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# CEREBELLUM-DEPENDENT LEARNING: The Role of Multiple Plasticity Mechanisms

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■ **Abstract** The cerebellum is an evolutionarily conserved structure critical for motor learning in vertebrates. The model that has influenced much of the work in the field for the past 30 years suggests that motor learning is mediated by a single plasticity mechanism in the cerebellum: long-term depression (LTD) of parallel fiber synapses onto Purkinje cells. However, recent studies of simple behaviors such as the vestibulo-ocular reflex (VOR) indicate that multiple plasticity mechanisms contribute to cerebellum-dependent learning. Multiple plasticity mechanisms may provide the flexibility required to store memories over different timescales, regulate the dynamics of movement, and allow bidirectional changes in movement amplitude. These plasticity mechanisms must act in combination with appropriate information-coding strategies to equip motor-learning systems with the ability to express learning in correct contexts. Studies of the patterns of generalization of motor learning in the VOR provide insight about the coding of information in neurons at sites of plasticity. These principles emerging from studies of the VOR are consistent with results concerning more complex behaviors and thus may reflect general principles of cerebellar function.

## INTRODUCTION

Motor learning is the process of improving the smoothness and accuracy of movements. It is obviously necessary for complicated movements such as playing the piano and climbing trees, but it is also important for calibrating simple movements like reflexes, as parameters of the body and environment change over time. The cerebellum is critical for motor learning. As a result of the universal need for properly calibrated movement, it is not surprising that the cerebellum is widely conserved in vertebrates. Thus the basic architecture of the cerebellum, renowned for its beauty, is also generally useful. In this review we describe the recent progress made in understanding the function of the cerebellum in encoding motor memories.

We begin by describing how the anatomy of the cerebellum inspired a model of motor learning that has influenced much of the research in the field for the

last 30 years. We then review the evidence for and against this model from studies of a simple behavior, the vestibulo-ocular reflex (VOR). This model and the main competing model each propose a single plasticity mechanism to explain motor learning, but neither model can account for all of the data regarding motor learning in the VOR. One resolution of these two competing hypotheses is that more than one plasticity mechanism may contribute to cerebellum-dependent motor learning. Recent work suggests that multiple plasticity mechanisms regulate the amplitude, dynamics, and consolidation of learned movements. The properties of motor learning also are influenced by the information-coding strategies used at the sites of plasticity. Studies of the generalization of learning to stimuli and contexts different from those present during learning are revealing constraints on these coding strategies. Analysis of the interaction of plasticity and coding in the VOR circuit is beginning to unveil how the cerebellum and related structures can support motor learning that is reliable yet flexible.

## A MODEL OF LEARNING INSPIRED BY THE UNIQUE ARCHITECTURE OF THE CEREBELLUM

The architecture of the cerebellum is often described as crystalline because it is composed of repeated modules, each containing the same few cell types connected in the same manner. Different regions of the cerebellum receive different inputs and project to different targets, yet the uniformity of the cerebellar architecture suggests that these modules process the signals they receive in similar ways. Thus one can be optimistic that studying the operation of the cerebellum during one learning task may reveal general principles that characterize the function of the cerebellum in many tasks.

An influential model of the cerebellum proposes that its general function is to act as a pattern classification device that can be taught to generate an appropriate output in response to an arbitrary input (Figure 1) (Albus 1971, Marr 1969). Mossy fibers provide sensory and motor inputs to the cerebellum. Purkinje cells provide the sole output of the cerebellar cortex and drive specific movements. The mossy fiber inputs are connected to the Purkinje cell outputs by a disynaptic pathway through cerebellar granule cells, as well as by pathways through inhibitory interneurons. Over a hundred thousand granule cell axons, known as parallel fibers, synapse onto a single Purkinje cell. The Marr-Albus model proposes that changes in the strengths of parallel fiber–Purkinje cell synapses could store stimulus-response associations by linking inputs with appropriate motor outputs.

The Marr-Albus model was inspired by some unusual and striking features of the architecture of the cerebellum. One striking feature is the enormous number of granule cells, which make up roughly half the neurons in the brain. According to the Marr-Albus model, the large number of granule cells enables this population of neurons to perform pattern separation. Similar patterns of mossy fiber activity would be sparsely reencoded into largely nonoverlapping populations of

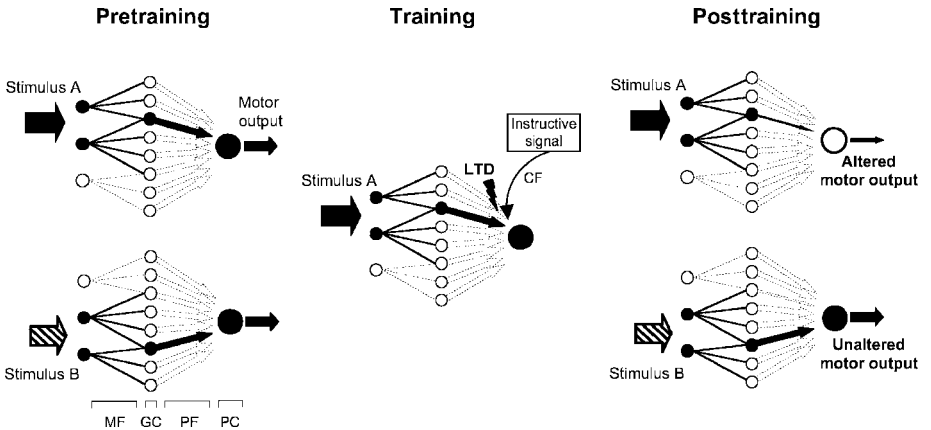


**Figure 1** The Marr-Albus model of motor learning. In this model, sparse reencoding in the cerebellum enables learning to create very precise stimulus-response mappings. Granule cells (GC) spike only when sufficient mossy fiber (MF) input is present, causing overlapping mossy fiber input patterns to be reencoded in nonoverlapping populations of granule cells. Plasticity controlled by climbing fibers (CF) weakens the strength of parallel fiber (PF)–Purkinje cell (PC) synapses (via LTD, indicated by the lightning bolt). LTD alters the efficacy of stimulus A firing the Purkinje cell and thus produces altered motor output. Because stimulus B activates different parallel fibers than stimulus A activates, the motor response to stimulus B is unaltered by training. Open circles and dotted lines indicate inactive neurons and synapses. Filled circles and solid lines indicate active neurons and synapses. The thin parallel fiber arrow indicates a synapse weakened by LTD.

granule cell activity, thereby allowing sensory events encoded by similar mossy fiber patterns to be associated with different motor outputs.

Another striking feature of the cerebellum is the climbing fiber input to Purkinje cells. Each Purkinje cell receives input from just one climbing fiber axon, which originates in the inferior olive. The climbing fiber forms a very strong synapse onto the Purkinje cell, with each presynaptic spike triggering a postsynaptic spike. Despite the powerful connection, the climbing fiber makes only a small contribution to the total spike output of the rapidly firing Purkinje cell because the climbing fiber fires at a much lower rate. Therefore it was postulated that the climbing fiber may serve a special function other than ordinary signal transmission. According to the Marr-Albus model, the climbing fiber provides the instructive signal that regulates the strength of parallel fiber–Purkinje cell synapses and thereby guides the encoding of new stimulus-response associations. Marr and Albus differed as to the nature of the instructive signal: Marr believed it to be a positive reinforcer, strengthening parallel fiber synapses when the Purkinje cell output was correct, whereas Albus believed it to be an error signal, weakening synapses when the output was incorrect. Consistent with the latter idea, electrical stimulation of climbing

fibers induces a decrease in synaptic strength, called cerebellar LTD, in parallel fibers that are active simultaneously (Ito et al. 1982b). The Albus model proposed that this single plasticity mechanism would mediate motor learning by restricting the expression of a movement coded for by a specific Purkinje cell to specific contexts in which that motor response was appropriate. For many years, the elegance of the Marr-Albus theory has focused attention on cerebellar LTD as a key candidate for the plasticity mechanism mediating motor learning.

## MOTOR LEARNING IN A SIMPLE BEHAVIOR: THE VESTIBULO-OCULAR REFLEX

Although motor learning is capable of achieving Olympic feats of skill, much has been learned from studies of simple behaviors. In this review we focus on recent advances in understanding motor learning from studies of the VOR. The VOR has many properties that make it amenable to experimentation, including easily controlled sensory inputs, quantifiable motor outputs, a well-characterized circuit anatomy, and the capacity to be studied in a variety of species.

The VOR is a reflex eye movement that stabilizes images on the retina during head movement by producing an eye movement in the direction opposite to head movement. The VOR elicits eye movements in response to both horizontal and vertical head rotations, as well as head translations. Although the function of the VOR is to support clear vision, the VOR is measured in the dark to isolate the eye movements driven by vestibular stimuli from eye movements driven by visual stimuli. The performance of the VOR is characterized by the gain, which is defined as the ratio between eye and head velocities. If the gain of the VOR is poorly calibrated, then head movements result in image motion on the retina, resulting in blurred vision. Under such conditions, motor learning adjusts the gain of the VOR to produce more accurate eye motion. Such adjustments are needed throughout life, as neurons and muscles develop, weaken, and die—or for humans, when a new pair of eyeglasses changes the magnification of the visual field. In the laboratory, we induce motor learning in the VOR by pairing image motion with head motion. Depending on the relative direction of head motion and image motion, the gain of the VOR can be adaptively increased or decreased. An increase in VOR gain is induced by image motion in the direction opposite that of the head (gain-up stimulus), and a decrease in VOR gain is induced by image motion in the same direction as the head (gain-down stimulus) (Figure 2).

The main neural circuit for the VOR is simple (Figure 3): Vestibular nuclei in the brainstem receive signals related to head movement from the vestibular nerve and project to oculomotor nuclei, which contain motoneurons that drive eye muscle activity. The flocculus and ventral paraflocculus of the cerebellum form an inhibitory side loop in the VOR circuit. Mossy fibers provide vestibular input to the cerebellum, and Purkinje cells inhibit VOR interneurons in the vestibular nucleus. For the VOR, the vestibular nuclei serve the role that the deep cerebellar

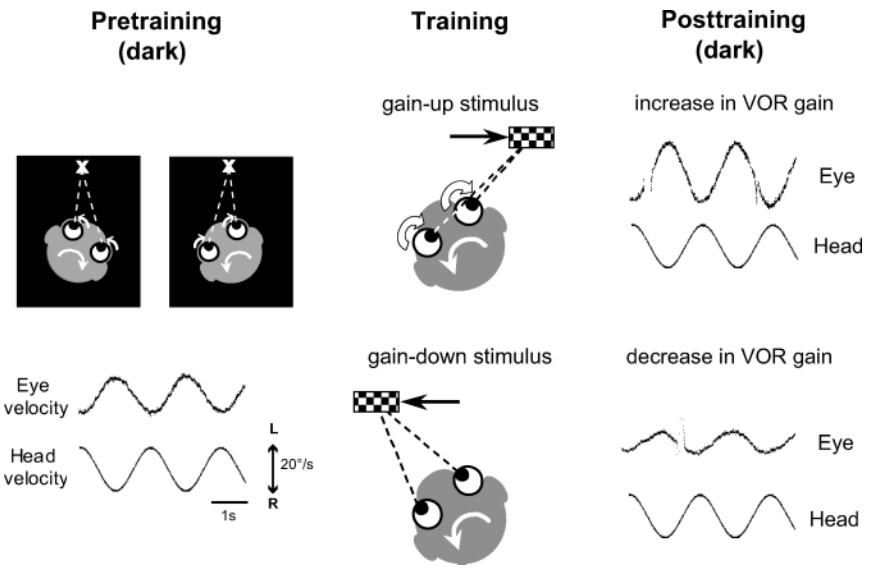


**Figure 2** Motor learning in the VOR. Before learning, eyes move with the same speed, but in the opposite direction, as the head, keeping the eyes stationary in world coordinates. Focal points of the eyes are indicated by an *x*. An increase in VOR gain is produced by training with image motion in the direction opposite that of the head (gain-up stimulus). A decrease in VOR gain is produced by training with image motion in the same direction as the head (gain-down stimulus). After each training session, the VOR is remeasured in the dark with the same head movement stimulus used in the pretraining measurements. The data shown are representative traces acquired from monkeys after 2 h of training.

nuclei serve for other cerebellum-dependent behaviors. Thus, when we refer to the contribution of the cerebellum to the VOR, we mean the cerebellar cortex.

## ROLE OF THE CEREBELLUM IN MOTOR LEARNING IN THE VOR: TWO INFLUENTIAL MODELS

Lesion and recording studies demonstrate the necessity of the cerebellum for motor learning in the VOR. Surgical lesions, pharmacological inactivation, and genetic disruption of the cerebellum all abolish the ability to adaptively modify VOR gain (Ito et al. 1982a, Koekkoek et al. 1997, Lisberger et al. 1984, Luebke & Robinson 1994, McElligott et al. 1998, Michnovicz & Bennett 1987, Nagao 1983, Rambold et al. 2002, Robinson 1976, Van Alphen et al. 2002), and Purkinje cells exhibit altered responses during the performance of the VOR after motor learning (Hirata & Highstein 2001, Lisberger et al. 1994a, Miles et al. 1980, Nagao 1989,

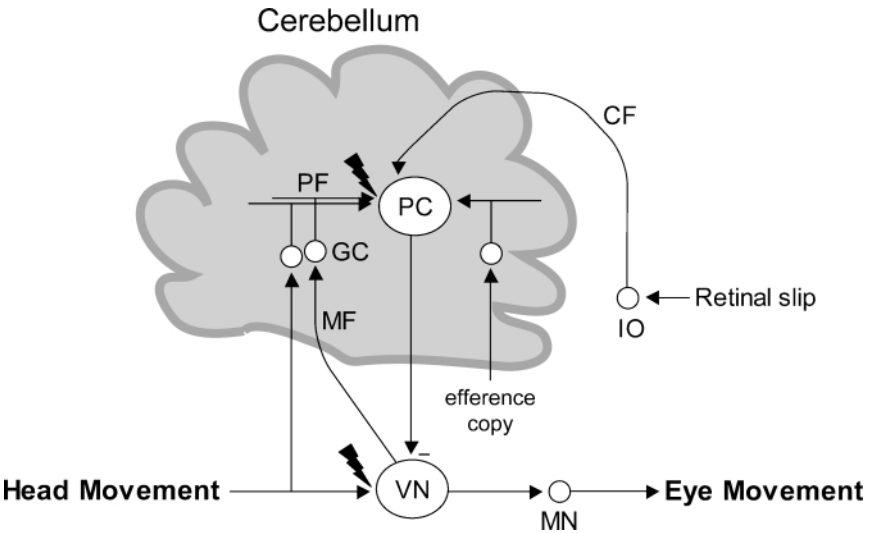


**Figure 3** Proposed sites of plasticity in the circuit for the VOR (indicated by lightning bolts). CF, climbing fibers; GC, granule cells; IO, inferior olive; MF, mossy fibers; MN, oculomotor nuclei; PC, Purkinje cells; PF, parallel fibers; VN, vestibular nuclei.

Watanabe 1984). On the basis of what is known about the contribution of Purkinje cells to eye movements, the responses of Purkinje cells during the VOR change in the correct direction to contribute to the altered eye movement response to head movement. This finding suggests that the cerebellum contributes to the expression of the altered VOR gain.

Despite general agreement that the cerebellum is important for motor learning in the VOR, there is disagreement over the specific role it plays; two long-standing hypotheses provide two very different accounts. Ito proposed an implementation of the Marr-Albus hypothesis (Ito 1972, 1982), in which the role of the cerebellum is to store the motor memory for the learned change in VOR gain. More specifically, Ito proposed that during training, the pairing of visual image motion and head motion causes coincident visually driven climbing fiber activity and vestibularly driven parallel fiber activity, which results in LTD of the active parallel fibers. The climbing fiber, which reports retinal slip and therefore the error in the function of the VOR, acts as the instructive signal guiding plasticity. The altered weights of the vestibular parallel fiber–Purkinje cell synapses would cause an altered eye movement response to the vestibular stimulus and thus could encode the motor memory for the altered VOR gain. An alternative model was proposed by Miles & Lisberger (1981). They proposed that the role of the cerebellum was not to store the motor memory but rather to compute the instructive signal guiding the induction of plasticity. According to this model, Purkinje cells convey the instructive signal to the vestibular nucleus, where it triggers heterosynaptic changes in the connections

between vestibular afferents and neurons in the vestibular nucleus. The Miles-Lisberger model attributes the altered responses of Purkinje cells to altered input to the cerebellum from mossy fibers carrying an efference copy of the altered eye movement command created in the vestibular nucleus. Thus the Purkinje cells could exhibit learning-related changes in their responses during performance of the VOR, even if no synaptic changes occur within the cerebellum. In contrast, the Marr-Albus-Ito model attributes altered Purkinje cell responses, recorded during performance of the VOR, to synaptic changes onto Purkinje cells themselves.

Thus two long-standing hypotheses propose (*a*) different sites of plasticity for motor learning, (*b*) different instructive signals guiding plasticity at these sites, and (*c*) different explanations for the changes recorded in Purkinje cells during performance of the VOR. Experimental tests of these three predictions provide support for and against each of these two hypotheses.

## Evidence for a Role of Plasticity in the Vestibular Nuclei

Support for plasticity in the vestibular nucleus comes from experiments that evaluate whether the changes in Purkinje cells are due to plasticity in the vestibular pathways through the cerebellum or are simply a reflection of altered efference copy resulting from plasticity elsewhere in the circuit. This issue cannot be resolved by recording from Purkinje cells during the performance of the VOR because both vestibular and efference-copy pathways are activated. Therefore, several investigators recorded from Purkinje cells during behavioral paradigms designed to independently assess the signals carried in these two pathways. One way to isolate the input to Purkinje cells carried by vestibular pathways is to rotate the animal while it holds its eyes still (VOR cancellation). Another way is to measure the input from efference-copy pathways during pursuit eye movements and to subtract this from the activity recorded during performance of the VOR. Measured in both of these ways, the sensitivity of Purkinje cells to vestibular input changes in the direction opposite to that predicted by the action of cerebellar LTD, and in the direction opposite that required to account for the change in VOR gain, given the known connectivity of Purkinje cells with their downstream targets (Hirata & Highstein 2001, Lisberger et al. 1994a, Miles et al. 1980). This result is difficult to reconcile with the idea that plasticity of the vestibular inputs to Purkinje cells is the primary mediator of the learned change in the gain of the VOR. Although some investigators have raised concerns about the assumptions associated with comparing neural responses across these different behavioral conditions (Ito 1993, Tabata et al. 2002), further comparisons between neural signals recorded in a single behavioral condition circumvent these concerns and provide sound evidence for extracerebellar plasticity. In particular, the responses of vestibular nucleus neurons during VOR cancellation exhibit learning-related changes that cannot be accounted for by the learning-related changes in the responses of Purkinje cells during VOR cancellation (Lisberger et al. 1994b). Because the changes recorded in the vestibular nucleus neurons cannot be accounted for by the input

they receive from Purkinje cells, the changes in the vestibular nucleus must result from plasticity at a site outside the cerebellum.

The latencies of learned responses are also consistent with plasticity in the vestibular nuclei (reviewed in detail in du Lac et al. 1995). Briefly, eye movements that depend only on the direct pathway through the vestibular nuclei should be executed with a shorter latency than eye movements that depend on the side loop through the cerebellum. The short latency of the first modified component of the VOR suggests that plasticity could occur in the direct pathway through the vestibular nuclei. However, in the broad distribution of Purkinje cells in the cerebellum, some cells respond with latencies short enough that they could contribute to the earliest modified component of the VOR. Furthermore, the pathway through the cerebellum could contribute to the modification of the VOR at longer latencies after onset of head movement.

A number of studies have used lesions or inactivation of the cerebellum after training to evaluate whether memory storage occurs outside the cerebellum. Investigators have obtained a variety of outcomes in such studies (Luebke & Robinson 1994, McElligott et al. 1998, Nagao & Kitazawa 2003, Partsalis et al. 1995, Pastor et al. 1994, Robinson 1976), with most finding that lesions did not completely eliminate the expression of learned changes in VOR gain. This retention of learned changes after lesions of the cerebellum would indicate a site of memory storage outside the cerebellum, if the lesion could be shown to be complete, which is difficult to do. In addition, several of these studies reported at least a partial loss of learned changes, which could reflect a site of memory storage in the cerebellum but could also simply reflect a requirement for the cerebellum for the expression of changes stored elsewhere in the VOR circuit.

Anatomical studies of another form of cerebellum-dependent learning also indicate a role for a site downstream of Purkinje cells in the storage of cerebellum-dependent memories. After a classical-conditioning paradigm in which rats were trained to blink in response to a tone (by pairing a tone with an airpuff), excitatory synapse number increased in the deep cerebellar nucleus (Kleim et al. 2002). No changes were found, however, in animals that experienced unpaired tones and airpuffs, which suggests that the anatomical changes observed could be attributed to learning. To the extent that changes in synapse number reflect plasticity, these results corroborate a contribution of the deep cerebellar nuclei to memory storage. In the cerebellar cortex, Purkinje cell morphology also changed after eyeblink conditioning, but these changes also were observed in the unpaired controls and therefore may be induced simply by activity in the cerebellar circuitry, rather than by learning (Anderson et al. 1999).

## Evidence for a Role of Cerebellar LTD

In the Marr-Albus-Ito model, changes in VOR gain result from LTD of parallel fibers carrying vestibular signals. In recent years several groups have disrupted molecular pathways required for cerebellar LTD and reported learning

impairments. The results of these studies are consistent with a role of cerebellar LTD in motor learning in the VOR, but in each of these studies the learning impairment could potentially be explained by disruption of plasticity mechanisms other than LTD or disruption of signal processing in the cerebellum, resulting in a functional cerebellar lesion. Although no individual result is conclusive, these studies collectively motivate further investigation of how LTD may contribute to motor learning.

Nitric oxide (NO) activity contributes to the induction of cerebellar LTD (Daniel et al. 1993, Lev-Ram et al. 1997, Shibuki & Okada 1991). Blocking cerebellar NO activity by applying scavengers or inhibitors prevents motor learning in the VOR in monkeys, rabbits, and goldfish (Li et al. 1995, Nagao & Ito 1991). Thus a NO-dependent process is important for changes in VOR gain. This NO-dependent process could be cerebellar LTD, but NO has additional actions on the VOR circuit that could potentially mediate its effects on learning. NO is involved in a form of parallel fiber–Purkinje cell long-term potentiation (LTP) (Lev-Ram et al. 2002), and it regulates the intrinsic spiking of Purkinje cells (Smith & Otis 2003), modulates synapses onto granule cells (Wall 2003), and alters processing in the vestibular nuclei (Moreno-Lopez et al. 2002).

Another manipulation that disrupts LTD targets the $\delta 2$ subunit of the glutamate receptor (GluR$\delta 2$), which is expressed selectively in Purkinje cells. Mice lacking GluR$\delta 2$ show neither cerebellar LTD nor motor learning in the VOR (Katoh et al. 2001). However, these mice have alterations in their basal VOR, so the impairment in motor learning may reflect a performance deficit rather than a learning deficit per se.

Another molecule important for cerebellar LTD is protein kinase C (PKC) (Crepel & Krupa 1988, Linden & Connor 1991). Transgenic mice expressing an inhibitor of protein kinase C (PKCI), under control of the Purkinje cell–specific promoter L7, showed impaired LTD in cultured Purkinje cells. These mice also exhibited no motor learning in the VOR with one hour of training (De Zeeuw et al. 1998). The impairment of LTD may have been responsible for the learning impairment. However, in Purkinje cells, PKC is a multifunctional enzyme that regulates potassium conductances and plasticity of the climbing fiber–Purkinje cell synapse, in addition to plasticity of the parallel fiber–Purkinje cell synapse (Hansel & Linden 2000, Widmer et al. 2003). Thus the transgene may disrupt normal signaling through the Purkinje cells during motor learning and thereby corrupt the instructive signals sent by Purkinje cells to downstream sites like the vestibular nuclei. These animals have normal resting levels of Purkinje cell activity (Goossens et al. 2001), but Purkinje cells have not been recorded during exposure to stimuli that induce motor learning to determine whether the signals they transmit to the vestibular nuclei are abnormal. Fortunately, enough is known about normal signaling in Purkinje cells during the induction and expression of motor learning that in vivo recording studies should readily resolve this confusion.

Consistent with these results from the VOR, studies using other cerebellum-dependent learning tasks have reported that pharmacological or genetic disruption

of molecules required for cerebellar LTD impairs motor learning (e.g., Aiba et al. 1994; Chapman et al. 1992; Katoh et al. 2000; Kishimoto et al. 2001a,b; Koekkoek et al. 2003; Nagao & Kitazawa 2000; Shibuki et al. 1996; Shutoh et al. 2002, 2003; Yanagihara & Kondo 1996).

Studies of the instructive signals controlling induction of plasticity also are consistent with a role of cerebellar LTD in motor learning in the VOR. In the Miles-Lisberger model the neural instructive signal is carried by Purkinje cells, which control the induction of plasticity in the vestibular nucleus. Alternatively, in the Marr-Albus-Ito model, the neural instructive signal controlling induction of motor learning is carried by climbing fibers. The climbing fibers can trigger LTD in parallel fibers. Climbing fiber inputs to the flocculus and ventral paraflocculus fire in response to image motion on the retina and thus can indicate errors in VOR performance when the reflex fails to stabilize images on the retina (Ghelarducci et al. 1975, Graf et al. 1988, Simpson & Alley 1974, Stone & Lisberger 1990). Destruction of the inferior olive or the nucleus of the optic tract (which provides input to the olive) alters visual tracking performance and abolishes the ability to change the VOR gain (Haddad et al. 1980, Ito & Miyashita 1975, Tempia et al. 1991, Yakushin et al. 2000b). An analysis of the two candidate instructive signals during motor learning in the VOR induced with high-frequency stimuli also suggests a role for climbing fibers in the induction of motor learning (Raymond & Lisberger 1998). For a neuron to provide an instructive signal for the VOR, its patterns of spiking must discriminate stimuli that increase and decrease VOR gain. During training with stimuli typically used to induce learning (low frequencies of head and visual stimulus oscillation), both climbing fiber and Purkinje cell responses discriminate the gain-up and gain-down stimuli (Simpson & Alley 1974, Watanabe 1984). Therefore, either population of neurons could, in theory, trigger the different changes required under these two conditions, and hence these findings are compatible with both the Marr-Albus-Ito and Miles-Lisberger models. However, during the induction of learning with high-frequency training stimuli, only climbing fibers, not Purkinje cells, discriminate the stimuli that increase or decrease VOR gain (Raymond & Lisberger 1998). This finding indicates that Purkinje cells cannot trigger the different changes induced by the gain-up and gain-down stimuli at high frequencies. Therefore, at least at high frequencies, the climbing fiber is the best candidate for the instructive signal guiding motor learning in the VOR.

## MULTIPLE PLASTICITY MECHANISMS CONTRIBUTE TO MOTOR LEARNING IN THE VOR

We have reviewed the support for both the Marr-Albus-Ito and the Miles-Lisberger models, and in brief, neither model can account for all of the experimental data accumulated to date. The single biggest challenge to the Marr-Albus-Ito hypothesis is the observation that after motor learning is induced in the VOR, the vestibular sensitivity of Purkinje cells changes in the wrong direction to account for changes

in the vestibular nucleus and to mediate the change in VOR gain. In addition, recordings of climbing fiber responses during exposure to a broad range of stimuli that induce motor learning suggest that the climbing fibers cannot serve as the sole instructive signal (Ke & Raymond 2001, 2002). A major challenge to the Miles-Lisberger hypothesis is the observation that adaptive changes in VOR gain can occur under some conditions in which the Purkinje cells fail to discriminate stimuli that increase and decrease VOR gain and therefore provide no useful instructive signal to guide plasticity (Raymond & Lisberger 1998). Also, the plasticity mechanism predicted by the Miles-Lisberger model has not been observed experimentally. Inputs to the vestibular nuclei undergo both potentiation and depression (Caria et al. 1996, 2001; Racine et al. 1986), but whether Purkinje cell spiking, the key instructive signal in the Miles-Lisberger model, can control the induction of plasticity at these synapses is not clear (Babalian & Vidal 2000).

One possible resolution of the conflicting data for and against these two models is that the plasticity mechanisms proposed by both models contribute to motor learning in the VOR. Recent studies using in vitro preparations have described many plasticity mechanisms in the cerebellum and related circuits (for review, see Hansel et al. 2001). In vivo evidence that multiple plasticity mechanisms contribute to motor learning is accumulating as well. In the next few sections we consider three properties of motor learning in the VOR that seem to be supported by multiple plasticity mechanisms.

## Regulation of Movement Dynamics

The contribution of multiple plasticity mechanisms to motor learning in the VOR was first proposed to explain why the vestibular sensitivity of Purkinje cells would change in the wrong direction to mediate the observed change in VOR gain. The VOR circuit contains a positive feedback loop: Purkinje cell activity can drive eye movements, and signals related to eye-movement commands then feed back to drive more Purkinje cell activity. One model postulates that the VOR circuit avoids the instability associated with feedback by using plasticity mechanisms distributed between the cerebellum and vestibular nuclei (Lisberger & Sejnowski 1992). According to this model, the change in VOR gain is due to plasticity in the vestibular nuclei. These nuclear changes alone would cause unstable eye movements, such as continuously accelerating eye movements in response to a constant-velocity head movement. However, additional changes in the cerebellar cortex could restore stability. The observed changes in the vestibular sensitivity of Purkinje cells are in the wrong direction to mediate the change in VOR gain, but they are in the right direction to maintain the proper time dynamics of movement (Hirata & Highstein 2001, Lisberger 1994, Lisberger et al. 1994a).

The cerebellar cortex regulates the timing of other learned movements as well (see Buonomano & Mauk 2004, in this volume). Although a posttraining lesion of the deep cerebellar nucleus abolishes conditioned eyeblink responses completely, a lesion of the cerebellar cortex primarily disrupts the timing of learned responses

(McCormick & Thompson 1984, Perrett et al. 1993). This finding suggests that the cerebellar cortex stores timing-related information, whereas the deep cerebellar nucleus is more important for storing the amplitude of the response. Accordingly, in human patients, disruption of the cerebellum results in deficits in the timing of movement (e.g., Ivry et al. 1988, Spencer et al. 2003).

## Consolidation of Memories

Multiple plasticity mechanisms may be used to maintain motor memories over different timescales. Many memories undergo consolidation after learning, making them less labile. Consolidation is a transformation in the way a memory is encoded, from using a short-term plasticity mechanism to using one that is distinctly long-lasting. Much work on consolidation has focused on the declarative memory system, but motor memories can undergo consolidation as well.

In humans learning to perform reaching movements in an altered force field, several hours must pass before the motor memory for one force field becomes resistant to erasure by the learning of a new force field (Brashers-Krug et al. 1996, Shadmehr & Brashers-Krug 1997). For this task, execution of movements immediately after learning results in frontal cortex activation, but in the hours after training is complete, the cerebellum becomes active during task performance (Shadmehr & Holcomb 1997). Thus the role of the cerebellum may change with time after acquisition of learning, which is consistent with the general notion that consolidation can involve redistribution of information between different parts of the brain, from short-term areas to long-term areas (Marr 1971).

Application of the information redistribution hypothesis to motor learning in the VOR has led to the idea that the motor memory for a learned change in VOR gain is transferred from the cerebellar cortex to the vestibular nuclei during long periods of training (Galiana 1986, Nagao & Kitazawa 2003, Peterson et al. 1991). This idea was inspired in part by the variable results obtained when various groups lesioned or inactivated the cerebellum after inducing motor learning in the VOR (Luebke & Robinson 1994, McElligott et al. 1998, Nagao & Kitazawa 2003, Partsalis et al. 1995, Pastor et al. 1994, Robinson 1976). Studies that reported small effects of lesions on the expression of previously acquired changes in VOR gain generally used longer training paradigms than did those that reported large effects. These results are consistent with the storage of motor memories initially depending on the cerebellum and with the storage of longer-term memories depending more upon other structures. However, the correlation was not perfect, and these studies were done with several different species and methods. A more systematic exploration of this hypothesis is currently underway (Kassardjian et al. 2003).

Studies of other cerebellum-dependent tasks provide additional evidence that multiple plasticity mechanisms support motor learning over different timescales. Inactivation of the cerebellum disrupted the expression of short-term, but not long-term, learned changes in visually driven eye movements (Shutoh & Nagao 2003). Similarly, inactivation of the cerebellar cortex with infusions of muscimol

abolished the retention of classically conditioned eyeblink responses when performed after the first through fourth training sessions, but it had no effect when infused after the ninth through twelfth training sessions (Attwell et al. 2002). This finding supports the idea that different mechanisms are used to maintain cerebellum-dependent memories induced with brief, versus extended, amounts of training.

## Bidirectional Changes in Movement Amplitude

The gain of the VOR can be adaptively increased or decreased. The Marr-Albus-Ito model attributes both an increase and a decrease in VOR gain to a single synaptic plasticity mechanism by suggesting that cerebellar LTD operates independently on parallel fibers that are active for head movements in different directions (Ito 1982). Specifically, the model proposed that LTD of parallel fibers firing during ipsiversive head turns would cause an increase in VOR gain, whereas LTD of parallel fibers firing during contraversive head turns would cause a decrease in VOR gain.

The Marr-Albus-Ito model predicts that increases and decreases in VOR gain would have similar properties stemming from their shared plasticity mechanism. In contrast, increases and decreases in VOR gain are different in several regards, which suggests they depend on different plasticity mechanisms. An early study found that increases in VOR gain passively decayed more rapidly than did decreases in VOR gain (Miles & Eighmy 1980). Furthermore, increases in VOR gain can be actively reversed more readily than can decreases in VOR gain (Boyden & Raymond 2003). Finally, increases in gain generalize less than decreases when measured in a context different from that used during training (see below). The distinct properties of increases and decreases in VOR gain suggest they are mediated by different plasticity mechanisms. Other movements may also depend on different plasticity mechanisms to implement bidirectional changes in movement amplitude. For example, increases and decreases in the gain of saccadic eye movements exhibit different behavioral properties (Robinson et al. 2003, Straube et al. 1997).

Further evidence for the idea that increases and decreases in VOR gain depend on different cellular mechanisms comes from the finding that some pharmacological and genetic manipulations differentially affect increases and decreases in VOR gain. Inhibiting NO or NMDA receptor activity impairs the ability of goldfish to increase, but not decrease, their VOR gain (Carter & McElligott 1995, Li et al. 1995). Mice lacking CaMKIV, a molecule necessary for long-lasting cerebellar LTD, have significantly impaired long-term memory for increases, but not decreases, in VOR gain (Boyden et al. 2003). In addition, a close examination of the published data for mutant mice expressing the PKCI transgene seems to suggest that they are more impaired for increases than decreases in VOR gain with long-term training (Van Alphen & De Zeeuw 2002). Together these pharmacological and molecular genetic studies indicate that increases and decreases in VOR gain depend on different plasticity mechanisms, and they raise the specific possibility

that increases in VOR gain, more than decreases in VOR gain, depend on cerebellar LTD.

If increases in VOR gain depend more on cerebellar LTD, decreases in gain may depend more on cerebellar LTP. Implementing bidirectional behavioral changes with a single plasticity mechanism such as cerebellar LTD could result, over time, in a state where the available plasticity had been consumed and no further learning was possible (Lisberger 1996, Sejnowski 1977). On the other hand, a model with inverse plasticity mechanisms operating at each synapse could allow for reversal of prior learning. In vitro, parallel fiber synapses exhibit not only LTD but also two different forms of LTP. Both forms of LTP are induced when parallel fibers are active in the absence of climbing fiber activity (Lev-Ram et al. 2002, Sakurai 1987, Salin et al. 1996). Thus the learning rule for induction of LTP is complementary to that for LTD: In the terminology of Boolean logic, LTD is induced when parallel fiber activity *AND* climbing fiber activity occur simultaneously, whereas LTP is induced when parallel fiber activity *AND NOT* climbing fiber activity, occur.

Bidirectional plasticity at the synaptic level could explain the capacity for bidirectional modifications at the behavioral level. In the VOR, an asymmetry exists in the reversal of increases and decreases in VOR gain: Increases in gain are readily reversed by subsequent gain-down training, but decreases in gain are harder to reverse by gain-up training (Boyden & Raymond 2003). This finding suggests that increases and decreases in VOR gain depend on different plasticity mechanisms that reverse each other with unequal efficacy. One specific model that can explain this asymmetric reversal invokes the asymmetric localization of LTP and LTD expression at the parallel fiber–Purkinje cell synapse. LTD is postsynaptically expressed. The two forms of LTP are expressed at different parts of the synapse: One is expressed presynaptically (Salin et al. 1996), and the other is expressed postsynaptically (Lev-Ram et al. 2002). This asymmetric localization at the anatomical level confers asymmetric reversal of plasticity at the physiological level (Bear & Linden 2000, Lev-Ram et al. 2003). If LTD contributes to an increase in VOR gain and the two forms of LTP contribute to a decrease in VOR gain, then this differential contribution could account for the asymmetric reversal seen at the behavioral level: The postsynaptic LTD contributing to an increase in gain would be fully reversed by the postsynaptic LTP contributing to a decrease in gain, but the presynaptic form of LTP contributing to a decrease in gain would not be reversed by the postsynaptic form of LTD contributing to an increase in gain (Boyden & Raymond 2003).

The plausibility of a role of cerebellar LTP in motor learning is supported by several additional results. A study of the strength of parallel fiber–Purkinje cell synapses in rat cerebellar slices estimates that only 7% of the connections are actually capable of driving postsynaptic responses (Isope & Barbour 2002). Thus in the basal state, there may be little additional room for LTD to navigate, and the greatest capacity for circuit modification could lie in potentiating the large number of silent parallel fiber synapses. In support of this view, a recent study in vivo found that stimulation of parallel fibers in zone C3 of the cerebellum

resulted in expansion of Purkinje cell cutaneous receptive fields, which the authors attributed to the action of LTP on parallel fiber–Purkinje cell synapses (Jorntell & Ekerot 2002). Contraction of Purkinje cell receptive fields became possible only after prior expansion had occurred, which suggests that one function of LTD is to reverse previously induced LTP. Evidence for a role of LTP in cerebellum-dependent learning also comes from the observation of an increase in the number of parallel fiber–Purkinje cell synapses after long-term training with an obstacle course (Anderson et al. 1996, Black et al. 1990). Presumably an increase in synapse number would be associated with LTP rather than LTD. Thus LTP may play roles both in the reversal of old memories and in the encoding of new ones.

The evidence described above suggests that increases and decreases in VOR gain depend on different plasticity mechanisms. One difference between increases and decreases in the gain of the VOR and other movements may be their dependence on LTD and LTP at parallel fiber–Purkinje cell synapses, but plasticity mechanisms at other sites may contribute differentially, as well.

## INTERACTION BETWEEN PLASTICITY AND CODING: SPECIFICITY AND GENERALIZATION OF LEARNING

Learning is useful only if it is expressed in appropriate contexts. Learning must generalize to situations slightly different from those present during training because, otherwise, natural situational variation could restrict learning from ever being expressed. Too much generalization, however, is not desirable: A learned response could be maladaptive if expressed in an inappropriate context. In the VOR, learning is sometimes expressed only in very specific contexts, and sometimes it generalizes to contexts other than that present during learning. The patterns of specificity and generalization provide insight into the encoding of information at the sites of plasticity.

### Specificity

One of the best-explored examples of the context dependency of motor learning in the VOR is the specificity of the adapted gain to the head tilt present during training. If during training the gain of the VOR is adaptively modified with the head tilted at a particular angle relative to gravity, much smaller gain changes are expressed when the VOR is measured with the same rotational stimulus but with the head tilted at a different angle (Baker et al. 1987). Thus, varying the angle of head tilt must cause different sets of neurons to be activated at the site of plasticity in response to the same rotational head movement. Indeed, the evidence suggests that varying the tilt angle of the head can cause the activation of completely nonoverlapping populations of neurons in response to the same rotational stimulus. Gain-up training of the rotational VOR with the head tilted 90° to the right induced an increase in gain that was not at all expressed when the head was

tilted 90° to the left (Yakushin et al. 2000a). This finding suggests a sparse, combinatorial encoding of information from the two types of vestibular end organs: the semicircular canals, which measure head rotation, and the otolith organs, which measure linear acceleration and head tilt. At the level of the primary afferents, these signals are in separate pathways. However, at the site of plasticity, the canal stimulus must activate totally different populations of neurons, depending on the otolith signal present, because no learning was expressed when the head was tilted in the direction opposite that present during training. The experiment was done in such a way that the canal afferents would be activated in the very same way regardless of whether the head was tilted 90° to the left or to the right. Also, the otolith signal was static in each condition, not varying with head rotation. Thus, at the site of plasticity the context provided by the static otolith input must gate the responses of neurons to their dynamic canal inputs. Then, during learning, plasticity would specifically alter synapses of the neurons activated in the context present during training.

Where might such a sparse combinatorial code exist in the VOR circuit? Many vestibular nucleus neurons are modulated by both rotation signals from the semicircular canals and dynamic head-tilt signals from otoliths (Angelaki et al. 1993, Baker et al. 1984, Bush et al. 1993, Endo et al. 1995, Kubo et al. 1977, Ono et al. 2000, Uchino et al. 2000). However, whether static head-tilt signals can gate rotational signals in the vestibular nuclei to a degree sufficient to account for the behavioral observations is unclear. If this interaction between dynamic canal and static otolith signals is not found in the vestibular nucleus, then the sparse reencoding may occur in the cerebellum. According to the Marr-Albus model, even if mossy fiber inputs carry the same head-rotation signals (Figure 4*A*, common stimulus), granule cells may fire only for specific combinations of head-rotation and static-tilt contexts (Figure 4*A*, Context A, Context B), with no overlap between the sets of granule cells that fire for different combinations. Then, the induction of plasticity of synapses from granule cells active only during rotations with leftward head tilt would not affect the flow of information through granule cells active only during rotations with rightward head tilt, even though their mossy fiber inputs could have identical head-rotation responses.

Another example of the stimulus specificity of motor learning in the VOR concerns the expression of learning when measured at head-rotation frequencies different from the training frequency. If training is induced with visual and vestibular stimuli at a single frequency, the observed change in VOR gain is much smaller when measured at head-movement frequencies different from the training frequency (Godaux et al. 1983, Iwashita et al. 2001, Lisberger et al. 1983, Powell et al. 1991, Raymond & Lisberger 1996). This finding suggests that the circuit for the VOR contains parallel, frequency-tuned, signal-processing channels, which are individually modifiable during training.

Such sparse encoding of head-movement frequency is not seen in early sensory afferent and vestibular nucleus neurons. Many of these neurons respond to head movements at a broad range of frequencies. Responses of some individual neurons

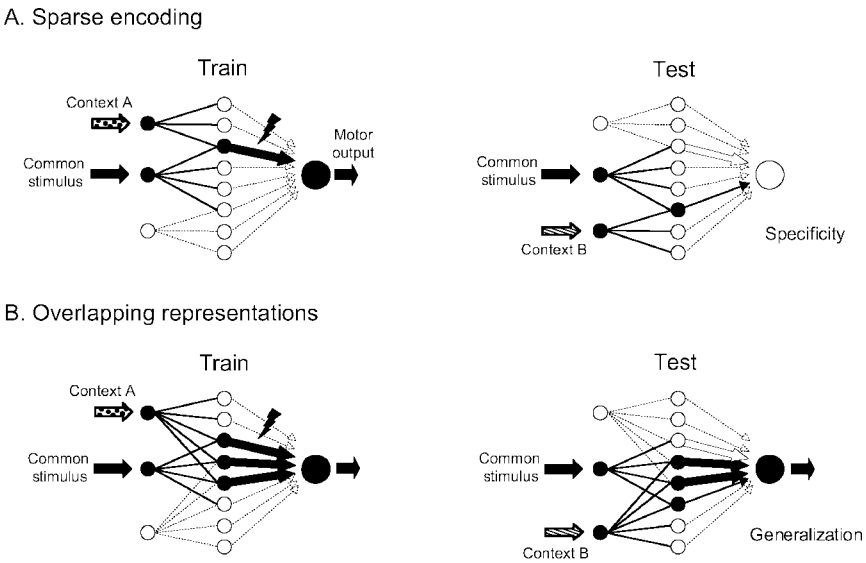


**Figure 4** General population coding schemes for achieving specificity and generalization in motor learning. The circuit is divided into three layers: an input layer, an association layer, and an output layer. (*A*) Sparse reencoding enables learning to link particular inputs to particular outputs, as in Figure 1. LTP (lightning bolt) strengthens the synapses active during training with the common stimulus and Context A, causing a learned motor output to be elicited when that combination is present. The common stimulus does not elicit the motor output in the presence of Context B because the neurons activated in the association layer were not active or modified during training. (*B*) Less-sparse representations have more overlap in the association layer, and the common stimulus can elicit the learned motor output in contexts different from those used during training. Open circles and arrows and dotted lines indicate inactive neurons and synapses. Filled circles and arrows and solid lines indicate active neurons and synapses. Thick arrows indicate synapses strengthened by LTP. Circuits using LTD instead of LTP would function in a similar manner.

vary with head-rotation frequency, with some acting as high-pass filters and others acting as low-pass filters (Angelaki & Dickman 2000, Buettner et al. 1978, Jones & Milsum 1971, Schneider & Anderson 1976). These neurons could support some degree of frequency selectivity, but they do not seem to have sufficient selectivity to explain the behavioral data. The cerebellum could act as an adaptive linear filter (Fujita 1982), which could have bandwidths that result in more tightly tuned frequency channels than found in early vestibular pathways.

Another demonstration of independently modifiable channels with different dynamic properties is a component of the VOR that is expressed specifically during fast accelerations (Clendaniel et al. 2002, Minor et al. 1999). Learned changes

in this component occur only when training is done with fast accelerations. In addition, if training is performed with stimuli of a particular velocity, the observed change in VOR gain is much smaller when measured with head-movement velocities different from that used during training (Fukushima et al. 1996, Iwashita et al. 2001).

Thus a simple model with parallel, sparsely coded channels, and with a single plasticity mechanism that alters a subset of these channels, can go a long way in explaining the general capacity of motor learning in the VOR to exhibit specificity for the particular stimuli present during training. Additional observations suggest, however, that less-sparse codes and multiple plasticity mechanisms may play an important role as well.

## Generalization

As described above, a change in stimulus parameters or context, such as rotation frequency or head tilt, can prevent the expression of learning. But some generalization of learning can be observed across these two sensory dimensions, and this generalization provides additional insight into how head tilt and frequency are coded in the circuit. For generalization of learning to occur, there must be overlap between the populations of neurons activated by the different stimuli or contexts (Figure 4*B*). In such a network, plasticity affecting the association between one stimulus and a motor output could change the association between another stimulus and the motor output, since some of the same neurons would be part of the representations of both stimuli at the site of plasticity. For example, training the rotational VOR with the head tilted 90° to the left induced learning that was partially expressed when the rotational VOR was measured with the head vertical (Yakushin et al. 2003). Hence there is some generalization of learning to different head tilts, which limits the sparseness of the representation of otolith and canal inputs at the site of plasticity. Some of the neurons at the site of plasticity, which are activated and undergo plasticity during rotations with the head tilted 90° to the left, also must respond to a rotation when the head is upright. Thus observing the degree to which learning generalizes can provide insight about coding at the site of plasticity.

The situation is slightly more complex for frequency selectivity because the amount of generalization depends on the frequency of the training stimulus. When training is done with 0.5 Hz stimuli, there is little expression of learning when the VOR gain is measured with 5 Hz head rotation. When training is done with 5 Hz stimuli, however, learning is expressed when the VOR gain is measured with 0.5 Hz head rotation (Raymond & Lisberger 1996). This asymmetric pattern of generalization could potentially result from a coding scheme in which neurons active during low-frequency head rotation are a subset of those active at high frequencies. Consider a simple coding scheme wherein most of the neurons active at 0.5 Hz are also active at 5 Hz, but a relatively small fraction of the neurons active at 5 Hz are active at 0.5 Hz. Then plasticity induced in the neurons active

during training at 5 Hz would affect the VOR gain measured at 0.5 Hz because most of the neurons mediating low-frequency head movements would have been activated and altered by the training. However, plasticity induced in the neurons active during 0.5 Hz training would have little effect on the VOR gain measured at 5 Hz because the neurons activated and altered during training would make up only a small fraction of those mediating the VOR response at 5 Hz. Thus, asymmetric generalization of learning could, in theory, result from a single plasticity mechanism acting on a single population of synapses.

However, another possibility is that the different patterns of generalization observed with high- and low-frequency training result from their dependence on different plasticity mechanisms, which operate on separate representations of head movement in the circuit for the VOR. One representation would be sparse like the network shown in Figure 4*A* (intermediate-layer neurons tightly tuned for frequency), and one would be less sparse like that in Figure 4*B* (intermediate-layer neurons responding to a broad range of frequencies). If low-frequency training produced changes in the sparse network, there would be little or no generalization when tested at high frequencies, and if high-frequency training produced changes in the less-sparse network, there would be generalization of learning when tested at low frequencies. One proposal is that the cerebellar cortex could contain the sparse network, and the deep cerebellar nuclei (or for the VOR, the vestibular nuclei) could contain the less-sparse network (Thach et al. 1992). This model would predict that changes induced with low-frequency rotation, which do not generalize, would be localized to the cortex, whereas changes induced with high-frequency rotation, which generalize to lower frequencies, would be localized to the brainstem. However, studies of the instructive signals available to guide motor learning would predict the opposite. At low frequencies, the instructive signals present in the Purkinje cells could potentially drive appropriate changes in the vestibular nuclei, whereas at high frequencies, the best candidate for the instructive signal is the climbing fiber (Raymond & Lisberger 1998). Another challenge to the idea that the cerebellar cortex is responsible for the specificity of learning comes from eyeblink conditioning. With the output of the cerebellar cortex inactivated, the expression of the conditioned response was no less specific for the stimuli used during training (Ohyama et al. 2003).

Even if different plasticity mechanisms are responsble for specific and generalized changes, they need not be located in separate parts of the circuit. For the case of frequency generalization in the VOR, the high- and low-frequency information-processing channels could be carried in the same neurons but by different subcellular signaling pathways. The observation that frequency-tuned coding channels seem to have distinct pharmacological properties supports this idea. Administration of NMDA receptor antagonists reduces low-frequency, but not high-frequency, VOR gain (Priesol et al. 2000). Thus NMDA receptors may be selectively present in the low-frequency coding channels, and they could endow the low-frequency channels with plasticity mechanisms different from those found in the high-frequency channels.

## Refinement of Generalization Across Multiple Sensory Dimensions

The extent to which learning generalizes often depends on the precise training paradigm. Additional training can prevent the generalization of learning that would otherwise occur. For example, changes in the rotational VOR gain induced when the head is tilted 90° to one side result in learning expressed when the rotational VOR is measured with the head in the upright position. However, this generalization is not observed if periods of gain-up training with the head tilted 90° to the right are alternated with periods of gain-down training with the head tilted 90° to the left (Yakushin et al. 2003). Appropriate changes in the rotational VOR are expressed when the head is tilted to each side, but no changes are observed when the VOR is measured with the head upright. The changes in the VOR circuit induced by the gain-up and gain-down training, which normally would have each been expressed when measured with the head upright, must somehow cancel each other. This cancellation could occur either by summation (masking) or by reversal of the effects of each training protocol on the neurons activated with the head upright. One hint about whether masking or reversal occurs comes from the observation that gain-down training with the head tilted 90° results in changes expressed in the head-upright position that are significantly larger than those induced by gain-up training with the head tilted 90° (Yakushin et al. 2003). If pure masking occurred, then the alternating-training protocol should result in a net decrease in gain when measured with the head upright. However, no change in gain was observed. Therefore, the changes induced by gain-up and gain-down training did not simply sum linearly when measured in the head-upright position, but rather interacted via a nonlinear process, perhaps involving reversal of plasticity at the cellular level.

This example shows that for a given context, generalization can be actively refined during the training process. To successfully stabilize images on the retina across varying conditions, the circuit for the VOR must coordinate the specificity or generalization of learning across many dimensions of sensory input, including both vestibular stimulus parameters and context cues. For example, the vertical VOR can be adapted to different gains during upward, versus downward, head turns (Hirata et al. 2002). Subjects can be trained to have different horizontal VOR gains when their eyes are angled upward versus downward (Shelhamer et al. 1992). Learning is also specific for the vergence angle held by the eyes during training (Lewis et al. 2003). Motor learning in the translational VOR is expressed only in one eye, if the other is not required to move in response to the training stimulus (Zhou et al. 2003). Despite the large number of dimensions that can provide contexts for specifically expressed learning, not all contexts are equally potent for regulating the expression of learning. For example, the vertical canal-mediated VOR can express different gains for rightward, versus leftward, head tilts, but head tilt that is pitched forward or backward is a less-effective contextual cue (Shelhamer et al. 2002). In the real world, learning is regulated by all of these dimensions simultaneously, and so the underlying coding and plasticity mechanisms in the VOR must be of sufficient richness to enable regulation of learning by multiple dimensions of sensory input.

Sparse, combinatorial coding of multiple dimensions may allow the expression of learned output only when the right combination of stimuli and contexts is present.

Investigators are exploring the patterns of specificity and generalization for other forms of motor learning, as well (a few examples include Collewijn & Grootendorst 1979; Kahlon & Lisberger 1999; Kramer et al. 1995, 1998; Lisberger et al. 1981; Ohyama et al. 2003; and Park et al. 2003). As behavioral observations are combined with studies of how information is encoded in the relevant neural circuits, these studies will constrain hypotheses concerning the sites of plasticity storing motor memories.

## Generalization of Increases Versus Decreases in VOR Gain

Increases in VOR gain generalize less than decreases in VOR gain across a number of sensory dimensions. For example, decreasing VOR gain by training with only one eye viewing generalizes to a decreased VOR gain in the other eye, but increasing the gain in one exposed eye does not result in transfer to the other eye (McElligott & Wilson 2001). Gain-down training generalizes across head rotation velocity and frequency more than gain-up training generalizes (Hirata et al. 2002, Iwashita et al. 2001, Kimpo & Raymond 2002, Raymond & Lisberger 1996). Finally, gain-down training of the rotational VOR generalizes more across head tilt angles than gain-up training generalizes (Yakushin et al. 2000a, Yakushin et al. 2003).

These results provide an important new insight about the plasticity mechanisms for increasing and decreasing VOR gain. To account for the above results, the gain changes induced in opposite directions must not simply involve opposite changes in the strength of the same synapses. Rather, different sets of synapses must be modified for increases and decreases in VOR gain. Even though the same vestibular neurons are activated in each case, the visual and other instructive signals must change different subsets of synapses for increases and decreases in gain. One possibility is that synapses at different sites in the circuit could be modified by training paradigms that increase and decrease VOR gain. Neurons at the site storing decreases in gain could encode for head rotation regardless of context or particular stimulus features (like the network in Figure 4*B*), whereas neurons at the site storing increases in gain could be strongly modulated by context (like the network in Figure 4*A*). One specific proposal is that the cerebellar cortex contributes more to gain-up learning, whereas the vestibular nucleus contributes more to gain-down learning (Li et al. 1995). On the other hand, the difference in generalization of increases and decreases in VOR gain could result from the properties of different plasticity mechanisms at a single site. For the model where LTD mediates an increase in gain and LTP mediates a decrease in gain, the patterns of generalization observed at the behavioral level suggest that LTP could spread to nonactivated synapses more than LTD spreads.

Thus the patterns of generalization support the idea that increases and decreases in VOR gain must use different plasticity mechanisms, and these mechanisms must affect different sets of synapses. Whether gain-up and gain-down

training are inducing changes at different anatomical sites in the circuit, or just affecting different subpopulations of synapses at the same site, remains to be determined.

## CONCLUSION

During the last several decades, attempts to discriminate between the Marr-Albus-Ito and Miles-Lisberger models have dominated research on motor learning in the VOR. Each model can explain some of the data regarding motor learning in the VOR with a single plasticity mechanism. However, several lines of evidence indicate that multiple plasticity mechanisms contribute to the regulation of this simple behavior. Multiple mechanisms may refine the time dynamics of learned responses, enable storage of motor memories over different timescales, and enable bidirectional alteration of movement amplitude.

These multiple plasticity mechanisms must act in combination with appropriate information-coding schemes to equip motor-learning systems with the ability to express learning in correct contexts. Studies of the generalization patterns of motor learning in the VOR provide insights about the coding of information in neurons at the site of plasticity. For a simple system like the VOR, it should be possible to map particular aspects of learning onto specific plasticity mechanisms, thus illuminating how movements can be precisely regulated in a complex world.

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