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A Mathematical Model of the Cerebellar-Olivary System II: Motor Adaptation Through Systematic Disruption of Climbing Fiber Equilibrium

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Abstract. The implications for motor learning of the model developed in the previous article are analyzed using idealized Pavlovian eyelid conditioning trials, a simple example of cerebellar motor learning. Results suggest that changes in gr→Pkj synapses produced by a training trial disrupt equilibrium and lead to subsequent changes in the opposite direction that restore equilibrium. We show that these opposing phases would make the net plasticity at each gr→Pkj synapse proportional to the change in its activity during the training trial, as influenced by a factor that precludes plasticity when changes in activity are inconsistent. This yields an expression for the component of granule cell activity that supports learning, the across-trials consistency vector, the square of which determines the expected rate of learning. These results suggest that the equilibrium maintained by the cerebellar-olivary system must be disrupted in a specific and systematic manner to promote cerebellar-mediated motor learning.

Keywords: eyelid conditioning, Purkinje, nictitating, LTP, LTD

In the preceding article we used a mathematical model to study how the synaptic organization of the cerebellar-olivary system (cerebellum and climbing fiber inputs from the inferior olive) influences plasticity at granule cell to Purkinje cell (gr→Pkj) synapses in the cerebellar cortex. The results suggest that the plasticity observed empirically at these synapses—they decrease in strength when active during climbing fiber input (long-term depression, LTD) and increase when active without a climbing fiber input (LTP) (Ekerot and Kano, 1985; Hirano, 1990; Ito and Kano, 1982; Kano and Kato, 1988; Linden et al., 1991; Sakurai, 1987, 1989; Salin et al., 1996; Schreurs and Alkon, 1993; Shibuki and Okada, 1992)—maintains an equilibrium level of climbing fiber activity at which LTD and LTP balance and the expected net change in the weights of gr→Pkj synapses is zero (Kenyon et al., 1997). Here, we consider how motor learning may be affected by a self-regulating equilibrium of climbing fiber activity.

The cerebellum is clearly important for the appropriate execution of movements as revealed by the severe motor impairments associated with cerebellar pathology (Dow and Moruzzi, 1958; Gilman et al., 1981) and by the numerous examples of motor deficits produced by experimental manipulations of the cerebellum (McCormick and Thompson, 1984a, 1984b; Nagao, 1983; Optican and Robinson, 1980; Robinson, 1976; Thach et al., 1992; Westheimer and Blair, 1973; Zee et al., 1981). Recently, doubts regarding the role of the cerebellum in motor function have stemmed from studies implicating cerebellar involvement in nonmotor tasks (Bracke-Tolkmitt et al., 1989; Fiez et al., 1992; Ivry et al., 1988; Kim et al., 1994; Leiner et al., 1991; Middleton and Strick, 1994). Although the question of motor and nonmotor roles for the cerebellum is

sometimes portrayed as an either/or issue (Gao et al., 1996), there is no compelling reason to believe that they are mutually exclusive. Since the regularity of the cerebellum's synaptic organization suggests that all regions perform a common computation, the application of this computation to both motor and nonmotor behaviors seems neither implausible nor inconsistent with current data. Indeed, this potential versatility represents an especially exciting aspect of current cerebellar research. The specific mechanisms of cerebellar information processing—which may be most easily identified by studying movements—may also provide inroads into a deeper understanding of the mechanisms of cognitive processes.

Many theories have attempted to relate the anatomy and physiology of the cerebellum to different aspects of sensory-motor function (Bloedel, 1992; Bower and Kassel, 1990; Bullock et al., 1994; Fujita, 1982; Gao et al., 1996; Gilbert, 1974; Ito, 1982; Kawato and Gomi, 1992; Llinas and Welsh, 1993; Moore et al., 1989; Pellionisz and Llinas, 1980; Sejnowski, 1977; Thach et al., 1992; Thompson, 1986). One influential class of theories suggests that the cerebellar-olivary system contributes to motor learning. These theories share basic features that were originally proposed by Marr (1969) and Albus (1971): (1) stimuli that precede movements are encoded by mossy fiber driven patterns of activity in specific subsets of cerebellar granule cells, (2) climbing fiber inputs to Purkinje cells are activated by movement errors and as such signal the need for adaptation of the recently executed movement, (3) gr→Pkj synapses that are coactive with the climbing fiber input are modified in strength such that subsequent movements under the same circumstances are improved. In support of these features, results from several preparations indicate that gr→Pkj synapses undergo climbing fiber-dependent LTD (Ito, 1989; Linden et al., 1991; Sakurai, 1987) and that several forms of motor learning, including Pavlovian eyelid conditioning (McCormick and Thompson, 1984a, 1984b; Perrett et al., 1993; Perrett and Mauk, 1995; Thompson, 1986), adaptation of the vestibular-ocular reflex (VOR) (du Lac et al., 1995; Ito, 1982; Lisberger, 1988; Nagao, 1983; Raymond et al., 1996; Robinson, 1976), and learning of wrist movements (Gilbert and Thach, 1977; Thach, 1980; Thach et al., 1992), depend on the cerebellum in a manner consistent with these theories.

There is not, however, complete agreement regarding role of the cerebellum in motor learning (Bower and Kassel, 1990; De Schutter, 1995; Llinas and Welsh, 1993; Pellionisz and Llinas, 1980; Houk and Wise, 1995). There even remain debates about the primary lesion, stimulation, and recording data that support a role for the cerebellum in motor learning (Kelly et al., 1990; Welsh and Harvey, 1989). Although these debates are beyond the scope of this article, the present analysis is motivated in part by a number of the empirical observations and conceptual arguments that identify apparent inconsistencies with basic aspects of cerebellar motor learning theories. These potential problems have been addressed to varying degrees by certain cerebellar models, but no single model addresses all criticisms. We do not attempt an exhaustive review of these models but only touch on representative examples to highlight the potential problems of existing motor learning theories of cerebellar function. Also, analysis of both eyelid conditioning and adaptation of the vestbulo-ocular reflex indicate that plasticity can occur in both the cerebellar cortex and nuclei (see Raymond et al., 1996; Mauk, 1997). Here, we focus only on the contributions of plasticity in the cerebellar cortex.

One argument relates to an array of difficulties posed by the spontaneous activity of climbing fibers (Keating and Thach, 1995). Although the original Marr/Albus theories did not address spontaneous climbing fiber activity, with the addition of such activity these theories appear to predict that all gr→Pkj synapses will saturate at maximum (Marr) or minimum (Albus) values, which would preclude the possibility for storing motor memories. It is also unclear how the occasional error-evoked climbing fiber inputs can convey information against a background of the more abundant spontaneous inputs. Gilbert (1975) addressed this issue by assuming that LTD only persists when its induction occurs during a noradrenergic input. However, this idea is directly contradicted by numerous *in vitro* LTD studies (see Ito, 1989).

Another criticism relates to the inability of most cerebellar theories to explain bidirectional adaptation of movements, which is required to explain the ability of the VOR to both increase or decrease in gain, and by the ability of Pavlovian eyelid responses to be acquired and extinguished. Although ignored by the Marr and Albus theories, this issue was addressed by more recent models that employ bidirectional plasticity controlled by the level of climbing fiber activity. For example, both Fujita (1982) and Sejnowski (1977) assume that gr→Pkj synapses decrease in strength when active during climbing fiber activity above a critical

level and increase in strength when active during lower levels of climbing fiber activity. It is clear how movement errors could drive climbing fiber activity above the critical value, which would lead to acquisition or increased amplitude/gain of the response. However, neither model specifies how spontaneous climbing fiber activity could fall below the critical value to permit extinction or decreased amplitude of the movement. Moreover, neither model specifies how the climbing fiber activity remains at the critical value, which is essential for maintaining the present pattern of synaptic weights when movements do not require adaptation.

In general, an inability to explain how synaptic weights remain constant when movements are appropriate is a weakness of all cerebellar motor learning models. As noted above, some models touch on this issue by assuming plasticity does not occur when climbing fiber activity is at a critical level, although how this level is maintained is not specified. Alternatively, some models employ the biologically unrealistic simplification that activity is limited to discrete "learning" and "retention or readout" periods (for example, Bullock et al., 1994). Plasticity controlled by error signals is only operable during the learning phase, and the effects of this plasticity are subsequently probed in the readout phase without affecting synaptic weights. This ensures that changes in synaptic weights will reliably survive until the readout phase and thus ensures the stability in the pattern of synaptic weights encoding memories.

However, the cerebellum represents a system in which the assumptions that both activity and plasticity are limited to discrete learning periods are untenable. Evidence indicates that LTD and LTP at gr→Pkj synapses is activity dependent; synapses are eligible to change only when they are active (for example, Linden and Connor, 1993). Given the variety of stimuli that can activate mossy fibers (Bloedel and Courville, 1981), it seems likely that there is always a nonzero amount of mossy fiber input to the cerebellum and that there is always a subset of granule cells that is active at any given time. Thus, activity-dependent plasticity suggests that there are ongoing opportunities for plasticity at these synapses and that stability in the pattern of synaptic weights encoding memories cannot arise from a lack of such opportunities. We suggest that realistic attempts to understand or model the cerebellum must apply the same rules for plasticity at all times and must consider the ongoing activity of cerebellar neurons.

Another apparent problem that has not been addressed by theories of the cerebellum relates to the discrepancy between the rate of induction of LTD and the rate of acquisition of cerebellar-mediated responses. Although LTD can be induced *in vitro* in six paired presentations of transmitter and postsynaptic depolarization intended to mimic a climbing fiber response (Linden and Connor, 1993), the acquisition of Pavlovian eyelid responses generally requires more than 100 training trials. If LTD is a putative mechanism of motor learning, how can this discrepancy be explained?

Finally, in attempting to address certain limitations, many models have departed from the direct, neuron-based language that contributed to the elegance of the Marr/Albus theories. The rules for plasticity at gr→Pkj synapses were stated in terms of the local and immediate effects that synaptic inputs produce, without assuming critical intermediate steps. For example, Albus assumed that gr→Pkj synapses decrease in strength when coactive with a climbing fiber input. In contrast, many of the more recent models employ less direct language in which critical intermediate steps are assumed but are not specified in biological terms. For example, both Fujita (1982) and Sejnowski (1977) assume gr→Pkj synaptic changes are related to climbing fiber activity that is different from a critical level, but it is not clear how gr→Pkj synapses could detect such changes.

Here we extend the analysis presented in the preceding article to address the criticisms outlined above with a "continuous activity" model that acknowledges spontaneous climbing fiber activity and uniformly applies the same plasticity rules at all times. The model builds on the preceding results in which (1) plasticity rules are stated in terms of local and direct effects of synaptic inputs and (2) climbing fiber activity is regulated by the cerebellar-olivary system to an equilibrium at which gr→Pkj synaptic weights undergo no net changes (Kenyon et al., 1997). Using a simple representation of Pavlovian eyelid conditioning, we show how error-evoked climbing fiber inputs can be detected against a background of spontaneous inputs, how this spontaneous climbing fiber activity can be increased or decreased to produce acquisition or extinction, respectively, and how the rate of motor learning should be significantly slower than the rate of LTD induction. Thus, our results suggest that cerebellar-mediated motor learning can be understood in terms of the conditions under which cerebellar-olivary equilibrium must be disrupted: (1) conditioning trials disrupt climbing fiber equilibrium and induce plasticity at gr→Pkj synapses, (2) this initiates a second phase of plasticity

after the trial that restores equilibrium, and (3) the net effect of these two phases allows learning to occur only when the climbing fiber equilibrium is repeatedly disrupted during a pattern of granule cell activity that is relatively consistent from one trial to the next. These processes cast new light on many of the apparent problems of motor learning theories of cerebellar function.

Methods

Results from Previous Model

In the preceding article (Kenyon et al., 1997), we developed a mathematical model of the cerebellar-olivary system using discrete time steps of duration Δt, corresponding to the time over which a climbing fiber input can induce LTD in coactive grPkj synapses. For completeness, the basic mathematical formalism and main results of this analysis are summarized here (Fig. 1B).

The activity of a Purkinje cell, denoted by P_{pc} and defined as the number of spikes per time step, is assumed to be a function of the linear sum of its active inputs weighted by the strength of each synapse. Thus,

$$P_{\text{pc}} = \sum_{i=1}^{m} P_i w_i, \tag{1}$$

where P_i represents the background likelihood of activity and w_i the synaptic weight of the ith gr→Pkj synapse, m gives the total number of such synapses, and the weights are scaled such that $0 \leq P_{\text{pc}} \leq 1$. Similarly, the activity of the associated climbing fiber, denoted by P_{cf}, is given by the sum of its input from cerebellar output, P_{pc}, and its input related to the unconditioned stimulus in eyelid conditioning, E_{US}, such that

$$P_{\text{cf}} = P_{\text{pc}} + E_{\text{US}}. \tag{2}$$

Plasticity at gr→Pkj Synapses

Based on empirical evidence, gr→Pkj synapses are assumed to display LTD in which the synapses decrease in strength when active with a climbing fiber input and LTP in which they increase in strength when active in the absence of a climbing fiber input. As in the preceding article, this plasticity can be expressed by an equation of the form

$$\Delta w_i = P_i(\delta^+ + \delta^-)\left[P_{\text{cf}}^{(\infty)} - P_{\text{cf}}\right], \tag{3}$$

in which δ^- and δ^+ are constants that represent the step decreases and increases in w_i resulting from LTD and LTP events, respectively, and $P_{\text{cf}}^{(\infty)}$ denotes the equilibrium level of climbing fiber activity,

$$P_{\text{cf}}^{(\infty)} = \delta^+/(\delta^+ + \delta^-), \tag{4}$$

at which the effects of LTD and LTP balance. For convenience, the time step Δt is taken to reflect the duration of influence of a single climbing fiber input to a Purkinje cell.

Climbing Fiber Equilibrium

The analysis described in the preceding article suggests that these forms of LTD/P combine with the synaptic organization of the cerebellar-olivary system to regulate spontaneous climbing fiber activity to the equilibrium level, $P_{\text{cf}}^{(\infty)}$. Since, the effects of LTD and LTP would balance at this level of climbing fiber activity, both spontaneous Purkinje cell and climbing fiber activity would also remain at their respective equilibrium levels. The preceding results also suggest that any perturbation of this equilibrium results in net changes in gr→Pkj synapses that restore climbing fiber and Purkinje cell equilibrium.

Mathematical Representation of Pavlovian Eyelid Conditioning

Although we expect the present results to apply to other forms of cerebellar-mediated motor learning (Raymond et al., 1996), we make use of the relatively direct association between the stimuli used in Pavlovian eyelid conditioning and the input/output pathways of the cerebellum (Fig. 1). As shown in Fig. 1A, eyelid conditioning typically involves the paired presentation of a conditioned stimulus (for example, a tone) with an unconditioned stimulus (puff of air to the eye). Under appropriate conditions, repeated presentation of these conditioned stimulus + unconditioned stimulus trials promotes the acquisition of conditioned eyelid responses that are elicited by the conditioned stimulus (Gormezano et al., 1962), as also shown in Fig. 1A. A number of laboratories have provided evidence that the conditioned stimulus is conveyed to the cerebellum via mossy fibers (Lewis et al., 1987; Solomon et al., 1986; Steinmetz et al., 1985, 1986, 1987, 1988), the unconditioned stimulus by climbing

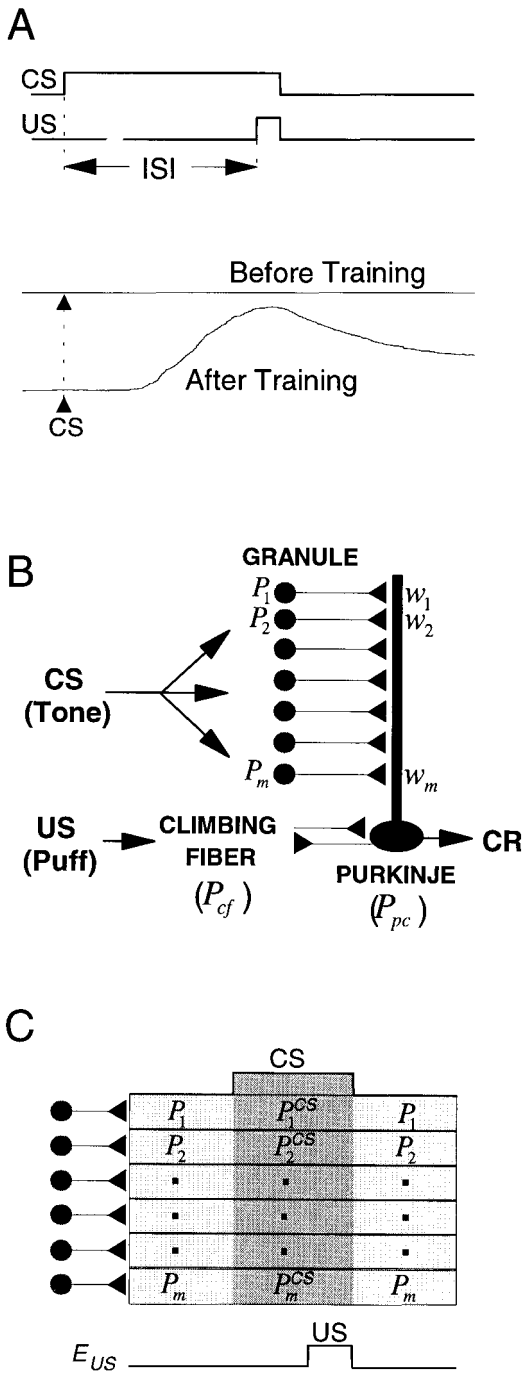

Figure 1. The relationships between eyelid conditioning, the synaptic organization of the cerebellum, and their mathematical representation in the present model. A. Eyelid conditioning involves the paired presentation of a conditioned stimulus, such as a tone, with a unconditioned stimulus, such as a puff of air in the eye. Under appropriate circumstances, the presentation of many such trials promotes the acquisition of a conditioned eyelid response. B. Simplifications of the synaptic organization of the cerebellum employed in the fibers (Mauk et al., 1986; McCormick et al., 1985), and that cerebellar output drives the expression of conditioned responses (McCormick and Thompson, 1984a). This is most directly demonstrated by studies in which normal conditioning occurs when the conditioned stimulus and unconditioned stimulus are replaced by direct stimulation of mossy fiber and climbing fiber pathways, respectively (Steinmetz et al., 1989).

Given these relationships between the mossy fiber inputs and the conditioned stimulus, climbing fiber inputs and the unconditioned stimulus, and the output of the cerebellum and the expression of conditioned responses, eyelid conditioning can be represented relatively simply in the present model (Fig. 1B). As illustrated schematically in Fig. 1C, the presentation of a conditioned stimulus and the corresponding activation of certain mossy fibers can be represented by activity in granule cells that may be different from the background activity. Thus, through the activation of mossy fibers, the conditioned stimulus is assumed to change the activity of the ith granule cell from P_i to $P_i^{(CS)}$, and thus the granule cell activity vector during the conditioned stimulus, $\vec{P}^{(CS)}$, may be distinct from the background activity vector $\vec{P}$. Unconditioned stimulus presentations can be represented by transiently assigning a positive value to E_{US}, which briefly increases the activity of the climbing fiber (Fig. 1C). Finally, since Purkinje cells inhibit the output cells of the cerebellar nuclei, a decrease in Purkinje activity during the conditioned stimulus can be taken as a measure of the magnitude of the conditioned response. Evidence suggests that this pattern and timing of stimuli is common to other forms

the analysis. Since increased cerebellar output appears the to drive expression of conditioned eyelid responses and since Purkinje cells inhibit the output cells (not shown), we assume that decreases in Purkinje cell activity produce conditioned responses. Moreover, since cerebellar output also inhibits climbing fibers, we have simplified the pathway between the Purkinje cells and climbing fibers, which contains two inhibitory synapses in series, to a simple excitatory connection. The stimuli used in eyelid conditioning are conveyed to the cerebellum via two cerebellar afferents—the unconditioned stimulus via climbing fibers, which project to the Purkinje cells, and the conditioned stimulus via mossy fibers, which make excitatory connections onto the granule cells. C. The present analysis ignores the mossy fiber synapses onto granule cells and simply assumes that the conditioned stimulus can alter granule cell activity. Each of the m granule cells is assumed to have a background level of activity P_i and a potentially different activity during the conditioned stimulus $P_i^{(CS)}$. Each granule cell contacts the Purkinje cell with a strength or weight w that can change when the synapse is active depending on the presence or absence of the climbing fiber input (see text).

of cerebellar motor learning such as VOR adaptation (Raymond et al., 1996).

Results

Eyelid Conditioning Trials Initiate Two Phases of Plasticity

To analyze the expected consequences of eyelid conditioning trials on the cerebellar-olivary system, we first consider the effects of a conditioned stimulus + unconditioned stimulus trial on a single gr→Pkj synapse. With the simplifying assumption that the unconditioned stimulus reliably elicits a climbing fiber input ($P_{\mathrm{cf}} = 1$ during the unconditioned stimulus), Eq. (3) describing the expected change in synaptic weights becomes

$$\Delta w_i^{(\mathrm{CS})} = -P_i^{(\mathrm{CS})}(\delta^+ + \delta^-)\left[1 - P_{\mathrm{cf}}^{(\infty)}\right], \quad (5)$$

where $\Delta w_i^{(\mathrm{CS})}$ is the change in synaptic weight of the ith synapse during the conditioned stimulus + unconditioned stimulus trial. Using Eq. (4) to substitute for $P_{\mathrm{cf}}^{(\infty)}$, Eq. (5) simplifies to

$$\Delta w_i^{(\mathrm{CS})} = -\delta^- P_i^{(\mathrm{CS})}, \quad (6)$$

showing that each synaptic weight is expected to decrease to the extent that it is active during the conditioned stimulus, which is simply a stochastic expression of the plasticity rule proposed by Albus (1971).

Since gr→Pkj synaptic weights can only decrease in strength if they are active during the conditioned stimulus, and remain unchanged if they are not, Eq. (6) shows that the conditioned stimulus + unconditioned stimulus trial will necessarily disturb the Purkinje cell and climbing fiber equilibria existing before the trial. Both Purkinje cell and climbing fiber activity will be lower than their equilibrium levels since the reduction in some gr→Pkj synaptic weights will decrease the sum of the synaptic inputs ($\sum P_i w_i$) below equilibrium. This implies that (1) a second phase of plasticity occurs *after* each conditioned stimulus + unconditioned stimulus trial during which synaptic weights increase according to their background activity until equilibrium is restored, and (2) the effects of a conditioned stimulus + unconditioned stimulus trial can be understood in terms of the net difference between these two phases, as is shown schematically in Fig. 2. Since this renormalization of synaptic weights will occur over time, we

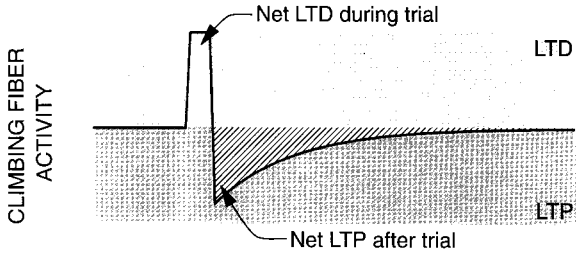

Figure 2. Paired conditioned stimulus + unconditioned stimulus trials disrupt the climbing fiber equilibrium existing before the trial and promote two phases of plasticity. The gr→Pkj synapses active during the trial undergo net LTD due to the increase in climbing fiber activity produced by the unconditioned stimulus. This decreases climbing fiber activity below equilibrium after the trial. During this phase gr→Pkj synapses undergo net LTP according to their background activity until climbing fiber equilibrium is restored.

let $\Delta w_i^{(R)}$ denote the total change in synaptic weight during the return to climbing fiber equilibrium, such that

$$\Delta w_i^{(R)} = \sum_{t_n} \Delta w_i(t_n), \quad (7)$$

where the sum is over all time steps following the conditioned stimulus + unconditioned stimulus trial. From our general expression for LTD/P (Eq. (3)), this sum is given by

$$\Delta w_i^{(R)} = -P_i \sum_{t_n} (\delta^+ + \delta^-)\left[P_{\mathrm{cf}}(t_n) - P_{\mathrm{cf}}^{(\infty)}\right], \quad (8)$$

where $P_{\mathrm{cf}}(t_n)$ denotes climbing fiber activity as a function of time after the conditioned stimulus + unconditioned stimulus trial. Equation (8) shows that during return to equilibrium the total change in the weight of each synapse is a function of its background activity and a sum that is the same for all synapses. Thus, letting this sum be denoted as x, Eq. (8) can be written more simply as

$$\Delta w_i^{(R)} = x P_i. \quad (9)$$

During return to equilibrium the change in background synaptic input to the Purkinje cell produced by the conditioned stimulus + unconditioned stimulus trial is reversed (that is, $\Delta \sum P_i w_i^{\mathrm{CS}} = -\Delta \sum P_i w_i^{(R)}$). This equality permits a solution for x in terms of P_i and $P_i^{(\mathrm{CS})}$, such that Eq. (9) becomes

$$\Delta w_i^{(R)} = \delta^- s P_i, \quad (10)$$

where s is given by

$$s = \frac{\sum P_j P_j^{(CS)}}{\sum P_j^2}. \tag{11}$$

The expected net change in synaptic weights produced by both phases of plasticity ($\Delta w_i^{(net)}$) is then given by combining Eqs. (6) and (10):

$$\Delta w_i^{(net)} = \delta^- \left[s P_i - P_i^{(CS)} \right]. \tag{12}$$

Equation (12), which is the main result of this section, shows that grPkj synaptic weights generally decrease when they are more active than normal during the conditioned stimulus and increase when less active during the conditioned stimulus. However, this relationship is modified by the factor s, the implications of which we consider next.

Net Plasticity is Selectively Sensitive to the Across-Trials Consistency of Granule Activity

Any form of Pavlovian conditioning requires a degree of across-trials consistency in the neural activity elicited by the conditioned stimulus. Conditioning would clearly be retarded or prevented should the conditioned stimulus activate a different subset of synapses each trial. With no background activity the expected change in the strength of the ith synapse produced by a conditioned stimulus + unconditioned stimulus trial would be related to its conditioned stimulus activity, P_i^{CS}, which is also a reasonable definition of the across-trials consistency for that synapse. With the arguments that follow we suggest that the expected change in synaptic weights during conditioning indicated by Eq. (12) represents a more general expression for across-trials consistency necessitated by the presence of background activity. In particular, the term s prevents learning when there is no consistency but when the conditioned stimulus produces an overall change from background in the number of active granule cells.

To illustrate this we use the hypothetical scatter plot shown in Fig. 3A in which the conditioned stimulus activity for each synapse, $P_i^{(CS)}$, is plotted as a function of its background activity P_i. This scatter plot illustrates three points. First, the term s from Eq. (12) defines the slope of the least-squares linear regression line that is constrained to pass through the origin. Second, for any given value of background activity P_i, the corresponding y-axis value of the point on the regression line (the term sP_i in Eq. (12)) is proportional to the amount of LTP that a synapse with that background activity will contribute to the plasticity that restores climbing fiber equilibrium (Fig. 3A, dotted arrow). The slope term would be relatively high for large amounts of gr→Pkj activity during the conditioned stimulus, indicating that a relatively large amount of LTD was induced during the trial, there was a relatively large displacement of climbing fiber activity away from equilibrium, and therefore a relatively large amount of LTP will be required to return to equilibrium. Whatever the total amount of LTP required to restore equilibrium, it will be distributed across synapses according to their background activities, as reflected by the line described by s. Third, the difference between each point and the corresponding point on the regression line (Fig. 3A, solid arrow) represents the amount of net plasticity for that synapse, and thus the conditionability of a conditioned stimulus is related to the sum of these vertical distances over all synapses. Therefore, synapses whose conditioned stimulus and background activities place them above the line with slope s will undergo more LTD during the trial than LTP during return to equilibrium (lighter region in Fig. 3B). Conversely, those below the line will undergo less LTD than subsequent LTP (darker region in Fig. 3B).

Figure 3 illustrates that the expected net changes in synaptic weights produced by a conditioned stimulus + unconditioned stimulus trial are related to the across-trials consistency of the granule cells activated by the conditioned stimulus. With perfect across-trials consistency the subset of granule cells activated by the conditioned stimulus is identical each trial, which means that each $P_i^{(CS)}$ is either zero or one. In contrast, it is more difficult to define precisely the complete lack of across-trials consistency. Although without background activity across-trials consistency is related to the conditioned stimulus activity (P_i^{CS}), with background activity, across-trials consistency is presumably related in some way to the differences between background and conditioned stimulus activities for each synapse. For example, a synapse that is always active during the conditioned stimulus (perfect across-trials consistency without background activity) could not make a significant contribution to a conditioned response if its background activity is equally high. This suggests the possibility that difference between background and conditioned stimulus activity ($P_i - P_i^{(CS)}$)

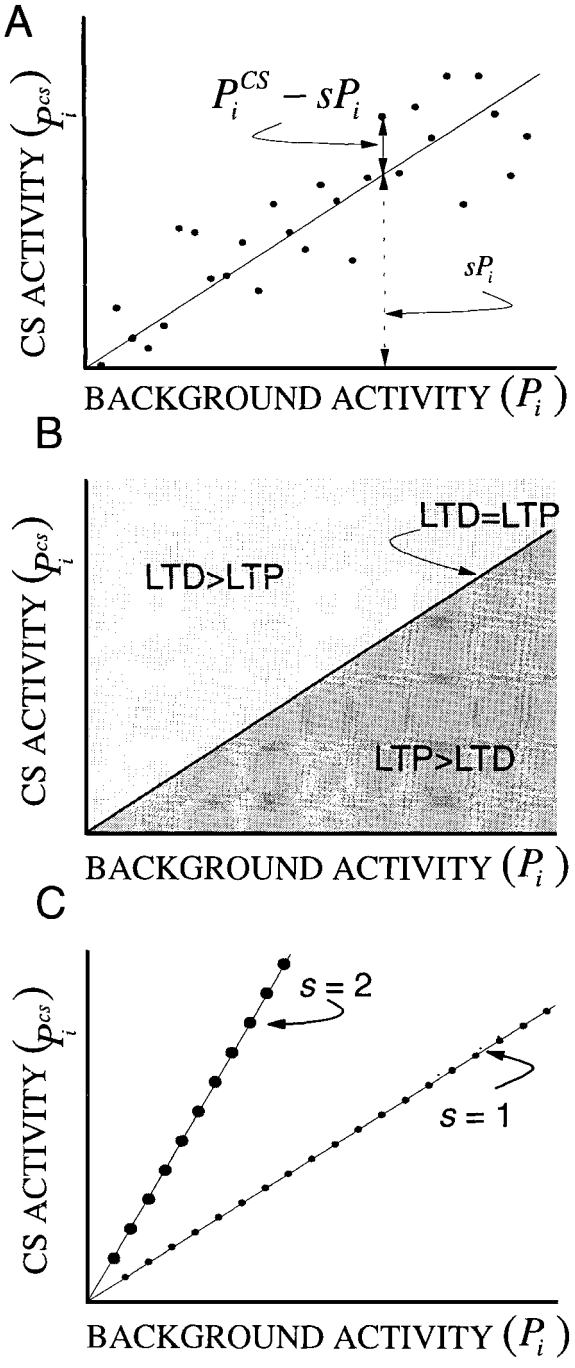

Figure 3. A graphical view of Eq. (12) and its relationship to across-trials consistency of the granule cells activated by the conditioned stimulus. Each graph shows a hypothetical scatter plot in which the probability of conditioned stimulus-evoked activity for each synapse ($P_i^{(CS)}$) is plotted as a function of its probability of background activity (P_i). A. An example showing a nonzero amount of across-trials consistency. The line represents the least squares regression line described by the points and constrained to pass through the origin. The slope of this line is the term s from Eq. (12). As also implied by Eq. (12), the conditioned stimulus activity for each synapse can be decomposed into two components. First, the expected activity during the conditioned stimulus, given the background activity of the synapse and the behavior of all other synapses, is the height of the regression line for that level of background activity (sP_i, dotted arrow). This also corresponds to the amount of net LTP that a synapse with that background activity will undergo during return to equilibrium. Second, the distance from the regression line ($P_i^{(CS)} - sP_i = P_i^{(atc)}$, solid arrow) represents both the difference between the actual and expected conditioned stimulus-related activities and the amount of net plasticity expected for that synapse. B. Since the line passing through the origin and with slope s represents the activities for which LTD during a conditioned stimulus + unconditioned stimulus trial is exactly reversed by LTP during return to equilibrium, (1) all synapses whose activity falls above the line (lighter shading) will decrease in strength since LTD is expected to be greater than LTP, and (2) all synapses whose activity falls below the line (darker shading) will increase in strength since LTP exceeds LTD. C. Two examples of zero across-trials consistency. The small dots illustrate the situation in which the conditioned stimulus related activity $P_i^{(CS)}$ is the same as the background activity P_i for all synapses ($s = 1$). The large dots illustrate a situation in which the conditioned stimulus increases the activity of all synapses by the same factor (that is, doubles), such that the predicted conditioned stimulus related activity sP_i equals the actual activity $P_i^{(CS)}(s = 2)$. In both cases the amount of LTD expected during the conditioned stimulus + unconditioned stimulus trials is equal to the expected amount of LTP during the subsequent return to equilibrium.

may approximate the degree of across-trials consistency. However, the apparent importance of the term s in Eq. (12) is that a simple "activity difference" rule can inappropriately predict across-trials consistency when the conditioned stimulus changes the overall number of granule cells that are active. Consider an example in which the conditioned stimulus activates a random subset of granule cells each trial (that is, no consistency), yet makes twice as many cells active as during background. This is the situation shown in Fig. 3C (larger dots). The overall increase in granule cell activity would make each $P_i^{(CS)}$ greater than its associated P_i, despite the absence of across-trials consistency. In this case the "activity difference" rule would indicate a high degree of conditionability. By adding the slope term s to the activity difference rule, Eq. (12) compensates for such changes in the overall granule cell activity.

In summary, conditioned stimulus activity is comprised of two components that correspond respectively to the two phases of plasticity initiated by a conditioned stimulus + unconditioned stimulus trial. The term $P_i^{(CS)}$ in Eq. (12) represents the granule cell activity that leads to LTD during the trial and sP_i represents the activity

associated with the net LTP during the return to equilibrium. The difference, which we call the across-trials consistency, $P_i^{(\mathrm{atc})}$, represents the component of the conditioned stimulus granule cell activity that is associated with the *net* changes in synaptic weights produced by a conditioned stimulus + unconditioned stimulus trial and the subsequent return to equilibrium. Thus, we can write the conditioned stimulus related activity, summed over all granule cells, as the sum of two components,

$$\vec{P}^{(\mathrm{CS})} = \vec{P}^{(\mathrm{atc})} + s\vec{P} \tag{13}$$

When the conditioned stimulus-evoked granule cell activity $\vec{P}_i^{(\mathrm{CS})}$ is the same as that component that is increased in strength during return to equilibrium ($s\vec{P}$), then the across-trials consistency is zero, and no learning is expected (as illustrated in Fig. 3C). In the next section we illustrate further that it is the across-trials consistency component $\vec{P}_i^{(\mathrm{atc})}$ that contributes to the acquisition of conditioned responses.

Acquisition and Extinction

Here we illustrate how acquisition and extinction of conditioned responses are influenced by the two phases of plasticity and by the across-trials consistency of the gr→Pkj synapses activated by the conditioned stimulus. Since evidence indicates that conditioned responses are elicited by increases in the appropriate cerebellar nucleus cells (McCormick and Thompson, 1984a) and since Purkinje cells inhibit nucleus cells, the decrease in Purkinje cell activity during the conditioned stimulus can be taken as a convenient measure of conditioned responses. Thus, we define the term $R = P_{\mathrm{pc}}^{(\infty)} - P_{\mathrm{pc}}^{(\mathrm{CS})}$, where $P_{\mathrm{pc}}^{(\infty)}$ is the equilibrium activity of the Purkinje cell and $P_{\mathrm{pc}}^{(\mathrm{CS})}$ is the Purkinje activity during the conditioned stimulus. For simplicity we make four assumptions: (1) the initial values of the synaptic weights are such that there is no change in Purkinje cell activity during the conditioned stimulus and thus no conditioned response (that is, initially $R = 0$), (2) the strength of the unconditioned stimulus is initially such that a climbing fiber input is reliably activated (initially $P_{\mathrm{cf}}^{(\mathrm{CS+US})} = 1$), (3) conditioned stimulus-related granule cell activity is different from background activity in a manner that makes across-trials consistency nonzero ($\vec{P}^{(\mathrm{atc})} \neq 0$) and (4) the time between conditioned stimulus + unconditioned stimulus trials is sufficient to restore equilibrium.

Figure 4 illustrates the processes predicted to occur during conditioned stimulus + unconditioned stimulus training under these conditions (see the appendix for mathematical details). The filled circles in Fig. 4A are a conventional representation of the acquisition and extinction curves (the expected magnitude of R) during simulated conditioned stimulus + unconditioned stimulus acquisition (left half of figure), and conditioned stimulus-alone extinction training (right half). The acquisition curve shows a negatively accelerating increase in R that is qualitatively similar to acquisition curves observed in eyelid conditioning (Gormezano et al., 1962). The extinction curve is also qualitatively similar to empirically observed extinction curves. For comparison, the expected climbing fiber activity elicited during the trial is shown by the filled circles in Fig. 4B. Each conditioned stimulus + unconditioned stimulus trial produces a transient increase in climbing fiber activity due to the presentation of the unconditioned stimulus.

One useful feature of this mathematical analysis is the ability to plot a continuous representation of the conditioned response expected had the conditioned stimulus been presented at any given time, as is shown in the solid trace in Fig. 4A. This continuous display of R illustrates that through the induction of LTD, each conditioned stimulus + unconditioned stimulus trial elicits a step increase in the magnitude of the expected conditioned response (see inset, Fig. 4A). This LTD also produces a step decrease below equilibrium in the probability of a climbing fiber input (Fig. 4B). As seen in Fig. 4B, and shown in more detail in the insets, there follows a second phase of plasticity during which net LTP restores climbing fiber equilibrium. During return to equilibrium the expected magnitude of the conditioned response (R) declines. These two phases of the expected amplitude of R illustrate the relative contributions to conditioned responses made by the two components of conditioned stimulus-activated granule cell activity as described in the previous section (that is, $\vec{P}^{(\mathrm{CS})} = s\vec{P} + \vec{P}^{(\mathrm{atc})}$). The LTD induced at gr→Pkj synapses active during the conditioned stimulus ($\vec{P}^{(\mathrm{CS})}$) produces the step increase in R and the step decrease in climbing fiber activity. The subsequent reduction of R during return to climbing fiber equilibrium is produced by net LTP at the gr→Pkj synapses proportional to the background activity ($s\vec{P}$). Thus, the *net* change in R is due to *net* LTD produced by the difference of these two components ($\vec{P}^{(\mathrm{atc})}$), which is related to the across-trials consistency of the granule

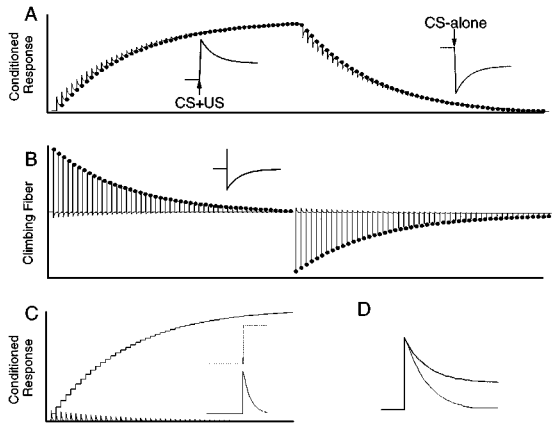

Figure 4. The role of across-trials consistency in the acquisition and extinction of Pavlovian conditioned responses. A. A measure of the conditioned amplitude R is plotted as a function of repeated conditioned stimulus + unconditioned stimulus training trials. The dots indicate the conditioned response expected during the presentation of each conditioned stimulus + unconditioned stimulus training trial and as such represent a conventional representation of acquisition and extinction curves. The curves exhibit the negatively accelerating changes in responding that are observed empirically. The curves between the dots show a continuous representation of the conditioned response amplitude had the conditioned stimulus been presented at that time. This trace illustrates that during acquisition (left half of figure) each trial is associated with two phases of plasticity: (1) an LTD-dominated phase during the conditioned stimulus + unconditioned stimulus presentation that produces a step increase in the expected amplitude of the conditioned response and (2) a subsequent LTP-dominated phase in which climbing fiber equilibrium is restored and in which the conditioned response can be partially or fully extinguished. The inset on the left shows this behavior more clearly for one conditioned stimulus + unconditioned stimulus trial. Conditioned stimulus-alone extinction trials (right half of figure) exhibit a complementary series of events. B. A plot of climbing fiber activity, P_{cf}, during the same acquisition and extinction training. Each conditioned stimulus + unconditioned stimulus training trial elicits (1) a brief increase in climbing fiber activity due to the unconditioned stimulus, (2) a subsequent decrease in activity below the equilibrium level due to the net LTD induced at gr→Pkj synapses during the trial, and (3) a subsequent return to equilibrium due to net LTP at certain gr→Pkj synapses. The inset shows these three phases more clearly for a single trial. Following the trial, P_{cf} returns to $P_{\mathrm{cf}}^{(\infty)}$ with an exponential time course. As acquisition proceeds the step increase in climbing fiber activity due to the unconditioned stimulus decreases because of the response-related inhibition from the cerebellum (modeled here as a decrease in excitation). The right side of the figure again shows the complementary processes that occur during extinction. There is a transient decrease below equilibrium during the trial due to the response-related inhibition of climbing fibers that is unopposed by the excitatory drive from the unconditioned stimulus. C. The contributions from $s\vec{P}$ and $\vec{P}^{(\mathrm{atc})}$ are plotted separately as a function of training trials. The partial extinction of conditioned responses following each paired trial is due entirely to net LTP produced in synapses according to the contribution from $s\vec{P}$, whereas the contribution from $\vec{P}^{(\mathrm{atc})}$ is unaffected by the return to equilibrium. The inset shows the separate contributions from $\vec{P}^{(\mathrm{atc})}$ and $s\vec{P}$ at an expanded time scale for a single trial. D. The increase in the conditioned response for a single trial is shown for a case with zero (dotted) and nonzero (solid) across-trials consistency. With no across-trials consistency the increase in the expected magnitude of the conditioned response produced by the conditioned stimulus + unconditioned stimulus trial is completely reversed by the subsequent LTP that returns climbing fiber activity to equilibrium. With nonzero across-trials consistency the return to equilibrium only partially reverses the increase in the expected conditioned response.

cells activated by the conditioned stimulus. This is shown in Fig. 4C where the contributions to R made by $s\vec{P}$ and $\vec{P}^{(\mathrm{atc})}$ have been plotted separately (again, a convenience permitted by the mathematical model). During the return to equilibrium the contribution of $s\vec{P}$ is completely reversed, while the contribution due to $\vec{P}^{(\mathrm{atc})}$ is unchanged. In the absence of across-trials consistency, the entire step increase in R produced by the conditioned stimulus + unconditioned stimulus trial would be completely reversed during the return to equilibrium (since $\vec{P}^{(\mathrm{CS})} = s\vec{P}$), and there would be no increase in conditioned responding (Fig. 4D). These results again illustrate that the across-trials consistency vector of gr→Pkj activity, $\vec{P}^{(\mathrm{atc})}$ determines the net amount of learning produced by conditioned stimulus + unconditioned stimulus trials.

Although these two phases of plasticity are repeated each conditioned stimulus + unconditioned stimulus trial throughout acquisition, the unconditioned stimulus-evoked increase in climbing fiber activity decreases, as does the step increase in conditioned response magnitude (Figs. 4B and 4A, respectively). These decreases are due to the response-related inhibition in climbing fiber activity during the unconditioned stimulus. As the conditioned response-related increase in cerebellar output (here a decrease in Purkinje activity) increases during acquisition, the ability of the unconditioned stimulus to activate climbing fibers decreases and the rate of further acquisition slows. This illustrates that the excitatory drive from the unconditioned stimulus is effectively canceled by the decreased Purkinje cell activity during the conditioned stimulus. This is consistent with evidence that the unconditioned stimulus-evoked climbing fiber responses decrease as conditioned responses are acquired (Sears and Steinmetz, 1991). Thus, inhibitory feedback from the cerebellum to the climbing fibers (see Fig. 1B) can explain (1) the negatively accelerating acquisition curves observed in eyelid conditioning, as has been previously

suggested (Donegan et al., 1989; Sears and Steinmetz, 1991), and (2) the attenuation of climbing fiber activity as movement performance improves (Gilbert and Thach, 1977; Thach, 1980). These processes also illustrate that once acquisition is complete, climbing fiber activity is in equilibrium during background and during the conditioned stimulus + unconditioned stimulus trial, despite the excitatory influence of the unconditioned stimulus on the climbing fibers.

The right halves of Figs. 4A and 4B illustrate that the processes predicted to occur during conditioned stimulus-alone extinction training are identical to those of acquisition, but opposite in polarity. Early in extinction training, climbing fiber activity is less than equilibrium during the conditioned stimulus-alone trial (Fig. 4B, right side). This is the result of the conditioned response-related increase in inhibition of climbing fibers during the conditioned stimulus (modeled here as a decrease in excitation) that is no longer opposed by the excitatory drive from the unconditioned stimulus. Since climbing fiber activity is no longer in equilibrium during the conditioned stimulus, gr→Pkj synapses must undergo net LTP to restore equilibrium. Thus, each conditioned stimulus-alone trial produces a step decrease in R that is partially reversed after the trial to restore equilibrium during background (see inset, right half of Fig. 4A). These processes continue until climbing fiber activity is again in equilibrium both during the conditioned stimulus and during background. These results indicate the importance of response-related inhibition of climbing fibers in extinction. Without the response-related inhibition, climbing fiber activity could not fall below equilibrium in the absence of the unconditioned stimulus, net LTP would not occur, and extinction would not be possible.

Across-Trials Consistency Determines the Magnitude of Synaptic Changes and the Rate of Learning

The above results demonstrate that the across-trials consistency vector $\vec{P}^{(\mathrm{atc})}$ represents the only component of the granule cell representation of the conditioned stimulus that contributes to the acquisition of conditioned responses. It follows that the magnitude of $\vec{P}^{(\mathrm{atc})}$ should determine the rates of acquisition and extinction. In the absence of background activity, across-trials consistency for each synapse is its conditioned stimulus-related activity (P_i^{CS}) and the rate of learning is proportional to the sum of the squares of the conditioned stimulus activities. This can be shown by defining a conditioned response as the change in conditioned stimulus-related Purkinje cell activity ($P^{\mathrm{CR}} = \Delta P_{\mathrm{pc}}^{\mathrm{CS}}$) and combining the expression for synaptic weight changes ($\Delta w_i^{\mathrm{CS}} = -\delta^- P_i^{\mathrm{CS}}$) with the expression for Purkinje activity during the conditioned stimulus ($P_{\mathrm{pc}}^{\mathrm{CS}} = \sum P_i^{\mathrm{CS}} w_i$). This yields the expression for the amount of learning produced each trial:

$$\Delta P_{\mathrm{pc}}^{\mathrm{CS}} = -\delta^- \sum \left(P_i^{\mathrm{CS}}\right)^2. \tag{14}$$

Here we show that with background activity the same general result applies; the rate of learning is proportional to the square of the across trials consistency vector ($(\vec{P}^{\mathrm{atc}})^2 = \sum (P_i^{\mathrm{atc}})^2$). Figure 5 shows that the predicted rate of acquisition is related to across-trials consistency as described by the term

$$\beta = \frac{|\vec{P}^{(\mathrm{atc})}|}{|\vec{P}|}, \tag{15}$$

where β represents a scalar measure of the magnitude of $\vec{P}^{(\mathrm{atc})}$ relative to the magnitude of the background activity vector $\vec{P}$. Using R as a measure of the amplitude of conditioned responses, acquisition curves for several values of β are shown in Fig. 5. Results demonstrate that the rate of acquisition increases as a function of β^2. Indeed, it is possible to show (see appendix) that in the linear model the number of trials to approach asymptotic response levels, denoted by N_{CR}, is given

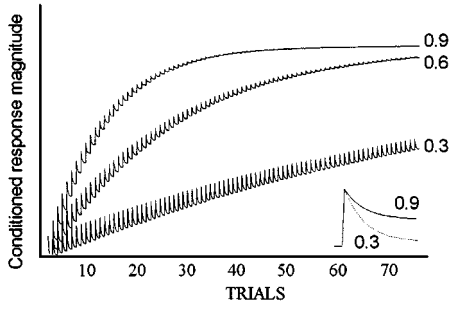

Figure 5. The role of across-trials consistency in the number of trials to acquire conditioned responses. Acquisition, as measured by R, is plotted as a function of the number of training trials for three values of β (.3, .6, .9). The inset shows that the step increase in responding is the same for high and for low values of β. Rather, β influences the extent to which the plasticity/responses induced during the trial are reversed during return to equilibrium.

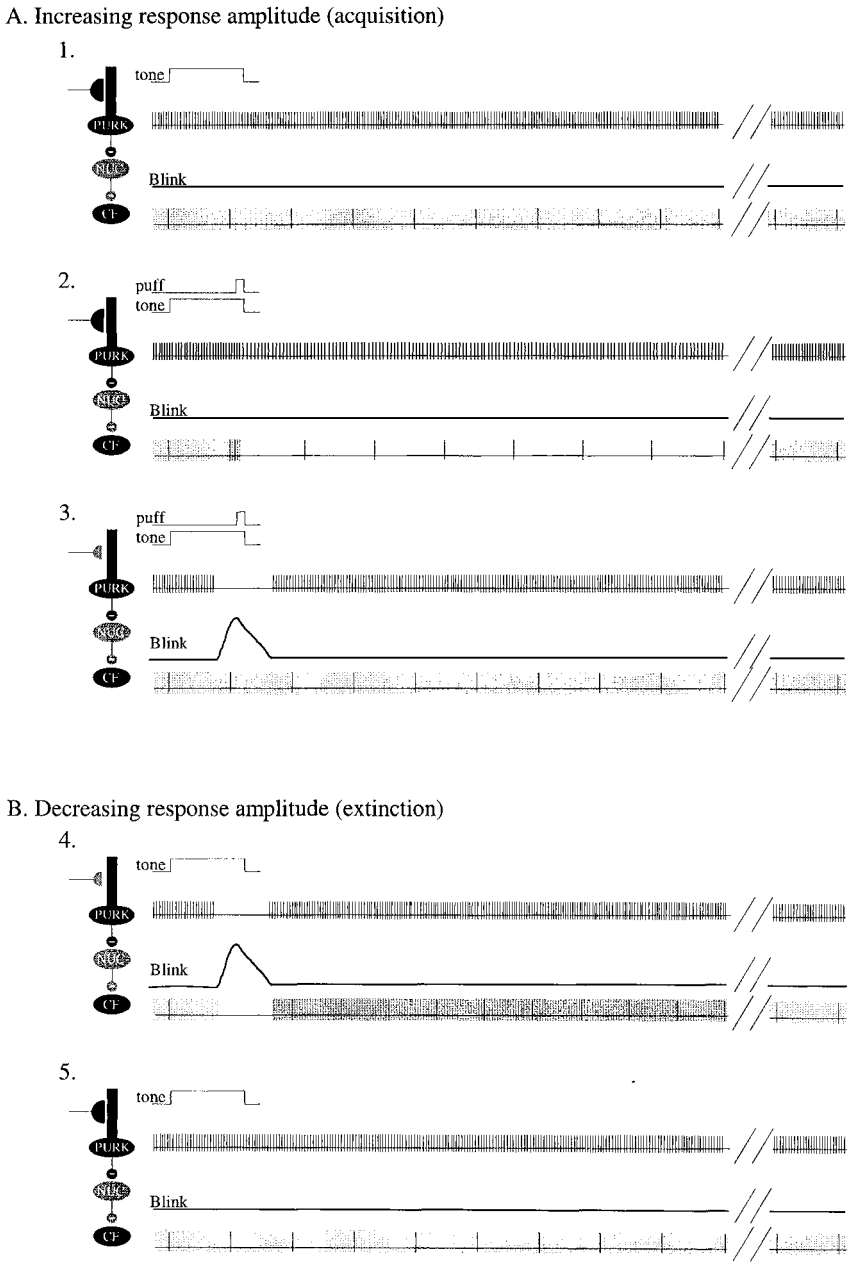

Figure 6. A summary diagram showing predicted changes in neural activity during acquisition and extinction training. Idealized representations of neural activity are shown to the right of the corresponding neuron in the simplified circuit diagram. In the circuit diagrams, the nucleus cells are shown in gray to highlight that their influence was modeled as a virtual excitatory connection between Purkinje cells and climbing fibers. For the climbing fiber activity shown at right, light gray shading depicts equilibrium activity, wherease darker gray denotes activity above equilibrium, and no shading denotes subequilibrium activity. A. The events predicted to occur during acquisition training are shown in panels A1 through A3. (1) Before training, presentation of a tone conditioned stimulus (stimulation protocol illustrated at top of figure) produces no effect on either Purkinje cell or climbing fiber action potential activity. (2) Paired presentation of tone and a reinforcing unconditioned stimulus produces an increase in climbing fiber activity during the unconditioned stimulus. Owing to the LTD induced by this trial, there follows a period during which both climbing fiber activity and Purkinje cell activity may be at times reduced below equilibrium levels. The magnitude of this reduction, which depends both on the number of gr→Pkj synapses active during the tone as well on the overlap between synapses active during the tone and the period following the tone, has been exaggerated for clarity. Eventually, gr→Pkj synaptic weights increase in proportion to their background activity until equilibrium is restored. (3) When conditioned responses have been acquired, climbing fiber activity remains in

by

$$N_{CR} = \frac{N}{\beta^2}, \tag{16}$$

where N denotes the number of time steps to restore equilibrium (see preceding article).

As in Fig. 4, Fig. 5 shows a continuous representation of R, depicting the conditioned response expected should the conditioned stimulus be presented at any given time. This trace illustrates that the step increase in conditioned responses elicited by paired conditioned stimulus + unconditioned stimulus trials at the beginning of training is independent of β. Instead, Eq. (6) suggests that the amplitude of this step is determined by the total conditioned stimulus-related activity ($\vec{P}^{CS}$) and by the amplitude of LTD events (δ^-). Thus, the larger number of trials to acquire with smaller values of β is not due to a decrease in the magnitude of plasticity induced by conditioned stimulus + unconditioned stimulus trials; rather, it reflects that more of the plasticity is erased during the return to equilibrium.

This analysis also demonstrates that the amount of across-trials consistency influences the average change in gr→Pkj synaptic weights required to produce a criterion or asymptotic level of conditioned responses. With high across-trials consistency, where gr→Pkj synapses reliably signal the conditioned stimulus, the changes in gr→Pkj synaptic weights required to produce a given increase in R are relatively small compared to lower levels of across-trial consistency. As across-trials consistency decreases—either because each synapse signals the conditioned stimulus less reliably or because there are fewer synapses whose activity is consistently altered by the conditioned stimulus or both—each synaptic weight must change by a greater amount to produce the same conditioned response. In the biologically realistic case where synaptic weights are bounded (that is, there are maximum and minimum values) decreasing amounts of across-trials consistency also affects the maximum level that R can reach (Medina and Mauk, 1995). This limit would be imposed by the inability of synaptic weights to obtain the extreme values required to produce conditioned responses given the low degree of across trials consistency.

Discussion

Results of the preceding article paper suggest that spontaneous climbing fiber activity may be regulated to an equilibrium level at which LTD and LTP balance at gr→Pkj synapses, and the net plasticity at each synapse is zero independent of its activity. Here we have examined the consequences of this equilibrium on cerebellar-mediated motor learning using an idealized representation of Pavlovian eyelid conditioning. The main results are that eyelid conditioning trials may disrupt cerebellar-olivary equilibrium and in doing so elicit two competing phases of plasticity. The net effects of these two phases would make the conditioning-induced changes in synaptic weights selectively sensitive to the consistency from one trial to the next in the gr→Pkj synapses activated by the conditioned stimulus. Thus, the systematic disruption of cerebellar-olivary equilibrium required for conditioning is comprised of two components: (1) nonequilibrium climbing fiber activity and (2) granule cell activity that is sufficiently consistent from one trial to the next. For eyelid conditioning these conditions occur during acquisition training when a conditioned stimulus precedes an unexpected unconditioned stimulus and during conditioned stimulus-alone extinction training when the conditioned stimulus predicts an expected unconditioned stimulus that is omitted.

Studies of both eyelid conditioning and of VOR adaptation have provided evidence that plasticity can occur in both the cerebellar cortex and cerebellar nuclei during motor learning. For example, previously learned changes in the gain of the VOR can be partially retained following lesions of the vestibular cerebellum. Similarly, lesions of the cerebellar cortex have on partial effects on the expression of previously learned eyelid responses. Specifically, cerebellar cortex lesions

←

equilibrium during the tone (due to increased climbing fiber inhibition associated with expression of the response) as well as before and after the tone. B. The events predicted to occur during extinction training are shown in panels B4 to 5. (4) In a well trained animal, presentation of a tone-alone extinction trial brings climbing fiber activity below equilibrium during the expression of the response. The reduction, which reflects the response-related inhibition of climbing fibers in the absence of the unconditioned stimulus, induces LTP at gr→Pkj synapses. In a manner similar to acquisition training, this produces a tendency for increased climbing fiber activity (above equilibrium) for a period following the trial. (5) As extinction training continues and the LTP reduces response amplitude, climbing fiber activity again returns to being in equilibrium, before, during, and after the trial.

have been shown to abolish the learned timing and to decrease the amplitude of conditioned eyelid responses. The implications of these sorts of observations on the relative contributions of plasticity at gr→Pkj synapses in the cerebellar cortex and mossy fiber to nucleus cell synapses in the cerebellar nuclei have been reviewed recently (Raymond et al., 1996; Mauk, 1997; Mauk and Donegan, 1997). Despite, this evidence for at least two sites of plasticity in the cerebellum, the purpose of the present analysis was to obtain a better understanding of the contribution of plasticity in the cerebellar cortex and of processes modulating the activity of climbing fibers. Preliminary analyses indicate suggest that the results presented here apply with or without nucleus plasticity and are not qualitatively affected by interactions with plasticity processes in the cerebellar nuclei (see Medina and Mauk, 1995).

Conditioned Stimulus + Unconditioned Stimulus Trials Produce Two Phases of Plasticity

Our results suggest that the effects of training can be understood in terms of the net difference between two phases of plasticity—the LTD induced during the conditioned stimulus + unconditioned stimulus trial, which disrupts equilibrium and initiates a second phase in which synapses undergo net LTP to restore equilibrium. Similarly, our results predict that a conditioned stimulus-alone extinction trial should produce the opposite effects—LTP during the trial and subsequent net LTD to restore equilibrium. Our results also suggest that the net difference makes plasticity at gr→Pkj synapses sensitive to the across-trials consistency of the conditioned stimulus-evoked granule cell activity. With no across-trials consistency, the changes induced during the trials are reversed during return to equilibrium. These processes are similar to those that presumably occur with spontaneous climbing fiber inputs or with unconditioned stimulus-alone trials. Each climbing fiber input induces LTD at the synapses that happen to be active at that time, and this disrupts climbing fiber equilibrium. However, since these synapses are as equally likely to undergo LTP during the return to equilibrium, the expected net change for each synapse is zero.

These results suggest an explanation for the slow rate of cerebellar-mediated motor learning relative to the rate of induction of LTD. These rates should be the same only when the conditioned stimulus elicits granule cell activity with perfect across-trials consistency. We have shown that the rate of learning should fall rapidly as across-trials consistency decreases. Since perfect across-trials consistency seems extremely unlikely, a rate of learning that is slower than the induction of LTD is expected from our results.

Within the context of our model, conditioning involves synapses that both decrease and increase in strength. Just as the expression of conditioned responses requires that some conditioned stimulus-activated synapses have decreased in strength, maintaining equilibrium requires that other synaptic weights increase. This may have important implications for studies attempting to measure or image training-induced plasticity at gr→Pkj synapses. Any technique that averages changes over many synapses may not report plasticity since there should be as many changes in one direction as changes in the other.

Cerebellar-Olivary Equilibrium and Motor Learning

The functionally important role for spontaneous climbing fiber activity suggested by our results highlights the value of considering the cerebellum as well as its inputs and outputs as a complete system. Considered in isolation, the spontaneous activity of climbing fibers, as well as the ongoing opportunities for activity-dependent plasticity at gr→Pkj synapses, appear to represent serious faults of the Marr/Albus theories. However, together these features may perform an important function by preventing unwanted synaptic changes when movements do not require adaptation.

One way to view the implications of our results is that motor learning represents a special case of returning to climbing fiber equilibrium. The stimulus patterns that promote acquisition or extinction simply impose an additional equilibrium constraint on the cerebellum. In acquisition, the unconditioned stimulus produces an above equilibrium level of climbing fiber activity during granule cell activity that is consistently different from background. Synapses change to achieve climbing fiber equilibrium, both during the conditioned stimulus + unconditioned stimulus trial and during background activity. The result of acquisition then is that climbing fiber activity is in equilibrium during the trial despite the unconditioned stimulus-evoked excitatory drive on the climbing fibers. This is consistent with the finding that unconditioned stimulus-evoked climbing fiber activity decreases as conditioned responses are acquired (Sears and Steinmetz, 1991) and with learning theories that are based on modulations

of unconditioned stimulus effectiveness (Rescorla and Wagner, 1972). Extinction can also be seen as a return to equilibrium when an expected unconditioned stimulus is withheld and response-related inhibition decreases climbing fiber activity below equilibrium during the conditioned stimulus. We suggest that by maintaining climbing fiber equilibrium the cerebellum keeps responses the same except under two conditions—when a conditioned stimulus reliably predicts an unexpected unconditioned stimulus (acquisition) and when the conditioned stimulus reliably predicts an expected unconditioned stimulus that is withheld (extinction).

Limitations of Cerebellar Models of Motor Learning

As discussed in the introduction, the present analysis was motivated in part by apparent limitations of cerebellar motor learning models. In particular, our results suggest that spontaneous climbing fiber activity is not incompatible with cerebellar motor learning but rather is necessary to maintain the pattern of synaptic weights in the presence of ongoing background activity while allowing reversible motor adaptation. We have shown, using empirically derived plasticity rules expressed in terms of the direct, local effects of synaptic inputs, how movement errors can be encoded by the probabilities of climbing fiber inputs that are different from an equilibrium probability. Moreover, results from the preceding article suggest that climbing fiber activity is self-regulated to the equilibrium probability, which was a gratuitous assumption of previous models. In addition, our results suggest how less than perfect across-trials consistency in the granule cells activated by a conditioned stimulus can explain the discrepancy between the number of training trials required to promote conditioned responses and the number of conjunctive inputs required to induce LTD at gr→Pkj synapses. In summary, our results show how the response-related inhibition of climbing fibers represents a mechanism that (1) helps regulate spontaneous climbing fiber activity to an equilibrium level that prevents unwanted drift or saturation of synaptic weights and (2) allows climbing fiber activity to fall below equilibrium when movements need to be decreased or extinguished. These key features have not been addressed by previous models of cerebellar motor learning.

Temporal Aspects of Learning Models

Models of Pavlovian learning have been divided into three broad categories: trials-level, temporal, and real-time models (see Gluck et al., 1990). Trials-level models treat the conditioned stimulus as a unitary event and consider only the net effects of each trial. Temporal models include factors that address the limited range of interstimulus intervals that promote conditioning (the ISI function), and real-time models also address the timing or temporal properties of conditioned responses. In this respect, the present model is a trials-level analysis, although we have reported preliminary computer simulation results from a real-time extension of this model (Medina and Mauk, 1995). Although our results do not directly address temporal and real-time issues, the effects of gr→Pkj across-trials consistency on learning may relate relatively directly to the ISI function, as has been suggested previously (Buonomano and Mauk, 1994; Mauk and Donegan, in press; Perrett et al., 1993). For eyelid conditioning, acquisition occurs for ISIs between about 80 and 2000 ms. Since our results suggest that acquisition is sensitive to the across-trials consistency of granule cell activity, variation in this consistency during the conditioned stimulus represents a possible mechanism for the ISI function. Results from previous computers simulations are consistent with this idea (Buonomano and Mauk, 1994).

Our approach suggests another distinction in categorizing models that we might call discrete activity versus continuous activity. We suggest that discrete-activity models are those that exclusively consider events activated by the conditioning trials and exclude consideration of activity or plasticity between trials. In contrast, continuous activity models acknowledge both activity and the opportunity for plasticity between trials and apply the same rules for plasticity at all times. In this respect, the present analysis is a continuous-activity model. We adopted this approach due to likelihood that the activity evoked by the conditioned stimulus and unconditioned stimulus represents a vanishingly small percentage of total cerebellar activity.

Empirically Testable Predictions

The main prediction of the present article is that as a function of motor learning, those Purkinje cells that receive climbing fiber inputs activated by movement errors should show training induced decreases in simple spike activity. Although training-dependent decreases in simple spike activity have been observed during the learning of wrist movements (Thach, 1980) and during eyelid conditioning (Berthier and Moore, 1986; Gould and Steinmetz, 1996; McCormick and Thompson, 1984a), increases in simple spike activity

have also been observed during eyelid conditioning (Gould and Steinmetz, 1996). Since conditioned "eyelid" responses include movements of the head and neck, one explanation relates to the likelihood that many Purkinje cells could be contributing to these responses. For example, conditioned responses include head movements away from the side to which the unconditioned stimulus is applied. Thus one key electrophysiological criterion required for our predictions is that the target Purkinje cell must receive input from a climbing fiber that is activated by the unconditioned stimulus. For example, the Purkinje cell recordings presented by Thach and colleagues in the context of wrist movement adaptation met this criterion.

Our results also suggest that there may be certain differences in the induction of LTD and LTP using *in vivo* versus *in vitro* preparations. The induction of LTD *in vivo* is similar to the events putatively associated with acquisition; certain granule cells are stimulated consistently in the presence of above equilibrium levels of climbing fiber activity. Our results predict that climbing fiber activity will be below equilibrium following the induction stimulation, and thus there should occur a period in which synapses increase in strength according to their background activity until equilibrium is restored. Thus, we expect that when induced *in vivo*, LTD should partially reverse. Although this has not been systematically tested, some previous results appear to be consistent with this prediction (Ekerot and Kano, 1985; Ito and Kano, 1982; Kano and Kato, 1988). This prediction does not apply to *in vitro* studies, since there should be no spontaneous climbing fiber activity. Similarly, our results also suggest that it should be difficult to induce LTP at gr→Pkj synapses *in vivo* since the stimulation-induced parallel fiber activity will occur during spontaneous climbing fiber activity regulated to the equilibrium level. Thus, to induce LTP *in vivo*, it may be necessary to produce a temporary block of spontaneous climbing fiber activity.

There are a number of unique predictions of our model that relate to the expected effects of disrupting the equilibrium level of climbing fiber activity. Since our results suggest that an equilibrium level of climbing fiber activity can prevent unwanted drift of synaptic weights to maximum or minimum values, prolonged disruption of climbing fiber equilibrium should abolish the memory for previously learned responses with a time course that parallels the drift of synaptic weights to saturated values. This prediction is significant because the abolition of learned responses by a climbing fiber lesion has at times been used as evidence that the memory for motor learning is conveyed to the cerebellum via climbing fiber inputs (see Llinas et al., 1975). Indeed, the time-dependent nature of this prediction may explain the discrepant results obtained with lesions of the inferior olive made after initial eyelid conditioning. McCormick et al. (1985) found that rabbits retain conditioned eyelid responses after a climbing fiber lesion, but that the responses extinguish with further conditioned stimulus + unconditioned stimulus training—as if the unconditioned stimulus was no longer effective. In contrast, Yeo et al. (1986) found that lesions of the inferior olive abolish the previously learned eyelid responses. Our results suggest that observations can be explained by different delays between the lesion and testing. However, since plasticity is activity dependent, even the ambient noise levels in the home cages could influence how rapidly responses are abolished following the lesions.

Our results also yield the novel prediction that temporary disruption of the inhibition of climbing fibers by cerebellar output should prevent the extinction of conditioned responses. Disrupting this inhibition should prevent climbing fiber activity from falling below equilibrium and thus prevent the induction of net LTP that our results suggest is necessary for response extinction. This disruption might be accomplished several ways, including infusion of a GABA antagonist into the inferior olive or a local anesthetic into the anterior interpositus or red nuclei. However, as above, if the infusion is sufficiently prolonged, our results predict that it would eventually abolish the retention of previously learned responses.

Generalization to Other Response Systems

Although we have used eyelid conditioning as a model for cerebellar motor learning in the present analysis, recent results suggests that eyelid conditioning reveals processes that generalize to other forms of cerebellar motor learning. For example, cerebellar-dependent adaptation of the VOR involves patterns of cerebellar inputs that parallel those for eyelid conditioning (Raymond et al., 1996). When mossy fiber vestibular input—which is analogous to a conditioned stimulus—reliably predicts greater than equilibrium climbing fiber activity due to slip of the image across the retina (unconditioned stimulus) then the gain of the VOR is increased (analogous to the conditioned response). If

conditions subsequently change and the VOR gain is too high, then the head turn predicts less than equilibrium climbing fiber activity and return to equilibrium involves changes in the VOR gain in the opposite direction. However, it remains to be determined whether cerebellar inhibition of climbing fibers plays a role in adaptation of the VOR. Nonetheless, these similarities between eyelid conditioning and VOR adaptation suggest that our results may apply to other forms of cerebellar-mediated motor adaptation. Even though the parallels between eyelid conditioning and other nonmotor tasks that appear to engage the cerebellum are not yet clear, the homogeneous synaptic organization of the cerebellum suggests that the computation that the cerebellum contributes to each is similar. Thus, our results may also help provide a better understanding of the cerebellum's role in these nonmotor tasks.

Appendix: Formal Expressions for the Acquisition and Extinction of Conditioned Responses

In this section, we derive formal expressions that describe the acquisition and extinction of conditioned responses predicted by the present model. To begin, we recapitulate some results from the previous paper showing that during normal background granule cell firing, climbing fiber activity returns to an equilibrium level, $P_{\mathrm{cf}}^{(\infty)}$, according to the equation

$$\Delta P_{\mathrm{cf}} = \frac{1}{N}\left[P_{\mathrm{cf}} - P_{\mathrm{cf}}^{(\infty)}\right], \tag{17}$$

where the number of time steps to relax to equilibrium is represented by the parameter N, given by

$$N = \frac{1}{\vec{P}^2(\delta^+ + \delta^-)}. \tag{18}$$

Due to the coupling between the Purkinje cell and the climbing fiber, under the same conditions of normal background activity the Purkinje cell will return to equilibrium according to an equation identical in form

$$\Delta P_{\mathrm{pc}} = -\frac{1}{N}\left[P_{\mathrm{cf}} - P_{\mathrm{cf}}^{(\infty)}\right]. \tag{19}$$

As described above, during acquisition training the climbing fiber approaches a state of equilibrium both in the presence and absence of paired conditioned stimulus + unconditioned stimulus presentations. Early in training, the climbing fiber responds strongly to paired conditioned stimulus + unconditioned stimulus presentations, but eventually these responses go to zero as training is completed. The process whereby the climbing fiber approaches equilibrium during conditioned stimulus + unconditioned stimulus presentations is mathematically identical to the analogous process in which the climbing fiber approaches equilibrium during normal background activity. The only difference is that during the conditioned stimulus + unconditioned stimulus trial, granule cell activity is given by $\vec{P}^{(\mathrm{CS})}$ rather than $\vec{P}$. This implies that we should make the substitution $\vec{P} \to \vec{P}^{(\mathrm{CS})}$ in the quantity N appearing in Eq. (18). However, we know that it is only the across-trials consistency vector, $\vec{P}^{(\mathrm{atc})}$, that contributes to the acquisition of conditioned responses, so that we must actually make the substitution $\vec{P} \to \vec{P}^{(\mathrm{atc})}$ in Eq. (18). The amplitude of the climbing fiber response to the successive conditioned stimulus + unconditioned stimulus trials, denoted by $P_{\mathrm{cf}}^{(\mathrm{CS+US})}$, therefore obeys the equation

$$\Delta P_{\mathrm{cf}}^{(\mathrm{CS+US})} = -\frac{\beta^2}{N}\left[P_{\mathrm{cf}}^{(\mathrm{CS+US})} - P_{\mathrm{cf}}^{(\infty)}\right], \tag{20}$$

where we assume that on the first trial $P_{\mathrm{cf}}^{(\mathrm{CS+US})} = 1$, $P_{\mathrm{pc}}^{(\mathrm{CS})} = P_{\mathrm{pc}}^{(\infty)}$, and β is given by Eq. (15). From Eqs. (2) and (20), the development of conditioned responses is then described by the equation

$$\Delta R = -\Delta P_{\mathrm{pc}}^{(\mathrm{CS})} = -\Delta P_{\mathrm{cf}}^{(\mathrm{CS+US})}. \tag{21}$$

Our results above showed that conditioned responses are acquired only to the component of $\vec{P}^{\mathrm{CS}}$ possessing finite across-trials consistency, $\vec{P}^{(\mathrm{atc})}$, whereas responses acquired to $s\vec{P}$ are extinguished during the return to equilibrium following each conditioned stimulus + unconditioned stimulus trail according to Eqs. (17) to (19). Defining the quantity α as

$$\alpha = \frac{|s\vec{P}|}{|\vec{P}|} = s, \tag{22}$$

the amplitudes of the responses acquired to $s\vec{P}$ for each trial are also given by Eqs. (20) and (21) but with the substitution $\beta \to \alpha$.

Finally, we note that the analogous expressions for the extinction of conditioned responses are identical to the expressions given above except that the initial conditions are such that $P_{\mathrm{pc}}^{(\mathrm{CS})} = P_{\mathrm{cf}}^{(\mathrm{CS+US})} = 0$.

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