EYE POSITION FEEDBACK IN A MODEL OF THE VESTIBULO-OCULAR REFLEX FOR SPINO-CEREBELLAR ATAXIA 6

J. H. Anderson[1], M. C. Yavuz[2], B. M. Kazar[3], P. Christova[1], C. M. Gomez[4]
[1]Department of Otolaryngology, University of Minnesota, Minneapolis, MN, USA
[2]Department of Computer Science and Engineering, University of Minnesota, Minneapolis, MN, USA
[3]Department of Electrical and Computer Engineering, University of Minnesota, Minneapolis, MN, USA
[4]Department of Neurology, University of Minnesota, Minneapolis, MN, USA

Abstract- **The autosomal dominant spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterized by progressive instability of posture and gait, incoordination, ocular motor dysfunction, and dysarthria due to degeneration of cerebellar and brainstem neurons. Recent studies have established that there are more than 16 genetically distinct subtypes. Clinical observations suggest that eye movements and postural stability are universally but differentially impaired in the SCAs. The aim of the present work was to study the horizontal vestibulo-ocular reflex (VOR) in SCA6 patients to understand the pathophysiology of the VOR due to cerebellar Purkinje cell degeneration. The VOR was recorded in patients with genetically defined SCA6 during rotation in the dark. Severely affected subjects had an intact VOR, but there were quantitative differences in the gain and dynamics compared to normal controls. During angular velocity ramp rotations, there was a reversal in the direction of the VOR that was more pronounced in SCA6 compared to controls. Modeling studies indicate that abnormal feedback of an eye position signal into the velocity storage network can account for this reversal. These and other results will help to identify features that are diagnostic for SCA subtypes and provide new information about selective vulnerability of neurons controlling vestibular reflexes.**

Keywords **- Vestibulo-ocular reflex, eye velocity storage, spino-cerebellar ataxia, motor control**

I. INTRODUCTION

The vestibulo-ocular reflex (VOR), initiated by stimulation of hair cells in the inner ear that are sensitive to linear and angular acceleration, helps to maintain gaze, the position of the eyes in space, during head movement. To a first approximation (neglecting the depth of focus, binocular convergence, and differences between the axes of rotation for the eyes and the head) the angular VOR causes the eyes to rotate opposite in direction and equal in magnitude to the head rotation, thereby helping to keep the visual world stable. However, when vision is absent and the head velocity is constant, the eye velocity is not maintained but decays to zero, although there is a neural network, referred to as velocity storage [1, 2], that helps to prolong the time course for decay so that the VOR continues after the neural activity in the vestibular nerve (from the inner ear to the brainstem) has returned to baseline. In addition, there can be a reversal in the direction of the eye velocity that is dependent on brainstem pathways.

The aim of the present work was to develop a model for the decay and reversal of the horizontal VOR in patients who have spinocerebellar ataxia (SCA) subtype 6 [3]. The pathology in SCA6 includes a degeneration of the cerebellum [4], a structure that is important for controlling the gain and direction of the VOR [5] and the spatial relationship of the VOR to a gravitoinertial reference frame [6, 7]. The SCAs are a group of neurodegenerative diseases characterized by progressive instability of posture and gait, incoordination, ocular motor dysfunction, and dysarthria due to degeneration of cerebellar and brainstem neurons. Recent studies have established that there are more than 16 genetically distinct subtypes, and clinical observations suggest that eye movements and postural stability are universally but differentially impaired across the subtypes.

In the present study we propose a model to characterize the horizontal VOR in SCA6. It includes an eye position signal that feeds into the velocity storage network. This is based on the model of Raphan et al [1] wherein the pathways carry physiological signals, and there are so-called direct and indirect (which contribute to the velocity storage) pathways that represent projections to the motor neurons innervating the eye muscles. There is feedback of an eye position signal into the velocity storage and this gives rise to the reversal in the direction of the VOR.

II. METHODOLOGY

Data were collected from four normal control subjects and three patients with SCA6. EOG electrodes were used to record the position of the eye in the head while the subjects sat on a chair (attached to a Contraves-Goerz 826 rate table) that was rotated in the horizontal plane. The head was held in a restraint attached to the chair (so that there was no neck movement), and the subject was in complete darkness so that only the rotation sensitive hair cells of the inner ear were stimulated. The reflex eye movement (VOR) was initiated by a short period of constant angular acceleration, 10 deg/sec^2 (for 18 seconds) or 20 deg/sec^2 (for 9 seconds), causing a ramp change in angular velocity of the head. A LabVIEW (National Instruments) data acquisition program was used to sample the EOG recording of the VOR and the tachometer signal (angular velocity of the rate table) at 200 Hz.

Matlab (The Mathworks) programs were used to digitally filter the sampled data, differentiate the eye position signal, and remove the quick phases from the eye velocity. The resulting slow phase eye velocity, referred to as the compensatory part of the VOR, was used for the modeling studies. Simulink (The Mathworks) was used to set up the

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Abstract

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model shown in Fig. 1. It includes the eye velocity storage mechanism proposed by Raphan et al [1] and also an additional pathway identified as "Eye Position Feedback." The eye velocity signal is integrated by the term, $1/(s + a_3)$, and feeds into the velocity storage network as negative feedback. Four parameters in the model (g_1, g_2, g_3, h) were adjusted in order to fit the model to the eye velocity data from individual trials. g_1 is the gain for a direct vestibular pathway relaying a velocity signal from the inner ear to the extra-ocular motoneurons; g_2 is the gain for the pathway to the integrator, 1/s, of the velocity storage mechanism; h is the gain for negative feedback to that integrator; g_3 is the gain for the eye position feedback. The fitting was done using fmincon, a Matlab routine for minimizing the RMS error with constraints. The constraints were the following: $g_1 > 0$, $g_2 > 0$, $g_3 < 0$ and $h < 0$. Note that a_3 was set equal to 0 and the cupula dynamics were the following:

$\frac{s}{t_c s + 1}$, where $t_c = 7$ and s is the Laplace operator.

III. RESULTS

An example of the VOR response for one trial in one SCA6 patient is shown in Fig. 2. The head acceleration was 20 deg/sec^2, causing a counterclockwise rotation. The circles are the maximum eye velocity for individual slow phases of the VOR and the solid line is the fit of the model (see Fig. 1 and Methods) to the data. Note that initially the eye velocity was to the right, opposite to the direction of head rotation, but 20 to 30 sec. after the acceleration had ceased and the head velocity was constant, the direction of the eye velocity reversed and was to the left.

Fig. 3 shows the eye velocity curves for the model based on the fits to the data from the normals (A) and SCA6 patients (B). The parameter values that were obtained from the fit to each trial (for accelerations in both directions and with both magnitudes) were used to simulate a VOR during a head acceleration of 10 deg/sec^2 in the counterclockwise direction (rotation to the left). The reversal for the patients is greater and occurs earlier for most trials compared to normals.

Table 1 shows the mean and standard deviation of the values for the four parameters that were optimized. A multiple ANOVA and univariate F tests showed that only g_3, the gain for the eye position feedback, was significantly different ($p < 0.01$) between normals and the SCA6 patients. The mean values were –0.0095 and -0.0005 for the patients and normals, respectively.

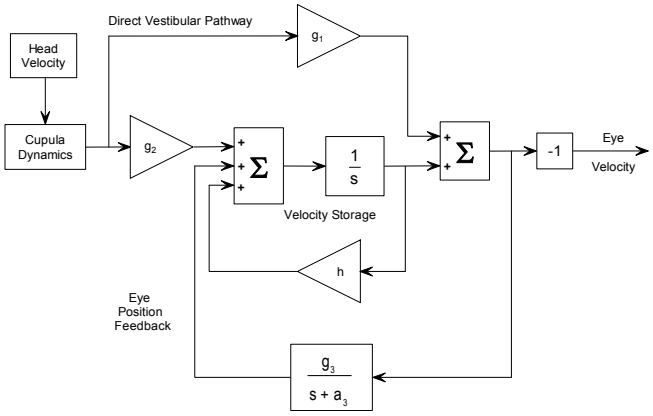

Fig. 1. Model of the horizontal vestibulo-ocular reflex.

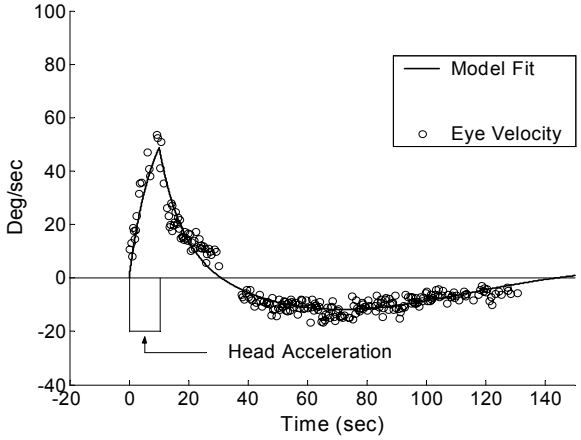

Fig. 2. Fit of model to eye velocity for one trial in SCA6.

The effect of this difference is demonstrated in Fig. 4. Fig. 4A shows the eye velocity curves for the model using the mean values for the four parameters. In addition, there are curves using the mean for three of the parameters and the mean minus one standard deviation for g_3. This depicts the variation in eye velocity and it can be seen that the reversal is greater with the values for the patients compared to normals. Finally, Fig. 4B shows the model responses when the g_3 term is set equal to zero, but keeping the mean values for the other three terms. In this case there is no reversal for either the patients or the normals.

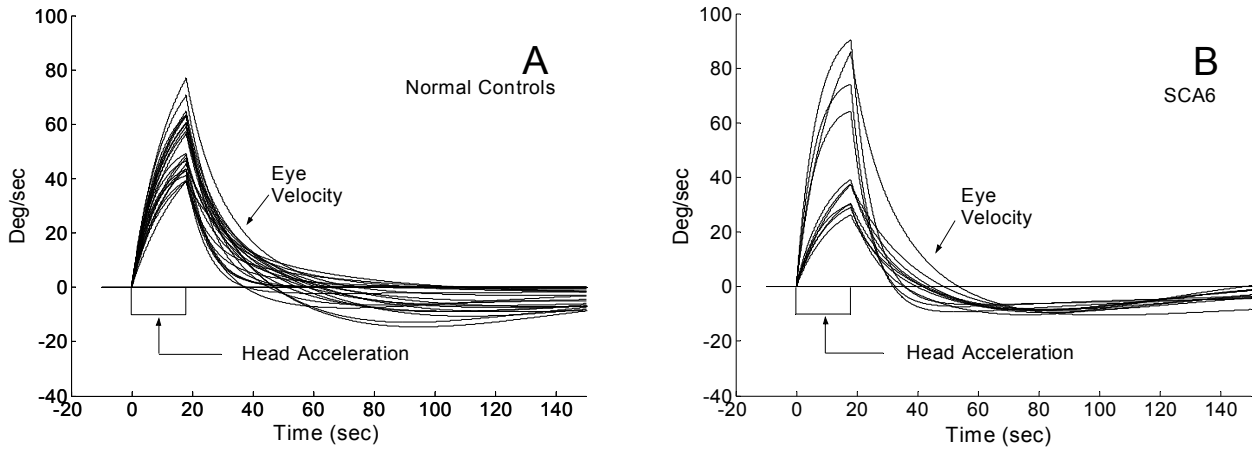

Fig. 3. Eye velocity of the model based on fits to the data from normal subjects (A) and SCA6 patients (B).

TABLE I
Values of the model parameters that were optimized.

	Head Acc.	h		g_1		g_2/g_1		g_3		Trials
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
NORMALS	10	-0.839	1.718	4.308	0.789	0.409	0.971	-0.0006	0.0017	15
	20	-1.283	3.522	4.455	1.256	0.432	1.118	-0.0003	0.0003	8
	10+20	-0.993	2.423	4.359	0.950	0.417	0.999	-0.0005	0.0014	23
SCA6	10	-1.799	2.430	5.178	2.701	0.278	0.657	-0.0127	0.0173	8
	20	-0.029	0.006	2.505	0.437	0.031	0.014	-0.0009	0.0000	3
	10+20	-1.316	2.195	4.449	2.589	0.210	0.561	-0.0095	0.0155	11

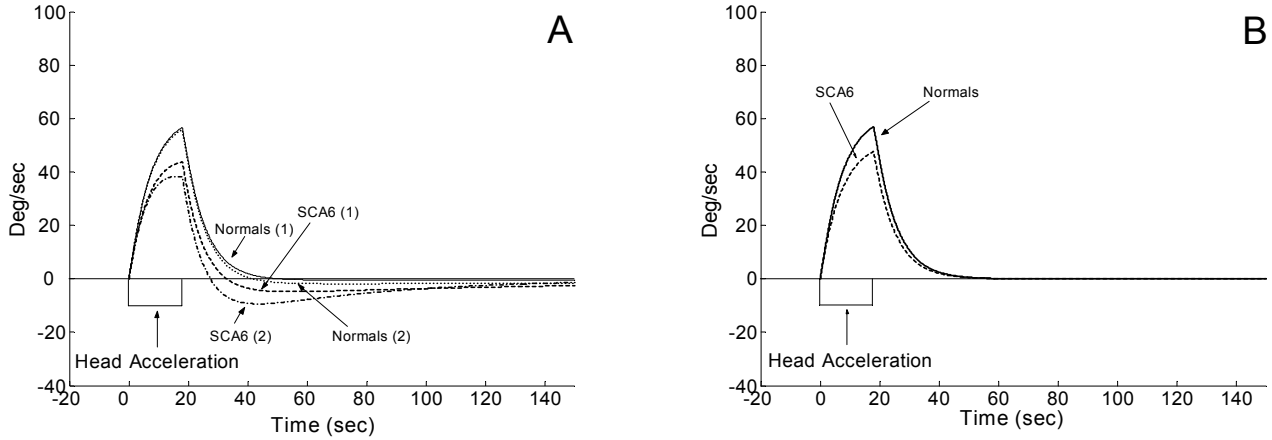

Fig. 4. Eye velocity of the model based on the mean values for fits to the data for normals and SCA6 patients. A: Mean values for all four optimized parameters (1) and mean for g_1, g_2, and h and mean minus one standard deviation for g_3 (2). B: Mean values for g_1, g_2, and h; $g_3 = 0$.

IV. DISCUSSION

The present results show that there is a significant reversal in the direction of the horizontal VOR that is more pronounced in SCA6 compared to normals. Furthermore, simulations of a model suggest that this could be due to an increase in the feedback of an eye position signal into the eye velocity storage network in the brainstem. It should be noted that the present model does not include any peripheral (inner ear and/or vestibular afferent) adaptation. This was done to simply the model and because any differences between the SCA6 patients and normals could not be due to any peripheral mechanisms.

Previous models of the VOR and the velocity storage mechanism have included a central adaptation operator that gives rise to a reversal in the direction of the VOR after a brief period of acceleration [8, 9]. Those models were based on a positive feedback pathway for the velocity storage [2] and feedback of an eye position signal that would combine with the vestibular afferent inputs to the brainstem. Consequently, all the vestibular pathways would be affected by the adaptation operator. In contrast for the present model it is proposed that the eye position feedback acts only on the velocity storage network as proposed by Raphan et al. [1] and not on the direct vestibular pathway to the oculomotor neurons. This implies that only a subset of vestibular nuclei neurons would be affected by the eye position feedback. Furthermore, if those neurons were strongly influenced by the cerebellum, then that could account for the greater reversal in SCA6.

It has been suggested that reversals in the direction of a vestibular nystagmus [10], rebound nystagumus [10], and periodic alternating nystagmus [9] are all caused by the same central adaptation mechanism that is influenced by cerebellar dysfunction. The VOR data for SCA6 provide further evidence for this. The neurodegeneration in SCA6 involves the cerebellar Purkinje cells and neurons in the inferior olive with little evidence for direct involvement of other regions in the brain [4]. In particular there is no cell loss in the vestibular nuclei.

Further studies with SCA6 and future work with other SCA subtypes, including those that have predominantly cerebellar pathology, should provide new information about the selective vulnerability of neurons controlling vestibular reflexes.

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