Cerebellar Involvement in Motor Learning

MICHAEL D. MAUK, PHILIP M. STEELE, and JAVIER F. MEDINA
Department of Neurobiology and Anatomy
University of Texas Medical School at Houston
Houston, Texas

For decades, cerebellar research has been guided by the central hypothesis that plasticity at synapses in the cerebellar cortex mediates motor learning. This hypothesis has been challenged especially strongly in recent years by data that contradict the original theories of cerebellar motor learning. These data form the basis for strong arguments to the contrary and have inspired new, non-motor theories of cerebellar function. We consider key data that are contrary to the motor learning hypothesis and develop the argument that both old and new data are best explained by extending, rather than rejecting, the basic tenets of the original motor learning theories of cerebellar function. NEUROSCIENTIST 3:303–313, 1997

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The most obvious symptoms associated with pathology of the cerebellum are severe motor deficits of voluntary movements characterized by ataxia and dysmetria (1, 2). An important goal of cerebellar research is to provide increasingly detailed and mechanistic descriptions of cerebellar function and how the dysfunction or absence of these mechanisms produces cerebellar symptoms. A central theme that has emerged from such work is the involvement of plasticity at cerebellar synapses in the adaptation or learning of movements (3, 4). The basic notion is that the cerebellum uses inputs encoding movement errors to improve subsequent motor performance through changes in the strength of certain cerebellar synapses. In this context, cerebellar ataxia is thought to reflect the execution of movements without the benefit of adaptive adjustments.

This view of the cerebellum has been strongly criticized, particularly in recent years (5–9). These criticisms are based on a variety of observations that appear to contradict the seminal theory, proposed by Marr (3), suggesting how the cerebellum could adapt movements. These observations are compelling and challenge ideas about cerebellar function. Is Marr's theory wrong? Do these new observations indicate that the cerebellum is involved in cognitive or sensory functions rather than motor learning (8)? Should we discard the idea that cerebellar plasticity mediates motor learning and look to alternative ideas and mechanisms? Although some have argued that we should, we will develop the arguments that 1) the basic tenets of motor learning theories of cerebellum are sound and 2) contrary observations illustrate that early motor learning theories were incomplete rather than wrong. We start with a basic description of cerebellar anatomy and then present an overview of Marr's ideas suggesting how this anatomy could mediate motor learning. We will then address objections to this theory and show how recent data suggest how we should extend, rather than reject, the notion that the cerebellum mediates motor learning.

Address reprint requests to: Michael D. Mauk, M.D., Department of Neurobiology and Anatomy, University of Texas Medical School at Houston, 6431 Fannin, Houston, Texas 77030 (email: mmauk@nba19.med.uth.tmc.edu).

The Synaptic Organization of the Cerebellum

The well-characterized and relatively simple synaptic organization of the cerebellum is central to ideas about its role in motor learning (Fig. 1). Outputs from the cerebellum arise from the cerebellar deep nuclei. These outputs are controlled by inhibitory inputs from Purkinje cells in the cortex of the cerebellum and by excitatory inputs from two classes of afferent projections to the cerebellum.

The properties of these two afferent types are quite different (10, 11). Mossy fibers make excitatory synapses directly onto the cerebellar nucleus cells, and they also project to the cerebellar cortex where they branch profusely. This branching allows the mossy fibers to make excitatory synapses onto a very large number of granule cells and onto Golgi cells. The granule cells, whose activity is also influenced by inhibition from Golgi cells, make excitatory synapses onto many Purkinje cells—the large output neurons of the cerebellar cortex. The divergence of mossy fibers onto granule cells and from granule cells onto Purkinje cells is so great that each Purkinje cell receives synapses from 100,000 to 200,000 granule cells (gr→Pkj synapses). Moreover, the convergence of inhibitory Purkinje cell inputs is such that the number of gr→Pkj synapses that influence each output cell in the nucleus is on the order of 10^8. Thus, the nucleus output cells are controlled by direct excitation from mossy fibers and by inhibition arising from an enormous network of neurons in the cerebellar cortex.

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In contrast, climbing fiber inputs are quite specific; each Purkinje cell receives only one climbing fiber input, and each climbing fiber contacts no more than about 10 Purkinje cells. Climbing fibers derive their name from the way they branch extensively and "climb" over the Purkinje cell dendrites. In doing so, each climbing fiber makes repeated synaptic contacts onto the same Purkinje cell, forming probably the strongest functional input in the CNS. Remarkably, this spatially distributed synaptic input has relatively small effects on the action potential activity of Purkinje cells. Each climbing fiber input does, however, produce a transient and cell-wide increase in intracellular calcium (12) that is believed to play a role in the induction of plasticity at granule cell synapses onto Purkinje cells (see below).

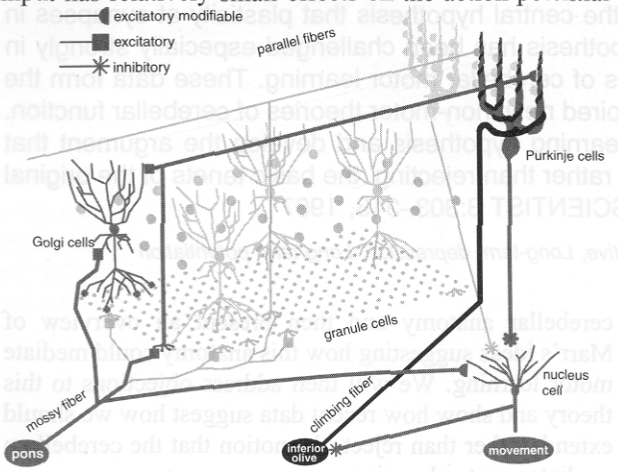


Fig. 1. A schematic representation of the synaptic organization of the cerebellum. The cerebellum is comprised of two anatomical components: 1) the cerebellar cortex with its granule, Golgi, stellate/basket (not shown), and Purkinje cells; and 2) the cerebellar nuclei, which provide the sole output of the cerebellum to other brain regions. Inputs to the cerebellum are provided by two quite different afferent types.

Climbing fibers (bold black) originate in the inferior olive nuclei and project to Purkinje cells. Each climbing fiber contacts 10 or fewer Purkinje cells, and each Purkinje cell receives input from only one climbing fiber. Climbing fibers make numerous, spatially distributed synapses with the Purkinje cells. This strong connection produces an all-or-none response in the Purkinje cell, characterized by a transient and cell-wide influx of calcium. This input is thought to control the induction of plasticity at the granule cell synapses on the Purkinje cell.

Mossy fibers, in contrast, arise from many nuclei, including many in the pons, and branch extensively. The mossy fibers begin two parallel pathways—they make excitatory connections directly onto the output cells (mf→nuc synapses), and they branch extensively in the cerebellar cortex, making excitatory synapses onto many granule and Golgi cells.

Granule cells make excitatory connections onto Purkinje cells (the gr→Pkj synapses), and the Purkinje cells, in turn, inhibit cells in the cerebellar nuclei. Activity in the enormous population of granule cells is modulated by feedback inhibitory input from Golgi cells, which receive excitatory inputs from mossy fiber and granule cells.

Plasticity is thought to occur at two sets of synapses: the gr→Pkj synapses in the cerebellar cortex and the mf→nuc synapses in the nuclei. Thus, the output cells are controlled by two parallel pathways (*shown in blue*), both containing modifiable synapses. The direct pathway using the mf→nuc synapses is relatively simple, whereas the less direct pathway through the cerebellar cortex involves complex interactions that control granule cell activity and involves plasticity at the gr→Pkj synapses.

Marr's Theory of Cerebellar Motor Learning

In 1969, Marr proposed a theory of cerebellar cortex based on these notable anatomical characteristics. The theory's three main propositions were: 1) the mossy fiber/granule cell inputs encode the specific circumstances in which movements occur, with the abundance of granule cells providing a rich representation and the ability to discriminate many similar circumstances, 2) climbing fibers signal that the movement controlled by their target Purkinje cells requires change, and 3) climbing fiber inputs induce plasticity at co-active gr→Pkj synapses, improving subsequent movement performance under similar circumstances. The elegance of this theory derives from the clarity and specificity with which it was stated. It makes a number of clear predictions; 1) forms of motor learning should engage cerebellar inputs and outputs in particular ways, 2) specific patterns of inputs should induce plasticity at the gr→Pkj synapses, 3) climbing fiber inputs should display a specialized role in conveying signals about movement errors, 4) lesions of the cerebellar cortex should abolish the motor memories encoded at the gr→Pkj synapses, and 5) lesions of the inferior olive (the source of climbing fibers) should prevent further motor learning.

Albus (13) argued that Marr's theory was analogous to Pavlovian conditioning, in which (for conditioning of eyelid responses) a tone paired with a puff of air in the eye promotes the acquisition of a conditioned eyelid response. In Albus' view, stimuli like tones are conveyed to the cerebellum via mossy fibers, error signals like the air puff are conveyed to the cerebellum via climbing fibers, and the learned response is mediated by plasticity at the gr→Pkj synapses. Analysis of Pavlovian eyelid conditioning and of adaptation of the vestibulo-ocular reflex (VOR) suggests cerebellar involvement in the way Albus envisioned (Box 1).

Objections to Theories That Assert Cerebellar Synaptic Plasticity Contributes to Motor Learning

Despite the general support for a role of the cerebellum in motor learning, many observations appear to contradict the predictions of Marr's theory. These observations have inspired strongly stated objections to the ideas that climbing fiber inputs signal movement errors and that the climbing fiber-induced plasticity in the cerebellar cortex mediates motor learning. A number of non-motor-learning and even non-motor theories of cerebellar function have been proposed as alternatives (5, 6, 9). Because many recent reviews have addressed this ongoing debate, providing arguments for (4, 14–16) and

against (6–9, 17) the motor learning hypothesis of cerebellum, another such review would be of limited value. Instead, our goal is to consider the information conveyed by the data that contradict the role for cerebellar synaptic plasticity in motor learning envisioned by Marr. We will develop the ideas that the data as a whole are best explained by elaborating, rather than rejecting, Marr's theory and that this extended theory provides a more detailed and complete understanding of the cerebellum.

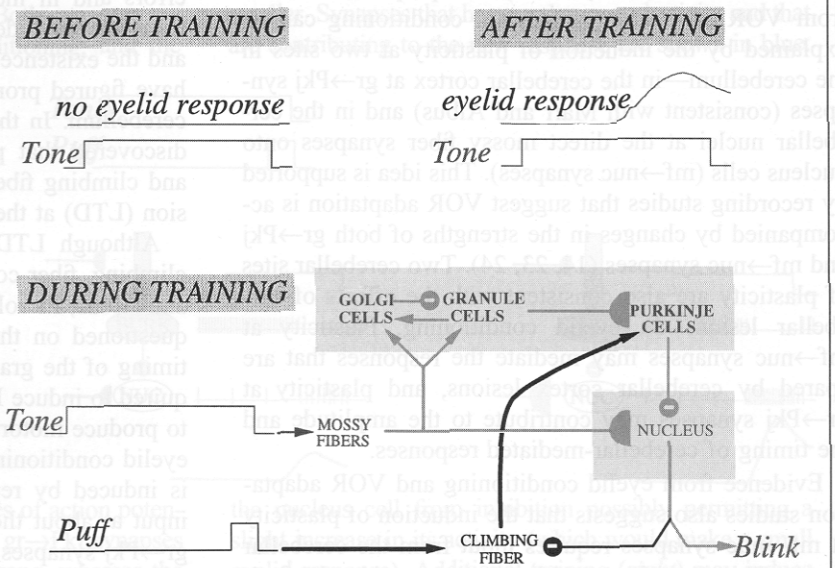
Cerebellar Cortex Lesions Don't Always Abolish the Memory for Previous Motor Learning

A fundamental tenet of Marr's theory is that memories for motor learning are stored as patterns of strengths at the gr→Pkj synapses. This leads to the obvious prediction that cerebellar cortex lesions should abolish previously learned motor responses. This prediction is clearly not supported by evidence from such systems as VOR

Box 1: Cerebellar Involvement in Eyelid Conditioning and VOR Adaptation

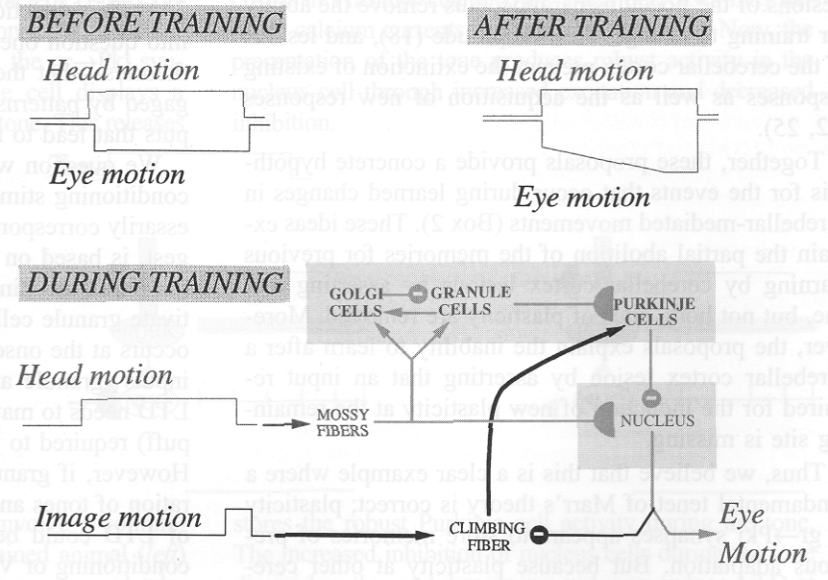
Eyelid Conditioning

Pavlovian eyelid conditioning typically involves the paired presentation of a tone with a puff of air directed at the eye. Before training, no detectable eyelid response is elicited by the tone. Following many training trials, the tone elicits an eyelid response that peaks near the time that the puff was presented. Evidence indicates that 1) the responses are elicited by output from the cerebellar nucleus, 2) the tone is conveyed to the cerebellum via mossy fibers, and 3) the puff activates climbing fibers. For example, stimulation of the cerebellar nucleus can elicit eyelid responses, even in untrained animals. Lesions of the cerebellar nucleus abolish the expression of the learned responses and electrical stimulation of mossy fibers and climbing fibers can substitute for tone and puff to produce normal learning (4, 16, 47).



VOR Adaptation

The vestibulo-ocular reflex (VOR) stabilizes images on the retina by producing eye motion that exactly counteracts head motion. The reflex remains accurate through adaptation, where paired occurrence of head motion with image motion (indicating incorrect VOR performance) can change the amplitude of the reflex. As with eyelid conditioning, evidence indicates that head motion activates mossy fibers, whereas image motion activates climbing fibers (23, 24).



adaptation and eyelid conditioning, which indicate that cerebellar cortex lesions only partially abolish the memories for previous adaptation. Lesions of the flocculus/paraflocculus regions of cerebellar cortex only partially remove learning-induced changes in VOR amplitude (18). For eyelid conditioning, lesions of the cerebellar cortex do not abolish previously learned eyelid responses (19); instead, they reduce the amplitude and disrupt the learned timing of the responses that are spared (20). Do these data necessarily indicate that VOR adaptation and eyelid conditioning do not involve climbing fiber-induced plasticity at gr→Pkj synapses?

We and others (4, 14, 20–22) have proposed that data from VOR adaptation and eyelid conditioning can be explained by the induction of plasticity at two sites in the cerebellum—in the cerebellar cortex at gr→Pkj synapses (consistent with Marr and Albus) and in the cerebellar nuclei at the direct mossy fiber synapses onto nucleus cells (mf→nuc synapses). This idea is supported by recording studies that suggest VOR adaptation is accompanied by changes in the strengths of both gr→Pkj and mf→nuc synapses (14, 23, 24). Two cerebellar sites of plasticity are also consistent with the effects of cerebellar lesions on eyelid conditioning. Plasticity at mf→nuc synapses may mediate the responses that are spared by cerebellar cortex lesions, and plasticity at gr→Pkj synapses may contribute to the amplitude and the timing of cerebellar-mediated responses.

Evidence from eyelid conditioning and VOR adaptation studies also suggests that the induction of plasticity at mf→nuc synapses requires input from the cerebellar cortex. This second proposition is supported by the findings that no further learning of the VOR or eyelid conditioning is possible after a cerebellar cortex lesion. Lesions of the flocculus/paraflocculus remove the ability for training to change VOR amplitude (18), and lesions of the cerebellar cortex prevent the extinction of existing responses as well as the acquisition of new responses (22, 25).

Together, these proposals provide a concrete hypothesis for the events that occur during learned changes in cerebellar-mediated movements (Box 2). These ideas explain the partial abolition of the memories for previous learning by cerebellar cortex lesions by asserting that one, but not both, sites of plasticity are removed. Moreover, the proposals explain the inability to learn after a cerebellar cortex lesion by asserting that an input required for the induction of new plasticity at the remaining site is missing.

Thus, we believe that this is a clear example where a fundamental tenet of Marr's theory is correct; plasticity at gr→Pkj synapses appears to store memories of previous adaptation. But because plasticity at other cerebellar synapses can also contribute, lesions of the cerebellar cortex do not completely erase the memory of previous learning. Indeed, we have suggested previously that the relative contributions of plasticity at gr→Pkj and mf→nuc synapses may vary depending on the amount and type of training that the animal has experienced (4, 14, 40). As a final comment on this issue, it seems fair to note that because Marr's work was entitled "A Theory of Cerebellar Cortex," the potential for plasticity in the cerebellar nuclei is not inconsistent with his theory.

The Timing of Inputs Required To Induce Plasticity Is Different Than the Timing of Stimuli Required To Produce Motor Learning

The other central feature of Marr's theory is the proposed role of climbing fibers in conveying movement errors and in inducing plasticity at gr→Pkj synapses. Consequently, identifying the function of climbing fibers and the existence and importance of cerebellar plasticity have figured prominently in attempts to understand the cerebellum. In the early 1980s, Ito and colleagues (26) discovered that paired activation of gr→Pkj synapses and climbing fiber inputs produces a long-term depression (LTD) at the gr→Pkj synapses.

Although LTD at gr→Pkj synapses is the type of climbing fiber-controlled plasticity proposed by Marr and Albus, its role in motor learning has been seriously questioned on the basis of the mismatch between the timing of the granule cell and climbing fiber inputs required to induce LTD and the timing of stimuli required to produce motor learning, such as VOR adaptation and eyelid conditioning (7, 8, 27). Specifically, robust LTD is induced by repeatedly activating the climbing fiber input at about the same time as (or a little before) the gr→Pkj synapses (Fig. 2B) (28, but see 29). In contrast, eyelid conditioning requires that the tone (which activates granule cells) must precede the onset of the puff (which activates climbing fibers) by about 100 ms (Fig. 2A). This objection is potentially quite serious as it calls into question one of the key features of the Marr/Albus theories—that the plasticity at gr→Pkj synapses is engaged by patterns of mossy fiber and climbing fiber inputs that lead to motor learning.

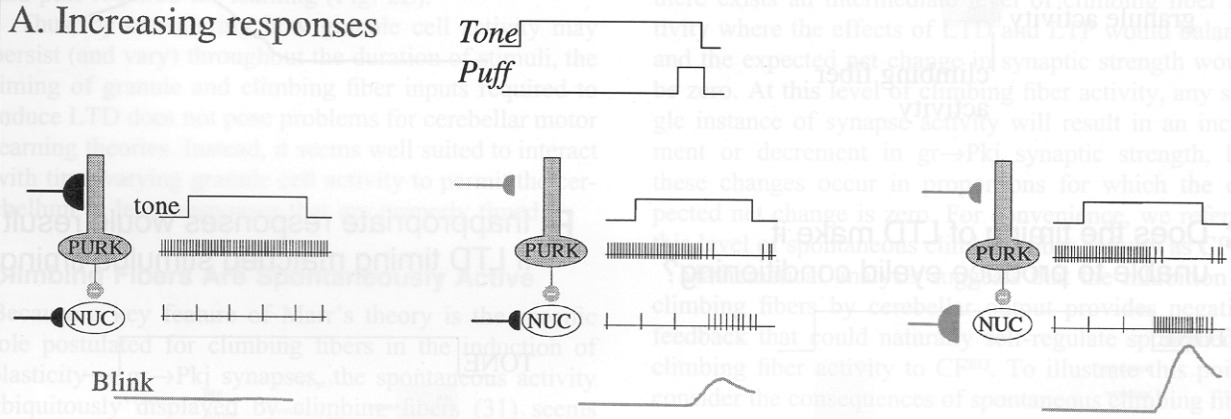
We question whether the timing displayed by eyelid conditioning stimuli and by LTD induction should necessarily correspond. Expecting that they should, we suggest, is based on the implied assumption that it is only the onsets of stimuli like tones and head turns that activate granule cells. That is, if granule cell activity only occurs at the onsets of tones, then indeed, the timing of inputs (granule and climbing fiber) required to induce LTD needs to match the timing of stimuli (e.g., tone and puff) required to produce eyelid conditioning (Fig. 2C). However, if granule cells are active throughout the duration of tones and head turns, then the observed timing of LTD could be quite appropriate to promote eyelid conditioning or VOR adaptation (compare Figs. 2D and 2E).

Studies attempting to understand cerebellar cortex mechanisms that mediate the timing of VOR adaptation and eyelid responses help illustrate this point. Both VOR

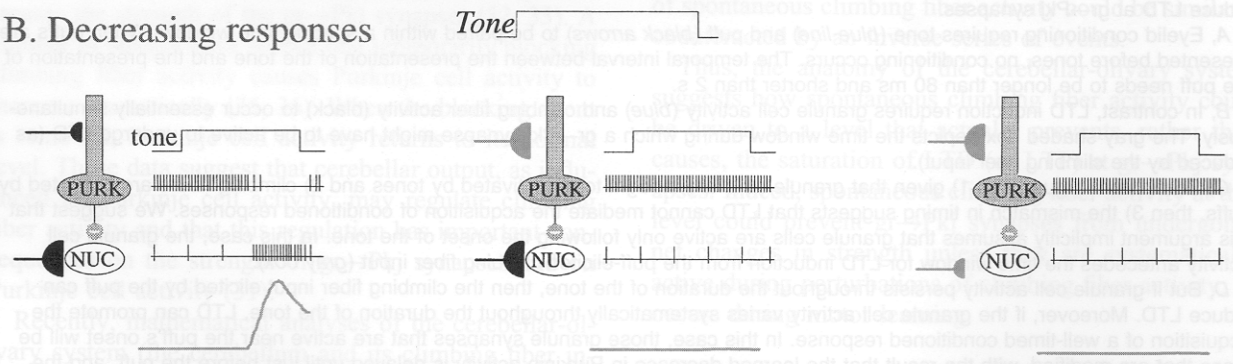
adaptation and eyelid conditioning show such a capacity for learned timing (14, 30). In VOR adaptation, changes in the amplitude of the VOR are largest for the time at which the error signal arrives (14). In eyelid conditioning, training with a short interval between tone and puff onsets produces fast, short-latency conditioned responses, whereas training with longer intervals produces slower, longer-latency responses (30). Evidence indicates that this learned timing is abolished by lesions of the cerebellar cortex. Large-scale computer simulations of cerebellar cortex suggest that mossy fiber inputs, like those activated by a tone, produce time-varying activa-

Box 2: Hypothesized Relationship Between Cerebellar Plasticity and Motor Learning

The illustrations show the events thought to occur during changes in the strength of eyelid responses. Each panel shows the two putative sites of plasticity, the gr→Pkj synapses and the mf→nuc synapses. Both synapses are activated by the tone in eyelid conditioning, and the climbing fiber input to the Purkinje cell (not shown) is assumed to be activated by the puff. Strong gr→Pkj synapses are shown relatively large; weak synapses are smaller. Synapses that have undergone plasticity and that are contributing to the new response are shown in blue.



Purkinje cells normally show high rates of action potential activity. Before training (*left*), the gr→Pkj synapses activated by the tone are relatively strong, whereas the mf→nuc synapses are relatively weak. Thus, presenting the tone does not decrease the ongoing Purkinje activity and does not increase activity in the nucleus cells. Correspondingly, there is no eyelid response. With paired presentation of tone and puff (*center*), the gr→Pkj synapses undergo LTD and the Purkinje cell displays a learned decrease in activity during the tone. This releases the nucleus cell from inhibition possibly permitting a slight increase in its activity (which would make a small eyelid response). Additional training (*right*) may induce LTP at the mf→nuc synapses because that activity of those synapses is repeatedly paired with a transient decrease in Purkinje cell activity. Such decreases may activate calcium currents in the nucleus cells (4). Now, the presentation of the tone produces robust activity in the nucleus cell through increased excitation and decreased inhibition.



Decreasing responses is believed to involve a complementary series of events. The well-trained animal (*left*) begins with relatively weak gr→Pkj synapses and relatively strong mf→nuc synapses. With tone-alone training (*center*), the gr→Pkj synapses undergo LTP, which restores the robust Purkinje cell activity during the tone. The increased inhibition of nucleus cells during the tone diminishes the eyelid response and may induce LTD at the mf→nuc synapses (*right*).

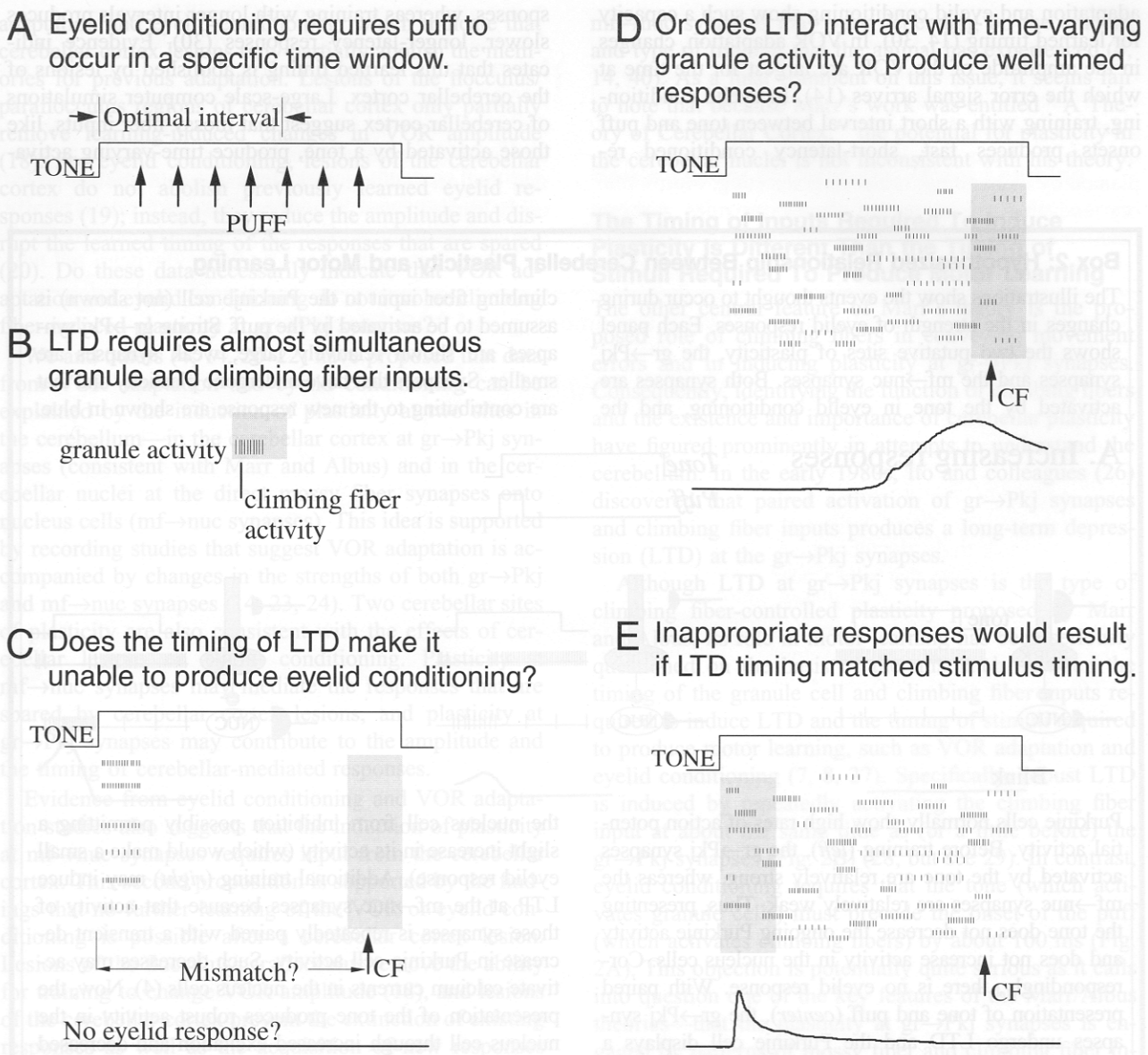


Fig. 2. The timing of stimuli required to produce motor learning, such as eyelid conditioning, does not match the timing required to induce LTD at gr→Pkj synapses.

A, Eyelid conditioning requires tone (*blue line*) and puff (*black arrows*) to be paired within a specific time window. When puffs are presented before tones, no conditioning occurs. The temporal interval between the presentation of the tone and the presentation of the puff needs to be longer than 80 ms and shorter than 2 s.

B, In contrast, LTD induction requires granule cell activity (*blue*) and climbing fiber activity (black) to occur essentially simultaneously. The gray shaded box depicts the time window during which a gr→Pkj synapse might have to be active to undergo LTD (as induced by the climbing fiber input).

C, Some have argued that 1) given that granule cells are thought to be activated by tones and 2) climbing fibers are activated by puffs, then 3) the mismatch in timing suggests that LTD cannot mediate the acquisition of conditioned responses. We suggest that this argument implicitly assumes that granule cells are active only following the onset of the tone. In this case, the granule cell activity antecedes the time window for LTD induction from the puff-elicited climbing fiber input (*gray box*).

D, But if granule cell activity persists throughout the duration of the tone, then the climbing fiber input elicited by the puff can induce LTD. Moreover, if the granule cell activity varies systematically throughout the duration of the tone, LTD can promote the acquisition of a well-timed conditioned response. In this case, those granule synapses that are active near the puff's onset will be those that are modified, with the result that the learned decrease in Purkinje activity is delayed until just before the puff, and the conditioned responses would be appropriately timed.

E, If 1) granule cell activity does persist throughout the tone and 2) the timing of LTD matches the timing of tone and puff required to promote learning (as some argue it should), then the timing of the learned responses would be likely to display inappropriately short latencies rather than being appropriately delayed.

tion of different subsets of granule cells at different times during the stimulus, as shown schematically in Figures 2C–E. The simulations show that if granule cell activity varied systematically during the tone or head turn, then LTD could modify only those synapses active around the time at which the error signal arrives. This could allow the learned response to be delayed until the appropriate time—just before the arrival of the error signal occurs. The key point is that this capability to time the response requires the type of timing that LTD induction displays—approximately simultaneous activation of gr→Pkj synapses and climbing fiber inputs (Fig. 2D). Indeed, abnormally timed responses would be produced if the granule/climbing fiber timing required for the induction of LTD were more like the timing of tone and puff required for learning (Fig. 2E).

Thus, by considering how granule cell activity may persist (and vary) throughout the duration of stimuli, the timing of granule and climbing fiber inputs required to induce LTD does not pose problems for cerebellar motor learning theories. Instead, it seems well suited to interact with time-varying granule cell activity to permit the cerebellum to learn responses that are properly timed.

Climbing Fibers Are Spontaneously Active

Because a key feature of Marr's theory is the specific role postulated for climbing fibers in the induction of plasticity at gr→Pkj synapses, the spontaneous activity ubiquitously displayed by climbing fibers (31) seems particularly damaging. This spontaneous activity raises many troubling questions. What prevents the saturation of LTD at all gr→Pkj synapses? How can the occasional error-evoked climbing fiber input convey information against this background activity? Recent results showing that gr→Pkj synapses also undergo LTP and results obtained from reversible inactivation of climbing fiber activity have provided clues to these questions. Several groups have now shown that the activation of gr→Pkj synapses in the absence of a climbing fiber input increases the strength of the gr→Pkj synapses (32, 33). A number of studies have shown that temporarily blocking climbing fiber activity causes Purkinje cell activity to increase dramatically (35, 36). When the blocking agent is removed, Purkinje cell activity returns to its normal level. These data suggest that cerebellar output, as influenced by Purkinje cell activity, may regulate climbing fiber activity and that this regulation has important consequences on the strength of gr→Pkj synapses and on Purkinje cell activity (31).

Recently, mathematical analyses of the cerebellar-olivary system (the cerebellum and its climbing fiber inputs from the inferior olive) have been used to address the interactions between the cerebellum and the climbing fibers of the inferior olive. The results of these mathematical analyses and computer simulations (34), are relatively easy to appreciate intuitively. The two key features of these results are the properties of plasticity at the gr→Pkj synapses and the inhibition of climbing fibers by projections from the cerebellar nuclei to the inferior olive (Fig. 1). The properties of LTD and LTP imply that gr→Pkj synapses will undergo plasticity whenever they are active (''active'' may mean one spike or a burst of spikes); they undergo LTD when there are chance pairings of granule cell activity with a spontaneous climbing fiber input, and they undergo LTP when granule cell activity occurs alone. Thus, the expected direction of change at a gr→Pkj synapse will depend on the likelihood that its activity is paired with a climbing fiber input. When climbing fiber activity is high, the expected result is a net decrease in synaptic strength (LTD), whereas a net increase (LTP) is expected when climbing fibers are silent. Between these two extremes, there exists an intermediate level of climbing fiber activity where the effects of LTD and LTP would balance and the expected net change in synaptic strength would be zero. At this level of climbing fiber activity, any single instance of synapse activity will result in an increment or decrement in gr→Pkj synaptic strength, but these changes occur in proportions for which the expected net change is zero. For convenience, we refer to this level of spontaneous climbing fiber activity as CF^{EQ}.

Mathematical analysis suggests that the inhibition of climbing fibers by cerebellar output provides negative feedback that could naturally self-regulate spontaneous climbing fiber activity to CF^{EQ}. To illustrate this point, consider the consequences of spontaneous climbing fiber activity above CF^{EQ} (Fig. 3). LTD would occur too frequently relative to LTP, resulting in a net decrease in Purkinje cell activity and a net increase in the activity of cerebellar nucleus cells through reduced inhibition from Purkinje cells. The increased inhibitory input from the nucleus cells would, in turn, cause a corresponding decrease in the activity of climbing fibers. Thus, the expected consequence of excess climbing fiber activity is an increased inhibition of climbing fibers resulting from net LTD at gr→Pkj synapses. Inappropriately low rates of spontaneous climbing fiber activity could be similarly counteracted by an inverse series of events.

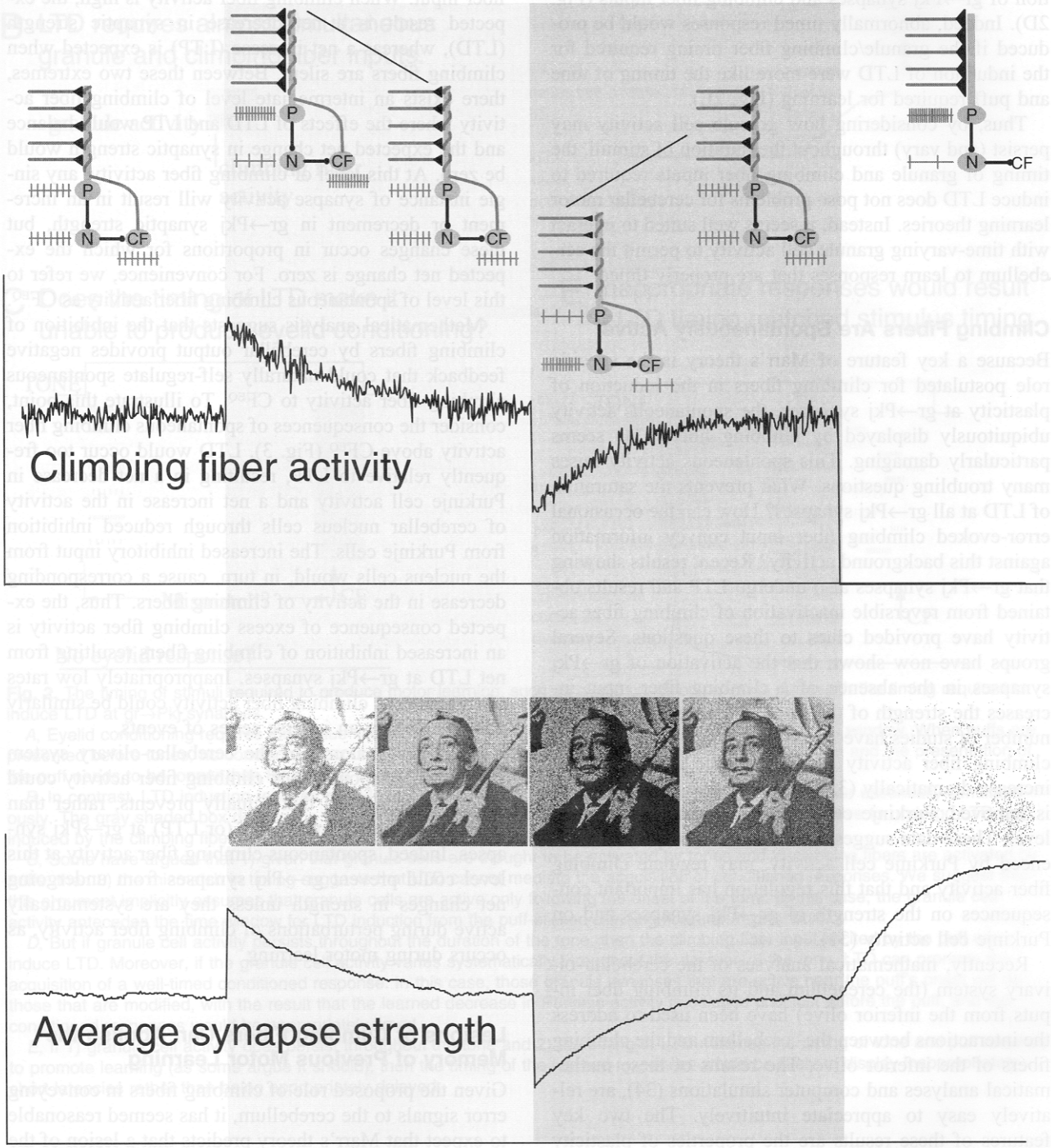
Thus, the anatomy of the cerebellar-olivary system suggests how spontaneous climbing fiber activity could be driven to a level that actually prevents, rather than causes, the saturation of LTD (or LTP) at gr→Pkj synapses. Indeed, spontaneous climbing fiber activity at this level could prevent gr→Pkj synapses from undergoing net changes in strength unless they are systematically active during perturbations of climbing fiber activity, as occurs during motor learning.

Lesions of Climbing Fibers Can Abolish the Memory of Previous Motor Learning

Given the proposed role of climbing fibers in conveying error signals to the cerebellum, it has seemed reasonable to expect that Marr's theory predicts that a lesion of the

climbing fibers (by destroying the inferior olive) should not affect the memories of previous learning but should prevent all subsequent learning. Several studies have provided evidence that contradicts this prediction by showing that lesions of the inferior olive abolish the memory for previous learning (37, 38). Such observations have been interpreted as evidence that the memory is stored outside of the cerebellum and its effects are conveyed to the cerebellum via the climbing fiber system (6, 37).

If, however, spontaneous climbing fiber activity helps prevent saturation of LTD or LTP at gr→Pkj synapses, climbing fiber lesions should have profound effects on the memories for previous learning. Following the ideas presented in the section above, removal of climbing fibers should allow LTP to go unchecked at gr→Pkj synapses. This would allow gr→Pkj synapses only to increase in strength, perhaps eventually reaching their maximal possible level (Fig. 3, *blue panel*). This would increase ongoing Purkinje activity (as is seen with re-



versible inactivation of climbing fibers) and, more important, would erase the pattern of gr→Pkj synaptic weights that encode the memories for previous learning. In the extreme, if all gr→Pkj synapses are saturated at their maximal possible strength, all previously learned memories would be erased. Note that these ideas allow the possibility that the effects of these lesions could increase with time following the lesion. It is possible, though not demonstrated, that this may explain the variable effects that have sometimes been observed with inferior olive lesions (38, 39).

An Extended Theory of Cerebellar Motor Learning

In summary, we have systematically examined several key objections to Marr's seminal theory of cerebellar-mediated motor learning. In each case, we have argued that the data can be explained not by rejecting Marr's theory, but rather by adding new and specific features (Fig. 4). These extensions to the original theory suggest 1) that an additional site of plasticity exists in the cerebellar nuclei, 2) that LTD, with its observed timing, combines with time-varying activation of granule cells to mediate the timing of cerebellar-mediated learned responses, and 3) that spontaneous climbing fiber activity is self-regulated to a level that prevents, rather than causes, drift of gr→Pkj synaptic strengths. The specificity of Marr's theory makes it, like all good theories, open to experimental evaluation and, potentially, to criticism. We have argued that criticisms of Marr's theory have led to new experiments and new ideas that elaborate the propositions of the original work. This extended theory also makes many experimentally testable predictions (40).

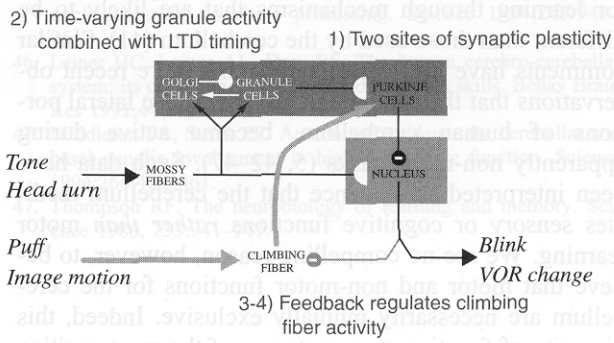


Fig. 4. A schematic representation of the extensions to Marr's theory suggested by recent data (*new features shown in blue*). *1*) The inability of cerebellar cortex lesions to produce complete abolition of previously learned responses can simply reflect an additional site of synaptic plasticity in the cerebellar nucleus. *2*) Interactions between persistent, time-varying granule cell activity with LTD obviates the apparent mismatch in the timing of stimuli required for learning and the timing of inputs required to induce LTD. These interactions may contribute to the appropriate timing of the learned responses. *3–4*) The regulation of spontaneous climbing fiber activity to an equilibrium level may help prevent, rather than cause, saturation of LTP or LTD at gr→Pkj synapses. The disruption of this equilibrium may explain the effects of climbing fiber lesions on the retention of previously learned responses.

Although our ideas address data apparently contrary to a role for the cerebellum in motor learning, it seems equally important to consider the conceptual limits of this hypothesis. Ideas like Marr's, for example, have been criticized because although cerebellar patients and experimental animals with cerebellar lesions show deficits in motor learning, they can show improvements in their movements (6). Observations like this undoubtedly reflect that other brain regions can also contribute to mo-

Fig. 3. A schematic representation of the pathways that could regulate spontaneous climbing fiber activity to an equilibrium (CF) at which LTD and LTP balance at gr→Pkj synapses. The circuits shown along the top row show how climbing fiber activity would be driven to the equilibrium level. The strength of the granule cell synapses onto Purkinje cells is coded by size; large synapses are strong, and small synapses are weak. The graph in the middle row shows hypothetical climbing fiber activity, whereas the lower graph shows the average strength of the gr→Pkj synapses.

Left panel (no background shading), shows the equilibrium level of spontaneous climbing fiber activity produces as much LTD as LTP at gr→Pkj synapses. Consequently, Purkinje, nucleus, and climbing fiber activity are relatively stable.

Middle left panel, If for some reason many gr→Pkj synapses were increased in strength, Purkinje cell and climbing fiber activity would be above equilibrium, and nucleus cell activity would be lower. The increased climbing fiber activity would lead to increased LTD relatively to LTP at gr→Pkj synapses. This would act to restore Purkinje and climbing fiber activity to the equilibrium level.

Middle right panel, If many gr→Pkj synapses were decreased in strength, climbing fiber activity would fall below equilibrium. This would lead to increased LTP relative to LTD at gr→Pkj synapses. Again, this would restore climbing fiber activity to the equilibrium level.

Right panel, If climbing fibers were silent, as with reversible cooling or with a lesion, LTP would occur at gr→Pkj synapses unopposed by LTD. This would cause gr→Pkj synapses to increase in strength gradually, perhaps eventually saturating at their maximal value.

The effects of these various events on the retention of memories are illustrated by assuming that the pattern of strengths at gr→Pkj synapses corresponds to the picture of Salvador Dali. Light pixels correspond to strong synapses, and dark pixels could correspond to weak synapses. Initially (*leftmost picture*), previous learning may have produced the particular pattern of strengths that encodes the Dali picture. When many synapses are increased in strength, the picture becomes lighter overall, but the pattern can remain if not too many synapses saturate at maximal strength. As synapses change to bring climbing fiber activity back into equilibrium, the picture darkens again, and the image remains relatively intact. The opposite events would happen if many synapses are decreased in strength. The darkened picture returns to near normal with little loss of information in the image. However, as shown in the rightmost image, with unregulated spontaneous climbing fiber activity (or none at all, as would be the case following a lesion of the inferior olive), gr→Pkj synapses would increase in strength. As more and more of them saturate at their maximal possible strength, the image is destroyed. Presumably, at this point there would be no further retention of the previously learned responses.

tor learning through mechanisms that are likely to be different than those used by the cerebellum (41). Similar comments have been prompted by the more recent observations that the cerebellum, especially the lateral portions of human cerebellum, become active during apparently non-motor tasks (5, 42–47). Such data have been interpreted as evidence that the cerebellum mediates sensory or cognitive functions *rather than* motor learning. We see no compelling reason, however, to believe that motor and non-motor functions for the cerebellum are necessarily mutually exclusive. Indeed, this diversity of function represents one of the most exciting aspects of current cerebellar research. The uniformity of the synaptic circuits displayed across the extent of the cerebellum suggests that whatever it is that the cerebellum computes, the computation is applied to all putative cerebellar functions (i.e., motor, cognitive, etc.). This leaves open the exciting possibility that the specific neural mechanisms of cerebellar information processing identified by studying motor learning, which is relatively tractable experimentally, can then become the foundation for a more concrete understanding of cerebellar, and perhaps non-cerebellar, mechanisms of cognitive processes.

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