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LEARNING AND MEMORY IN THE VESTIBULO-OCULAR REFLEX

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Studies of the neural basis of learning and memory in intact animals must, by their nature, start "from the top" by choosing a behavior that can be modified through learning, revealing how neuronal activity gives rise to that behavior, and then investigating, in the awake, behaving animal, changes in neural signaling that are associated with learning. Such studies also must recognize that the learning and memory expressed in the behavior of an animal will reflect both the properties of the neural network that mediates the behavior and the nature of the underlying changes in the operation of cells or synapses. In the past 10 years, there has been an explosion of information about learning and memory in the vestibulo-ocular reflex (VOR) of the awake, behaving monkey. At the same time, there have been unprecedented advances in understanding mechanisms of cellular plasticity such as long-term potentiation (LTP) in the hippocampus and long-term depression (LTD) in the cerebellum. A prerequisite for understanding learning and memory is to elevate specific mechanisms of cellular plasticity into cellular mechanisms of learning by establishing their function in the context of a neural system that mediates learning and memory in a particular behavior. Our review synthesizes the

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combined behavioral, physiological, anatomical, cellular, and computational analyses needed to understand learning and memory in the VOR.

INTRODUCTION TO THE VOR AND RELATED BEHAVIORS

Under normal behavioral conditions, the VOR prevents images of the stationary world from slipping across the retina. Inertial sensors in the vestibular apparatus detect head motion and send signals into the brain to generate compensatory eye movements that are opposite in direction to head motion. In the laboratory, the VOR is evoked by passive head rotation in darkness. The behavior is quantified by measuring the evoked eye motion and computing the *gain* of the VOR, defined as eye speed divided by angular head speed in darkness. We define the gain of the *normal* VOR as that recorded during passive head rotation in a naive subject that has not yet been subjected to conditions that cause learning.

The VOR is a fast reflex that operates without visual feedback, at least on the time scale of individual head turns. In monkeys, this is ideal because the normal gain of the VOR is near 1.0, and the VOR alone is nearly sufficient to stabilize retinal images. In other species, including humans, the normal gain of the VOR is less than one, so visual-tracking systems must cooperate with the VOR to prevent retinal-image motion during head turns. One such system, the optokinetic response (OKR), operates in all species. It responds to smooth motion of images that cover a large portion of the visual field and generates compensatory eye movements in the same direction as the visual stimulus. A second tracking mechanism, smooth-pursuit eye movements, operates effectively only in primates. It responds to the motion of small targets by keeping the eyes moving at approximately the same speed as that of the target. The OKR and pursuit must be included in any discussion of neural expressions of learning and memory in the VOR because these two visual-tracking systems share circuitry with the VOR and place constraints on the sites of the neural changes, and possibly on the mechanisms that underlie learning in the VOR.

For the purposes of this review, we define *learning* as the acquisition of behavioral changes and *memory* as the changes themselves. Learning occurs in the VOR under most conditions that provide persistent image motion during head turns. If monkeys wear spectacles that magnify or miniaturize vision, then the gain of the VOR that is measured in darkness increases or decreases over a time course of hours or days (Miles & Fuller 1974). Learning occurs during the vestibular stimulation provided either by the subject's active head turns or by passive oscillation. The visual conditions provided by spectacles can be mimicked by arranging for a large visual stimulus to move either exactly

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with or opposite to the rotation of the subject's head (e.g. Collewijn & Grootendorst 1979). The learned changes in the gain of the VOR are remembered for days if the subject is deprived of either visual (Robinson 1976) or vestibular (Miles & Eighmy 1980) stimuli after the VOR has been modified.

PROPOSED SITES OF MEMORY IN THE VOR

A decade ago, the location of memory in the VOR was highly controversial, and two reviews by different groups of investigators espoused very different views (Miles & Lisberger 1981, Ito 1982). The past ten years, however, have seen a large increase in the amount of data and models relevant to the sites of memory in the VOR. In this section of our review, we outline the available data on the sites of memory and present a testable hypothesis that accounts for available data. We also discuss the remaining areas of disagreement and outline the kinds of experiments that would resolve these outstanding issues.

Behavioral Analysis of Memory in the VOR

We can learn a good deal about sites of memory from a careful analysis of behavioral changes, even before examining the organization of the essential neural network or the responses of its constituent neurons. For example, behavioral studies have shown that learning in the VOR is more complex (and interesting) than a simple scaling of reflex commands.

LATENCY OF THE MODIFIED COMPONENT OF THE VOR The use of brief pulses of head motion as a vestibular stimulus revealed that the first 5 ms of the VOR do not change even after large changes in the steady-state gain of the VOR (Lisberger 1984). These data divided the VOR into separate modified and unmodified components and demonstrated that the earliest part of the VOR is driven entirely by the unmodified component. For the stimulus used by Lisberger (1984), the latencies of the unmodified and modified components are 14 and 19 ms, respectively. For other stimuli, however, the unmodified and modified components of the VOR cannot be distinguished based on their latencies. Broussard et al (1992) found that changes in the gain of the VOR caused small but consistent changes in the earliest portion of the eye movements evoked by electrical stimulation of the vestibular apparatus with a single pulse. Khater et al (1993) found that learning-related changes could be detected as soon as the eyes started to move when a natural vestibular stimulus provided extremely rapid head accelerations.

Because changes in the gain of the VOR appear in the earliest eye movements evoked by some stimuli (Broussard et al 1992, Khater et al 1993), one site of memory for the VOR is likely to be found in the shortest-latency VOR pathways, which reside entirely in the brainstem and include just two synapses (e.g. Precht & Baker 1972). If the disynaptic VOR pathways contain a site of

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memory, why did Lisberger (1984) not find any changes in the first 5 ms of the responses to a pulse of head velocity? We suggest that the answer lies in the latencies of the responses of vestibular primary afferents for the vestibular stimuli used in different studies. Primary afferents respond with latencies that range from 5 to 18 ms (Lisberger & Pavelko 1986) for the relatively low head accelerations in the stimulus used by Lisberger (1984). If the afferents with shorter latencies (5 ms) project into unmodified pathways and those with longer latencies (>10 ms) project into modified pathways, then the first 5 ms of the VOR should not be modified even if the site of memory is in disynaptic VOR pathways. In contrast, we know that all afferents respond synchronously within 1 ms for stimulation with single electrical pulses (Brönte-Stewart & Lisberger 1994), and we presume that all afferents also respond synchronously for the very rapid head acceleration used by Khater et al (1993). For these stimuli, a site of memory in disynaptic modified pathways should cause learning to be expressed in the earliest part of the evoked eye movement. Even though this logic suggests that one site of memory is in the disynaptic brainstem VOR pathways, the experiments of Brönte-Stewart & Lisberger (1994) suggest that there may be additional sites of memory in pathways that have additional intervening synapses.

DYNAMICS OF THE MODIFIED COMPONENT OF THE VOR The time course, or "temporal dynamics," of the VOR changes as a function of the gain of the VOR. For the natural stimulus provided by a ramp of head velocity, the evoked eye velocity only slightly overshoots a final steady eye velocity when the gain of the VOR is normal (Figure 1). The overshoot is much larger after the gain of the VOR has been lowered, and it is barely evident when the gain of the VOR is high (Lisberger & Pavelko 1986). For electrical stimulation with single pulses, the effects of changing the gain of the VOR were larger in the later portion of the evoked eye movements than at their onset or peak (Broussard et al 1992). For electrical stimulation with trains of pulses, there was a complex temporal structure in the relationship between the gain of the VOR and the evoked eye movements. The magnitude and time course of the effects depended critically on which afferents were activated by the stimulus, and the learning-related changes were larger in the later portions of the evoked eye movements, growing over a time course of about 40 ms (Brönte-Stewart & Lisberger 1994). These data imply that the memory of a modified VOR cannot be implemented simply as a scale factor in one or more VOR pathways. If it were, learning in the VOR would cause simple increases or decreases in the speed of compensatory eye movement at all times, both a few milliseconds and tens of milliseconds after the onset of the modified component of the response. If, for example, the mechanism responsible for memory were a change in strength of transmission (e.g. LTP or LTD) at the synapse from

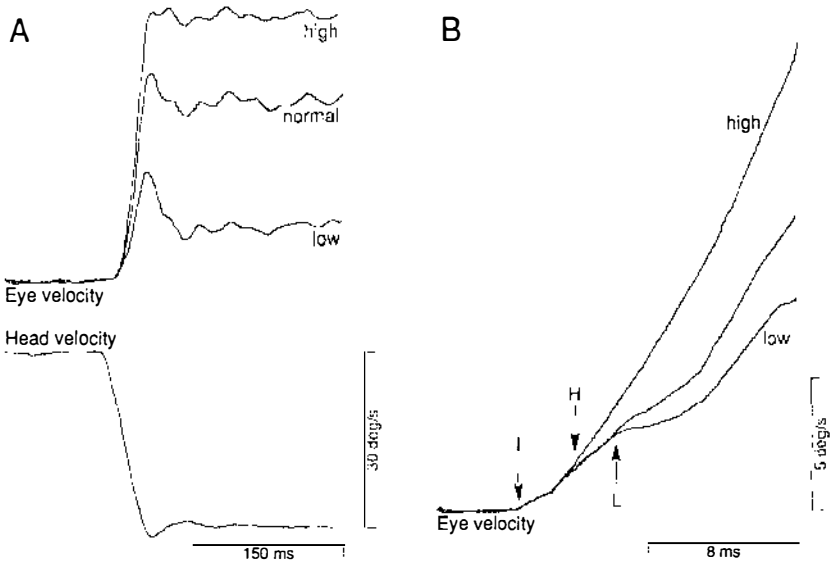

Figure 1 Effect of learning in the VOR on the eye movements evoked by ramps of head velocity. Each trace shows the average of 10 traces of eye or head velocity. (*A*) Slow-sweep records showing the VOR before learning (*normal*) and after learning induced by magnifying (*high*) or miniaturizing (*low*) spectacles. (*B*) Fast-sweep records showing the events at the initation of the VOR for the data in *A*. The arrow labeled "I" indicates the initation of the VOR, and those labeled "H" and "L" point out the times when the high-gain and low-gain records of eye velocity diverge from the control record. The gain of the VOR was 0.32, 1.05, and 1.57 for the records labeled low, normal, and high, respectively. Upward deflections are rightward motion. Reprinted with permission from Lisberger et al (1990).

primary afferents onto secondary vestibular neurons, then the eye movements evoked by electrical stimuli should scale uniformly as a function of the gain of the VOR. Neither of these predictions is supported by data.

Both the architecture of the neural network that mediates the VOR and the properties of the cellular mechanisms of learning may contribute to the complex relationship between the gain of the VOR and the temporal dynamics of the evoked eye movements. 1. Changes in the VOR could result from changes in the relative strengths of pathways with different dynamics (Lisberger et al 1983, Minor & Goldberg 1991, Quinn et al 1992a) or changes in the dynamics of the VOR pathways themselves (Lisberger & Sejnowski 1992). 2. Memory may reside in a small amount of synaptic potentiation or depression that is amplified over a time course of tens of milliseconds by neural feedback loops. 3. Memory could result from changes in cellular properties that have a long time course, such as the ionic conductances that determine the repetitive firing

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properties of the relevant neurons or a long-duration synaptic potential, rather than in the strength of fast synaptic transmission.

Essential Circuit for the VOR

The most direct VOR pathway comprises a three-neuron reflex arc that includes afferents from the vestibular nerve, interneurons in the vestibular nucleus, and extraocular motoneurons (e.g. Precht & Baker 1972, Highstein 1973). In addition to this basic pathway, there are a number of less direct pathways, including projections across the midline that relay vestibular afferent information between the vestibular nuclei on the two sides of the brainstem (Shimazu & Precht 1966) and projections from the vestibular nucleus to the motoneurons through the nucleus prepositus (Baker & Berthoz 1975). Important side loops include projections from the nucleus prepositus and the vestibular nucleus to a portion of the cerebellum called the flocculus/ventral paraflocculus (F/VPF) (Langer et al 1985b) and back from the F/VPF to the vestibular nucleus (Langer et al 1985a). We know these side loops are important because complete bilateral ablations of the F/VPF or the whole cerebellum abolish learning in the VOR while having little or no effect on the normal VOR (Robinson 1976, Nagao 1983, Flandrin et al 1983, Lisberger et al 1984).

Much is known about the connections, signal processing, and firing properties of three types of neurons whose firing patterns change consequent to learning in the VOR. Based on their responses during a variety of behavioral paradigms and some direct evaluations of their connections, the neurons appear to be interconnected in the pattern illustrated by Figure 2. Position-Vestibular-Pause cells (PVPs), so-named because they fire in relation to eye position and vestibular rotation and they pause during saccades, are in the vestibular nuclei and are some of the principal interneurons in the disynaptic VOR pathways. PVPs receive monosynaptic inputs from the vestibular nerve (Scudder & Fuchs 1992) and project monosynaptically to extraocular motoneurons (Scudder & Fuchs 1992, McCrea et al 1987). Flocculus Target Neurons (FTNs), so-named because they are the targets of monosynaptic inhibition from the F/VPF (Lisberger & Pavelko 1988, Lisberger et al 1994b), also are in the vestibular nuclei and also receive monosynaptic inputs from the vestibular nerve (Broussard & Lisberger 1992). Available data imply that at least some FTNs project directly to ocular motoneurons (Scudder & Fuchs 1992, Lisberger et al 1994b). Horizontal-Gaze Velocity Purkinje cells (HGVPs) are so-named because they discharge in relation to horizontal-gaze velocity during interactions of visual and vestibular stimuli (Miles et al 1980b, Lisberger & Fuchs 1978a) and are Purkinje cells in the flocculus and ventral paraflocculus. HGVPs project directly to the vestibular nucleus (Langer et al 1985a), where they monosynaptically inhibit interneurons in the brainstem VOR pathways (e.g. Baker et al 1972, Highstein 1973), almost certainly including FTNs.

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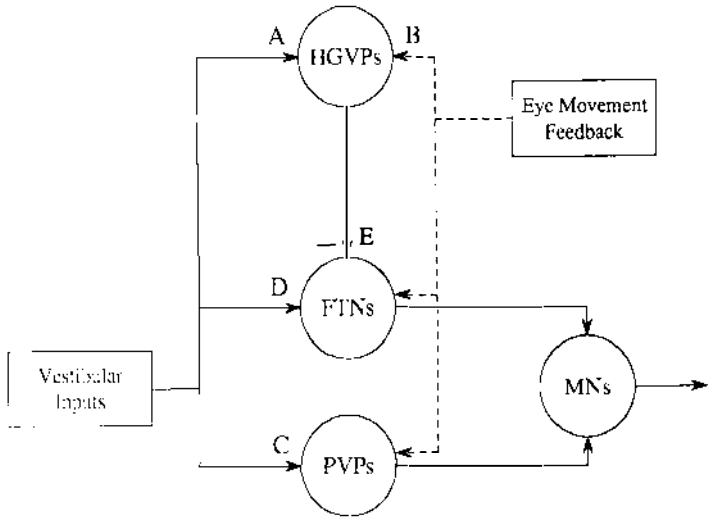

Figure 2 Schematic diagram showing the key neurons that participate in learning and memory in the VOR and the flow of signals within the neural network. The large circles represent horizontal-gaze velocity Purkinje cells (*HGVPs*) in the flocculus/ventral paraflocculus, the flocculus target neurons (*FTNs*) and position-vestibular-pause cells (*PVPs*) in the vestibular nucleus, and extraocular motoneurons (*MNs*). The letters (*A, B, C, D, E*) provide a vocabulary for discussing possible sites of learning and memory. Dashed lines refer to feedback connections, and solid lines show feed-forward connections. Note that HGVPs have an inhibitory influence on FTNs, as shown by the minus sign.

Because most of the electrophysiological recordings in awake, behaving animals have been made in rhesus monkeys, we discuss data primarily from this species. However, because the cell types and connections in the VOR pathways appear to be highly conserved across vertebrate animals (e.g. Dieringer 1986, du Lac & Lisberger 1992, Pastor et al 1994), we expect that much of what we describe applies to other species as well.

A major advance in localizing sites of memory in the VOR has come from the recognition that primary changes in neuronal activity due to local changes in synaptic transmission or cellular sensitivity must be distinguished from secondary changes that are simply transmitted from the primary site via changes in the activity of inputs to the secondary site. It is difficult to distinguish primary from secondary effects of learning because the extensive feedback in the VOR pathways makes it impossible to interpret the responses of neurons in the context of serial connections from the vestibular apparatus to the motoneurons. In the oculomotor system, feedback provides signals related to eye movement. These eye-movement signals are thought to be feedback of

the motor command and to arise from neurons that drive eye movement, rather than from proprioceptors in the eye muscles or the orbital tissues (Keller & Robinson 1971, Lisberger & Fuchs 1978b). For example, PVPs, FTNs, and HGVPs all receive inputs related to eye movement, as evidenced by their responses during pursuit eye movements with the head stationary. Accordingly, during the VOR, the responses of neurons in the VOR pathways result from a combination of head- and eye-movement inputs, even for PVPs and FTNs, which receive monosynaptic inputs from vestibular primary afferents.

With the feedback organization of the VOR pathways in mind, consider the problem of comparing a neuron's responses during the VOR before and after changes in the gain of the VOR. Suppose that none of the synaptic connections or intrinsic properties of the neuron become modified consequent to learning. Learning, by definition, causes a change in the eye movement evoked by a given head movement. The amplitude of the response will be changed in the afferents that provide eye-movement inputs to a neuron, and that change will be reflected in the neuron's response during the learned VOR, even though there have not been any cellular changes in the neuron or its afferent synapses. In PVPs, FTNs, and HGVPs, the component of neuronal firing rate that is due to eye-movement feedback can be dissociated from that component due to head-movement inputs by taking advantage of the fact that different oculomotor behaviors produce different combinations of head-movement signals and eye-velocity feedback signals. During smooth pursuit, the eyes move, but the head does not. During the VOR, both the eyes and the head move. During a paradigm called "cancellation of the VOR," the head moves, but the eyes are stationary in the orbit because the subject tracks a target that moves exactly with the head. Cancellation of the VOR provides a means to behaviorally eliminate the eye-movement feedback to a neuron. Therefore, the components of neuronal firing caused by eye-movement feedback and vestibular inputs can be distinguished by comparing neuronal responses during pursuit (eye movement only) and VOR cancellation (head movement only) to those during the VOR (eye and head movement). This method of analysis is based on the assumption that neuronal firing rates during the VOR can be predicted by the sum of firing during pursuit and during cancellation of the VOR, an assumption that has been verified for HGVPs (Lisberger & Fuchs 1978a, Lisberger et al 1994a) and FTNs (Lisberger et al 1994c).

Neural Correlates of Memory in the VOR Pathways

The responses of FTNs, PVPs, and HGVPs during the VOR are each modified after changes in the gain of the VOR. In describing these changes in neuronal responses, we address the following issues: Are the changes in the responses measured during the VOR in the correct direction to account for the changes in the learned behavior? Is the latency from head movement to neuronal

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response short enough to account for the short-latency component of the learned response? Do the changes associated with learning simply correlate with the altered eye movement or do they reflect alterations in the sensitivity to head-movement inputs? Because of the technical difficulties associated with recording from individual neurons during the several hours required to get a large change in the gain of the VOR, most studies of learning-related changes in neuronal responses have compared populations of neurons recorded while the gain of the VOR is low, normal, and high.

We define the "correct" direction of changes in neuronal responses according to the connections of each class of neurons. FTNs and PVPs are in the direct pathways that drive the VOR and during the normal VOR show responses that will drive the associated eye movement. Therefore, increases in the amplitude of the responses of FTNs or PVPs would be in the correct direction to drive increases in the gain of the VOR. Decreases in the amplitude of the responses of FTNs or PVPs would be in the correct direction to reduce the gain of the VOR. A change in the sign of the response would cause FTNs or PVPs to counteract rather than drive the VOR and would be in the correct direction to reduce the gain of the VOR. Because HGVPs inhibit their target neurons in the brainstem (presumably FTNs), different logic must be used to define the correct direction of changes in the responses of HGVPs. Consider a head turn that causes an increase in the firing of the vestibular inputs to FTNs. If the same stimulus normally causes little or no response in HGVPs, then FTNs will increase their firing and the vestibular signal will be forwarded to ocular motoneurons to drive the VOR. If, however, the firing of HGVPs increases at the same time as the firing in the vestibular inputs to FTNs increases, then the responses of FTNs will be reduced by inhibition from the HGVPs, and the gain of the VOR will be lower than normal. If the firing of HGVPs decreases at the same time as the firing in the vestibular inputs to FTNs increases, then the responses of FTNs will be amplified, and the gain of the VOR will be higher than normal. Thus, increases in the size of the vestibular responses of HGVPs would be in the correct direction to cause decreases in the gain of the VOR, and vice versa.

FLOCCULUS TARGET NEURONS Changes in the gain of the VOR cause dramatic changes in the responses of FTNs during the VOR (Lisberger & Pavelko 1988, Lisberger et al 1994c). When the gain of the VOR is normal, FTNs exhibit large responses that consist of increases in their firing rate during the VOR evoked by head turns toward the side of recording (henceforth called *ipsiversive* head turns). When the gain of the VOR is high, the responses are larger but maintain the same direction selectivity so that firing rate still increases during ipsiversive head turns. When the gain of the VOR is low, the sign of the responses of FTNs reverses so that firing rate decreases during the

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same ipsiversive head rotation. As outlined above, the changes in FTN responses recorded by Lisberger et al (1994c) are in the correct direction to mediate the associated changes in the gain of the VOR. Recordings from individual FTNs during brief periods of learning (Partsalis et al 1993) have suggested that individual FTNs undergo changes similar to those documented by comparing populations of FTNs recorded when the gain of the VOR was low, normal, and high (Lisberger et al 1994c).

The latencies of FTN responses during the VOR make them good candidates to mediate the earliest modified component of the VOR. Table 1 provides the logic on which we base this suggestion. During ramps of head velocity (cf Figure 1), FTNs responded with a median latency of 11 ms (Lisberger et al 1994c). Since at least some FTNs project monosynaptically to ocular motoneurons, we assume that a response in FTNs will influence motoneuronal firing within 1 ms. In turn, motoneurons respond an average of 7 ms before the onset of the eye movements evoked by ramps of head velocity (Lisberger et al 1994c). Thus, signals transmitted from the vestibular apparatus through FTNs to motoneurons will introduce a latency of about 19 ms (11 + 1 + 7 ms) between the onset of head motion and the onset of eye motion. Because the latency of the VOR is 14 ms for ramps of head velocity, the pathway through FTNs has a latency that is too long to drive the initial unmodified eye velocity of the VOR. However, the median latency of the pathway through FTNs agrees well with the latency of 19 ms measured for the modified component of the VOR induced by ramps of head velocity.

Comparison of the firing rates of FTNs when VOR gain was high and when it was low indicates that the effects of motor learning on the responses of FTNs are too large to be explained by eye-movement feedback signals alone (Lisberger et al 1994c). Moreover, recordings from FTNs during cancellation of the

Table 1 Latencies from head turn to eye movement during ramps of head velocity[a]

	PVPs	FTNs	HGVPs
Head turn to neuron[b]	7	11	23
Neuron to motoneuron	1	1	2
Motoneuron to eye movement	7	7	7
Head turn to eye movement[c]	15 ms	19 ms	32 ms

[a] Responses to ramps of head velocity (600°/s²). Columns show the latencies for pathways through each of three different interneurons. The numbers in the first three rows add up to the total latency for each pathway, given in the bottom row.

[b] This row gives the median latencies for the full sample of each class of neuron.

[c] These latencies should be compared with the latency of 14 ms for the unmodified, earliest component of the VOR and 19 ms for the modified component of the VOR, using the same ramp of head velocity.

VOR reveal that motor learning causes a change in the sensitivity to head-velocity inputs that is in the correct direction to account for motor learning (Lisberger et al 1994c). From these data we conclude that changes in the responses of FTNs are caused partly by a primary change in the transmission of vestibular inputs to FTNs.

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POSITION-VESTIBULAR-PAUSE CELLS Changes in the gain of the VOR cause small changes in the responses of PVPs under some behavioral conditions. These changes in the responses of PVPs are in the correct direction to support the change in the gain of the VOR. During contraversive head turns (away from the side of recording), PVPs have larger responses when the gain of the VOR is high than when it is low (Lisberger et al 1994c). During ipsiversive head turns, however, the amplitude of the responses of PVPs does not depend on the gain of the VOR.

The latency of their responses make PVPs good candidates to subserve the earliest unmodified component of the VOR. During the VOR induced by the ramps of head velocity used in our experiments, PVPs respond with a median latency of 7 ms. Since they project directly to extraocular motoneurons, PVPs, like FTNs, will influence eye movements after a latency of about 8 ms (1 ms to influence motoneuronal firing, plus 7 ms from motoneuronal firing to the onset of eye movement). Thus, signals transmitted from the vestibular apparatus through PVPs to extraocular motoneurons will introduce a latency of about 15 ms from head movement to eye movement (Table 1); this latency is in good agreement with the 14 ms latency of the VOR evoked by ramps of head velocity.

Two lines of evidence suggest that the learning-associated changes in the responses of PVPs are secondary to feedback of eye-velocity signals, rather than a reflection of primary changes in the strength of the head-velocity inputs to PVPs (Lisberger et al 1994c). 1. The responses of PVPs during cancellation of the VOR are not modified in association with changes in the gain of the VOR. Because the responses during cancellation of the VOR provide a direct estimate of the strength of the vestibular input to these cells, we would have expected a change in the strength of vestibular transmission to PVPs to cause a measurable change in responses under this condition. 2. The changes in the responses of the PVPs can be explained simply by taking into account their innate sensitivity to eye velocity, measured during pursuit with the head stationary, and the learning-associated changes in the eye velocity during the VOR. We conclude that PVPs contribute to the expression of memory in the VOR but only by virtue of their inputs from eye-velocity feedback. The data are not consistent with the conclusion that there is a primary site of memory in the vestibular inputs to PVPs.

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HORIZONTAL-GAZE VELOCITY PURKINJE CELLS HGVPs express marked changes in their responses after learning has induced increases or decreases in the gain of the VOR. When the gain of the VOR is normal, HGVPs show little or no response during the VOR (Lisberger & Fuchs 1974). After the gain of the VOR has become low or high, HGVPs exhibit pronounced responses during the VOR. During a low-gain VOR, HGVPs and the vestibular inputs to FTNs show increased firing at the same time. During a high-gain VOR, the firing of HGVPs decreases at the same time as the firing in the vestibular inputs increases. According to the logic outlined at the start of this section, the changes in the responses of HGVPs, if measured during the VOR, are in the correct direction to cause changes in the gain of the VOR. These data are not controversial: Similar results have been obtained by multiple investigators in monkeys (Miles et al 1980a, Watanabe 1984, Lisberger & Pavelko 1988, Lisberger et al 1994a) and rabbits (Dufosse et al 1978). In addition, recordings that followed individual Purkinje cells during brief periods of learning (Watanabe 1984) have revealed the same neural expression of memory found by comparing large populations of HGVPs recorded at different gains of the VOR (Lisberger et al 1994a).

The modified responses of most HGVPs occur with a latency that is too long to contribute to the earliest modified component of the VOR. During the VOR induced by ramps of head velocity, HGVPs respond with a median latency of 23 ms. Stimulation of the F/VPF produces eye movements after latencies of at least 9 ms, consistent with a latency of 2 ms for the firing of HGVPs to affect the firing of motoneurons. The total latency from head to eye movement for signals transmitted from the vestibular apparatus through HGVPs to extraocular motoneurons is 32 ms (Table 1). We conclude that most HGVPs respond too late to contribute to the earliest expression of memory in the VOR[1] but that changes in the responses of HGVPs during the VOR do contribute to later components of the modified VOR.

Analysis of the firing of HGVPs during cancellation of the VOR has demonstrated changes in the amplitude of responses to vestibular inputs that are in the wrong direction to account for learning-induced changes in VOR gain or in the firing of HGVPs during the VOR (Miles et al 1980a, Lisberger et al 1994a). If the sole site of the cellular changes associated with VOR memory

[1]In the case of HGVPs, the distribution of latencies is quite broad. The median latency is not a good estimate of the responses of the full population and it may be important to consider the possibility that individual cells with different latencies subserve different functions. A small fraction (5%) of the HGVPs recorded during the VOR induced by ramps of head velocity (Lisberger et al 1994a) responded with latencies of 10 ms or less and therefore had the potential to contribute to the earliest part of the modified VOR. In the case of FTNs and PVPs, however, the distribution of latencies was much narrower and the median latency provided a good estimate of the latency of the full sample (Lisberger et al 1994c).

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were in the vestibular inputs to HGVPs, then we would have expected the responses of HGVPs during cancellation of the VOR to become larger after the gain of the VOR had been lowered and smaller after the gain of the VOR had been raised. The opposite occurs. The same "wrong-way" results were obtained when the sensitivity to vestibular inputs was estimated by subtracting the eye-velocity component of the firing rate from the firing of HGVPs during the VOR (Lisberger et al 1994a).

Controversy has surrounded interpretation of the recordings from HGVPs because of the paradox that HGVPs show changes in the correct direction to support the modified VOR if measured during the VOR (Miles et al 1980a, Watanabe 1984, Lisberger et al 1994a) and in the wrong direction to cause the modified VOR if measured during cancellation of the VOR (Miles et al 1980a, Lisberger et al 1994a). Computer modeling (Lisberger & Sejnowski 1992, Lisberger 1994) has now demonstrated that that the paradoxical data are predicted if (*a*) there are sites of memory in the vestibular inputs to both FTNs and HGVPs, and (*b*) the memory in the inputs to HGVPs consists of changes in the time course and strength of vestibular transmission. Explanation of the paradox hinges on the assumption that changes in the responses of neurons that transmit eye-velocity feedback to HGVPs are responsible for some of the changes in the firing of HGVPs measured during the VOR. New data have also excluded a number of previous explanations for this paradox. The possibility of species differences (Lisberger 1982, Kawato & Gomi 1992) has been ruled out by the similarity of the data from monkeys (Watanabe 1984) and rabbits (Dufosse et al 1978). The possibility that eye-velocity feedback is important in monkeys but not in rabbits is negated by the finding of pronounced eye-movement responses in Purkinje cells in the flocculus of rabbits (Leonard & Simpson 1985, Nagao 1991). The possibility that different studies were recorded from different populations of Purkinje cells is negated by the finding that the paradox exists in almost all individual HGVPs (Lisberger et al 1994a).

A current controversy stems from the question of whether it is correct to judge the function of the F/VPF from the responses of HGVPs. Some HGVPs have been recorded in the flocculus (Lisberger et al 1994a), but most of the HGVPs in the literature have been recorded in the ventral paraflocculus. There is now evidence of some anatomical differences in the source of the visual inputs to the flocculus vs the ventral paraflocculus (Gerrits & Voogd 1989). New experiments are required to determine whether the flocculus performs a function that is different from that of the HGVPs. This issue could be addressed by extensively recording from the flocculus and/or by determining the effects on learning of lesions that remove the flocculus but spare the ventral paraflocculus. Nagao (1992) has claimed to find differences in the responses of Purkinje cells recorded in the flocculus and the ventral paraflocculus in monkeys. However, his conclusions are compromised by a number of technical

problems (for a more extensive discussion, see Lisberger et al 1994a). Even if future recordings reveal that non-HGVPs in the F/VPF also contribute to memory in the VOR, the demonstration of learning-related changes in the responses of HGVPs during the VOR in the dark (Miles et al 1980a, Lisberger et al 1994a) requires that HGVPs be included in any theory of learning and memory in the VOR.

Further Constraints on the Sites of Memory in the VOR

The evidence that we have presented so far implicates the vestibular inputs to FTNs as one candidate locus of memory in the VOR. FTNs receive information about head movement from multiple sources: monosynaptic input from afferents traveling in the ipsilateral vestibular nerve, polysynaptic inputs from the contralateral vestibular nerve (Broussard & Lisberger 1992), and inhibition from Purkinje cells in the F/VPF (Lisberger et al 1994b). In addition, FTNs probably receive disynaptic inputs from the ipsilateral vestibular nerve (Broussard & Lisberger 1992). In theory, changes in the amplitude of any of these input signals or in the strength of synapses from any or all of these inputs, or postsynaptic changes in the intrinsic properties of FTNs could produce the changes observed in FTN response properties. However, the fact that the VOR circuitry also mediates visual-tracking eye movements of pursuit and the OKR places significant constraints on which of these potential candidates could mediate learning-related changes in the responses of FTNs during the VOR.

Because pursuit is driven, at least in part, by inputs to FTNs from the F/VPF, we would expect that changes in the strength of transmission from HGVPs onto FTNs would result in parallel changes in the pursuit eye movements. Such changes do not occur (Lisberger 1994). From this finding, we conclude that the synapse between HGVPs and FTNs is not a site of memory in the VOR. This conclusion is supported by the finding that changes in the gain of the VOR affect neither the magnitude nor the time course the eye movements evoked by electrical stimulation of the F/VPF (Lisberger 1994).

In monkeys, changes in the gain of the VOR cause parallel changes in a part of the OKR that has a very slow time course, building up over 5 to 15 s and lasting as long as 1 min in the dark after the moving stimulus is turned off. This "long time constant" component of the OKR becomes smaller than normal when the gain of the VOR is low and larger than normal when the gain of the VOR is high (Lisberger et al 1981). Because vestibular primary afferents do not carry signals related to the OKR (Buttner & Waespe 1981), changes in the synapses between vestibular afferents and FTNs would not affect the OKR. Therefore, these synapses cannot be the sole site of memory in the brainstem. However, secondary vestibular neurons do carry signals related to the long time constant component of OKR (Henn et al 1974), and changes in transmission from secondary neurons to FTNs would affect the

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OKR. For the remainder of the paper, we use the term *vestibular inputs to FTNs* to refer to the full set of possible brainstem vestibular inputs and not just to the inputs from primary afferents.

Use of Computer Models to Reveal Possible Sites of Memory

In neural circuits that contain feedback (as do most circuits in the brain), the expression of memory in the responses of cells is determined partly by the site and nature of the cellular mechanism of memory and partly by the architecture of the neural network in which the memory mechanism is embedded. Positive feedback, such as exists in the oculomotor system, can act as an amplifier to convert small cellular changes into large neural and behavioral expressions of memory (Miles et al 1980a,b) or as an integrator to convert transient changes in input signals into sustained changes in behavioral output (Lisberger & Sejnowski 1992). The possible effects of positive feedback on the operation of a neural network invalidate reasoning that is based on purely feedforward neural connections and demand the quantitative analysis that is provided by dynamic, recurrent models to form hypotheses about the site of memory. In addition, the relationship between the dynamics and gain of the VOR is an important constraint on the sites and mechanisms of memory, but it is too complex to be evaluated without quantitative modeling.

Lisberger & Sejnowski (1992) and Lisberger (1994) used computer simulations to search for a combination of sites of memory that could account for the gain and dynamics of the VOR in the dark; the gain and dynamics of pursuit with the head stationary; and the responses of FTNs, PVPs, and HGVPs during the VOR, cancellation of the VOR, and pursuit when the gain of the VOR was high, normal, or low. Figure 2 summarizes the possible sites of memory that were tested by the modeling and provides a vocabulary for expressing the results of the computer simulations. The models were able to reproduce available behavioral and neural data only if there were sites of memory in the brainstem vestibular inputs to FTNs (site D) and in the vestibular inputs to HGVPs (site A). Part of the change in the gain of the VOR was accomplished by varying the strength of transmission in parallel at these sites. The amount of change at these sites in the model was selected to reproduce the measured effect of changes in the gain of the VOR on the responses of HGVPs during cancellation of the VOR. Changes in the strength of vestibular inputs to FTNs were in the correct direction to cause changes in the gain of the VOR. Changes in the strength of vestibular inputs to HGVPs were in the wrong direction to cause changes in the gain of the VOR but were in the right direction to maintain stability in the VOR.

Further changes in the gain of the VOR and the required change in dynamics were attained by altering the time course but not the strength of the vestibular inputs to HGVPs. When the input was made more transient, either by adding

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some overshoot to the vestibular input (Lisberger 1994) or by shortening the time constant of filtering at that site (Lisberger & Sejnowski 1992), the gain of the VOR was reduced and the response to ramps of head velocity became more transient. In principle, a change in the time course of a neural input could result from changes in cellular or circuit properties. A faster time course could be obtained by (*a*) differentially changing the weights of inputs with different time courses (e.g. Lisberger 1994), (*b*) using changes in strength of transmission to alter the temporal filtering properties of a local neural network (e.g. Fujita 1982, Lisberger & Sejnowski 1992), or (*c*) altering a cellular mechanism in a way that changes the temporal filtering properties of a synapse or the spike generator in the postsynaptic cell.

Within the context of the connections shown in Figure 2, models were created that could reproduce available data only if they implemented sites of memory at both A and D. Changes in the strength of transmission at sites A or D alone caused the model to exhibit unstable runaway behavior, because of the eye-velocity feedback pathway through HGVPs. Parallel changes in the strength of transmission at sites A and D maintained stability but did not produce either changes in the dynamics of the VOR or large enough changes in the gain of the VOR without requiring changes in the strength of transmission at site D much larger than demonstrated in recordings from HGVPs during cancellation of the VOR. Changes in the strength of transmission within the eye-velocity feedback pathway (site B) caused changes in the gain and dynamics of pursuit eye movements, contradicting the lack of effect of changes in the gain of the VOR on pursuit (Lisberger 1994). Altering the time course of the vestibular inputs to FTNs (site D) caused the dynamics of the VOR to vary in the wrong direction: Decreases in the gain of the VOR were associated with decreased rather than increased overshoot during ramps of head velocity. Altering the strength or time course of the vestibular inputs to PVPs (site C) incorrectly predicted that changes in the gain of the VOR should be associated with changes in the responses of PVPs during cancellation of the VOR. As discussed above, learning-related changes in the inhibitory inputs to FTNs from HGVPs (site E) can be ruled out by the failure of changes in the gain of the VOR to cause parallel changes in pursuit eye movements or in the eye movements evoked by electrical stimulation of the F/VPF.

Other attempts have been made to model the site or sites of memory in the VOR, but none have been successful at reproducing the internal signals recorded from neurons at different gains of the VOR, and some have ignored important constraints imposed by well-documented parts of the essential neural network. One class of models (Lisberger et al 1983, Quinn et al 1992a, Minor & Goldberg 1991) was based on a model proposed by Skavenski & Robinson (1973). Each of these models consists of two or more parallel VOR pathways with different temporal-filtering properties, and each accomplishes changes in

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the gain and temporal dynamics of the VOR by adjusting the weights differentially in the pathways. Lisberger et al (1983) used this approach to reproduce data showing that learning in the VOR is frequency-selective when the vestibular stimulus for adaptation is a sine wave at a single frequency. Minor & Goldberg (1991) demonstrated that it was possible to reproduce the general temporal trajectory of eye velocity evoked by ramps of head velocity when the gain of the VOR was low, normal, and high. Quinn et al (1992a) reproduced changes in the gain and phase of the VOR during sinusoidal rotation of the visual scene and the animal at single frequencies. Each of these models demonstrates the feasibility of accomplishing some aspects of adaptive changes in the VOR by distributing sites of memory across parallel neural pathways that have different temporal dynamics. Quinn et al (1992b) demonstrated that it is feasible to implement this class of model as a neural network that has an architecture derived from the basic organization of the brainstem VOR pathways. However, none of these models were helpful in localizing the sites of memory in the brain because they did not attempt to emulate the flow of neural signals in the biological VOR pathways, and they did not contain nodes that represented PVPs, FTNs, and HGVPs.

A second class of models was based on the original proposal by Ito (1972) that the sole site of memory in the VOR is in a pathway from the vestibular labyrinth through the flocculus to the vestibular nucleus. Fujita (1982) demonstrated that this model can produce realistic learning and memory in the eye movements of the VOR, if eye-velocity positive feedback to the F/VPF plays little or no role in the operation of the system. Gomi & Kawato (1992) used a model that included the possibility of eye-velocity positive feedback through the F/VPF and employed an automatic-optimization algorithm to adjust the weights of transmission of vestibular and eye-movement signals through the node that represented Purkinje cells in the flocculus. The model selected a large weight for the eye-velocity input to the flocculus. Without systematically exploring why eye-velocity inputs to the flocculus were strong in their model, Gomi & Kawato (1992) concluded that eye-velocity positive feedback was not important for the operation of the biological system. Because they were based on the preconception that the sole site of memory for the VOR is in the flocculus, these models have not elucidated the sites of memory in the VOR pathways in the brain.

The model of Lisberger (1994) is one of a third class of models that attempts to represent the known architecture of the biological neural network for the VOR. One of the deficiencies of Lisberger's model is that it lumps the two sides of the brain together and fails to represent the commissural connections between the two vestibular nuclei. Galiana (1986) used a model that included both sides of the brain and explicitly represented many of the neurons that are known to participate in the VOR. Her model demonstrated that the commis-

sural connections between the vestibular nuclei would be feasible sites of memory in the VOR. Available data are compatible with Galiana's suggestion. Lisberger et al (1994c) have provided evidence that one site of memory is in the vestibular inputs to FTNs, and Broussard & Lisberger (1992) have shown that one potential vestibular input to FTNs is an excitatory connection that is transmitted from the contralateral vestibular nucleus. However, there are two problems with Galiana's (1986) model: 1. The model fails to replicate the equal amplitude eye-velocity and head-velocity inputs to HGVPs in monkeys (Lisberger & Fuchs 1978a, Miles et al 1980b), and 2. Galiana's (1986) contention that the gain-of-pursuit eye movement should not change even if the site of memory in the VOR is in feedback loops overlooks the temporal dynamics of pursuit evoked by target motion at constant speed. Lisberger (1994) has shown that the temporal dynamics of eye velocity during pursuit are affected by changing the gain of positive feedback in the model, not by changing the gain of the VOR in monkeys.

A Unifying Hypothesis for the Sites of Memory in the VOR

We suggest that there are multiple sites of memory in the VOR and that each site performs a different function. A site of memory in the brainstem appears to drive the earliest modified component of the VOR. Because Lisberger & Miles (1980) looked for and did not find changes in the vestibular responses of non-FTN vestibular neurons in the vestibular nucleus, the primary site of memory in the brainstem is likely to be in synapses onto FTNs or in the intrinsic properties of the FTNs themselves.[2] A second site of memory, in the vestibular inputs to HGVPs, may be in the F/VPF. The memory in the vestibular inputs to HGVPs has been modeled so that separate changes in the strength and time course of vestibular inputs have different functions. Although the change in the strength of vestibular inputs is in the wrong direction to cause the associated changes in the gain of the VOR, it is in the correct direction to maintain stability in the system in the face of changes at the brainstem site of memory. The change in the time course, once amplified and integrated by the rest of the VOR pathways, is converted into a signal that would cause part of the associated changes in the gain of the VOR.

POSSIBLE MECHANISMS OF LEARNING IN THE VOR

Conclusions about the mechanisms of learning require an integrated understanding not only of the details of mechanisms of cellular plasticity operation,

[2]If the site of memory is in the intrinsic properties of FTNs, then it must be localized so that changes in the gain of the VOR do not affect the responses of FTNs to inhibitory inputs from F/VPF. Otherwise, changing the gain of the VOR would affect the eye movements evoked by electrical stimulation in the F/VPF as well as the gain of pursuit, which it does not (Lisberger 1994).

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but also of the operation of those mechanisms in the context of the presynaptic and postsynaptic activity at a putative site of memory. In particular, the mere existence of a mechanism for cellular plasticity does not constitute evidence that the mechanism participates in a specific form of behavioral learning. In this section of our review, we evaluate how known mechanisms of cellular plasticity might work in the context of the presynaptic and postsynaptic activity at the putative sites of memory in the VOR. For learning in the vestibular inputs to HGVPs, we evaluate the available presynaptic signals in the context of cerebellar LTD, which has been proposed as a specific cellular mechanism for learning in the VOR (Ito 1989). For learning in the vestibular inputs to FTNs, where mechanisms of cellular plasticity have not yet been described, we evaluate the available presynaptic and postsynaptic activity in the context of current ideas about mechanisms of cellular plasticity in the hippocampus and cerebral cortex. This part of our paper is, by its nature, speculative, and we conclude that available data are far too fragmentary to allow any firm conclusions about mechanisms of learning in the VOR. We present this section as a framework for designing experiments that will examine the mechanisms of learning in the realistic conditions imposed by the operation of the neural network for the VOR in awake, behaving animals.

Anatomical Structures Involved in Learning in the VOR

Ablation studies have identified anatomical structures that may be involved in learning in the VOR. Removal of the whole cerebellum or bilateral ablation of the entire flocculus and ventral paraflocculus prevented learning in the VOR but had relatively little effect on the normal VOR (e.g. Robinson 1976, Lisberger et al 1984, Barmack & Pettorossi 1985, Nagao 1983). In contrast, ablation of the uvula and nodulus in the midline vestibulo-cerebellum had no effect on learning or memory in the VOR (Cohen et al 1992). One possibility is that ablation of the F/VPF abolishes learning in the VOR because it removes the site(s) of memory. However, this is not consistent with evidence that at least one site of memory for the VOR is in the brainstem. As a resolution to this problem, Miles & Lisberger (1981) suggested that output signals from the F/VPF were essential as "teachers" to guide learning, independent of the role of the F/VPF as a site of memory for the VOR.

A recent experiment by Luebke & Robinson (1994) provides strong support for the idea that the output from the F/VPF might guide learning. They first demonstrated that stimulation of the inferior olive at 7 Hz causes Purkinje cells in the cat's flocculus to cease firing simple spikes, thereby eliminating all functional output from the flocculus. They then used this paradigm to reversibly inactivate the flocculus in cats that had been preadapted to have increased or decreased VOR gains. Luebke & Robinson (1992) found that the memory of the adapted VOR was retained during inactivation of the F/VPF and that

rotation with normal viewing did not cause the VOR to relearn a gain of 1.0. Thus, inactivation of the flocculus had no effect on memory, but it prevented learning in the VOR. Surgical lesions of the inferior olive also prevent learning (Barmack & Simpson 1980, Tempia et al 1991). This result could reflect a direct contribution of climbing-fiber inputs to learning in the cerebellar cortex, but it might also reflect disruption of a direct contribution of climbing fibers to learning in the brainstem or alteration of the normal operation of Purkinje cells.

Behavioral Rules for Learning in the VOR

At the behavioral level, an adequate condition for learning in the VOR is the association of visual and vestibular inputs. The gain of the VOR can be modified if visual experience is altered so that the directions of image motion and head motion are correlated consistently during head turns. If a subject wears magnifying spectacles, for example, then the normal VOR will be too small, images will move in the opposite direction from each head turn, and the gain of the VOR will increase. Likewise, if a subject wears miniaturizing glasses, then the normal VOR is too large, images will move in the same direction as the head turn, and the gain of the VOR will decrease. These behavioral considerations suggest a head-plus-image-motion learning rule for the VOR:

If image motion is in the same direction as head turns, then the gain of the VOR should decrease.

If image motion is in the opposite direction from head motion, then the gain of the VOR should increase.

Possible Rules for Learning in the Brainstem

At the neural level, the visual and vestibular sensory inputs that guide learning must be represented in the discharge of neurons that converge on the sites of memory. As we have already mentioned, FTNs receive vestibular inputs from multiple sources. Because of the clear necessity of the F/VPF for learning, we focus on the potential visual error signals from the HGVPs, even though visual inputs reach the vestibular nucleus from a variety of sources. Two previous papers (Miles & Lisberger 1981, Lisberger 1988) have proposed that correlated changes in the activity of HGVPs and vestibular inputs provide error signals that guide cellular mechanisms of learning at FTNs in the vestibular nuclei. To analyze this hypothesis, we consider the neural error signals available as inputs to FTNs from HGVPs and from the vestibular system when the gain of the VOR is 1.0 and the monkey is subjected to head turns under altered visual conditions that, if prolonged, would cause learning. The left-most column in Table 2 describes the visual conditions used to cause learning as $\times N$, where N is the ideal

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gain of the VOR for that visual condition. From left to right, the next four columns represent the direction of the change in the gain of the VOR required to eliminate image motion during head turns, and the direction of the change of firing in vestibular inputs, HGVPs, and FTNs for an ipsiversive head turn during each of the conditions used to cause learning.[3] The right-most column represents the absolute firing rate of FTNs during ipsiversive head turns for each adapting condition. During ipsiversive head turns, the vestibular inputs to FTNs will show increases in firing rate. Under conditions that call for a decrease in the gain of the VOR (×0, ×0.4, ×0.7), ipsiversive head turns are associated with increases in the firing rates of HGVPs. Under conditions that call for an increase in the gain of the VOR (×2), ipsiversive head turns are associated with decreases in the firing rate of HGVPs . Under normal (×1) viewing conditions, an ipsiversive head turn does not cause any change in the simple-spike firing rate of HGVPs, and no learning occurs. Thus, the neural signals available as inputs to FTNs suggest a neural learning rule for the VOR:

If changes in the firing rate of vestibular and HGVP inputs to FTNs are in the same direction, then the gain of the VOR should decrease.

If changes in the firing rate of vestibular and HGVP inputs to FTNs are in opposite directions, then the gain of the VOR should increase.

Table 2 Evaluation of possible rules for learning in the vestibular inputs to FTNs[a]

Behavioral condition[b]	Required change in VOR gain	Modulation of vestibular inputs[c]	Modulation of HGVP firing	Modulation of FTN firing	Absolute firing rate of FTNs[d]
×0	−	++	+++	−	***
×0.4	−	++	++	0	****
×0.7	−	++	+	+	*****
×1	0	++	0	++	******
×2	+	++	−−−	+++++	*********
Pursuit	0	0	+++	−−−	*
Baseline	0	0	0	0	****

[a] The table represents responses of vestibular afferents, HGVPs, and FTNs to ipsiversive head turns under various adapting conditions when the gain of the VOR is 1.0. The entries were inferred from average responses measured during sinusoidal vestibular rotation under behavioral conditions that simulated ×0, ×1, and ×2 adapting conditions or during pursuit with the head stationary (Lisberger & Fuchs 1978a, Lisberger et al 1994b).

[b] Behavioral conditions are indicated as ×*N*, where *N* is the gain of the VOR required to eliminate image motion during head turns. Also shown are the responses during ipsiversive pursuit eye movements and the baseline firing rate in the resting condition with the head stationary and eyes stationary at straight-ahead gaze.

[c] Modulation of firing is represented by "−" signs for a decrease, "+" signs for an increase, and zero for no change in firing rate from baseline.

[d] The number of asterisks indicates the absolute firing rate of the FTNs.

[3]Because HGVPs, FTNs, and PVPs are all spontaneously active, signals related to the sensory stimuli are encoded in changes in the firing rate from the resting rate.

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CONSTRAINTS ON CELLULAR MECHANISMS OF LEARNING AT FTNs At least two classes of mechanisms of cellular plasticity would allow correlated changes in firing rate of the vestibular and cerebellar inputs to FTNs to guide changes in the strength of vestibular inputs to FTNs. 1. Purkinje cell terminals could release modulatory substances (e.g. Chan-Palay et al 1982) that would interact directly in an activity-dependent way with the terminals of neurons that provide vestibular inputs to FTNs to cause synaptic potentiation or depression. 2. Because HGVPs directly inhibit the FTNs, activity in HGVPs could guide learning through its effects on the level of activity in the postsynaptic neurons, the FTNs. Following the examples of activity-dependent plasticity now known at numerous sites in the brain, modification of the synapses between vestibular inputs and FTNs might depend on the relationship between activity in the presynaptic vestibular axons and some aspect of activity in FTNs.

A mechanism based on comparison of the absolute firing rate of FTNs with that of vestibular inputs would provide consistent guidance for learning in the VOR. Consideration of Table 2 reveals that the gain of the VOR increases when the firing rates are high both in FTNs and in their vestibular inputs. The gain of the VOR decreases when firing rates are low in FTNs and high in their vestibular inputs. In contrast, any variable correlated with the direction of modulation of the firing of FTNs cannot control learning because the direction of modulation of FTN firing is not consistently related to the direction of change in the gain of the VOR. For example, ipsiversive head turns under $\times 2$ and $\times 0.7$ viewing conditions would be associated with an increase in both the postsynaptic activity of FTNs and the presynaptic activity of vestibular inputs, but the changes in the gain of the VOR associated with these conditions are in opposite directions. Furthermore, a comparison of the changes in the firing rate of the FTNs during $\times 0$, $\times 0.4$, and $\times 0.7$ viewing conditions shows that a decrease in the gain of the VOR can occur under conditions associated with either a decrease, an increase, or no change in the firing rate of the FTNs during an ipsiversive head turn. Because of the high level of spontaneous activity in FTNs and their vestibular inputs, a simple correlation of presynaptic and postsynaptic activity cannot provide a complete learning rule because the resting activity would cause transmission to become potentiated maximally, even in the absence of the requisite association of vestibular and cerebellar input signals. Instead, a neural mechanism that depends on activity in the FTNs and their vestibular inputs must involve set points or thresholds as reference points to control whether transmission is potentiated or depressed. In the case of FTNs, the set point for postsynaptic activity must be at a firing rate above the resting rate, corresponding to an absolute firing rate of +6 in Table 2. If the firing rate of the vestibular inputs to FTNs is above resting rate and the firing of FTNs is above the set point of +6, then the gain of the VOR increases. If the firing rate of the vestibular inputs to FTNs is above resting rate and the

firing of FTNs is below the set point of +6, then the gain of the VOR decreases. If the firing rate of FTNs is at the set point of +6, then the gain of the VOR does not change. Several authors have proposed mechanisms that could be used to implement a set point to regulate the levels of synaptic depression and potentiation in neurons that are spontaneously active (reviewed by Artola & Singer 1993).

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OUTPUT OF HGVPs AS AN ERROR SIGNAL TO GUIDE LEARNING? The firing of HGVPs has a feature that may prove to be necessary for a neural error signal that guides learning in the VOR. The simple-spike firing of HGVPs contains useful information about the need to change the gain of the VOR whether or not the subject is using the OKR and/or pursuit eye movements to eliminate the image motion caused by a VOR that is too large or too small. The activity of HGVPs has separate components driven by visual motion and eye motion (Stone & Lisberger 1990a). Either ipsiversive image motion or ipsiversive eye motion alone is sufficient to increase the simple-spike firing rate of HGVPs. When a subject executes a head turn under conditions that cause learning in the VOR, image motion will accompany at least the first 100 ms of the head turn. If the direction of the image motion is ipsiversive, then the firing rate of HGVPs will increase. If the subject fails to initiate visual tracking, then the image motion will persist throughout the head turn, and the firing of HGVPs will remain high. If the subject does initiate visual tracking, then the image motion may disappear, but the ipsiversive smooth eye velocity initiated by visual tracking will cause the firing of HGVPs to remain high for the duration of the head turn. Even during sinusoidal oscillation at low frequencies, when image motion is eliminated almost completely by the visual-tracking system, the output of HGVPs continues to provide useful information about the direction of errors in the VOR. The consistent modulation of HGVPs would be one way to explain the finding that the VOR undergoes learning during sinusoidal oscillation at low frequencies, even if the visual stimulus is a small spot that is tracked almost perfectly (Lisberger et al 1984).

The firing of HGVPs also has a feature that may not be appropriate for an error signal that guides learning. This problem does not arise when the gain of the VOR is 1.0, because the simple-spike firing rate of HGVPs is unmodulated during head rotation in the dark or in normal visual conditions (×1). In some conditions, however, HGVPs provide an error signal even though the gain of the VOR is appropriate and visual inputs do not provide an adequate condition for learning. After the gain of the VOR has been adapted to be high or low, for example, the simple-spike firing rate of HGVPs is modulated consistently during the VOR in the dark (Miles et al 1980a, Watanabe 1984, Lisberger et al 1994a). The direction of the response of HGVPs is such that if simple-spike firing guides learning in the vestibular inputs to FTNs, then

the combination of vestibular inputs and simple-spike firing would cause a VOR with a low gain to get still lower and a VOR with a high gain to get still higher. In practice, this situation could prevent forgetting by causing automatic reinforcement of short-term potentiation or depression in the vestibular inputs to FTNs. In principle, however, it contradicts our assumption that a useful error signal for guiding learning in the VOR should be present only when there is visual feedback and not during the VOR in the dark.

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A POSSIBLE ROLE FOR CLIMBING FIBERS IN LEARNING IN THE BRAINSTEM? *Climbing fibers* and *mossy fibers* provide two different kinds of inputs to the cerebellum. Mossy fibers synapse on granule cells. The axons of granule cells ascend in the cerebellar cortex and form *parallel fibers,* which make excitatory connections onto Purkinje cells. Mossy fiber inputs to the cerebellum cause Purkinje cells to emit simple spikes, which fire at rates as high as 200 or 300 spikes/s (until now our discussion of the firing of HGVPs has concerned only the simple spikes). Climbing fibers make extensive synaptic contacts directly on Purkinje cells and cause them to emit *complex spikes,* which fire at low rates that seldom exceed 1 or 2 spikes/s. In many parts of the cerebellum, climbing fibers send collaterals to the regions of the deep cerebellar nucleus that are related to the Purkinje cells that are the primary targets of the climbing fibers.

Climbing-fiber collaterals to the FTNs provide a potential solution to the problem outlined in the previous section, i.e. that a cellular learning rule based on the simple-spike firing of HGVPs might guide inappropriate learning during head turns in the dark when the gain of the VOR is high or low. The complex spike activity of Purkinje cells in the F/VPF is driven by visual inputs related to the motion of small targets or large textures in primates (Stone & Lisberger 1990b) and to the motion of large textures in rabbits (Alley et al 1975, Graf et al 1988). Available anatomical evidence is consistent with the possibility that the climbing-fiber inputs to the F/VPF send collaterals to FTNs (Balaban et al 1981). Therefore, climbing fibers may transmit information about the presence and direction of image motion to the FTNs. Since the visual inputs provided by climbing fibers would not be modulated consistently during the VOR in the dark or in the absence of visual image motion, they could serve as an absolute indicator of the need for learning in the VOR. They could operate either as a primary error signal to guide learning or as a permissive influence that would enable a learning mechanism based on activity in FTNs, HGVPs, and the vestibular inputs to FTNs.

LTD as a Cellular Mechanism of Learning in the Cerebellar Cortex

Ito (1972, 1982) proposed the "flocculus hypothesis" of motor learning in the VOR, based on a model of associative learning in the cerebellum suggested

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by Brindley (1964) and developed more thoroughly by Marr (1969) and Albus (1971). In this class of models, the climbing fiber acts as a teacher that instructs the synapses from parallel fibers to Purkinje cells by a mechanism that depends on paired activity between these two inputs. According to the flocculus hypothesis, climbing-fiber activity related to contraversive image motion causes long-term depression (LTD) at the synapses from vestibular parallel fibers onto Purkinje cells. Under stimulation conditions that require an increase in the gain of the VOR, vestibular inputs to Purkinje cells originating from the ipsilateral vestibular labyrinth would be more active during complex spikes and would undergo LTD (Ito 1982). Under conditions that require decreases in the gain of the VOR, vestibular inputs originating from the contralateral labyrinth would be more active during complex spikes and would undergo LTD (Ito 1993).

LTD IN THE CEREBELLUM Experiments in a variety of preparations have provided evidence that a cellular mechanism for LTD exists in the cerebellar cortex. Conjunctive stimulation of parallel- and climbing-fiber inputs to a Purkinje cell causes depression of transmission in the synapses from the parallel fibers to the Purkinje cell (see Ito 1989, Linden & Connor 1993).

We must assume that cerebellar LTD has a companion LTP and that the absence of conjunction between climbing- and parallel-fiber inputs potentiates a synapse, while conjunction depresses the synapse. If LTD existed without either LTP or, at least, decay of LTD, then the spontaneous activity of parallel fibers and climbing fibers would cause parallel-fiber synapses onto Purkinje cells to become terminally depressed. In cerebellar slices, LTP can be induced in parallel fiber–Purkinje cell synapses if the Purkinje cell is hyperpolarized and/or loaded with the Ca^{2+} chelator EGTA and the parallel fibers are activated (Sakurai 1987, Crepel & Jaillard 1991, Shibuki & Okada, 1992). We also adopt the suggestion by Ito (1993) that cerebellar LTD operates reciprocally on mossy-fiber inputs that respond to a given input but have opposite direction preferences. Thus, decreases in the amplitude of the responses of HGVPs to ipsiversive head motion could be mediated either by LTD of synapses from parallel fibers that show increased firing for ipsiversive head motion or by LTP of synapses from parallel fibers that show decreased firing for ipsiversive head motion. Likewise, increases in the amplitude of the responses of HGVPs to ipsiversive head motion could be mediated by LTD of synapses from parallel fibers that show decreased firing during ipsiversive head motion or by LTP of synapses from parallel fibers that show increased firing during ipsiversive head motion.

PREDICTIONS OF THE FLOCCULUS HYPOTHESIS FOR LEARNING AT PARALLEL-FIBER INPUTS TO HGVPs Evaluated in the context of the known mossy-fiber inputs to HGVPs, the flocculus hypothesis lacks the specificity needed to cause

changes in the gain of the VOR without affecting other functions of the HGVPs. In monkeys, HGVPs receive three separate mossy-fiber inputs related to head velocity, eye velocity, and image motion (Miles & Fuller 1975, Lisberger & Fuchs 1978b, Miles et al 1980b, Noda 1986, Stone & Lisberger 1990a), and the simple-spike firing of HGVPs is approximately equal to the sum of these three inputs (Lisberger & Fuchs 1978a, Miles et al 1980b). During conditions that cause learning, not only the vestibular parallel-fiber inputs, but also the eye-movement and visual parallel-fiber inputs to the HGVPs fire in conjunction with climbing-fiber activity. Thus, the flocculus hypothesis predicts that learning in the VOR would be associated with changes in the strength of eye-movement and visual parallel-fiber inputs as well as vestibular parallel-fiber inputs to HGVPs.

The predictions of the flocculus hypothesis for the effect of different adapting conditions on the strength of vestibular inputs to HGVPs are inconsistent with the observations by Miles et al (1980b) and Lisberger et al (1994). After monkeys had been exposed to conditions that caused learning in the VOR (Table 3), increases in the gain of the VOR were associated with increases in the vestibular sensitivity of HGVPs, and decreases in the gain of the VOR were associated with decreases in the vestibular sensitivity of the HGVPs. According to the flocculus hypothesis, the conjunction of increased activity in the vestibular parallel-fiber inputs and visual climbing-fiber inputs under conditions that require the gain of the VOR to be increased (×2) should cause decreases in the amplitude of the vestibular responses of HGVPs. The absence of conjunction of climbing-fiber inputs and vestibular parallel-fiber inputs during conditions that require the gain of the VOR to be decreased (×0) should cause increases in the amplitude of the vestibular responses of HGVPs. Although available data on the amplitude of the sustained vestibular inputs to HGVPs contradict the flocculus hypothesis, modeling studies by Lisberger (1994) and Lisberger & Sejnowski (1992) have raised the possibility that changes in the amplitude of transient vestibular responses of HGVPs, in the direction predicted by the flocculus hypothesis, could participate in changing the gain of the VOR. New experiments will be needed to test for the postulated changes in the transient vestibular responses of HGVPs and to understand whether oppositely directed changes in the transient and sustained vestibular sensitivity of HGVPs are compatible with learning mediated by LTD in the cerebellar cortex of the F/VPF.

Analysis of the flocculus hypothesis for eye-movement mossy-fiber inputs yields different predictions depending on whether or not visual-tracking mechanisms such as pursuit or the OKR are used during learning to generate smooth eye movements that reduce the image motion. When the subject does not track the moving images seen under the adapting conditions (Table 3), eye movements are always in the opposite direction from head movements: The direction

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Table 3 Evaluation of cerebellar LTD as a rule for learning in the parallel fiber inputs to HGVPs[a]

	Vestibular inputs				Eye-movement inputs							
					Not tracking				Tracking			
Behavioral condition[b]	Vestibular mossy fiber[c]	Climbing fiber[d]	Predicted change[e]	Recorded change[e]	Eye-movement mossy fiber[c]	Climbing fiber	Predicted change	Recorded change	Eye-movement mossy fiber	Climbing fiber	Predicted change	Recorded change
LR reversal	+	−	+	−	−	−	−	+	+	−	+	+
×0	+	−	+	NA[f]	−	−	−	NA	0	−	0	NA
×0.25	+	−	+	−	−	−	−	NA	−	−	−	NA
×2	+	+	−	+	−	+	+	+	−	+	+	+
Pursuit	0	−	0	NA	0	−	0	NA	+	−	+	NA
×1 (Rapid)	+	+	−	NA	−	+	+	NA	−	+	+	NA

[a] The table compares predicted and observed changes in the sensitivity of HGVPs to vestibular and eye-movement mossy-fiber inputs produced by various adapting conditions. Entries in the table are extrapolated from averaged responses of HGVPs (Lisberger & Fuchs 1978a).

[b] LR reversal indicates left-right reversal of vision with prisms. Other adapting conditions are indicated as ×*N*, where *N* is the gain of the VOR required to eliminate image motion during head turns. Also shown are the responses during ipsiversive pursuit eye movements and during rapid head turns with nonnal vision [× 1 (Rapid)].

[c] "+" and "−" signs indicate increases and decreases in the firing rates of the mossy fibers during ipsiversive head turns during the adapting conditions.

[d] "+" and "−" signs indicate increases and decreases in the firing rates of the climbing fibers due to retinal-image motion produced by head turns under the adapting conditions.

[e] "+" and "−" signs indicate increases and decreases in the sensitivity of HGVPs to the mossy-fiber inputs after exposure to the adapting conditions.

[f] Data not available.

of changes in the amplitude of the responses of HGVPs to eye velocity should be opposite that predicted for the responses to head velocity. The flocculus hypothesis predicts decreases in the strength of the eye-movement inputs for left-right reversal (LR reversal), ×0, and ×0.25 viewing conditions and increases for ×2 viewing conditions. When the subject does track the moving images seen under the adapting conditions (Table 3), the flocculus hypothesis predicts that the responses of HGVPs to eye velocity should get larger after learning in the LR reversal and ×2 viewing conditions, that they should get smaller after adaptation with ×0.25 viewing, and that they should not change after adaptation with ×0 viewing. In a partial test of these predictions, Miles et al (1980) found that both LR reversal of vision and ×2 viewing conditions caused small increases in the amplitude of the eye-movement responses of HGVPs during pursuit with the head stationary. These data would be consistent with the predictions of the flocculus hypothesis if the monkey were actually tracking the visual world during LR reversal of vision. However, the data are not conclusive, because it is unclear whether or not the monkeys were tracking the visual scene during adaptation.

Visual simple-spike responses of HGVPs are always modulated in the opposite direction from visual climbing fibers, and therefore the flocculus hypothesis predicts that the visual simple-spike responses of HGVPs will be maximally facilitated by any condition that causes image motion. No one has looked for increases in the amplitude of the image-motion response of HGVPs after learning. If such a change occurs, it should cause increases that were looked for but not seen in eye acceleration at the initiation of pursuit after the gain of the VOR had become high or low (Lisberger 1994). Either Lisberger's data contradict the predictions of the flocculus hypothesis or the visual parallel-fiber inputs to HGVPs are maximally potentiated even at the normal gain of the VOR.

Analysis of the parallel- and climbing-fiber inputs to HGVPs under tracking conditions that do not cause changes in the gain of the VOR reveals additional conditions under which the flocculus hypothesis lacks the specificity needed to control the gain of the VOR. During pursuit with the head stationary (Table 3), climbing fibers are silent when simple-spike activity increases (Lisberger & Fuchs 1978a, Stone & Lisberger 1990b), so the flocculus hypothesis predicts that the responses of HGVPs to eye velocity should get stronger. During rapid head turns under normal visual conditions with the lights on (Table 1), the 14-ms latency from the onset of head motion to the onset of the VOR causes a brief, transient image motion that affects climbing-fiber activity even if the gain of the VOR is 1.0 (Stone & Lisberger 1990b). According to the flocculus hypothesis, the conjuction of climbing- and parallel-fiber activity under this condition should cause depression of the vestibular responses of HGVPs and enhancement of their eye-movement responses. There is no evidence that these changes occur.

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The problems of specificity in the flocculus hypothesis could be circumvented by recent findings that the cellular mechanisms of LTD are more complex than assumed by the flocculus hypothesis. Simple conjunctive activation of parallel fibers and climbing fibers is not adequate for the induction of LTD. For example, Ekerot & Kano (1985) showed in an in vivo preparation that the induction of LTD by conjunctive stimulation of parallel fibers and climbing fibers was blocked if cerebellar inhibitory neurons were simultaneously activated. In vitro studies have confirmed their observation that inhibitory inputs to the Purkinje cells can prevent the induction of LTD (Crepel & Jaillard 1991, Shibuki & Okada 1992).

In the in vitro preparations used to study LTD, many cellular conditions do not pertain to those in the intact animal. Inhibitory inputs were blocked, many of the normals inputs to Purkinje cells were physically missing or damaged, and Purkinje cells were below threshold for firing. These factors must be considered in deciding whether the LTD studies in vitro can contribute to learning in the behaving animal, when Purkinje cells and their mossy-fiber inputs fire spontaneously at rates of about 100 spikes/s. In the vestibular nucleus, for example, the temporal dynamics of neurons depends critically on whether the membrane is above or below the threshold for repetitive firings of action potential (du Lac & Lisberger 1993).

We conclude that LTD remains a candidate mechanism for learning in the cerebellar cortex. However, the existence of multiple mossy-fiber inputs to the F/VPF requires a precisely regulated form of LTD and not a form that is invoked whenever there is conjunctive activation of parallel- and climbing-fiber inputs to a given Purkinje cell. Several questions must be answered before cerebellar LTD can be elevated from the status of a mechanism of cellular plasticity with unknown function: 1. Does learning in the VOR cause the changes predicted by Table 3 in the responses of HGVPs to eye movement and visual inputs? 2. What precisely are the cellular requirements for LTD and under what behavioral conditions does the activity in the relevant neurons meet those cellular requirements? 3. Can LTD provide the requisite synaptic specificity, and what are the factors that contribute to specificity in this form of cellular plasticity? and 4. How do the results obtained in brain slices and tissue culture relate to the conditions in vivo?

CONCLUSIONS

We have presented a new hypothesis concerning the sites of memory in the VOR and the contribution of network dynamics to the expression of memory. Based on extensive behavioral data and single-unit recordings, we suggest that one site of memory is in the vestibular inputs onto FTNs in the brainstem. We propose that a second site of memory is in the vestibular inputs to HGVPs in

the flocculus and ventral paraflocculus of the cerebellum. We have considered the details of possible mechanisms of cellular plasticity in the brainstem and in the cerebellum in relation to the neural signals produced by behavioral conditions that cause learning. Details of the cellular mechanisms of synaptic plasticity are of critical importance in the induction and specificity of learned behavioral changes in the VOR. Therefore, we suggest that future research on possible cellular mechanisms of learning in the VOR be performed in conditions that mimic as nearly as possible the neural activity that is present under behavioral circumstances that cause learning. We also suggest that future behavioral and neural analyses of learning in the VOR explicitly test the predictions made by possible cellular mechanisms of learning. An understanding of learning and memory in the VOR will result only from integration of the constraints and complexities provided by the real-world environment of the functioning brain with a detailed understanding of the in vivo operation of possible cellular mechanisms of learning.

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