Trying to Understand the Cerebellum Well Enough to Build One

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ABSTRACT: The development of an increasingly detailed computer simulation of the cerebellum is briefly described. Specific and relatively direct evaluation of the performance of this simulation is made possible by the straightforward way in which pavlovian eyelid conditioning engages the cerebellum. Inputs to the simulation are based on recordings of mossy fiber and climbing fiber responses to the stimuli used in eyelid conditioning, and the output of the simulation can be evaluated with respect to the extensively characterized behavioral properties of eyelid conditioning. Because construction of the simulation has been guided by a strong aversion to errors of commission, both failures and successes of the simulation have proven informative. The behavior of the simulation related to the inhibitory nucleo-olivary feedback connection and spontaneous activity of climbing fibers is described. A prediction of the simulation concerning extinction is confirmed by experiment.

KEYWORDS: cerebellum; extinction; eyelid conditioning; inferior olive; motor learning; Pavlov; rabbit; simulation

INTRODUCTION

The diversity of talks at a conference in St. Louis illustrates the variety of behaviors and neural processes to which the cerebellum is believed to contribute. Despite this variety there appears to be considerable uniformity of synaptic organization throughout all regions of the cerebellum.[1,2] For this reason it may be more productive to think of the cerebellum as having one function: it receives inputs, processes them according to the computation its synaptic organization supports, and sends the results to other brain regions. From this single computation, diversity of function arises from differences in what inputs encode and from differences in downstream targets. This view highlights the potential value of approaches characterizing the nature of the computation accomplished by the cerebellum.

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That such approaches are even possible is a tribute to the seminal work of Eccles, Ito, Szentàgothai, and many others who have provided a remarkably detailed characterization of the synaptic organization and physiology of the cerebellum.[1,2] With this advantage it should, in principle, be possible to accomplish for the cerebellum what Hodgkin and Huxley accomplished for the action potential.[3] It should be possible to understand the components of the cerebellum well enough to build one. Here we describe efforts to build a representation of the cerebellum in the computer, the ways in which the properties of pavlovian eyelid conditioning facilitate evaluation of cerebellar simulations, and the insights gained from a recent success of the simulation.

APPROACH TO AND SCOPE OF THE SIMULATIONS

During the development of the simulation we were mindful of the important distinctions between errors of omission and errors of commission.[4] Errors of omission refer to the unavoidable limitation that no simulation can contain the complete set of biological details at all levels. While errors of omission can cause a simulation to fail, this is simply part of the process of asking what set of details is required to produce certain capabilities. By contrast, errors of commission refer to the addition of unwarranted assumptions for which there is no independent evidence and whose inclusion is motivated primarily to allow a simulation to succeed in explaining only the phenomenon that the assumption was intended to explain. Thus, we suggest that the best we can do is to recognize errors of omission, while avoiding errors of commission at all cost. The latter is especially important since otherwise (1) the simulations cannot fail, (2) successes are only as informative as the hypothetical features that are added, and (3) the process is not a fair test of whether enough is known about the parts to explain the whole. By avoiding errors of commission, simulations can be informative with both their failures and their successes.

Building a computer simulation of the cerebellum is possible owing to the wealth of knowledge available for the anatomy and synaptic physiology of cerebellar neurons.[5,6] In our simulation, each cell is represented as a leaky integrate-and-fire neuron whose membrane potential is determined by both leak and synaptic conductances taken from available physiologic data. (See Ref. 6 for details.) The cells are interconnected with divergence and convergence ratios that closely conform to anatomic data, and connectivity in the cerebellar cortex is represented to respect the known two-dimensional geometry. The simulation incorporates plasticity at the granule cell-to-Purkinje cell (gr-Pkj) synapse.[7] As in early cerebellar models of motor learning,[2,8] the simulation incorporates long-term depression (LTD) at this synapse, as supported by a wealth of data.[2,9–15] In contrast to an early version of the simulation that included only LTD,[16] the current simulation also incorporates long-term potentiation (LTP) at the gr-Pkj synapse. Based on recent data,[17] the LTD and LTP in the simulation are mutually reversing. In the following sections, we describe how the incorporation of this bidirectional plasticity, together with the inhibitory nucleo-olivary connection, has greatly improved the performance of the simulation over that of its predecessor. In particular, we focus on a specific prediction that follows from the simulation regarding the extinction of conditioned eyelid responses (see below).

TESTING SIMULATIONS WITH PAVLOVIAN EYELID CONDITIONING

The properties of pavlovian eyelid conditioning provide us with a unique opportunity to test a simulation with realistic inputs, to compare outputs of the simulation to behavior, and to maintain close relations between simulations and experiments. In eyelid conditioning, rabbits are given repeated presentations of a neutral stimulus such as a tone paired with electrical stimulation of the periorbital muscles (or an airpuff to the eye), much in the way Pavlov originally conditioned his dogs to salivate to stimuli predicting food.[18] Initially, the tone or "conditioned stimulus" (CS) has no behavioral effect, whereas the stimulation or "unconditioned stimulus" (US) evokes a reflexive closure of the eyelids. With repeated pairings of the CS and US, the CS acquires the ability to evoke a conditioned eyelid response. If after acquisition the CS is repeatedly presented alone, the CS undergoes extinction, that is, it loses the ability to evoke conditioned responding. The wealth of parametric behavioral data on this form of associative learning[19] has made it a popular system for the neural analysis of learning. In particular, the learned timing of these responses[20–23] has proven to be especially informative about the cerebellar mechanisms that may be involved (FIG. 1).[5,6,24–29]

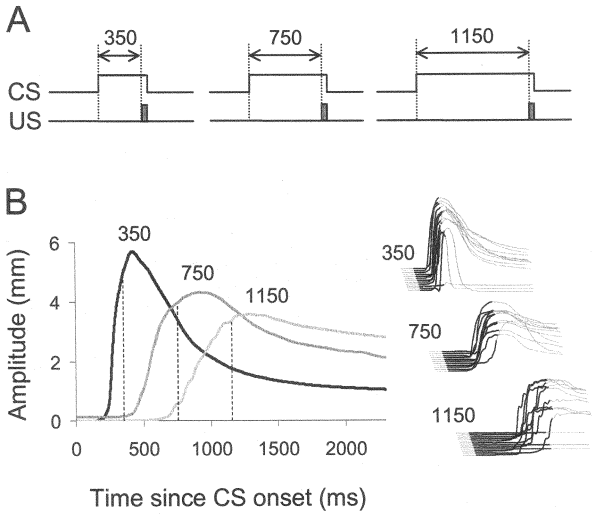

FIGURE 1. (**A**) Three conditioning protocols in which the conditioned stimulus (CS) duration (400, 800, and 1200 ms) and the interval between CS and unconditioned stimulus (US) onsets (350, 750, and 1,150 ms) are respectively varied. (**B**) Sample conditioned responses to auditory CSs from individual rabbits respectively trained on the protocols shown in **A**. (*Left)* Averages across 12 CS alone trials for each rabbit on the seventh day of training. (*Right)* Individual sweeps from which the average data were obtained. Note the sensitivity of the timing of the conditioned response to variation in the CS-US interval. (See Refs. 5, 6, and 24–29 for the role of the cerebellar cortex in response timing.) *Dark lines* indicate the presence of the CS.

For simulations, the key advantage of eyelid conditioning stems from evidence indicating the relatively direct relations between (1) the stimuli used in eyelid conditioning and afferent inputs to the cerebellum, and (2) output from the anterior interpositus nucleus of the cerebellum and the expression of the conditioned responses. These relations make it possible to provide inputs to the simulation and to test the outputs against the well-characterized behavioral properties of eyelid conditioning. Inputs to the simulation are taken from published peri-stimulus histograms of tone-elicited mossy fiber activity[30] and US-elicited climbing fiber responses.[31] Evidence from recording, stimulation, and lesion studies indicates that activation of certain cells in the anterior interpositus nucleus is responsible for driving the expression of the responses.[32,33] The output of the simulation can therefore be evaluated with respect to the behavioral properties of eyelid conditioning. Thus, our goal is to understand how the cerebellum takes a particular pattern of mossy and climbing fiber inputs and transforms them into the specific pattern of nucleus cell output that generates the conditioned eyelid response (FIG. 2).

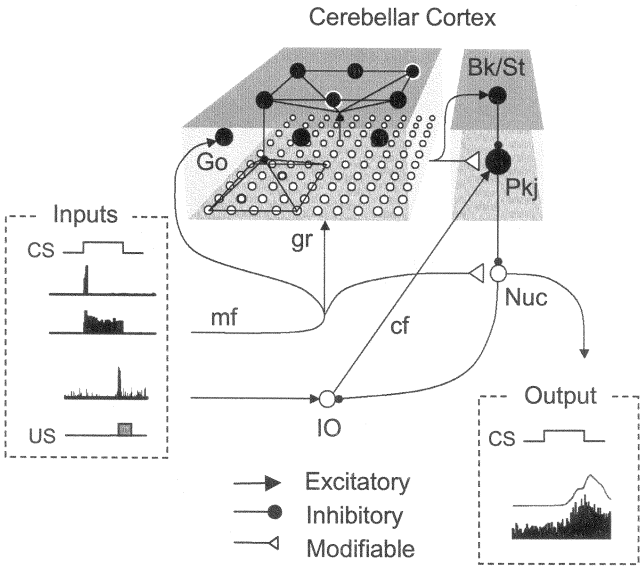

FIGURE 2. Basic eyelid circuitry of the cerebello-olivary system and the way in which it is engaged by pavlovian conditioning. The conditioned (CS) and unconditioned stimuli (US), respectively, activate mossy (mf) and climbing fibers (cf). Data for mossy and climbing fibers are taken from Aitkin and Boyd[30] and Sears and Steinmetz,[31] respectively. The granule cell-to-Purkinje cell (gr-Pkj) synapses in the cerebellar cortex are assumed to undergo plastic changes during conditioning. (See Refs. 5, 6, 26, and 27 for plasticity at a second site in the cerebellar nucleus.) As a result, deep nucleus cells acquire the ability to produce output that drives brain stem motor neurons. Data for interpositus nucleus cells are taken from McCormick and Thompson.[32] Bk/St, basket and stellate cells; gr, granule cell; Go, Golgi cell; IO, inferior olive; Nuc, cerebellar nucleus cell; Pkj, Purkinje cell.

As we argued previously,[34] LTD at the gr-Pkj synapses activated by the CS satisfies both the necessity of convergence and the capacity for expression criteria, which cannot be violated if LTD mediates the expression of conditioned eyelid responses. Inputs from the mossy and climbing fibers (respectively from the CS and US) converge at these synapses.[34–39] Since Purkinje cells are known to tonically inhibit cerebellar nucleus cells[2,40] and since Purkinje cell activity inhibits the expression of conditioned responses (FIG. 2),[41] LTD at the gr-Pkj synapses activated by a CS would promote changes in Purkinje cell activity capable of mediating response expression. Given a sufficient amount of LTD, the resulting decrease in Purkinje cell activity in response to the CS could release the deep nucleus from tonic Purkinje cell inhibition and generate a conditioned response. Conversely, increasing the strength of gr-Pkj synapses via LTP could increase Purkinje cell activity, thereby increasing the tonic inhibitory input to the nucleus cell. Such a process could account for why conditioned responses undergo extinction. Our simulations permit specific and detailed tests of the feasibility of these as yet unproven ideas.

Finally, the straightforward ways in which eyelid conditioning engages the cerebellum permit a close correspondence between experiments and simulations. Since we can train a simulation with the same patterns of inputs with which we can train rabbits, predictions from the simulations can be empirically tested directly.

RULES FOR PLASTICITY

The rules that govern the induction of synaptic plasticity are fundamentally important assumptions for a simulation of the cerebellum, for they determine the exact computations that the simulation will accomplish in response to the inputs with which it is provided. Fortunately, there now exists a large body of evidence on various forms of synaptic plasticity in the cerebellum and their rules for induction. (See Ref. 42 for a review.)

Consistent with early models of cerebellar motor learning, evidence is convincing that gr-Pkj synapses undergo LTD when presynaptic activity occurs in close temporal proximity to a climbing fiber spike.[2,9–15] The exact temporal relationship required for the induction of LTD is not yet well established. Various studies have suggested that LTD induction occurs when parallel fiber stimulation either precedes,[15] is simultaneous with,[2,9,11,13,14] or follows[10,12] climbing fiber stimulation. We have generally found that the ability of the simulation to learn properly timed responses and to show extinction of the responses is largely unaffected by the precise temporal assumptions regarding LTD induction. Based on indirect evidence from VOR studies in monkey,[43] LTD in the current simulations is induced when activation of the gr-Pkj synapse falls within a 100-ms window centered 100 ms prior to the climbing fiber input. However, the results presented here do not depend on the precise temporal assumptions for LTD induction. LTP at the gr-Pkj synapses has also been characterized, and the evidence suggests that gr-Pkj synapses are strengthened when presynaptic activity occurs in the absence of climbing fiber input.[11,13,17,44,45] We therefore incorporated an activity-dependent LTP rule at the gr-Pkj synapse, in which LTP occurs when a granule cell is active outside of the climbing fiber window.

Recent evidence suggests that LTD and LTP at gr-Pkj synapses induced by the presence or absence of climbing fiber inputs, respectively, are mutually revers-

ing.[17,46] In the cerebellum-like structure of mormyrid fish, it was found that the synapses corresponding to the gr-Pkj synapses in the mammalian cerebellum undergo presynaptic forms of mutually reversible LTP and LTD.[46] More recently, it was shown in rat cerebellar slices that there are two forms of cerebellar LTP, one of which is presynaptic and the other of which is postsynaptic.[17] The latter form of LTP has now been shown to be mutually reversing with LTD,[17] a process itself that is considered postsynaptic.[47] These data are fully consistent with the reversible LTP/LTD rule in the simulation. The simulation also incorporates plasticity in the cerebellar nucleus at the mossy fiber to nucleus synapses. Because this plasticity is not essential to the results that follow, we omit discussion. (See Ref. 48 for details.)

A BRIEF HISTORY OF FAILURES

The current simulations display many of the main behavioral properties of eyelid conditioning and have produced mechanistic predictions that were recently subjected to empirical test.[6,49,50] These are, however, relatively recent events. For many years the simulations failed to produce even the most basic aspects of eyelid conditioning. Here we briefly describe aspects of these failures, particularly of the transition from failures to successes, from which a degree of insight can be gleaned.

Due to limitations imposed by computer power and by lack of empirical information, our early simulations involved only the cerebellar cortex and were designed to address whether Purkinje cells could learn appropriately timed pauses in activity (and hence appropriately timed nucleus output) given eyelid conditioning-like inputs.[16] These simulations contained only a rule for LTD at the gr-Pkj synapses, in part because LTP at these synapses was less understood than LTD and in part because the focus was on acquisition (as opposed to extinction) of conditioned responses. The simulations were comprised of mossy fiber inputs, a layer of granule cells, a layer of Golgi cells, and a single Purkinje cell whose granule cell synapses could undergo LTD when a climbing fiber input was activated (as when the US was presented, for example). Thus, there was only unidirectional plasticity at the gr-Pkj synapses. Two other major features were missing from the early simulations: (1) a representation of the deep nuclei and its inhibitory connection to the inferior olive and (2) spontaneous climbing fiber activity. These were all errors of omission, because it had already been shown that LTP could be induced at the gr-Pkj synapse,[11,13,44] recording studies had found that climbing fibers were spontaneously active at 1 Hz,[31] and anatomic and physiologic studies supported the existence of the inhibitory nucleo-olivary projection.[51–54] Despite their capacity to generate a fine-grained temporal code in the cerebellar cortex that, in principle, might permit the proper timing of conditioned responses, these early simulations failed to learn when spontaneous climbing fiber activity was introduced between trials.

The problem posed by spontaneous climbing fiber activity was related to the eventual saturation of all synapses at their minimum strengths.[55] If climbing fibers were spontaneously active, then assuming only LTD, gr-Pkj synapses would continue to decrease in strength every time presynaptic activity coincided with a spontaneous climbing fiber spike. Because granule cells are also spontaneously active,[56] all gr-Pkj synapses exhibiting non-zero firing rates would be expected to decrease in strength and eventually saturate (albeit at different rates depending on their sponta-

neous firing rates) at their minimum strength, even without external input to mossy or climbing fibers. Such considerations reveal that a model assuming only LTD would fail to explain the stability of motor memories.[57] Indeed, this problem of saturation was the primary reason why our early simulations failed to learn properly.

The early failure of the simulation suggested that merely showing that cerebellar LTD occurs during learning would not be a sufficient explanation of eyelid conditioning. In the next section, we describe how a more detailed representation of the simulation can learn under realistic conditions in which climbing fibers are spontaneously active at their observed rate of 1 Hz. The success shows that far from posing a problem, spontaneous climbing fiber activity is central to the cerebellum's ability to learn and retain motor memories. As will become evident, the cerebellar features whose addition brought the simulation to a critical mass highlights a more systems-oriented view.

NUCLEO-OLIVARY FEEDBACK AND EXTINCTION

The failures just described clearly indicated that a more detailed simulation was needed even to explain the most basic learning features of the cerebellum. As noted above, there were three clear errors of omission in the early simulation: an LTP process at the gr-Pkj synapse,[11,13,44] spontaneous climbing fiber activity,[31,57] and a nucleus cell representation with its inhibitory connection to the inferior olive.[51–54] The most recent version of our simulation sets the leak conductance of the inferior olive such that action potentials are generated spontaneously at their natural firing rate of 1 Hz.[31] The inclusion of these features into the simulation marked a crucial turning point. By incorporating these crucial missing pieces into the simulation, we were able to account for various features of eyelid conditioning, including the timing of conditioned responses,[6] the rapidity with which reacquisition occurs to an extinguished CS,[46] and the ability of conditioned responses to extinguish.[58] These successes have led to novel and testable predictions that were recently subjected to empirical test.[6,49,50] Here, we focus on a specific prediction of the simulation that we recently tested involving the role of the inhibitory nucleo-olivary feedback loop in extinction.

Understanding the role of nucleo-olivary feedback in extinction requires an appreciation of the self-regulatory process accomplished by nucleo-olivary inhibition.[55] To begin with, the simulation suggests that the spontaneous activity of climbing fibers is self-regulated by the cerebellum to a special level. FIGURE 3 shows results from simulations that were initiated with starting synaptic weights that made the simulation badly out of equilibrium. Initially, the strengths of gr-Pkj synapses are at a minimum, and thus there is no Purkinje cell activity (FIG. 3A, left). Nucleus cells are therefore disinhibited (FIG. 3A, center), and the climbing fibers are silent due to the strong nucleo-olivary inhibition (FIG. 3A, right). As time elapses, however, the system eventually settles into an equilibrium state in which climbing fiber activity stabilizes at 1 Hz (FIG. 3A, right). The same equilibrium state is attained if the gr-Pkj synapses are initialized at strengths higher than those required for equilibrium (FIG. 3B). Thus, the spontaneous activity of climbing fibers is naturally and necessarily driven to the level where, on average, there are no net changes in the strength of gr-Pkj synapses and no net changes in the level of output of the deep nucleus neurons.[55]

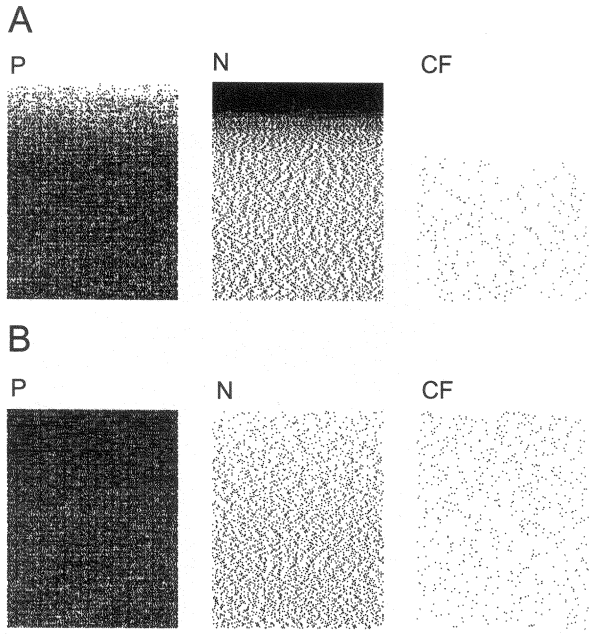

FIGURE 3. Simulated rasterplots of Purkinje cell (P), deep nucleus cell (N), and climbing fiber (CF) activity. The simulation runs from *top to bottom* and *left to right*. (**A**) Behavior of simulation initiated with synaptic weights that were minimal for gr-Pkj synapses. (**B**) Behavior of simulation initiated with synaptic weights that were maximal for gr-Pkj synapses. In both simulations, the synapses are eventually adjusted and stabilized to a level in which CF activity settles at its equilibrium level of 1 Hz.

It was largely the absence of this self-regulating equilibrium that precluded the proper behavior of our early simulations. The current simulation solves the aforementioned problem of synaptic saturation by accomplishing this self-regulation. Recall that with only LTD, spontaneous climbing fiber activity eventually drives spontaneously active gr-Pkj synapses to a minimum. By allowing LTD to be reversed by LTP, however, the synapses are freed from being pinned down to a minimum strength, because any LTD that occurs by chance will be reversed by LTP upon spontaneous occurrences of presynaptic granule cell activity in the absence of climbing fiber input. The result is that despite moment-to-moment changes in synaptic strength, each gr-Pkj synapse stabilizes on average at an intermediate strength determined by the spontaneous firing rate of the presynaptic granule cell.[51] By contrast, if the LTP and LTD are not mutually reversing, then the saturation problem remains unsolved, because spontaneous activity in both granule cells and climbing fibers eventually drives each of the processes to saturate to its minimum (for LTD) or maximum (for LTP), that is, the strengths of the gr-Pkj synapses spontaneously drift until they are either all as strong or all as weak as they can be. Eventually, the capacity for synaptic modification would permanently be lost for all gr-Pkj synapses, a condition that would preclude any new learning or the retention of previous learning.

The preceding analysis suggests that the spontaneous climbing fiber activity is fundamental for the capacity to retain learning and that learning in the cerebellum can only be understood in terms of the way training disrupts this equilibrium.[58] Because the equilibrium level of spontaneous climbing fiber activity precludes net changes in input and output, the training procedures involved in acquisition and extinction of conditioned responses must systematically disrupt this equilibrium to produce the observed changes in responding to the CS. How this would happen during acquisition is relatively intuitive. Normally, the gr-Pkj synapses activated by the CS would encounter a climbing fiber input at the equilibrium probability, but presentation of the US in conjunction with the CS ensures that the probability of a climbing fiber input is much higher in the latter situation. Accordingly, there is an accumulation of net LTD at these synapses as training proceeds. These changes are maintained because the modified synapses experience the equilibrium level of climbing fiber activity between training trials.

An important consequence of the inhibitory nucleo-olivary connection is that as the simulation acquires conditioned responses (and thus learns an increased output), the inhibition of climbing fibers by the cerebellum increases. In this way the simulation parallels the important empirical observation that the ability of the US to elicit a climbing fiber response diminishes as conditioned responses increase.[31,59,60] FIGURE 4 shows results from simulations that were trained from an equilibrium state. During repeated presentations of the CS alone (shown in gray), there is no change in the responses of Purkinje cells, nucleus cells, or climbing fibers (FIG. 4, light gray boxes). When the simulation is subsequently trained with repeated pairings of the CS and US, Purkinje cells gradually learn to pause and disinhibit deep nucleus cells in response to the CS (FIG. 4, thin dark gray box). As the nucleus output increases, the climbing fiber response evoked by the US becomes increasingly suppressed (FIG. 4, thick dark gray box).

The simulation makes specific and testable predictions about the mechanisms that operate during extinction of conditioned responses. As shown in FIGURE 4 (thin black box), if the CS is repeatedly presented alone after acquisition, Purkinje cell output increases and nucleus cell output decreases in response to the CS across trials. This extinction process is mediated by a restrengthening via LTP of those gr-Pkj synapses that had originally undergone net LTD during acquisition. What, however, is the signal that drives this process? Due to nucleo-olivary inhibition, climbing fiber activity is suppressed below equilibrium during extinction near the time the US had occurred during acquisition (FIG. 4, thick black box). In the simulation, it is this transient suppression of climbing fiber activity below the normal spontaneous level that drives the induction of LTP at gr-Pkj synapses consistently active in the absence of a climbing fiber input.[58] The simulation therefore predicts that if the inhibitory feedback from the deep nucleus to the inferior olive is blocked, climbing fiber activity should not be transiently suppressed, and hence extinction should be prevented.

We recently found strong evidence in support of this prediction.[50] Rabbits with a cannula implanted in the inferior olive were trained in a standard delay conditioning protocol for five sessions, during which a tone CS was paired with periorbital stimulation. After acquisition, they were given three separate extinction sessions (each preceded by two training sessions to establish baseline responding) in which the CS was repeatedly presented alone. A separate treatment occurred for each extinction session: a control treatment with no infusion, a control treatment with continuous in-

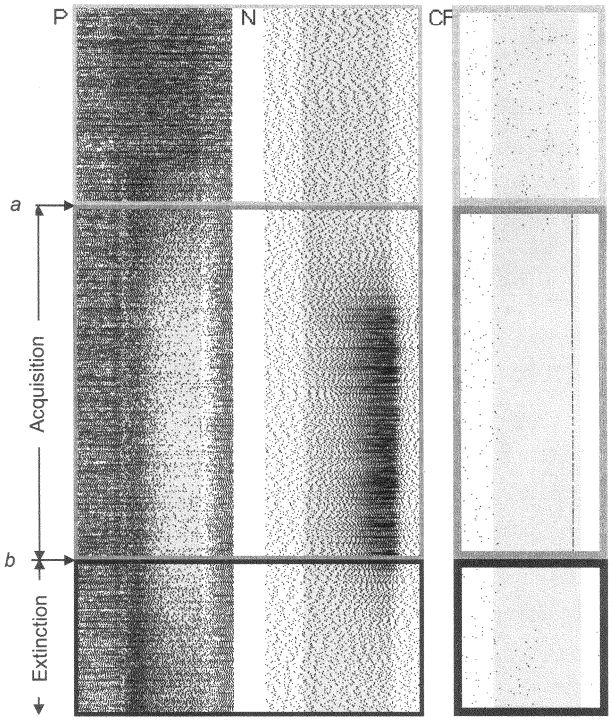

FIGURE 4. Simulated rasterplots of Purkinje cell (P), deep nucleus cell (N), and climbing fiber (CF) activity. Each sweep represents a segment of one trial cycle comprised of a 1-second CS (*shaded area*) and a 5-second intertrial interval. Trials run from *top to bottom* and *left to right*. The simulation begins at equilibrium and is initially given repeated presentations of the CS alone. No changes in activity are observed in response to the CS (*thin light gray box*), and the CF fires at its equilibrium rate in both the CS and the intertrial periods (*thick light gray box*). Acquisition training in which the CS and US are paired begins at **a** and continues until **b**. P activity gradually becomes suppressed and N activity becomes increased in response to the CS (*thin dark gray box*). CF responses evoked by the US occur 50 ms prior to the termination of the CS (*thick dark gray box*). Starting at **b**, the CS is extinguished. P activity increases and N activity decreases to the CS with repeated extinction trials (*thin black box*). Note the marked suppression of CF activity below its spontaneous firing rate near the time at which the US occurred during acquisition (*thick black box*).

fusion of artificial cerebrospinal fluid (ACSF), or a continuous infusion of the GABAA antagonist picrotoxin to block nucleo-olivary inhibition. Consistent with the prediction, extinction failed to occur when nucleo-olivary feedback was blocked (FIG. 5A, right), whereas extinction proceeded normally during the control treatments (FIG. 5A, left).

A second prediction was then tested: blocking excitatory transmission in the inferior olive should block the US signal and hence produce extinction, despite continued pairings of the CS and US. Consistent with this prediction, when the subjects

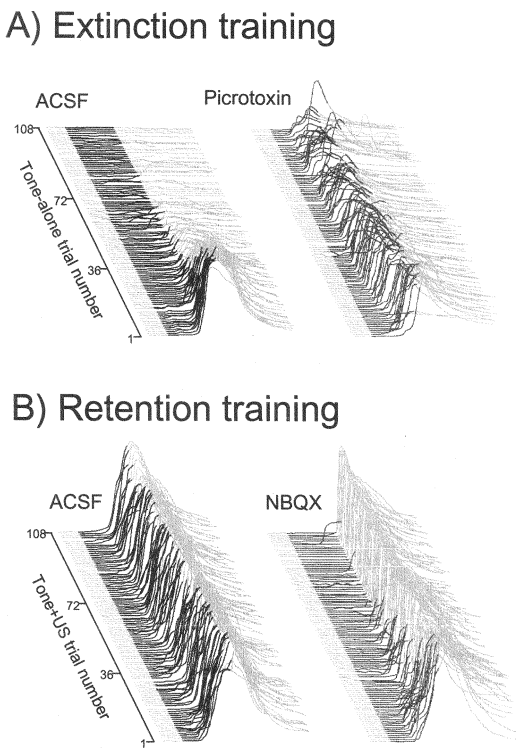

FIGURE 5. Trial-by-trial sweeps for different treatment sessions averaged across four rabbits given cannula implants in the inferior olive. (**A**) Average sweeps during extinction sessions in which either artificial cerebrospinal fluid (ACSF; *left*) or the GABAA antagonist picrotoxin (*right*) was continuously infused into the inferior olive. Extinction is blocked by picrotoxin. (**B**) Average sweeps during paired training (retention) sessions in which either ACSF (*left*) or the AMPA receptor antagonist NBQX (*right*) was infused continuously into the inferior olive. NBQX produced extinction. The concentration for both GABAA and NBQX was 150 μM; the rate of infusion was 0.1 μM min^{-1}. *Dark lines* indicate the presence of the CS.

were subsequently retrained and then tested with continuous infusions of the AMPA antagonist NBQX that began just before a paired training session, the conditioned responses extinguished (FIG. 5B, right). Extinction did not occur during sessions with ACSF infusions (FIG. 5B, left). A second control treatment showed that this extinction-like effect was due not merely to a time-dependent effect of the drug on response expression, but to an experience-dependent effect; when the session was begun 40 minutes after the start of the infusion, extinction still required a similar number of trials. These results confirmed the predictions of the simulation regarding extinction and suggest that extinction of conditioned eyelid responses is driven by the transient suppression of climbing fiber activity below equilibrium.

CONCLUSIONS

We have described a computer simulation of the cerebellum and the way in which it has been tested using Pavlovian eyelid conditioning. The simulation is based on integrate-and-fire neurons whose properties are based on available physiologic data and are wired in accord with the known synaptic organization of the cerebellum. The inputs to the cerebellum are based on recordings of mossy and climbing fiber responses to the stimuli used in eyelid conditioning. The output from the cerebellum can be evaluated with respect to the behavioral output of eyelid conditioning, because recording and stimulation studies suggest that the deep nucleus neurons of the anterior interpositus directly drive the conditioned response. The simulated gr-Pkj synapses in the cerebellar cortex undergo bidirectional changes in strength. Early failures of the simulation were due to the omission of a bidirectional plasticity rule at gr-Pkj synapses and the nucleo-olivary feedback connection. Recent tests of successful simulations incorporating both features suggest that the transient suppression of climbing fiber activity below equilibrium via nucleo-olivary inhibition is the signal that drives extinction.

The insights we have gained into the mechanisms of cerebellar computation may shed light on how the cerebellum operates in other domains.[26] If cerebellar function is considered in terms of how the cerebellum transforms its inputs into outputs, attempts to apply the simulation to data from VOR adaptation, saccade adaptation, and smooth pursuit, all of which are known to be affected by cerebellar lesions,[26,61] should prove highly informative. So long as the inputs to and outputs from the cerebellum are known in these preparations, the simulation can be applied to investigate whether and how its computational principles solve the required input-output transformations. Hopefully, we will then discover how a single computation allows the cerebellum to perform diverse functions.

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