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The vestibulo-ocular reflex as a model system for motor learning: what is the role of the cerebellum?

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Motor systems are under a continuous adaptive process to maintain behavior throughout developmental changes and disease, a process called motor learning. Simple behaviors with easily measurable inputs and outputs are best suited to understand the neuronal signals that contribute to the required motor learning. Considering simple behaviors, the vestibulo-ocular reflex (VOR) allows quantification of its input and motor output and its neural circuitry is among the best documented. The main candidates for plastic change are the cerebellum and its target neurons in the brainstem. This review focuses on recent data regarding the involvement of the cerebellum in VOR motor learning. Learning can be divided into that acutely acquired over a period of hours and that chronically acquired over longer periods. Both acute and chronic learning have three phases named acquisition, consolidation, and retention. The cerebellar role in retention is disputed, but there is a consensus on the need of an intact cerebellum for acquisition. Data from neuronal recording, lesion studies and transgenic mouse experiments is complex but suggests that the signal representation in the cerebellum contains aspects of both motor output and sensory input. The cerebellum apparently uses different mechanisms for acute and chronic learning as well as for increases and decreases in VOR gain. Recent studies also suggest that the signal content in the cerebellum changes following learning and that the mechanisms used for chronic adaptation involve not only changes in a head velocity component but also in the efference copy of an eye movement command signal reaching Purkinje cells. This data leads to a new conceptual framework having implications for developing theories on the role of the cerebellum in motor learning and in the search for plastic elements within the VOR circuitry. For chronic learning we hypothesize that changes in the head velocity information traveling through the circuitry occur in parallel with changes in the integrator pathway and the efference copy pathway. We further propose that these changes are necessary to maintain the broadband characteristics of the learned behavior.

Keywords:
vestibulo-ocular reflex – cerebellum – motor learning

Blazquez PM, Hirata Y, Highstein SM.
The vestibulo-ocular reflex as a model system for motor learning. What is the role of the cerebellum?
Cerebellum 2004; 3: 188-192

Introduction

Movements of the head are detected by the peripheral labyrinth and reported to the central vestibular system in the brainstem. Central vestibular neurons, in turn, command equal but oppositely directed reflexive eye movements that maintain the alignment of the retinal fovea on the visual target. This three-neuron pathway mediates the vestibulo-ocular reflex or VOR. The *gain* of the VOR (calculated as eye velocity divided by head velocity recorded in the dark) approximates unity, reflecting the ability of the reflex to generate eye movements of equivalent magnitude to the head movements in order to maintain stable gaze. The reflex is both spatially and temporally compensatory, and is also modifiable.[1] VOR circuitry includes a loop through the cerebellum which has provided one of the best known neuronal models for studies of cerebellar plasticity. The VOR carries several advantages for studies of motor behavior, including the elegant simplicity of its neuronal circuits (Figure 1), and the existence of well-established paradigms for induction and quantification of motor learning, as well as its evaluation using detectable error signals such as slippage of the image on the retina. However, there are highly recursive and reciprocal interconnections between the brainstem and cerebellar components of the VOR circuitry that render the task of signal extraction in relation to a particular set of parameters difficult and controversial.[2,3] Further, there are several candidate teaching signals for VOR motor learning, including retinal slip, motor error, and decorrelation control between the retinal slip signal and the motor command.[2,4,5]

Received 14 March 2004; Accepted 6 June 2004

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DOI 10.1080/14734220410018120

Evaluation of an inverse dynamic model in the cerebellum during VOR behavior

During the execution of a movement the central nervous system acts by controlling different muscles pairs and producing proper muscle contraction with appropriate

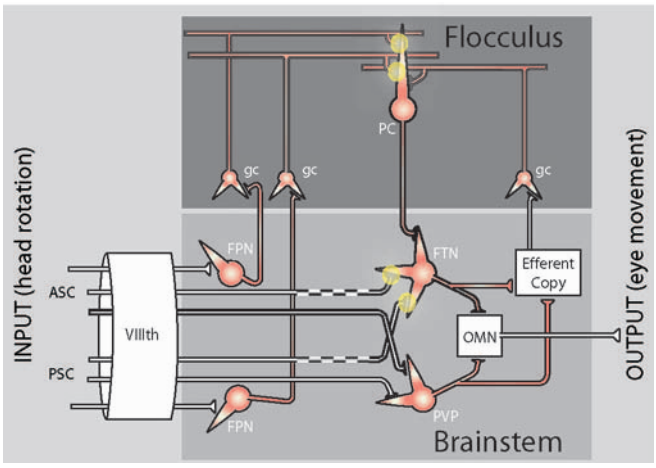

Figure 1
Schematic representation of the vertical VOR circuitry. Angular head acceleration is detected by the semicircular canals (anterior and posterior semicircular canals for vertical head rotations) and sent to secondary vestibular neurons in the brainstem (FPN, FTN and PVP).[24,29–30,38] FTN and PVP send direct projections to the oculomotor nucleus for the generation of compensatory eye movements while FPN, PC and FTN form a brainstem-flocculus loop.[24,29,38,39] In yellow we show the candidate synapses for plasticity according to Lisberger's model.[24] Abbreviations: ASC, anterior semicircular canal afferents; FPN, flocculus projecting neurons; FTN, flocculus target neurons; gc, granular cells; OMN, oculomotor nucleus; PC, Purkinje cells; PSC, posterior semicircular canal afferents; PVP, position vestibular pause neurons; VIIIth, eighth nerve.

timing. This might be performed by a *feed-back* system where actions are continuously controlled by sensory and proprioreceptor information or by using an *inverse dynamic* model in a feed-forward system. Both theories have their advantages but recent work has favored the existence of inverse dynamic models of muscle plants in order to achieve fast feed-forward motor control.[5–7] The cerebellum has been identified as a candidate structure where the inverse dynamic model may be stored. It has been demonstrated that the output of the cerebellum, represented by floccular Purkinje cell discharge, is equivalent to the dynamic component of the oculomotor motor command during a visually driven eye movement task called ocular following.[6–8] Thus, for the oculomotor system, Purkinje cell firing patterns can be reconstructed by a *linear combination* of eye position, velocity and acceleration as is the case for oculomotor neurons. This combination *is* the inverse dynamic model. However, one tenant of this theory is that, if we assume that the oculomotor plant does not change for different behaviors, the representation of the inverse dynamic model should be invariant across *different behavioral paradigms*. Experimental evidence has proven otherwise. Recently we have shown that different sets of coefficients for our parameters (eye position, velocity and acceleration) were required to reconstruct the discharge of a Purkinje cell during different visual-vestibular paradigms,[9] hence a pure inverse dynamic model resident within the cerebellar flocculus is not sufficient. To resolve this issue, we have studied the VOR within its linear range and have constructed a model of the Purkinje cell discharge patterns that assumes linear summation of input signals to flocculus (head, retinal slip, and efference copy of motor command signals).[9–11] Our model is consistent with the variety of signals arriving at the cerebellar cortex, and can account for Purkinje cell firing during all paradigms with a single parameter set at a given VOR gain.

Acute versus chronic VOR motor learning

Motor learning can be divided into that acutely acquired over a period of hours and that chronically acquired over longer periods. Both acute and chronic learning have three phases named acquisition, consolidation, and retention. Acute motor learning is usually achieved by providing visual-vestibular mismatch stimuli for a period of hours while chronic learning is achieved by the long-term application of magnifying or minifying lenses. Recent experimental results argue that acute and chronic VOR learning are the result of two different mechanisms that can be correlated with the acquisition and consolidation phases of learning. Although both, LTP and LTD have been suggested as possible mechanisms for cerebellar learning, LTD has been put forward as the major candidate for cerebellar plasticity.[2,12–14] Transgenic mice that contain protein kinase C (PKC) blockers (LTD is blocked in L7-PKCi at the granule cell-Purkinje cell synapses) can not modify their VOR gains acutely (hours), but can modify them chronically (weeks of training).[14] In agreement, flocculus inactivation after acute learning results in the disappearance of the learned changes while a large percent of these changes remain if the inactivation is performed following chronic training.[15–18] We recently showed that the quantity of memory retention is different for acutely and chronically trained animals.[19] A few hours after a 2–3 hour acute adaptation, only 40% of the new gain is retained, while more than 70% is retained after chronic adaptation. Further, Purkinje cell discharge demonstrates a monotonic change in head velocity sensitivity after acute learning and a non-monotonic change in both eye and head component signals following chronic training (compare ref. 10 and 11). In addition, cerebellar inactivation with muscimol (a GABA-A agonist) following training in the classical conditioning paradigm of the nictitacting membrane response in rabbits suggests the existence of cerebellar mechanisms that act up to 1 hour following the end of the training period and that can be part of the consolidation phase of new motor memories.[20,21] These evidence suggest that the cerebellum works to facilitate the consolidation of new memories and participates in storing new motor memories during the

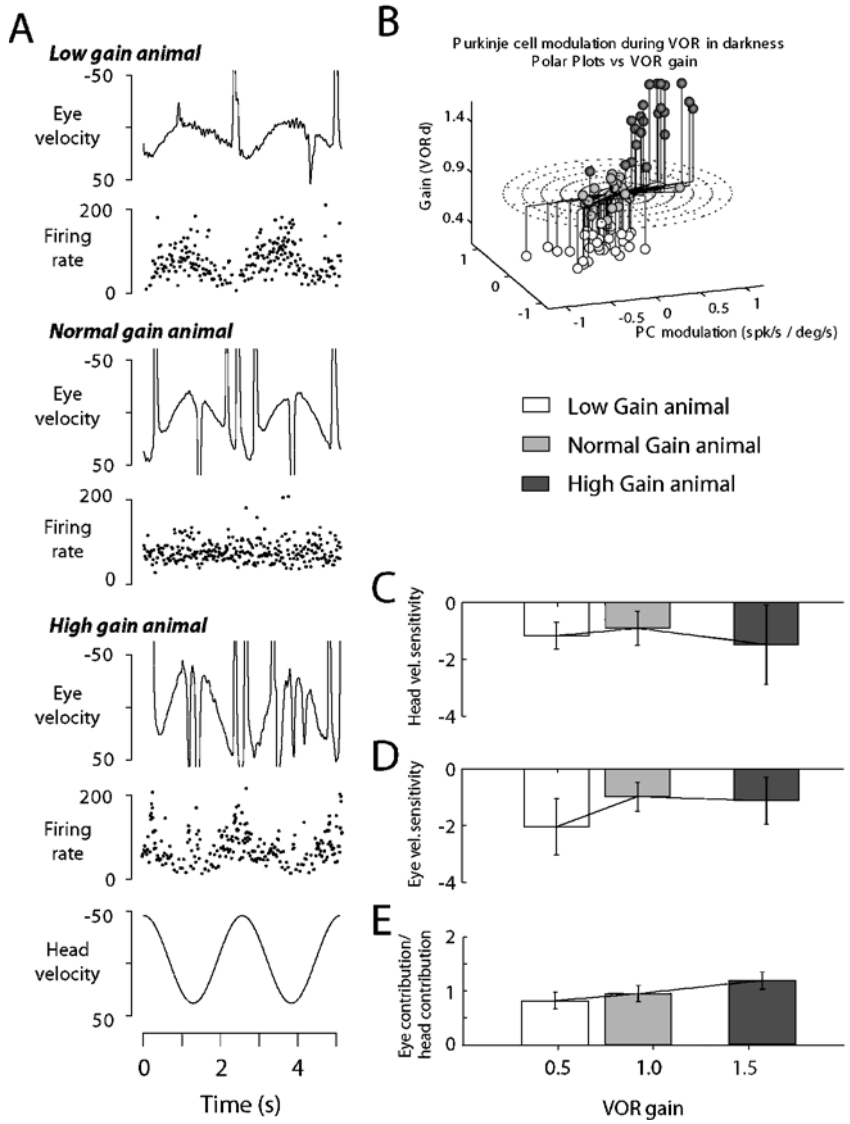

Figure 2
Changes in the Purkinje cells (PCs) response during head rotations in the dark after chronic VOR motor learning. (A) The behavior and the PC response for the low, normal and high gain adapted animal. For each section eye velocity is shown on top and firing rate (spikes/sec) on the bottom. Head velocity is shown only once at the bottom of figure A. PCs show a change in their response from *out of phase* modulation with respect to the head velocity (increasing firing rate for downward head movements) in the low gain animal to *in phase* modulation with respect to head velocity (increasing firing rate for upward head movements) in the high gain adapted animal. (B) A polar plot representation of the response (modulation) of individual PCs with respect to their phase and the VOR gain. This graph shows a 180 degrees phase shift from the high gain to the low gain animal. (C)–(D) Analysis of the signal content of each individual PC showed a non monotonic change of both eye and head velocity components after VOR adaptation, with a significant increases in the eye velocity component after low gain adaptation and a significant increase in the head velocity component after high gain adaptation. (E) The relative contribution of eye velocity and head velocity related inputs to the firing rate. This figure was constructed by multiplying the sensitivity of individual PCs to eye velocity times the VOR gain and normalizing this value with respect to the head velocity sensitivity.

acquisition phase of learning but not during the consolidation phase.

VOR gain increases versus VOR gain decreases

Experimental results suggest that the CNS mechanisms employed for gain decreases and increases are different. Miles and Eighmy[22] showed that behavioral VOR gain increases and decreases do not follow the same learning curves and we have shown that the same is true for memory retention.[19] Boyden and Raymond[23] showed an asymmetric reversibility of VOR gain in mice exposed to increases and decreases of VOR gain following previous exposure to decreases and increases of gains respectively. They argued that this asymmetry is a consequence of different forms of cerebellar learning, where postsynaptic

LTD causes gain increases and both postsynaptic and presynaptic LTP cause gain decreases by affecting the synapses that carry the head velocity information arriving to Purkinje cells. Since we have recently shown that neuronal eye and head signals can change after chronic adaptation[11] other interpretations are possible.

Purkinje cell activity in relation to VOR motor learning. Recent studies

Our recent study[11] highlighted the changes in the responses of Purkinje neurons following chronic adaptation, and the possible consequences of these changes. We used a multiple regression analysis method based on the assumption that Purkinje cell discharge can be modeled using sensory and motor signals. Changes in the value of each parameter before and after motor learning were quantified. We concluded that Purkinje neurons change their tuning during VOR in the dark (VORd) as a consequence of an increase in their head (high gain) and eye (low gain) velocity sensitivities (Figure 2). This result builds upon the previous view[24,25] that assumed that changes occur only in the head velocity pathway. Both studies agree that it is the change in eye velocity *magnitude* due to VOR motor learning that allows the Purkinje neurons modulation to support the new behavior (compare responses in the low and high gain adapted animal in Figure 2A and 2E). We propose that the same mechanism used for plasticity in the granule cell–Purkinje cell synapses that carry head velocity signals might also apply to those granule cell-Purkinje cell synapses that carry efference copy signals of the motor command.[25–28] This statement has two rationales: First, in some cases both, eye and head related information is confined within the same mossy fiber (input to the cerebellar cortex);[29–31] hence a change in the synaptic efficacy in this pathway will affect both signals. Second, other mossy fibers carry only head or only eye related information[25,29,30] and if we assume that the composition of those granule cell–Purkinje cell synapses that carry only eye velocity information is indistinguishable from those that carry only head velocity information, plasticity could occur in any granule cell–Purkinje cell synapse given the proper conditions. The functional implications of a change in the eye velocity sensitivity of Purkinje cells are revealed when simulating oculomotor behaviors different from VORd, for example ocular pursuit. Because the removal of the cerebellum completely abolishes pursuit behavior,[32] there can be no parallel pathways that compensate for a change in eye velocity sensitivity in Purkinje cells after VOR motor learning. Therefore we hypothesize that changes that compensate for an increase in eye velocity sensitivity in Purkinje cells must occur somewhere between the Purkinje cells and the motor neuron, at synapses located outside the cerebellar cortex.

Surpassing the restrictions of a velocity mode-model of VOR motor learning

An additional complication of our paradigm is that VOR output is frequency specific. At high frequencies of stimulation the gain of the VOR in the dark in the normal animal is close to 1 and is said to be dominated by a velocity component, while at low frequencies the gain in the dark decreases and is dominated by a position component. These particular dynamics of the VOR behavior are a consequence of the time constant of the semicircular canals and the eye plant.[33] *Acute* VOR motor learning has been shown to alter this dynamic. Lisberger and colleagues[34,35] showed that acute adaptation induces maximum gain changes at the adapted frequency and later proposed that VOR gain adaptation occurs in parallel pathways. Then, acute changes in VOR gain can be the result of changes in the high frequency or in the low frequency component and can cause changes in the dynamics of the VOR. Kramer and collegues[36,37] used different acute training paradigms that induce changes in the phase of the VOR and demonstrate that the eye velocity to position integrator can be selectively changed. *Chronic* adaptation, on the other hand, evokes gain changes over the broad band of the natural range of frequencies and maintains the dynamics of the reflex, reflecting another substantial difference between acute and chronic VOR motor learning (compare ref. 10 and 35). Because the low frequency band is dominated by an eye position component, and the dynamics of the reflex are preserved following chronic adaptation, we suggest that chronic adaptation causes plastic changes in the velocity to position integrator pathway as well. Changes are suggested at the input and output elements of the integrator. These changes are not thought to affect the properties of the integrator itself, since the dynamics of the VOR are maintained after chronic VOR adaptation.

Conclusions

An inverse dynamic model, if present somewhere other than at the motor neurons, does not reside solely in the cerebellum. Neuronal data as well as lesion studies suggest the presence of more than one cerebellar mechanism for VOR adaptation.[10–11,13–15] Classical models of motor learning in the VOR need reevaluation. The neuronal models employed to date to explain VOR adaptation assume changes in the cerebellum and in the brainstem target neurons in order to support the new behavior.[2,12,24] However, one caveat of these models is the simplification of the system to a velocity mode, specifically the input is head velocity, the efference copy is eye velocity and the output is eye velocity. This has a potential drawback of missing key plastic elements necessary to explain the new behavior.[11] In this respect, we hypothesize that for the chronically adapted animal additional plastic elements are located at the input or

output of the neuronal velocity to position integrator, that these changes do not affect the properties of the integrator itself, and that changes in the eye velocity sensitivity of the Purkinje cells must be compensated somewhere else to make the system stable during pursuit.

Acknowledgements

This work was supported by National Institutes of Health Grant EY05433. We thank Dora Angelaki, Gay Holstein and Shane A. Heiney for valuable comments on the manuscript.

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