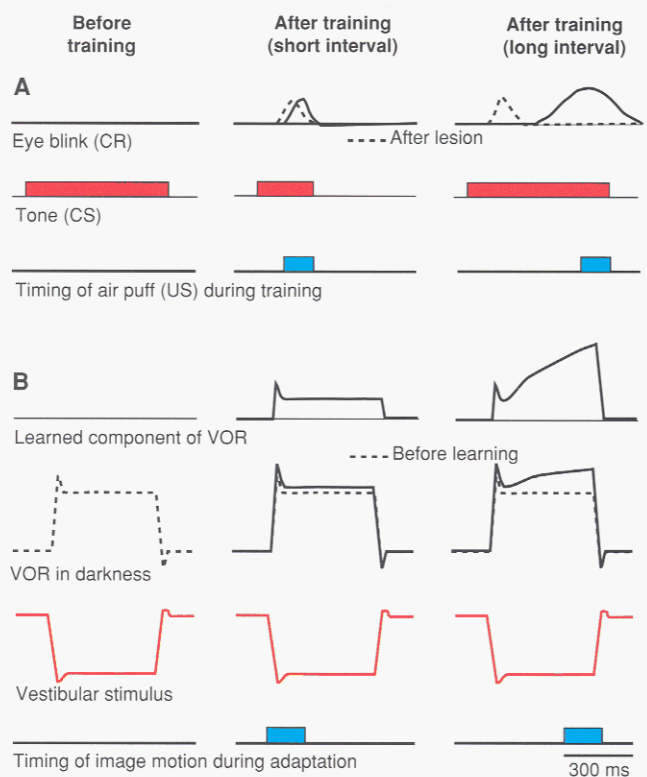
inactivation of the AIN with lidocaine prevents the expression but not the acquisition of eyelid conditioning (33); this finding suggests a site of plasticity in the cerebellar cortex. However, in both eyelid conditioning and motor learning in the VOR, ablations of the relevant parts of the cerebellar cortex remove only some of the memory acquired in previous training sessions, even though they prevent further learning. For the eyelid response, lesions that included the anterior lobe of the cerebellar cortex did not abolish a previously conditioned eyelid response but did change the amplitude and timing of the response (14–16). For the VOR, part of the memory of the modified VOR was lost, but much was retained if the floccular complex was removed after learning (34–36). These data argue that at least part of the memory for both the VOR and the eyelid response is stored outside of the cerebellar cortex, in the relevant deep cerebellar nucleus.

Electrical recordings have provided further information about the sites of memory, particularly for the VOR, although results from the two systems are again in excellent general agreement. For the VOR, single-unit recordings have suggested that memory is distributed between the cerebellar cortex of the floccular complex and its deep cerebellar nucleus in the brainstem (19, 36, 37). The recordings revealed large neural correlates of the learned component of the VOR in the Purkinje cells of the floccular complex, in FTNs, and in the extraocular motoneurons. Cause-and-effect relations among the learned responses in these neurons have been inferred from measurement of the latencies of the responses during the VOR and through computer simulations of neural networks with realistic architectures. These approaches have provided support for the lesion studies' conclusions that the memory for the VOR is stored partly in the vestibular inputs to FTNs in the vestibular nucleus and partly in the vestibular inputs to the cerebellar cortex. For eyelid conditioning, electrical recordings have revealed correlates of learning in the cerebellar cortex and the AIN as well as in the red nucleus, the motor nuclei, and even the hippocampus (12, 21, 38). The cerebellar loci that express correlates of learning in the circuit for the eyelid response agree with those for the VOR, but it has not yet been possible to establish cause-and-effect relations by comparing the neuronal latencies at different sites.

A Role for the Cerebellar Cortex in Learned Timing

The cerebellar cortex appears to play a special role in regulating the timing of learned movement. For the eyelid response, animals

Fig. 3. Learned timing in two cerebellum-dependent learning tasks. **(A)** Conditioned eyelid responses. Left panel: Before training, an auditory CS (red) elicits no eyelid response. Center panel: After a period of conditioning in which the CS is paired with a US such as a puff of air to the eye (blue) with a short CS-US interval, the CS elicits a brief, short-latency conditioned response (CR) of the eyelid (solid trace). Lesions that include the anterior lobe of the cerebellar cortex cause little change in the timing of the CR (dashed trace). Right panel: After conditioning with a long CS-US interval, the CS elicits a prolonged, long-latency eyelid response. Lesions that include the anterior lobe of the cerebellar cortex transform the prolonged, long-latency CR into a brief, short-latency CR. In the center and right panels, the tone (CS) and air puff (US) were presented together during conditioning, but the CR was measured for trials that presented only the tone. **(B)** VOR. Left panel: Before conditioning, a step of head velocity (vestibular stimulus; red) elicits a reflex eye velocity response (VOR; dashed trace) that is approximately equal in amplitude and opposite in direction to the vestibular stimulus. Center panel: After a training period in which image motion (blue) that renders the VOR too small is paired with the beginning of the vestibular stimulus, the amplitude of the VOR increases (solid traces). The learned component of the VOR (top traces) has the same amplitude throughout the duration of the head turn. Right panel: After a training period in which the same image motion is paired with the end of the vestibular stimulus, the learned component of the VOR is larger and has an increasing amplitude. Vertical calibration bars, 8° per second. In the center and right panels, the vestibular stimulus and image motion were presented together during conditioning, but the VOR and its learned component were measured during head turns in darkness.



were trained to emit differently timed responses for tone CSs of different frequencies (Fig. 3A) (14, 39). During conditioning, the air-puff US occurred at a short interval after the onset of one tone CS (Fig. 3A, center panel) and at a longer interval after the onset of a second tone CS (Fig. 3A, right panel). Both the short and long intervals produced conditioning. When delivered alone, the tone CS that had been paired with the US at a short interval evoked a brief, short-latency eyelid response. The tone associated with the long CS-US interval evoked a longer latency, more prolonged response. Lesions that included the anterior lobe of the cerebellar cortex had only a small effect on the short-latency, brief eyelid response but converted the longer latency, more prolonged response into a short-latency, brief response. Thus, the conditioned response after the lesion had the same short latency independent of its timing before the lesion. The interpretation of this experiment was that the cerebellar cortex is required for the expression of learned responses that are delayed relative to the stimuli that elicit them, and thus the cerebellar cortex may be the site where the memory of this type of learned timing is stored.

A similar kind of learned timing occurs in the VOR (40). Learning was induced by pairing 600-ms head turns with 150-ms pulses of image motion that were delivered at either the beginning or the end of the head turn (Fig. 3B). The VOR was first tested with a head turn in darkness (41); learning was then induced by delivering paired head turns and image motion for 3 hours, and finally the VOR was tested in darkness again. The learned component of the VOR was isolated from the prelearning VOR by subtracting the eye velocity evoked during a testing head turn in darkness before learning from that evoked after learning. The image motion presented during training was in a direction that rendered the VOR too small, and in each case learning caused an increase in the size of the VOR. However, the effect of learning on the dynamics of the VOR depended on the interval between the onset of the head turn and the image motion during learning. If learning was induced with image motion at the start of the head turn (Fig. 3B, center panel), then the learned component of the VOR was nearly constant in amplitude throughout the testing head turn. However, if learning was induced with image motion at the end of the head turn (Fig. 3B, right panel), then the learned component of the VOR was much larger at the end of the testing head turn than at the beginning. These data raise the possibility that there are two components of learning in the VOR. One component causes changes only in the size of the response. The other

component causes changes in the time course of the learned response, such that the largest learned changes in the response occur at some delay relative to the onset of the vestibular stimulus. Thus, both the conditioned eyelid response and the VOR show evidence of learned timing (42). For the VOR, the neural substrate of learned timing remains to be identified, but one experiment suggests that the cerebellar cortex may be involved, as it is for eyelid conditioning. In goldfish, lesions of the cerebellar cortex alter mainly the later part of the learned VOR response (35), much like the effect of lesions of the anterior lobe of the cerebellar cortex on the learned eyelid response.

Input Signals and Cellular Rules That Guide Learning

For a given brain locus to contribute to behavioral learning, that site must be endowed with a mechanism of cellular plasticity and must receive neural input signals that are appropriate to guide the local mechanism of plasticity. In both the eyelid response and the VOR, the cerebellar cortex and the relevant deep nucleus receive the proper signals. As discussed earlier (12, 20–24), information about the tone CS for the eyelid response and the vestibular stimulus for the VOR is transmitted to the cerebellum over mossy-fiber pathways. Information about the somatosensory US for the eyelid response and the image motion for the VOR is transmitted over both mossy-fiber and climbing-fiber pathways.

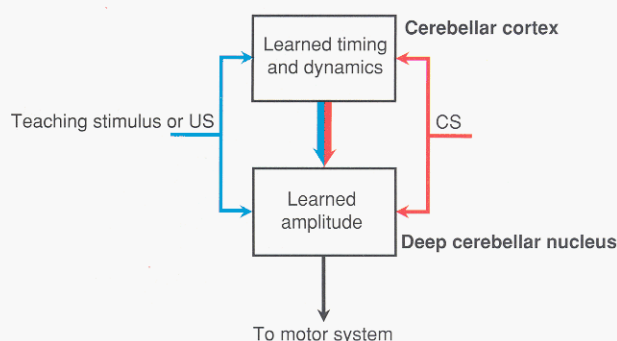
In the cerebellar cortex, the convergence of signals arriving over the climbing-fiber and mossy-fiber input pathways could cause learning through the well-known cellular mechanism of long-term depression (LTD) (43). Cerebellar LTD, a long-term decrease in the strength of transmission from parallel fibers to Purkinje cells, is caused by coincident activation of the climbing-fiber and parallel-fiber inputs to a

given cell. Because cerebellar LTD is present at a site where relevant input signals converge, it seems well positioned to participate in cerebellum-dependent learning. However, LTD may be just one of many cellular mechanisms of plasticity in the cerebellar cortex. Because information about the US also is conveyed to the cerebellar cortex over mossy-fiber pathways, learning in the cerebellar cortex could be mediated by any plasticity mechanism that depends on the conjunction of pre- and postsynaptic activity arising from either climbing-fiber or mossy-fiber inputs. Moreover, both synaptic potentiation and depression are undoubtedly involved in learning in intact, behaving animals.

In the deep cerebellar nuclei, major inputs arise from the Purkinje cell axons as well as from collaterals of both mossy fibers and climbing fibers, and there is little evidence to indicate which combinations of inputs contribute to plasticity. The finding that lesions of the cerebellar cortex prevent learning without abolishing previously learned responses suggests that the simple-spike output of Purkinje cells provides either a permissive or instructive input to a cellular mechanism of plasticity in the deep nuclei (14, 15, 44). If this mechanism depends on the correlation of pre- and postsynaptic activity, then the role of Purkinje cells could be to control learning by setting the postsynaptic activity of their target neurons. In the VOR, the simple-spike output from the floccular complex contains information that is appropriate to guide learning in the vestibular nucleus, at least for sinusoidal head motion at low frequencies (45). In the eye-blink system, it may be necessary for learning to occur first in the cerebellar cortex to create modulation of Purkinje cell simple-spike output, which in turn could guide learning in the AIN (15).

There is evidence that the climbing fibers from the inferior olive participate in learning. For the VOR, ablation of the in-

Fig. 4. Theory of cerebellum-dependent motor learning. Neural representations of the CS (red arrows) and the teaching stimulus or US (blue arrows) are conveyed in parallel pathways to the cerebellar cortex and the deep cerebellar nucleus. Learned changes occur both in the deep cerebellar nucleus and in the cerebellar cortex. Changes in the deep cerebellar nucleus mediate learned changes in the amplitude or strength of the response to the CS. Changes in the cerebellar cortex contribute to the learned timing or dynamics of movements elicited by the CS. The pathway from the cerebellar cortex to the deep cerebellar nucleus serves a dual role: It provides at least part of the neural signals that drive the conditioned response (red arrows), and it can convey teaching signals that contribute to plasticity in the deep cerebellar nucleus (blue arrows).



ferior olive prevents learning (46). For the eyelid response, ablation of the inferior olive prevents subsequent eyelid conditioning. In one study, ablation of the olive also abolished a previously conditioned eyelid response; in a second study, a previously established conditioned response remained after the lesion, and this response gradually diminished during continued conditioning trials, much as would be expected if the US were withheld during repeated trials that delivered only a CS (47). Moreover, electrical stimulation of the inferior olive was able to substitute for the somatosensory US and, when paired with a tone CS, induced eyelid conditioning (20). Further experiments will be needed to determine whether the site of climbing-fiber action during learning is in the cerebellar cortex, the deep nuclei, or both.

Cerebellum-Dependent Learning: A Hypothesis

On the basis of the many similarities of motor learning in the VOR and the eyelid response, we propose a hypothesis that could provide a framework for understanding all forms of cerebellum-dependent learning (Fig. 4). Many of the similarities in the neural implementations for conditioning of the eyelid response and motor learning in the VOR draw heavily on general features of cerebellar organization, and the uniform architecture of the cerebellum may prove to have correlates in the principles of operation of the cerebellum. Our view of the cerebellum is new only in the sense that it postulates a new combination of sites and mechanisms of learning. Almost all of its elements can be found in previous ideas regarding cerebellar function (2, 7, 14, 15, 44, 48).

Our hypothesis (Fig. 4) has three elements: (i) Learning occurs in both the cerebellar cortex and the deep cerebellar nuclei; memories can be stored at both sites. (ii) The component of learning that occurs in the cerebellar cortex is critical for regulating the timing of movements. (iii) The output from the cerebellar cortex guides learning in the deep cerebellar nucleus; hence, learning that occurs in the cerebellar cortex can be transferred partially or completely to long-term memory in the deep cerebellar nucleus.

The distribution of learning across multiple sites may enable the nervous system to meet the challenge of regulating multiple attributes of the signals that control movement. For example, accurate arm movement requires correct time courses in the commands for force generation in each muscle, as well as suitable amplitudes of the force created by each contraction. Separation of the learning of timing and amplitude

at different sites may render the computations more tractable for the brain.

Timing is a critical aspect of movement, and it may be necessary to use motor learning to regulate the timing of motor commands in all motor systems. However, learned "timing" may have different meanings in different motor systems. For eyelid conditioning, timing means regulation of the latency and duration of the response to ensure that the eyelid is closed and the cornea protected at the time of the air puff. For the VOR, it may mean adaptation of the time course of the motor commands to compensate for changes in the physical properties of either the sensory or motor apparatus. For the VOR, timing may also mean compensating for the natural instabilities that result from the use of efference copy in a positive feedback configuration (26). The intricate interneuronal networks in the cerebellar cortex may be ideally suited for learning the time course of the response.

Learning and memory at multiple sites will require coregulation of those sites. Part of the required coregulation would be provided if the simple-spike output of Purkinje cells guides learning in the deep cerebellar nucleus. Such a mechanism would allow learning in the cerebellar cortex to be transferred to the deep nuclei and potentially would eliminate the need for additional coordination of signals that guide learning in the cerebellar cortex and deep nuclei. Also, with this mechanism, some sites of learning and short-term memory may not be sites of long-term memory. In any given motor system, the exact division of memory between the cerebellar cortex and the deep nuclei may depend on the amount and type of training, as well as on the inherent biases (in individual species and in different movement systems) for plasticity in one site or another.

Although motor learning in the VOR and classical conditioning of the eyelid response are superficially quite different problems in motor control, the two systems appear to use remarkably similar neural mechanisms for learning. The eyelid response and the VOR are part of a large class of movements in which motor learning depends on the integrity of the cerebellum. The neural mechanisms of cerebellum-dependent learning revealed for these two behaviors may represent general principles that apply to all forms of cerebellum-dependent learning, including classical conditioning of limb movements and motor learning in saccadic eye movements and reaching arm movements (5, 49).

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