I. INTRODUCTION

Since Marr's groundbreaking theory on the cerebellar cortex (Marr, 1969), the issue of cerebellar learning has been actively if not harmoniously investigated. Marr's theory was based on the equally seminal work of Eccles, Ito, and Szenthágráti (1967), which laid the foundations for providing a nearly complete circuit diagram of the cerebellum. The nearly 40 years of cerebellar research since has provided not only a wealth of evidence in support of the theory, but additional evidence to include other sites of plasticity outside of the cerebellar cortex, including the deep cerebellar and vestibular nuclei.

Here we review evidence relating to three questions. (1) Does the cerebellum learn? (2) How is this learning accomplished? (3) What is the functional role of cerebellar learning? We first describe evidence of cerebellar involvement in a number of forms of motor learning and adaptation. Then, based on the unique advantages of eyelid conditioning, we review evidence on the mechanisms underlying cerebellar learning. The evidence suggests that cerebellar learning is mediated by plasticity in the cerebellar cortex and in its downstream targets in the deep cerebellar nuclei. Finally, we examine the behavioral
FIGURE 13-1 How Pavlovian eyelid conditioning, an associative form of motor learning, engages the cerebellum. In eyelid conditioning, repeated pairings of a peripheral stimulus such as a tone (the conditioned stimulus, or CS) and mild electrical stimulation around the eye (the unconditioned stimulus, or US) gradually establishes a conditioned eyelid response to the previously neutral CS. Research since the early 1980s has shown that the CS and US, respectively, activate the mossy and climbing fiber afferents to the cerebellum and that the activity of one of the deep cerebellar nuclei drives the expression of the conditioned response. Current evidence suggests that eyelid conditioning is mediated by plasticity at two sites, one at granule cell-to-Purkinje cell (gr-Pkj) synapses in the cerebellar cortex and another at the excitatory mf-nuc synapses of mossy fibers onto deep nucleus cells.

properties of eyelid conditioning to infer the contribution of this learning to cerebellar information processing. We conclude by suggesting that the cerebellum learns temporally specific feed-forward predictions that are used to improve the operation of any neural process occurring on a relatively short time scale.

II. SYNAPTIC ORGANIZATION OF THE CEREBELLM

As just noted, the architecture of the cerebellum — its cell types, connectivity, and synaptic organization — is known in great detail (Chan-Palay, 1977; Eccles et al., 1967; Ito, 1984; Llinas, 1981). The input to the cerebellum is conveyed by two major afferents, the mossy fibers and climbing fibers (Fig. 13-1). Mossy fibers arise from cells in various nuclei within the brainstem, thereby conveying activity from virtually every area in the brain, including the cerebral cortex. Mossy fibers project profusely into the cerebellar cortex, making excitatory contacts with inhibitory Golgi cells and granule cells and providing excitatory collaterals to cells in the deep cerebellar and vestibular nuclei. Thus, there is a great divergence of mossy fiber input onto granule cells, the most numerous type of cell in the brain. Granule cells give rise to parallel fibers
that course through the cerebellar folium and synapse on the inhibitory Purkinje cells, the sole output neurons of the cerebellar cortex projecting to the deep cerebellar and vestibular nuclei. Parallel fibers also contact inhibitory interneurons, which in turn make synapses with Purkinje cells. Purkinje cells receive inputs from up to 200,000 parallel fibers, making them one of the cells with the greatest convergence of inputs in the brain. Mossy fibers influence cerebellar output indirectly via a pathway through the cerebellar cortex and directly via their collateral projections to the deep cerebellar nuclei.

Climbing fibers arise in the inferior olivary nuclei and project directly onto Purkinje cells. Each climbing fiber contacts about 10 Purkinje cells, and each Purkinje cell receives input from only one climbing fiber. The connection between a climbing fiber and a Purkinje cell is one of the most powerful synapses in the brain. Climbing fibers also make far weaker synaptic contacts with cells in the deep cerebellar and vestibular nuclei via collaterals. Therefore, the divergence and convergence ratios for climbing fiber inputs are far less than those for mossy fiber inputs.

III. THE CEREBELLUM LEARNS

An extensive body of evidence from eyelid conditioning and adaptation of eye movements suggests that the cerebellum learns. To varying degrees, the evidence points to the cerebellum as a key site of plasticity for each of these forms of learning.

A. Adaptation of Smooth Pursuit

Smooth-pursuit eye movements are those that we and other primates make when tracking a moving stimulus. When the motion of the stimulus is predictable, an early open-loop portion of the eye movement also adapts to anticipate this stimulus (Barnes and Donelan, 1999; Kettner, Leung, and Peterson, 1996; Leung and Kettner, 1997; Medina, Carey, and Lisberger, 2005; Thier and Ilg, 2005). Currently, evidence for a cerebellar locus for this form of learning comes from lesion studies. Lesions of the cerebellum abolish smooth pursuit (Robinson, Straube, and Fuchs, 1997; Westheimer and Blair, 1974), and lesions specific to the dorsal (oculomotor) vermis prevent pursuit adaptation (Takagi, Zee, and Tamargo, 2000). Computer simulations are also consistent with a cerebellar locus for learning since they demonstrate that network models with plasticity in the cerebellar cortex (see later) can adequately reproduce complex predictive pursuit movements in monkeys (Kettner et al., 1997; Kettner, Suh, Davis, and Leung, 2002).
B. Saccade Adaptation

Saccades are rapid eye movements that redirect the gaze from one location to another. They are commonly studied by having humans or monkeys make an eye movement to a peripherally presented target stimulus. The amplitude of the saccade can be increased or decreased if during the primary saccade the target is moved horizontally in the same or the opposite direction of the initial saccade (forward or backward adaptation, respectively) (Hopp and Fuchs, 2004). Lesion studies suggest that the cerebellum is required for adaptation of saccades induced by artificially weakening extraocular muscles (Optican and Robinson, 1980) and that the oculomotor vermis is necessary for the behaviorally induced adaptation of saccades (Hopp and Fuchs, 2004). Lesions of the caudal fastigial nucleus downstream of the oculomotor vermis also lead to dysmetric saccades and prevent saccade adaptation (Robinson, Fuchs, and Noto, 2002; Robinson, Straube, and Fuchs, 1993). The caudal fastigial nucleus, which projects to the brainstem burst generators that drive saccades, exhibits neural activity that changes with saccade adaptation (Scudder, 2002; Scudder and McGee, 2003) and whose time of termination may be determined by population activity in the oculomotor vermis (Thier, Dicke, Haas, and Barash, 2000; Thier, Dicke, Haas, Thielert, and Catz, 2002). Although these data do not pinpoint the site of plasticity underlying saccade adaptation, they support a cerebellar locus for learning.

C. Adaptation of the Vestibulo-Ocular Reflex (VOR)

The VOR is a reflex that compensates for movements of the head to stabilize visual inputs on the retina (Ito, 1970). A turn of the head induces a compensatory turn of the eyes in the opposite direction, with an amplitude (referred to as gain, often taken as the ratio of the velocity of the eyes to that of the head) approximating that of the former (gain \( \approx 1 \)). The VOR gain can be modified by manipulations in which visual input is changed so that a gain of 1 does not appropriately compensate for head movement (Gonshor and Jones, 1973).

Based on the proposals by Marr (1969) and Albus (1971), Ito (1972) suggested that VOR adaptation could be mediated by changes in the strengths of granule cell–to–Purkinje cell (gr-Pkj) synapses. The VOR is mediated by a three-neuron arc consisting of the semicircular canals, the primary vestibular neurons, and the oculomotor neurons, with the cerebellum attached to this trisynaptic reflex pathway as a side loop (Ito, 1970, 1972). This constrains the possible sites of plasticity to a relatively small number (Miles and Lisberger, 1981). Although an enormous body of evidence now exists for plasticity at gr-Pkj synapses (Hansel, Linden, and D'Angelo, 2001; Ito, 2001), the evidence that VOR adaptation is mediated by this plasticity has come largely from
studies showing that cerebellar cortex lesions (including genetic modifications in mice that impair plasticity mechanisms) prevent adaptation and from recording studies showing activity patterns consistent with such a mechanism (Ito, 2001). Although there remains disagreement over the essential site(s) of plasticity, it is generally agreed that plasticity at one or more sites within the cerebellar cortico-nuclear microcomplex (i.e., a computational unit involving populations of neurons in the cerebellar cortex, their targets in the deep cerebellar or vestibular nuclei, and inferior olive) mediates VOR adaptation.

D. Eyelid Conditioning

With its long history of use in experimental psychology, eyelid conditioning is one of the most extensively characterized forms of associative learning. Eyelid conditioning involves repeatedly pairing a neutral stimulus such as a tone and either electrical stimulation of the periorbital muscles or a puff of air directed at the eye (the unconditioned stimulus, or US). This training eventually imbues the tone with the power to evoke eyelid closure on its own, rendering it a classical, or Pavlovian, conditioned stimulus (CS).

Several lines of evidence suggest that eyelid conditioning is mediated by learning in the cerebellum. First, lesions of a deep cerebellar nucleus, the anterior interpositus nucleus (AIN) ipsilateral to the trained eye, permanently abolishes learning and retention of eyelid conditioning (McCormick, Clark, Lavond, and Thompson, 1982; McCormick and Thompson, 1984a; Yeo, Hardiman, and Glickstein, 1985a). Since learning to the contralateral side is normal (McCormick et al., 1982; McCormick and Thompson, 1984a), the deficit is not due to perceptual, motivational, or motor impairments. Second, stimulation and recording studies indicate that neural activity in the AIN drives the learned response — stimulating the AIN drives eyelid closure, and activity in the AIN anticipates and models the learned response (McCormick and Thompson, 1984a, 1984b) and drives the premotor and motor neurons via the red nucleus (Chapman, Steinmetz, Sears, and Thompson, 1990). Third, reversible-lesion studies indicate that the underlying plasticity occurs at or upstream of the AIN — inactivation of the AIN but not the red nucleus or superior cerebellar peduncle prevents learning (Krupa, J.K. Thompson, and Thompson, 1993; Krupa and R.F. Thompson, 1995). Finally, stimulation studies show that learning occurs downstream from the pontine nucleus and inferior olive, the sources of cerebellar input from the CS and US, respectively (Fig. 13-1). That is, learning occurs when either a tone or mossy fiber stimulation is paired with stimulation of the inferior olive (Mauk, Steinmetz, and Thompson, 1986; Steinmetz, Lavond, and Thompson, 1989); and in decerebrate ferrets, conditioned responses to a forelimb stimulation CS can be elicited with mossy fiber stimulation even when antidromic activation of their cell
bodies in the pons is prevented (Hesslow, Svensson, and Ivarsson, 1999). Collectively, these data suggest strongly that eyelid conditioning is mediated by the cerebellum. They also indicate a remarkably direct mapping of the training stimuli of eyelid conditioning onto cerebellar afferents (CS — mossy fiber, US — climbing fiber) and cerebellar output onto behavioral output (AIN activity — eyelid closure). This implies that the behavioral properties of eyelid conditioning provide a relatively direct window into cerebellar learning and the computation that it supports.

IV. HOW THE CEREBELLUM LEARNS

A. Sites of Plasticity

As already noted, the inputs from the stimuli that induce learning in eyelid conditioning (e.g., the CS and US in eyelid conditioning) converge at the Purkinje cells and cells in the AIN. For this reason, the two sites that have received the greatest attention as candidate sites of plasticity are the \textit{gr-Pkj} synapses in the cerebellar cortex and the synapses of mossy fibers onto the AIN (\textit{mf-nuc synapses}) (Fig. 13-1).

1. Cerebellar Cortex

From the earliest studies in the 1980s, there were indications that plasticity in the cerebellar cortex contributed to eyelid conditioning, although its precise contribution was unclear. Whereas some early studies found that lesions of certain regions of the cerebellar cortex completely abolished previously acquired responses and prevent their reacquisition (Yeo, Hardiman, and Glickstein, 1984, 1985b), other studies showed that learning or relearning was slowed but not completely prevented (Lavond and Steinmetz, 1989; Yeo and Hardiman, 1992). Since 1994, several studies of eyelid conditioning in mice without Purkinje cells or with impaired long-term depression (LTD) at \textit{gr-Pkj} synapses (see later) have in general produced the latter pattern of results (Aiba et al., 1994; L. Chen, Bao, Lockard, Kim, and Thompson, 1996; Kishimoto et al., 2001; Koekkoek et al., 2003, 2005; Shibuki et al., 1996) [but see (Miyata et al., 2001)]. The discrepancies between the early rabbit studies prevented definitive statements about the precise contribution of the cerebellar cortex to learning. Similarly, the generally incomplete deficits in mouse studies have proved difficult to interpret due to numerous factors, including potential extracerebellar contributions to learning in mice (Koekkoek et al., 2003, 2005). Nonetheless, these studies are consistent with the hypothesis that the cerebellar cortex is one site of plasticity underlying cerebellar learning.

In part to clarify the disagreement between the early rabbit studies, in one of the first studies in our laboratory we removed large portions of the ipsilateral
cerebellar cortex via aspiration after training rabbits to respond to two separate CSs with differently timed responses (Perrett, Ruiz, and Mauk, 1993). Cerebellar cortex lesions did not abolish learned responses but disrupted their timing, revealing responses to both CSs with short, fixed latencies (Fig. 13-2A). This effect was correlated with the rostro-caudal extent of the lesion and whether or not it included the anterior lobe (Fig. 13-2B). Since the timing of conditioned eyelid responses is learned (Hoehler and Leonard, 1976; Kehoe, Graham-Clarke, and Schreurs, 1989; Mauk and Ruiz, 1992; Millenson, Kehoe,

FIGURE 13-2 Posttraining lesions of the cerebellar cortex abolish the timing of the conditioned response. A. Conditioned responses (top panels) established using a differential conditioning procedure to one stimulus (CS1) paired with the US at an interstimulus interval (ISI) of 150 ms (left) and a second stimulus (CS2) paired with the US at an ISI of 750 ms (right). Note that the timing of the learned eyelid closure (e.g., upward deflections of the trace) is maximal near the expected time of the US for each CS. B. Posttraining lesions of the cerebellar cortex including the anterior lobe (A) unmask responses with short, fixed latencies independent of the ISI. S, ansiform lobule; P, paramedian lobule. [Reprinted with permission from Perret, Ruiz, and Mauk (1993).]
and Gormezano, 1977) (see below), these data, together with recent studies in mice (Koekkoek et al., 2003, 2005), suggest that plasticity in the cerebellar cortex is essential for this component of learning. This lesion effect has now been replicated in a number of studies across different laboratories. The residual short-latency responses (SLRs) have been observed after electrolytic lesions (Garcia, Steele, and Mauk, 1999; Medina, Garcia, Nores, Taylor, and Mauk, 2000) and reversible lesions in which the GABA_A antagonist picrotoxin was infused into the AIN to disconnect it from the cerebellar cortex (Aksenov, Serdyukova, Irwin, and Bracha, 2004; Bao, Chen, Kim, and Thompson, 2002; Garcia and Mauk, 1998; Medina, Garcia, and Mauk, 2001; Ohyama and Mauk, 2001; Ohyama, Nores, and Mauk, 2003; Ohyama, Nores, Medina, Riusech, and Mauk, 2006).

As we describe later, SLRs reflect plasticity at a second site in the AIN. The presence of SLRs after a lesion of the cerebellar cortex is then taken as a functional index that a lesion of the cerebellar cortex is complete, and it provides a way to assess its precise contribution to learning. If the cerebellar cortex is necessary for inducing plasticity in the AIN (Medina and Mauk, 1999; Miles and Lisberger, 1981) (see upcoming Section B, on plasticity rules), then complete lesions should completely prevent further learning. In contrast, if plasticity is induced in the AIN independent of the cerebellar cortex, then complete lesions should only partly prevent new learning. We tested these alternatives by training subjects to one CS, after which we made electrolytic lesions of the cerebellar cortex to unmask SLRs (Fig. 13-3). After recovery, we then trained the subjects to a second CS of a different modality (Garcia, Steele, and Mauk, 1999). Subjects for whom the lesions unmasked SLRs completely failed to learn to the new CS. In contrast, control subjects with lesions outside of the anterior lobe learned to the new CS. These data, together with the results discussed earlier, indicate that the role of plasticity in the cerebellar cortex is two-fold — to mediate adaptive timing of learned responses and to provide a signal for inducing plasticity in the AIN.

2. Deep Cerebellar Nucleus

The SLRs spared by cerebellar cortex lesions are mediated by a form of neural plasticity in the AIN whose induction is associative. First, SLRs are associative, since they are observed neither before training nor after unpaired training but only after paired training (Medina, Garcia, and Mauk, 2001; Ohyama, Nores, and Mauk, 2003; Ohyama et al., 2006). Second, SLRs are highly input specific (Ohyama, Nores, and Mauk, 2003; Perrett and Mauk, 1995), in that they are less likely to be evoked by test stimuli that are less similar to the original CS. These data suggest that SLRs are caused not by a nonassociative process (Attwell, Ivarsson, Millar, and Yeo, 2002) but by an associative form of neural plasticity. Further evidence suggests that the essential site of the plasticity
Lesions of the cerebellar cortex prevent subsequent learning to a new CS. Rabbits were first trained to establish robust responding to either an auditory or a tactile CS, after which electrolytic lesions were made in the cerebellar cortex. Subsequently, they were trained for 15 sessions in which a new CS of the alternative modality was paired with the US. Lesions that unmasked short-latency responses to the previously trained CS completely prevented learning to the new CS (gray circles), whereas new learning was normal for lesions which did not unmask short-latency responses (black circles). This effect is not attributable to nonspecific sensory, motivational, or motor deficits since learning to the new stimulus proceeded normally when training was switched to the opposite eye (C5). Each trace in the upper panels show a response averaged across CS-alone test trials during a training session for a control (left) and lesioned (right) animal. [Reprinted with permission from Garcia, Steele, and Mauk (1999).]

underlying SLRs is in the AIN (Ohyama et al., 2006). First, SLRs are abolished when glutamatergic synaptic transmission in this nucleus is blocked, suggesting that the expression pathway underlying SLRs includes the AIN. Second, direct stimulation of mossy fibers supports SLRs, suggesting that the site of plasticity is downstream of these fibers. Finally, SLRs can be learned during inactivation of the red nucleus, suggesting that the site of plasticity is upstream of the red nucleus. Since the only site of plasticity downstream of mossy fibers and upstream of the red nucleus is in the AIN, these data collectively indicate that an input-specific form of plasticity in the AIN underlies SLRs (Ohyama et al., 2006).
B. Plasticity Rules

1. LTD at the gr-Pkj Synapse


First, gr-Pkj LTD occurs at a site where inputs from the to-be-associated stimuli converge — the tone and US, respectively, are conveyed to Purkinje cells via the mossy and climbing fibers. Second, the rules for inducing gr-Pkj LTD are consistent with those for establishing conditioning — both occur only when two stimuli occur close in time. It has been argued that because the fine temporal parameters for induction differ — LTD is induced optimally when parallel and climbing fibers are coactivated (Hirano, 1990; Ito and Kano, 1982; Ito, Sakurai, and Tongroach, 1982; Lev–Ram et al., 2003; Lev–Ram, Wong, Storm, and Tsien, 2002; Sakurai, 1987) (but see C. Chen and Thompson, 1995; Ekerot and Kano, 1985, 1989; Karachot, Kado, and Ito, 1994), whereas eyelid conditioning is optimal when the interval between tone onset and the US is 200–500 msec (Gormezano, Kehoe, and Marshall, 1983; Kehoe and Macrae, 2002) — gr-Pkj LTD cannot be the mechanism underlying learning (De Schutter, 1995; Llinas, Lang, and Welsh, 1997; Llinas and Welsh, 1993; Schreurs and Alkon, 1993). However, this argument requires that the tone CS activates granule cells only at its onset (Mauk and Donegan, 1997; Nores et al., 2000). This is highly unlikely, given that mossy fiber inputs are active throughout the extent of a tone (Aitkin and Boyd, 1978). If mossy fiber input is converted into a distributed time-varying granule cell representation (Buonomano and Mauk, 1994; Mauk and Donegan, 1997; Medina, Garcia, et al., 2000; Medina and Mauk, 2000; Nores et al., 2000), then the temporal requirements for eyelid conditioning (Gormezano et al., 1983; Kehoe and Macrae, 2002) can be reproduced, assuming that gr-Pkj synapses become eligible for LTD after 100 msec (Kettner et al., 1997; Raymond and Lisberger, 1998; Voicu and Mauk, in press).
Third, LTD of gr-Pkj synapses activated by the CS would enable expression of learned eyelid responses by decreasing the normally high rate of Purkinje cell activity during the CS, thereby driving eyelid closure via disinhibition of the AIN (Hesslow, 1994). In anesthetized ferrets in which conditioned eyelid responses were established by pairing a forelimb stimulation CS and a periorbital US, Purkinje cell activity showed decreases during the CS that were not evident before training (Hesslow and Ivarsson, 1994). Only Purkinje cells controlling eyelid closure were recorded in this study (selected based on whether stimulating them could evoke a delayed rebound in eyelid EMG activity), so it is likely that the pause in Purkinje cell activity was causing the conditioned responses. In addition, the finding that electrically stimulating Purkinje cells with pulse trains suppresses previously acquired conditioned responses (Hesslow, 1994) is consistent with the sufficiency-for-expression criterion.

Fourth, gr-Pkj LTD appears necessary for learning, since lesions of the cerebellar cortex prevent learning (Bao, Chen, Kim, and Thompson, 2002; Garcia, Steele, and Mauk, 1999). In a study using rabbits we lesioned the cerebellar cortex after first establishing learning to a tone or vibratory CS. Using the functional criterion that lesions should spare SLRs (Garcia, Steele, and Mauk, 1999), cerebellar cortex lesions completely prevented subsequent learning to a new CS, suggesting that gr-Pkj LTD is necessary for learning. This contrasts with prior studies in rabbits (Lavond and Steinmetz, 1989; Yeo and Hardiman, 1992) and various mouse knockout studies (Aiba et al., 1994; Bao, Chen, Qiao, Knusel, and Thompson, 1998; L. Chen et al., 1996; Shibuki et al., 1996) in which lesions of the cerebellar cortex (or deletion of processes necessary for gr-Pkj LTD) partly spared the capacity for learning. A major problem with such studies is that the lesions are often incomplete. Assessment of knockout mice is also complicated by numerous problems, including the potential for (1) compensatory processes, (2) movement artifacts in EMG recording studies, and (3) noncerebellar contributions to eyelid conditioning (Koekkoek et al., 2003, 2005). Future studies should address this issue using treatments that specifically and completely block gr-Pkj LTD as well as training protocols that preclude noncerebellar contributions to learning in mice.

2. LTP at the gr-Pkj Synapse

Although gr-Pkj LTD meets certain criteria for acquisition, other evidence suggests that it alone is not sufficient. Long-term potentiation (LTP) of gr-Pkj synapses is induced when granule cells are activated alone (Coemans et al., 2004; Hirano, 1990; Lev-Ram et al., 2003, 2002; Sakurai, 1987; Salin, Malenka, and Nicoll, 1996). Although both pre- and postsynaptic forms of LTP have been identified, only the latter reverses climbing fiber–induced LTD (Coemans et al., 2004; Lev-Ram, Mehta, et al., 2003; Salin et al., 1996) and
could thus prevent synapses from saturating (Kenyon, Medina, and Mauk, 1998a, 1998b). Synaptic saturation challenges the LTD hypothesis of learning because spontaneous activity of climbing fibers (1–2 Hz) and granule cells (10–50 Hz) (Eccles et al., 1967) would potentially depress all synapses with sufficient time and abolish any specificity to learning (Llinas, Lang, and Welsh, 1997; Llinas and Welsh, 1993). However, computational analyses suggest that a mutually reversing (but not independent) LTD/LTP plasticity rule combined with inhibitory nucleo-olivary feedback allows simulations of the olivocerebellar circuit to both acquire and extinguish conditioned responses without synaptic saturation (Kenyon et al., 1998a, 1998b) (see later). This suggests that postsynaptic gr-Pkj LTP is also necessary for proper learning. There is no direct evidence for this prediction.

LTP of gr-Pkj synapses could underlie extinction, or the gradual decline of learned responses with repeated presentation of the CS alone. As will be elaborated later, gr-Pkj LTP occurs at a site where CS-evoked granule cell activity and a suppression of climbing fiber activity due to the inhibitory nucleo-olivary feedback (Medina, Nores, and Mauk, 2002) converge at the Purkinje cell. Like LTD and acquisition, gr-Pkj LTP is induced when gr-Pkj synapses are activated in the absence of climbing fiber activity (Coemsans et al., 2004; Hirano, 1990; Lev-Ram et al., 2003, 2002; Sakurai, 1987; Salin et al., 1996), much as behavioral extinction is induced when the CS is presented in the absence of the US. Induction of gr-Pkj LTP during extinction could increase CS-evoked granule cell activity and thereby restore suppression of AIN cells, consistent with a recording study in which extinction was correlated with a disappearance of the CS-evoked Purkinje cell pause (Hesslow and Ivarsson, 1994). Finally, recent studies are consistent with the hypothesis that gr-Pkj LTP is necessary for extinction, since preventing inhibitory nucleo-olivary feedback prevents extinction (Medina, Garcia, et al., 2002; Nilaweera, Zenitsky, and Bracha, 2005; Ramnani and Yeo, 1996).

3. Plasticity Downstream of the Cerebellar Cortex

A number of plasticity mechanisms at neurons immediately downstream of the Purkinje cells (the deep cerebellar and vestibular nuclei, respectively, for eyelid conditioning and VOR adaptation) could contribute to cerebellar learning. For eyelid conditioning, at least three known forms of plasticity in the AIN could contribute to SLRs spared by cerebellar cortex lesions: the formation of new mf-nuc synapses, LTP at existing mf-nuc synapses, and/or increased intrinsic excitability of AIN neurons. A recent study using electron microscopy to count synapses in the AIN of rats found that whereas the number of inhibitory synapses remained unchanged after either paired or explicitly unpaired training, excitatory synapses increased only after paired training (Kleim et al., 2002). Since excitatory input to the AIN comes largely from mossy fibers, these results
raise the possibility that de novo formation of mf-nuc synapses is required before subsequent activity-dependent plasticity induced at these synapses (Pugh and Raman, 2006; Racine, Wilson, Gingell, and Sunderland, 1986) leads to the gradual emergence of SLRs. A cell-wide increase in the intrinsic excitability of AIN neurons (Aizenman and Linden, 2000) (although by itself this cannot account for the stimulus specificity of SLRs) could contribute to SLRs by modulating the induction of mf-nuc plasticity (Pugh and Raman, 2006).

Synaptic plasticity (de novo formation and/or LTP) of mf-nuc synapses meets the conditions of necessity for convergence, sufficiency for induction, capacity for expression, and necessity for acquisition of SLRs. As with gr-Pkj plasticity, CS and US inputs converge at the deep cerebellar nucleus. The conditions for inducing synaptic mf-nuc plasticity and learning agree. In intact rats, paired training selectively increases excitatory mf-nuc synapses as well as field potentials in the deep cerebellar nucleus driven by white-matter stimulation (Kleim et al., 2002), and mf-nuc LTP (Racine et al., 1986) is induced in cerebellar slices stimulated with parameters that mimicking the expected pattern of activity during eyelid conditioning (Pugh and Raman, 2006). Either form of synaptic mf-nuc plasticity would suffice to mediate SLRs observed in the absence of the cerebellar cortex. Finally, assuming that induction of SLRs is necessary for learning, that NMDA antagonists or protein synthesis/kinase inhibitors infused into the AIN impair acquisition of eyelid responses without preventing their expression (Bracha et al., 1998; G. Chen and Steinmetz, 2000a, 2000b) is also consistent with the notion that blocking mf-nuc plasticity prevents the induction of SLRs. Future studies should address this more directly using SLRs as a dependent measure.

In principle, three postsynaptic signals could control the induction of mf-nuc plasticity: (1) climbing fiber activity conveyed via collaterals to the deep nucleus, (2) deep nucleus activity (a Hebbian rule), and (3) Purkinje cell activity (Medina and Mauk, 1999). Several converging lines of evidence point to a Purkinje cell rule. For instance, in contrast to earlier work (Lavond and Steinmetz, 1989; Yeo and Hardiman, 1992), more recent studies show that physical or reversible lesions of the cerebellar cortex completely prevent new learning (Bao, Chen, Kim, and Thompson, 2002; Garcia et al., 1999). In vitro studies have also shown that transiently releasing the AIN neurons from hyperpolarization leads to the rebound excitation (Aizenman and Linden, 1999; Llinas and Muhlethaler, 1988) essential for inducing both increased excitability (Aizenman and Linden, 2000; Zhang, Shin, and Linden, 2004) and mf-nuc LTP (Pugh and Raman, 2006). These results suggest that input from the cerebellar cortex, in the form of either learned pause in Purkinje cell activity via LTD at gr-Pkj synapses (Hesslow and Ivarsson, 1994; Medina, Garcia et al., 2000) or a climbing fiber–induced pause in simple spike activity (Bell and Grimm, 1969; Eccles et al., 1967; Sato, Miura, Fushiki, and Kawasaki, 1992), is necessary for inducing mf-nuc plasticity. Proof of this concept is provided by
a recent computational analysis of cerebellar learning, which showed that only
a simulated cerebellum with the Purkinje rule could produce a stable set of
gr-Pkj weights maintained in the presence of background activity in the olivo-
cerebellar system (Medina and Mauk, 1999), consistent with earlier analyses
of VOR adaptation (Miles and Lisberger, 1981). Studies showing the dynamics
of plasticity induction in the cerebellar cortex and AIN (Medina, Garcia, and
Mauk, 2001; Ohyama and Mauk, 2001) as well as the differential effects of
cerebellar cortex lesions on adapted eye movements depending on the time of
the lesion (Broussard and Kassardjian, 2004; Kassardjian et al., 2005; Shutoh,
Ohki, Kitazwa, Itohara, and Nagao, 2006) are also consistent with the Purkinje
cell rule.

C. Relative Roles of the Cerebellar Cortex and Deep
Cerebellar Nuclei

1. The Cerebellar Cortex

Lesions of the cerebellar cortex affect the timing of learned eyelid responses.
Since adaptively timed responses are learned even when temporally invariant
mossy fiber stimulation is used as the CS (Hesslow, Svensson, and Ivarsson,
1999), precerebellar inputs with varying times to onset (Moore, Desmond, and
Berthier, 1989) are not necessary for proper timing. Together with evidence
pointing to the cerebellum as the essential site of plasticity, this suggests that
the cerebellar cortex generates a temporal code. Simulations of the cerebellum
(Buonomano and Mauk, 1994; Medina, Garcia et al., 2000; Medina and
Mauk, 2000) again provide proof of this concept. Presented with patterns of
mossy and climbing fiber inputs obtained from previous recording studies
(Aitkin and Boyd, 1978; Sears and Steinmetz, 1991), the simulations reproduce
adaptively timed learning (Medina, Garcia, et al., 2000; Medina and Mauk,
2000). An examination of the simulation revealed a spectrum of granule cells
peaking in activity at different times since the onset of the tone — some firing
only at the onset of the tone, some only during the early portion of the tone,
some only near the end of the tone, and others throughout the tone (Medina,
Garcia et al., 2000).

Adaptively timed cerebellar output is achieved by coupling the temporal
code with gr-Pkj plasticity. Selective LTD at gr-Pkj synapses active late in the
tone coinciding with the US is necessary, but not sufficient, to produce adap-
tively timed responses. Consistent with this view, a recent study showed that
gr-Pkj LTD is necessary for learning–dependent timing (Koekkoek et al., 2003).
Transgenic L7-PKCi mutant mice, deficient in gr-Pkj LTD due to selective
inhibition of protein kinase C in Purkinje cells, were trained with a tone CS
and periorbital US. These mice acquired eyelid responses with significantly
shorter latencies than wild-type mice late in training; but unlike their wild-
type counterparts, they could not adjust the timing of their responses when the ISI was increased. Interestingly, short-latency eyelid responses survived lesions of the AIN, pointing to a noncerebellar contribution to learning in mice (Koekkoek et al., 2003, 2005). Subtracting out the noncerebellar component, the data are consistent with the notion that gr-Pkj LTD is necessary (but not sufficient) for temporally specific learning.

Simulations and experiments indicate that gr-Pkj LTP is also necessary for acquiring adaptively timed responses. In a simulated cerebellum, the learned responses were not appropriately delayed when LTP was inactivated during training trials (Medina, Garcia et al., 2000). Thus, gr-Pkj LTP helps to shape appropriately delayed responses by selectively strengthening synapses active only during the early portion of the CS (in the absence of the US) to suppress the increased cerebellar output due to selective LTD of synapses active later in the CS (in the presence of the US) (Medina, Garcia et al., 2000). To test this hypothesis, we removed a fraction of the Purkinje cells after establishing robust learning to unmask responses with a small short-latency component in addition to a later adaptively timed component (Medina, Garcia et al., 2000). If the hypothesis is correct, then with continued training the short-latency component should eventually disappear due to LTP of the remaining early active gr-Pkj synapses. This prediction was confirmed when partial cerebellar cortex lesions initially unmasked a bimodal response whose early component gradually extinguished with further training (Medina, Garcia et al., 2000).

2. The Deep Cerebellar Nucleus

It has long been known that the AIN is required for the expression of learning, at least in rabbits (McCormick, Clark et al., 1982; McCormick and Thompson, 1984a). Current evidence is consistent with the hypothesis that the induction of plasticity at mf-nuc synapses is necessary for learning. Together with evidence from VOR adaptation, plasticity at mf-nuc synapses may consolidate long-term changes of cerebellar output in responses to stable changes in the pattern of cerebellar inputs. In addition, there is some evidence that these long-term changes mediate savings of learning (see later).

One line of evidence that the induction of mf-nuc plasticity is necessary for learning comes from reversible-lesion studies. A simulated cerebellum (Medina, Garcia, and Mauk, 2001) with bidirectional plasticity rules at gr-Pkj and mf-nuc synapses, respectively controlled by climbing fiber and Purkinje cells, respectively, predicts that learning in the cerebellar cortex should occur first, followed by an increase in cerebellar output as mf-nuc plasticity is induced. This prediction was confirmed when reversible lesions of the cerebellar cortex at different time points during acquisition revealed that learning and SLRs developed in parallel, suggesting that the induction of AIN plasticity (as measured
by the presence of SLRs) determines the rate of learning (Medina, Garcia, and Mauk, 2001). A related study tested whether the expression of learning required AIN plasticity by utilizing the temporal specificity of learning in the cerebellar cortex (Ohyama and Mauk, 2001). In the first phase, subjects were trained with a long tone/ISI to subthreshold levels in order to restrict plasticity to the cerebellar cortex. As expected, when the cerebellar cortex was pharmacologically disconnected, no SLRs were observed. In the second phase, subjects were trained robustly with a short tone/ISI to induce AIN plasticity. As expected, disconnecting the cerebellar cortex after this phase unmasked SLRs. In the crucial test, presenting the original long tone evoked conditioned responses with two peaks, each timed to the ISIs in the second and first phases, respectively. Although blocking glutamatergic transmission in the AIN does not significantly affect the expression of normal conditioned eyelid responses (Aksenov, Serdyukova, Bloedel, and Bracha, 2005; Attwell et al., 2002), this may indicate that an increased excitability of AIN neurons is sufficient for expressing the learning in the cerebellar cortex (Ohyama et al., 2006).

Several rabbit studies have shown that infusing agents into the AIN that might block cellular processes necessary for inducing mf-nuc plasticity prevents acquisition but not expression of conditioned eyelid responses. This pattern of results has been observed after infusing the NMDA receptor antagonist AP5 (G. Chen and Steinmetz, 2000b), the protein kinase inhibitor H7 (G. Chen and Steinmetz, 2000a), the transcription inhibitor actinomycin D (Gomi et al., 1999), or the protein synthesis inhibitor anisomycin (Bracha et al., 1998) during and after training. Although these studies are subject to the caveat that the drugs may have leaked to the cerebellar cortex, collectively they are consistent with the notion that induction of AIN plasticity is required for acquisition.

The induction of mf-nuc plasticity may contribute to savings (Medina, Garcia, and Mauk, 2001), which refers to the observation that relearning or learning to a new CS is faster than original acquisition (Kehoe, 1988). In conditioning of the rabbit’s third eyelid, both rapid reacquisition after extinction (Macrae and Kehoe, 1999; Napier, Macrae, and Kehoe, 1992) and cross-modal savings (Holt and Kehoe, 1985; Kehoe and Holt, 1984; Kehoe, Macrae, and Horne, 1995; Kehoe, Morrow, and Holt, 1984; Kehoe and Napier, 1991; Macrae and Kehoe, 1999; Schreurs and Kehoe, 1987) have been observed. Simulation analyses indicate that extinction is governed largely by reversal of gr-Pkj plasticity, which slows the reversal of mf-nuc plasticity (Medina, Garcia, and Mauk, 2001). This suggests that the degree of residual mf-nuc plasticity determines the degree of savings during subsequent acquisition (Medina, Garcia, and Mauk, 2001). This prediction was tested in animals trained for at least five sessions with a tone CS and US and then extinguished for up to 45 days. Querying mf-nuc plasticity at various time points during the course of
extinction revealed that SLRs could continue to be unmasked by reversible cerebellar cortex lesions despite the complete extinction of normal conditioned responses. The decline of SLRs was much slower than the extinction of normal learned responses, and the percentage of SLRs was correlated with the degree of savings observed during a subsequent reacquisition session.

These results suggest that other forms of savings, such as cross-modal savings (e.g., from tones to lights, and vice versa), might also be mediated by AIN plasticity (Hansel, Linden, and D'Angelo, 2001; Medina, Garcia, and Mauk, 2001). A recent study found that SLRs did not generalize across auditory and visual modalities. This suggests that mf-nuc plasticity is not involved in cross-modal savings. Instead, a global increase in intrinsic excitability of AIN neurons may be involved (Hansel, Linden, and D'Angelo, 2001; Ohyama, Nores, and Mauk, 2003). Future studies could address this hypothesis.

D. Bidirectional Learning and Control of Climbing Fiber Activity

As noted earlier, a major challenge for the gr-Pkj LTD hypothesis of learning (Albus, 1971; Ito, 1972) is that both granule cells (Eccles et al., 1967) (10–50 Hz) and climbing fibers are spontaneously active (De Schutter, 1995; De Zeeuw et al., 1998; Gilbert, 1975; Glickstein, 1992; Llinas and Welsh, 1993) (1–2 Hz). Hence, if gr-Pkj LTD were the only mechanism, all synapses would eventually become weakened. Recent studies suggest that bidirectional plasticity at the gr-Pkj synapse and inhibitory nucleo-olivary feedback (Kenyon et al., 1998a, 1998b; Medina, Garcia et al., 2000; Medina and Mauk, 1999) allow the cerebellum to learn and extinguish adaptively timed responses despite this spontaneous activity.

The key to success is the triple-negative feedback control implemented by the olivo-cortico-nuclear loop (Fig. 13-1). Coupled with bidirectional gr-Pkj plasticity, this loop is critical for keeping climbing fiber activity within the range of 1–2 Hz. For instance, a treatment that increased (decreased) climbing fiber activity (Llinas and Volkind, 1973) would lead to greater gr-Pkj LTD (LTP) and hence decreased (increased) simple-spike activity (i.e., the Purkinje cell spikes due to granule cell activity). The resulting increase (decrease) in AIN activity in turn would decrease (increase) the level of climbing fiber activity back to its spontaneous rate via increased (decreased) nucleo-olivary inhibition. This self-regulation stabilizes synaptic weights at gr-Pkj synapses and maintains climbing fiber activity at an equilibrium level (Bloedel and Bracha, 1998; Miall, Keating, Malkmus, and Thach, 1998) (Fig. 13-4A).

In this context, acquisition and extinction of adaptively timed conditioned responses are the olivo-cerebellar system's solutions to restoring the equilibrium level of climbing fiber activity (Kenyon et al., 1998a, 1998b) on
FIGURE 13-4 Inhibitory feedback from the deep cerebellar nucleus to the inferior olive contributes to self-regulation of climbing fiber activity and bidirectional learning. A. Simulated raster plots showing self-regulation of climbing fiber activity. The inhibitory feedback from the deep cerebellar nucleus (N) to the inferior olive completes a triple-negative feedback loop that drives climbing fiber (CF) activity back to an equilibrium firing rate (1–2 Hz, right panels) regardless of whether the initial conditions of the simulation promote high (top panels) or low (bottom panels) cerebellar output. B. Simulated raster plots showing Purkinje cell (P), deep cerebellar nucleus cell (N), and climbing fiber (CF) activity in response to a CS presented alone before training, during pairings of the CS and US, and extinction (i.e., the CS presented alone). Each row shows 2,000 ms from a single trial [500 ms before, 1,050 ms during (shaded area), and 450 ms after the CS]. During paired trials, the 50-ms US coterminates with the CS. Time progresses from top to bottom. Paired training gradually leads to a suppression of Purkinje cell activity (left) and increase in deep nucleus cell activity (center) during the CS, which in turn decreases the probability of the US activating a climbing fiber (right). Extinction leads to a gradual restoration of high Purkinje cell activity (bottom left) and decreased cerebellar output (bottom center), accompanied by a transient suppression of climbing fiber activity (bottom right) during the CS. C. Extinction of conditioned eyelid responses is blocked by preventing inhibition of climbing fiber activity via infusions of the GABA\(_A\) antagonist picrotoxin into the inferior olive (red traces). The left panel shows normal extinction during ACSF infusions into the inferior olive (blue traces). [Reprinted with permission from Medina, Nores, and Mauk (2002).]
a shorter time scale. For instance, acquisition disrupts climbing fiber equilibrium by systematically increasing activity at the end of the CS (Fig. 13-4B). Due to temporal coding and plasticity in the cerebellar cortex, Purkinje cells learn to suppress activity later in the CS (Hesslow and Ivarsson, 1994; Medina, Garcia et al., 2000). This allows greater activity in the cerebellar nucleus, which in turn suppresses climbing fiber activity via nucleo-olivary feedback (Hesslow and Ivarsson, 1996; Sears and Steinmetz, 1991), especially near the time of the US. In this way the acquisition of eyelid responses restores climbing fiber activity to its equilibrium level. The reverse occurs in extinction. The omission of the US causes a transient decrease in the probability of climbing fiber activity around its expected time of occurrence due to nucleo-olivary inhibition from the conditioned response. This signal for the absence of the US, which depends on a nonzero level of spontaneous climbing fiber activity (Albus, 1971; Medina, Nores, and Mauk, 2002), induces gr-Pkj LTP and decreases cerebellar output back to baseline (Fig. 13-4B).

One prediction of this view is that eliminating the inhibitory nucleo-olivary feedback should block the transient suppression of climbing fiber activity and thereby prevent the extinction of previously learned responses (Fig. 13-4C). This prediction was recently tested in rabbits trained to a tone CS and then given infusions of the GABA_A antagonist picrotoxin into the inferior olive to block nucleo-olivary feedback during extinction (Medina, Nores, and Mauk, 2002). Consistent with the prediction, conditioned responses failed to extinguish when nucleo-olivary inhibition was blocked, while infusing the AMPA antagonist NBQX into the inferior olive in a subsequent training session mimicked extinction despite continued presentation of the US. A similar effect was observed in an experiment in which training to one CS (CS1) normally prevents subsequent learning to a second CS2 paired with CS1 and the US. Consistent with the notion that this so-called blocking effect (Kamin, 1969) is due to suppression of the inferior olive by the learned response to CS1, infusing picrotoxin during the second phase of training rescued learning to CS2 (Kim, Krupa, and Thompson, 1998).

V. CONTRIBUTION OF LEARNING TO CEREBELLAR INFORMATION PROCESSING

Eyelid conditioning displays two temporal properties that provide insights into what the cerebellum computes. First, learning is associative and optimal within a limited range of interstimulus intervals (ISIs: intervals between CS and US onsets) (Gormezano et al., 1983; Kehoe and Macrae, 2002). Learning initially increases as the ISI increases above 100 ms and then decreases gradually as the ISI increases beyond 500 ms (Gormezano et al., 1983; Kehoe and Macrae, 2002; Ohyama, Nores, Murphy, and Mauk, 2003) (Fig. 13-5). This suggests
that for cerebellar output to increase, the CS-activated mossy fibers must reliably precede the US-driven climbing fiber input by at least 100 ms and no more than a few seconds. Second, learning is adaptively timed — the conditioned eyelid response is gauged such that maximum closure occurs at or near the expected time of the US (Frey and Ross, 1968; Schneiderman and Gormezano, 1964; Smith, 1968). Thus, when mossy fiber activity reliably signals a climbing fiber response, not only does cerebellar output increase, but it does so at the appropriate time.

These properties illuminate how the cerebellum contributes to movements. Sensory input is essential for motor control (Sanes, Mauritz, Evarts, Dalakas, and Chu, 1984), and one way in which it can be used to control movements is via feedback. A thermostat uses feedback to control temperature — on detecting a difference between actual and desired temperature, it activates the
cooler or heater. The problem with this strategy is that it is slow, since adjustments are made only after a difference between desired and actual values is detected. This leads feedback systems to oscillate when driven fast (Kawato and Gomi, 1992; Massaquoi and Topka, 2002; Wolpert and Miall, 1996). In contrast, feed-forward systems anticipate predictable events. If opening a window reliably decreases temperature, a well-adjusted feed-forward thermostat heats the room rapidly whenever the window is subsequently opened. This makes feed-forward systems fast, but at a price—they must first learn to associate changes (temperature drop) with cues (opening a window) to produce an anticipatory response. To be accurate, feed-forward systems must also anticipate when change occurs in relation to a particular cue. If opening a small window decreases temperature more slowly than opening a large one, a thermostat would need to know when to start heating in each case. Therefore, an accurate feed-forward control system displays learning that is both associative and temporally specific (Ohyama, Nores, Murphy, and Mauk, 2003; Wolpert and Miall, 1996).

This is precisely the kind of learning displayed by eyelid conditioning. The cerebellum thus computes a temporally specific feed-forward prediction that minimizes climbing fiber responses driven by either external (e.g., somatosensory) or internal (e.g., cortical) input. Like previous authors, we suggest that the cerebellum comprises part of a feed-forward controller (Ito, 1970; Kawato and Gomi, 1992; Massaquoi and Topka, 2002), but we additionally emphasize the temporal aspects of its computation. Temporally specific feed-forward predictions probably apply generally across the cerebellum, because the organization of the cerebellar cortex is remarkably uniform (Eccles et al., 1967; Ito, 1984) and strong parallels are observed across learned eye movements that depend on the cerebellum (Ohyama, Nores, Murphy, and Mauk, 2003; Raymond, Lisberger, and Mauk, 1996). For instance, like eyelid conditioning, adaptive gain modification of the VOR (Ito, 1982; Miles and Lisberger, 1981; Robinson, 1976), saccades (Barash et al., 1999; Takagi, Zee, and Tamargo, 1998) and smooth pursuit (Rambold, Churchland, Selig, Jasmin, and Lisberger, 2002; Takagi, Zee, and Tamargo, 2000) all require the cerebellum, and cerebellar output appears crucial for the timing of saccades (Barash et al., 1999; Robinson and Fuchs, 2001; Robinson, Straube, and Fuchs, 1993; Takagi, Zee, and Tamargo, 1998; Thier, Dicke et al., 2000), VOR (Pastor, de la Cruz, and Baker, 1994; Raymond, Lisberger, and Mauk, 1996), and predictive pursuit (Barnes and Donelan, 1999; Kettner et al., 2002; Medina, Carey, and Lisberger, 2005; Vercher and Gauthier, 1988). Studies of single- and multi-joint limb movements also suggest that the cerebellum learns internal models of movement dynamics (Ebner, 1998; Imamizu et al., 2000; Kawato, 1999; Mussa-Ivaldi, 1999; Thach, 1998; Thoroughman and Shadmehr, 2000), i.e., feed-forward control signals that compensate for climbing fiber inputs in an adaptively timed manner. Finally, the temporal constraints of eyelid condition-
ing suggest that the computation contributes to any process, be it sensory, cognitive (Highstein and Thach, 2002; Schmahmann, 1997), emotive, or motor, that occurs on a relatively short time scale.

VI. CONCLUSION

The cerebellum clearly learns. Recent studies involving detailed computer simulation analyses and permanent and/or reversible lesions suggest that the plasticity underlying this learning is distributed between the cerebellar cortex and its downstream targets, with plasticity at gr-Pkj synapses mediating temporally specific learning and plasticity at mf-nuc synapses increasing the gain of cerebellar output. Bidirectional plasticity in the cerebellar cortex and deep cerebellar nucleus, respectively, are controlled by climbing fibers and Purkinje cells. The network dynamics of the cerebellar cortex could create a temporal code in the form of granule cells firing with different temporal delays during a CS, which can help shape the timing of cerebellar output via gr-Pkj plasticity. Inhibitory nucleo-olivary feedback is crucial for controlling bidirectional plasticity in the cerebellar cortex, a notion that has yet to be tested in other forms of cerebellar learning and adaptation.

The remarkably straightforward way in which eyelid conditioning engages the cerebellum — the CS and US, respectively, activate the mossy and climbing fibers, and the learned behavioral response is driven by the output of a deep cerebellar nucleus — makes the behavioral properties of eyelid conditioning a relatively direct window into what the cerebellum computes. The temporal properties of eyelid conditioning suggest that the cerebellar learning is involved in making temporally specific feed-forward predictions, a computation that is likely across the cerebellum, given its uniform circuitry. Such a computation can encapsulate the many functions previously attributed to the cerebellum. It also offers an explanation for the dysmetric and uncoordinated movements seen in patients with cerebellar pathology, and it provides a foundation for understanding how the cerebellum might contribute to nonmotor functions.

REFERENCES


