NASA/CR-95-112614

NCC2-5081

IN-51-CR

005 [illegible]

Torsional Eye Movements Evoked by Unilateral Labyrinthine Galvanic Polarizations in the Squirrel Monkey

Lloyd B. Minor[1,2], David L. Tomko[2] and Gary D. Paige[2,3]

[1] *Department of Otolaryngology – Head & Neck Surgery, Johns Hopkins University School of Medicine*
[2] *Vestibular Research Facility, NASA Ames Research Center*
[3] *Department of Neurology, University of Rochester School of Medicine*

INTRODUCTION

Electrical stimulation of vestibular-nerve afferents innervating the semicircular canals has been used to identify the extraocular muscles receiving activation or inhibition by individual ampullary nerves. This technique was originally developed by Szentagothai (1950) and led to the description of three neuron reflex arcs that connect each semicircular canal through an interneuron traversing in the region of the medial longitudinal fasciculus to one ipsilateral and one contralateral eye muscle. Selective ampullary nerve stimulation was subsequently used by Cohen and colleagues (Cohen and Suzuki, 1963; Cohen *et al.*, 1964; Suzuki *et al.*, 1964; Cohen *et al.*, 1966) to study movements of the eyes and activation of individual extraocular muscles in response to stimulation of combinations of ampullary nerves. This work led to a description of the now familiar relationships between activation of a semicircular canal ampullary nerves and the anticipated movement in each eye. Disconjugacy of eye movements induced by individual vertical canal stimulation and dependence of the pulling direction of vertical recti and oblique muscles on eye position were also defined in these experiments.

Subsequent studies have defined the mechanisms by which externally applied galvanic currents result in a change in vestibular-nerve afferent discharge. The currents appear to act at the spike trigger site. Perilymphatic cathodal currents depolarize the trigger site and lead to excitation whereas anodal currents hyperpolarize and result in inhibition. Afferents innervating all five vestibular endorgans appear to be affected equally by the currents (Goldberg *et al.*, 1984). Irregularly discharging afferents are about 5–10 times more sensitive than regularly discharging ones because of the steeper slope of the former's faster postspike recovery of excitability in encoder sensitivity (Smith and Goldberg, 1986). Response adaptation similar to that noted during acceleration steps is apparent for longer periods of current administration. This adaptation is manifested as a perstimulus return toward resting discharge and poststimulus after-response in the opposite direction (Goldberg *et al.*, 1984; Minor and Goldberg, 1991). Cathodal currents (with respect to the perilymphatic space of the vestibule) are excitatory whereas anodal currents are inhibitory.

Horizontal eye movements evoked by unilateral galvanic polarizations administered through chronically implanted labyrinthine stimulating electrodes have been studied in alert squirrel monkeys (Minor and Goldberg, 1991). We sought to extend this analysis by recording three-dimensional eye movements during galvanic stimulation. As predicted based upon roughly equal stimulation of ampullary nerves innervating the vertical canals, a substantial torsional component to the nystagmus is noted. The trajectory of torsional slow phases and nystagmus profile after the polarization provide insight into the central mechanisms that influence these responses.

METHODS

Eye Movement Recording

Three squirrel monkeys were each implanted with three scleral search coils. Frontal coils measuring 11 mm in diameter and consisting of three turns of teflon insulated stainless steel wire (Cooner AS632) were implanted on the right and left eyes. A sagittal coil measuring 8 mm in diameter and consisting of four turns of the same wire was implanted laterally on the right eye. Each animal was held with its head restrained by a bolt implanted at the occiput such that the horizontal semicircular canals were in the earth-horizontal plane with the animal upright (Minor and Goldberg, 1990). During the experiments, the animals sat in the upright position in a hollow cube with a side length of 18 cm and with one pair of field coils mounted along the interaural (IA) axis and the other pair along the dorsoventral (DV) axis of the head. All testing was performed in darkness.

Horizontal and vertical eye position were recorded with two independent coil position detection circuits (CNC Engineering). The frontal search coil provided horizontal eye position from the detector circuit driven by the IA-axis field and vertical eye position form the detector driven by the DV-axis field. Torsional eye position was recorded from the search coil mounted laterally on the right eye through a detector driven by the DV-axis field. Errors introduced by misalignment of the sagittal search coil in the horizontal plane were corrected by subtracting a component of the vertical eye position signal from the torsional signal through a variable-gain summing amplifier (Paige and Tomko, 1991). For these torsional signals, the subtracted component of the vertical eye position signal was that required to minimize cross-talk during head pitch. Eye position and current monitor signals were sampled at 200 Hz. Eye velocity was calculated by digital differentiation of the eye position signal with a four-point central difference algorithm.

Labyrinthine Stimulating Electrodes

A chlorided silver wire, 250 μm in diameter and insulated to within 1 mm of its tip, was fit through a hole in the bony promontory and into the perilymphatic space of the vestibule. A second chlorided silver wire was placed in the hypotympanum (Minor and Goldberg, 1991). Constant DC currents, typically 5–8 sec duration, were delivered by a stimulus isolator (A-M Systems) and monitored with an in-series digital ammeter. Currents are designated as cathodal (excitatory) or anodal (inhibitory) to indicate polarity of the perilymphatic electrode.

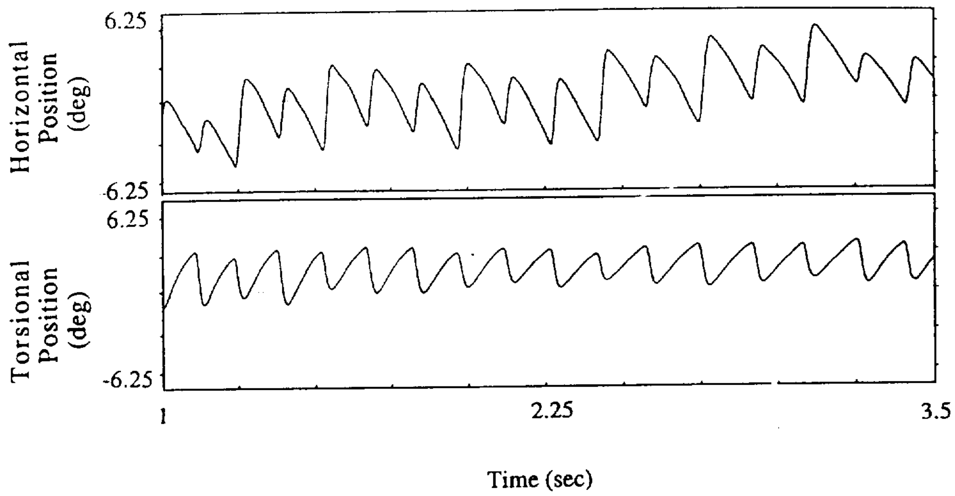

Figure 1 Horizontal-torsional nystagmus evoked by 100 μA cathodal polarization of the right ear. Positive values of horizontal position correspond to rightward eye position and positive values of torsional position represent intorsion of the right eye (counterclockwise movement of the right eye with respect to the animal).

RESULTS

A horizontal, torsional nystagmus was evoked by the unilateral galvanic polarizations (Figure 1). A vertical component of lower and more variable slow phase velocity was occasionally present. Cathodal stimulation in the right ear resulted in slow phases directed to the left and counterclockwise (with respect to the animal, corresponding to intorsion of the right eye). When a vertical component to the nystagmus was present, slow phases were typically upward for cathodal and downward for anodal stimulation of either ear. Mean horizontal and torsional slow phase velocities for 100 μA cathodal and anodal stimuli are given in Table 1.

Table 1 Predicted and observed eye movements evoked by unilateral galvanic polarizations.

			Predicted eye velocity 100 μA		*Observed eye velocity 100 μA*	
	β	g_{rot}	$\dot{e}_{hor}$	$\dot{e}_{tor}$	$\dot{e}_{hor}$	$\dot{e}_{tor}$
cathodal	0.27	0.40	28	28	26.5 ± 8.9	29.0 ± 10.1
anodal	0.19	0.40	19	19	17.7 ± 5.8	15.7 ± 3.8

Predicted and observed horizontal and torsional eye velocity in response to 100 μA unilateral galvanic polarizations. Calculation of predicted eye velocity as described in the text. Observed eye velocity is mean ± s.d. of data pooled from three animals.

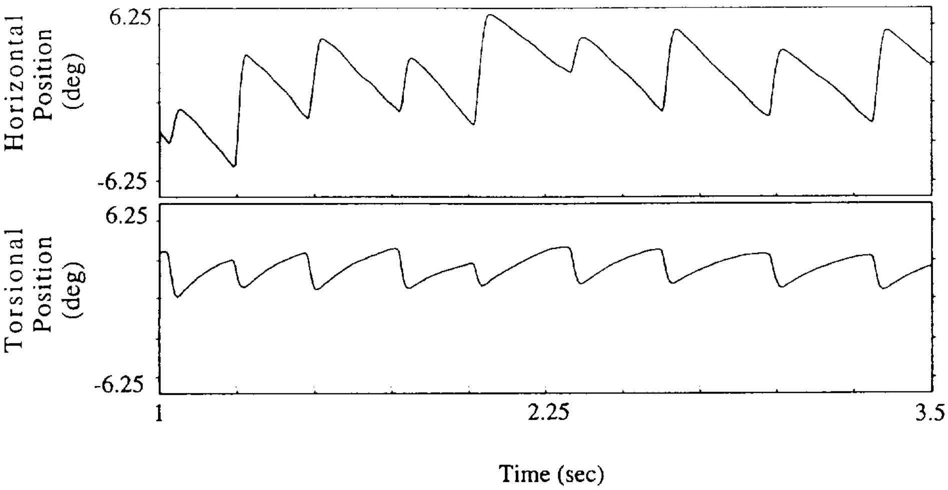

Figure 2 Horizontal-torsional nystagmus evoked by 75 μA cathodal polarization of the right ear. Eye position is displayed with the same direction convention as in Figure 1.

Examination of nystagmus evoked by unilateral currents less than 100 μA revealed clear differences in the profiles of horizontal and torsional slow phases. Horizontal slow phases were relatively linear whereas torsional ones showed a decay of slow phase velocity that could be approximated by a single exponential (Figure 2,3). The time constant of this exponential decay in each torsional slow phase evaluated for 50 and 75 μA cathodal and anodal stimulation in two animals measured 259 ± 73 msec (mean ± s.d.). The third animal had a longer time constant of 382 ± 49 msec (t-test, $p < .05$).

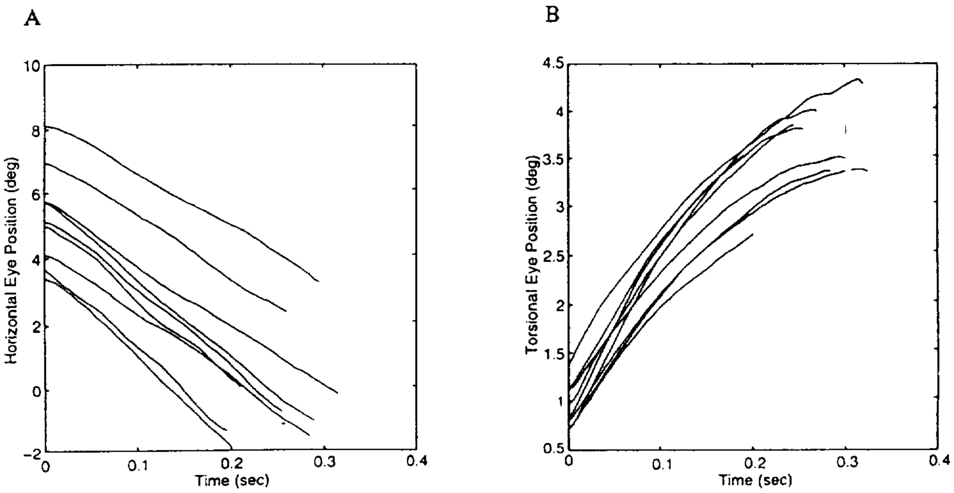

Figure 3 Slow phases from 75 μA cathodal polarization of the right ear displayed with respect to time from onset of each slow phase. An exponential fit to each torsional slow phase was used to obtain the first-order time constants described in the text.

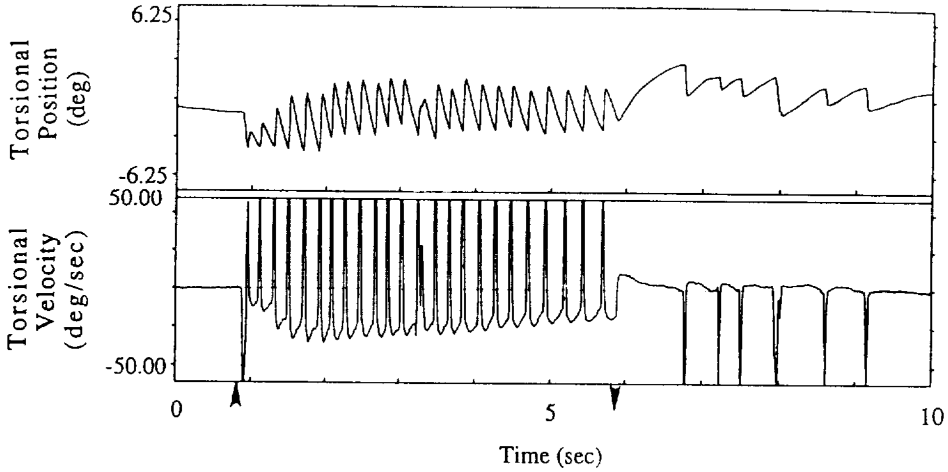

Figure 4 Torsional eye position and eye velocity (recorded from the right eye) in response to 100 μA cathodal polarization of the left ear. Time at which current was turned on and off indicated by upward and downward arrows, respectively. Direction convention for eye position and velocity as described in Figure 1.

Torsional responses typically showed declining eye velocity during administration of current followed by an after-response in the opposite direction (Figure 4). This profile of perstimulus response decline followed by an after-response in the opposite direction after cessation of current was present for torsional responses evoked by anodal and cathodal stimuli.

DISCUSSION

Relationship Between Peripheral Stimulation and Eye Velocity

Slow phase eye velocity of nystagmus evoked by unilateral labyrinthine polarizations provides insight into the vestibular endorgans activated by the currents. As previously noted (Minor and Goldberg, 1991), horizontal slow phase velocity closely resembles that predicted according to the following relationship:

$$\dot{e} = (1/2) \cdot I \cdot (\beta/g_{rot}) \cdot (g_{vor}) \, .$$

In this formula, I is the applied current (in μA), β is the mean polarization sensitivity of regularly discharging vestibular-nerve afferents, g_{rot} is the mean rotational sensitivity of these afferents , and g_{vor} is the gain of the VOR which, for the horizontal VOR, averages 0.8 in squirrel monkeys (Paige, 1983; Minor and Goldberg, 1990). The factor of $1/2$ is introduced because the currents are only being applied unilaterally and VOR gain is thought to typically be established by push-pull inputs from vestibular-nerve afferents on both sides.

The computation is similar for torsional responses except that torsional VOR gain in the squirrel monkey averages $1/2$ of horizontal VOR gain (Bello *et al.*, 1991). Galvanic polarizations are thought to activate vestibular-nerve afferents innervating all five vestibular endorgans (Goldberg *et al.*, 1984) so posterior and anterior canal afferents would be expected to contribute to the torsional response (Cohen *et al.*, 1964).

Table 1 presents the observed and predicted responses for horizontal and torsional slow phase eye velocity evoked by unilateral 100 μA galvanic polarizations. Rotational and galvanic sensitivity of regular afferents are chosen because these afferents are thought to provide prinicipal inputs to the VOR. Anodal responses are appoximately two-thirds as large as cathodal responses. A similar asymmetry is seen in the galvanic responses of regularly discharging afferents (Minor and Goldberg, 1991). Torsional slow phase eye velocity for each current magnitude was close in amplitude to horizontal slow phase velocity. One possible explanation for the equivalence of these slow phase velocity components may lie in the contribution of afferents from ampullary nerves to the horizontal and torsional eye movements. The torsional response would seem to be due to activation of two endorgans (anterior and posterior canal ampullary nerves) with summation of inputs whereas the horizontal response would seem to be principally due to inputs from one endorgan (horizontal ampullary nerve). The presence of an intermittent upward component in the slow phases evoked by cathodal stimuli and downward in anodal responses may indicate that currents may have a somewhat stronger effect on the anterior than the posterior canal ampullary nerve. Such an interpretation is offered with caution because differential effects of individual ampullary nerve signals in the generation of nystagmus as well as modulation of the nystagmus by otolith activation cannot be excluded.

Dynamics of Nystagmus Slow Component

Torsional eye velocity decreases during the course of an individual slow phase whereas horizontal slow phase velocity remains relatively linear (Figure 2). This decline in torsional slow phase velocity that appears to be "reset" by each fast phase is most obvious for responses to 50 and 75 μA stimuli. Magnitude of slow phase velocity is lower at these lower current strengths. Consequently, duration of slow phases is longer and the velocity decay, fit by a first-order process, is more obvious.

Interactions between torsional slow and fast phases are reminiscent of eye movements seen in the horizontal system when the velocity-to-position integrator has been made leaky. Such effects are noted after injections of neurotoxins (kainate or ibotenate) or muscimol into the region of the nucleus prepositus hypoglossi or central medial vestibular nucleus (Cannon and Robinson, 1987; Mittens *et al.*, 1994). A reduction in time constant of the velocity-to-position integrator often occurs in association with imbalance in tonic activity between the two vestibular nerves. Its occurrence most likely accounts for Alexander's Law, the phenomenon in which spontaneous nystagmus due to such an imbalance in vestibular activity is more intense when the subject looks in the fast-phase than in the slow-phase direction (Robinson *et al.*, 1984).

Effects on velocity-to-position integration induced by imbalance in tonic vestibular activity are more apparent for torsional than horizontal eye movements. The differential effect seems likely to be related to organization of the two neural integrators. Time constant of the torsional velocity-to-position integrator, measured from position-step displacements of the human eye, is approximately 2 sec whereas that of the horizontal velocity-to-position integrator is >20 sec (Seidman *et al.*, 1995). A small reduction of the

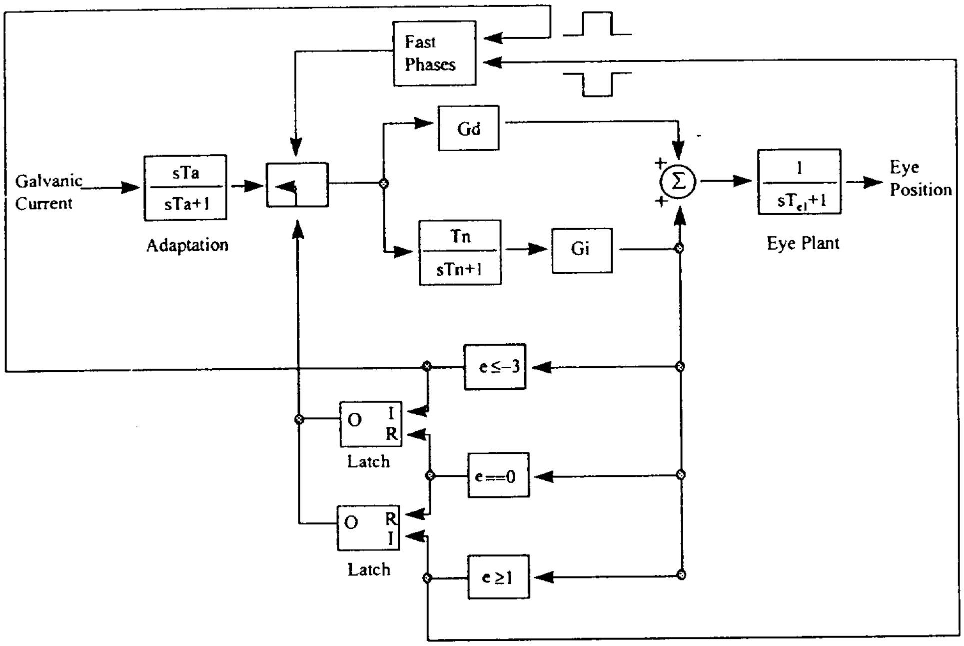

Figure 5 A model of torsional nystagmus evoked by unilateral galvanic polarizations. The applied current results in a step change in vestibular-nerve afferent discharge. This change in afferent discharge is then affected by processes of peripheral and central adaptation. The dominant time constant that results in best fit to the data is $T_a = 20$ sec. The signal then passes through direct and indirect pathways with gains G_d and G_i. The indirect pathway is represented by a leaky velocity-to-position integrator with $T_n = 0.3$ sec. G_d and G_i are adjusted to cancel the pole ($T_{el} = .24$ sec) of the oculomotor plant (Robinson, 1981).

Fast phases in the model are triggered when the eye reaches an eccentricity of 3 deg for perstimulus response and 1 deg for poststimulus response. Each fast phase consists of a step change in eye position that brings the eye back to center of the torsional oculomotor range. Fast-slow phase interactions are controlled by a latch-switch mechanism. The latch consists of an input, reset, and output. The latch is engaged when eye position exceeds the specified eccentricity values. The switch is then closed for slow phases and opened for fast phases. It remains in the fast phase mode until the eye returns to 0 position at which time a reset signal changes the switch back to the slow phase mode.

Signal transmission from the adaptation operator through the direct and indirect pathways is interrupted during a fast phase. A latch holds the output from adaptation processes during the fast phases. The change in eye position induced by the fast phase passes through the leaky velocity-to-position integrator and effectively "resets" the integrator.

torsional time constant would, therefore, be more apparent than the same reduction in the horizontal time constant.

Per-stimulus Decline in Torsional Eye Velocity with Inverted After-response

Initial rise in torsional slow phase velocity at the onset of stimulation was variable and influenced by a blink that frequently occurred when polarizations began. Torsional slow phase velocity typically reached a peak within 500 msec after stimulus onset and then declined during the following 4–8 sec of current administration. An after-response in the opposite direction was frequently noted immediately after the current was turned off (Figure 4). Responses have been modeled as shown in Figure 5. Vestibular-nerve afferents are directly activated by the currents thereby bypassing transduction mechanisms and peripheral mechanics. Modulated afferent activity induced by the currents passes through an adaptation operator. Velocity storage is not included in the model because animals were in the upright position during testing. Torsional velocity storage with the head in this position is expected to have minimal effect on these responses due the mismatch between the plane of the torsional eye movement and orientation of the head relative to gravity (Raphan and Sturm, 1991; Raphan *et al.*, 1992).

Adaptation is representative of two processes (Furman *et al.*, 1989). Vestibular-nerve afferents show adaptation to prolonged acceleration steps manifested as a per-acceleration response decline and post-acceleration response reversal prior to return to resting activity. The time constant of this peripheral adaptation process averages 80 sec for constant-amplitude acceleration stimuli (Goldberg and Fernandez, 1971). Similar responses have been observed in the eye velocity profiles evoked by long-duration accelerations (Paige, 1983). Central adaptation processes have been suggested based upon the observed reversal phases of both postrotatory nystagmus and optokinetic after nystagmus (Young and Oman, 1969; Furman *et al.*, 1989). Such central adaptation may have a role in decreasing the spontaneous nystagmus seen in cases of imbalanced vestibular activity such as following a unilateral vestibular lesion (Courjon *et al.*, 1977).

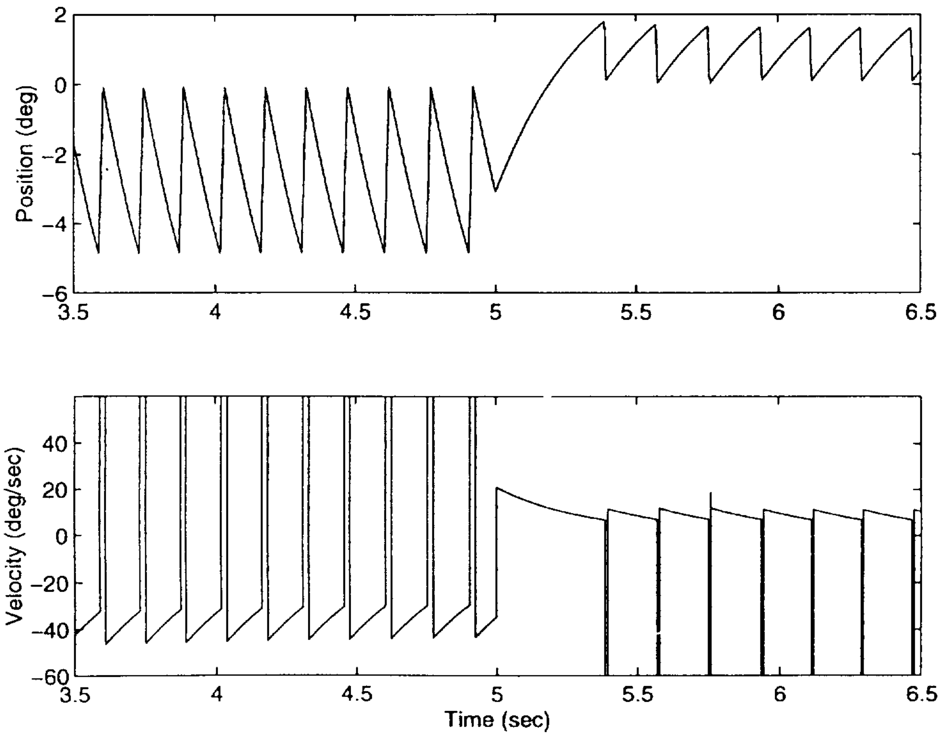

Figure 6 The model described in Figure 5 was run in Simulink® (The MathWorks, Inc.). Runge-Kutta 5 with a minimum step size of 0.001 sec was used. In the stimulation, the polarizing current step is turned off at 5 sec. Predicted torsional eye position and velocity are shown.

In simul
time const
operator cc
is interrupt
physiologi
vestibular-
are attribut
by a reset
of the tors
position re
direction d
per- and p
and poststi
phase velo
Followir
and indirec
plant. A si

Acknowle

This work
NIH Grant

REFERE

Cannon, S.C.
stem le
Cohen, B. an
204, 34
Cohen, B., Su
cat. *An*
Cohen, B., To
76, 523
Courjon, J.H.,
ocular r
Furman, J.M.
optokin
Goldberg, J.M
of the sq
34, 635
Goldberg, J.M
to exter
51, 123
Minor, L.B. a
by calo
Minor, L.B.
ablation
Mettens, P., C
preposit
Paige, G.D. (
monkey.

In simulation of the model, adaptation (T_a) and velocity-to-position integrator (T_n) time constants were determined from the data. Signal transmission from the adaptation operator corresponds to vestibular inputs controlling slow phases. This slow phase signal is interrupted during fast phases by changing the switch to the fast phase mode. The physiological correlate of this process corresponds to pause in activity of the position-vestibular-pause neurons during saccades and fast phases of nystagmus. Fast phase pulses are attributable to activity in burst neurons. The switch is returned to the slow phase mode by a reset from the latch that is triggered by return of torsional eye position to 0 (center of the torsional oculomotor range). Onset of the fast phase occurs when torsional eye position reaches an eccentricity of 3 deg during the polarization and 1 deg in the opposite direction during the after-response. These eye position set points for fast phases during per- and poststimulus responses are clearly reflected in the data. The difference in per- and poststimulus values may indicate that initiation of a fast phase is dependent upon slow phase velocity and duration in addition to eye position.

Following adaptation and fast-slow phase interaction, the signal passes through direct and indirect pathways the gains of which are set to cancel the pole of the oculomotor plant. A simulation of the model is shown in Figure 6.

Acknowledgment

This work was supported by NASA Space Medicine Tasks 199-16-12-17 and -24 and by NIH Grant DC 00979. Mr. David Lasker provided advice on the Simulink® model.

REFERENCES

Cannon, S.C. and Robinson, D.A. (1987) Loss of the neural integrator of the oculomotor system from brain stem lesions in the monkey. *J. Neurophysiol.*, **57**, 1383–1409.

Cohen, B. and Suzuki, J-I. (1963) Eye movements induced by ampullary nerve stimulation. *Am. J. Physiol.*, **204**, 347–351.

Cohen, B., Suzuki, J-I., Bender, M.B. (1964) Eye movements from semicircular canal nerve stimulation in the cat. *Ann. Otol. Rhinol. Laryngol.*, **73**, 153–169.

Cohen, B., Tokumasu, K., Goto, K. (1966) Semicircular canal nerve eye and head movements. *Arch. Ophthal.*, **76**, 523–531.

Courjon, J.H., Jeannerod, M., Ossuzio, I. and Schmid, R. (1977). The role of vision in compensation of vestibulo-ocular reflex after hemilabyrinthectomy in the cat. *Exp. Brain Res.*, **28**, 235–248.

Furman, J.M.R., Hain, T.C. and Paige, G.D. (1989). Central adaptation models of the vestibulo-ocular and optokinetic systems. *Biol. Cybern.*, **61**, 255–264.

Goldberg, J.M. and Fernandez, C. (1971). Physiology of peripheral neurons innervating semi-circular canals of the squirrel monkey. I. Resting discharge and response to constant angular accelerations. *J. Neurophysiol.*, **34**, 635–660.

Goldberg, J.M., Smith, C.E. and Fernandez, C. (1984). Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J. Neurophysiol.*, **51**, 1236–1256.

Minor, L.B. and Goldberg, J.M. (1990) Influence of static head position on the horizontal nystagmus evoked by caloric, rotational and optokinetic stimulation in the squirrel monkey. *Exp. Brain Res.*, **82**, 1–13.

Minor, L.B. and Goldberg, J.M. (1991) Vestibular-nerve inputs to the vestibulo-ocular reflex: A functional ablation study in the squirrel monkey. *J. Neurosci.*, **11**, 1636–1648.

Mettens, P., Godaux, E., Cheron, G. and Galiana, H.L. (1994) Effect of muscimol microinjections into the prepositus hypoglossi and medial vestibular nuclei on cat eye movements. *J. Neurophysiol.*, **72**, 785–802.

Paige, G.D. (1983) Vestibuloocular reflex and its interactions with visual following mechanims in the squirrel monkey. I. Response characteristics in normal animals. *J. Neurophysiol.*, **49**, 134–151.

Paige, G.D. and Tomko, D.L. (1991) Eye movement responses to linear head motion in the squirrel monkey. I. Basic characteristics. *J. Neurophysiol.*, **65**, 1170–1182.

Raphan, T., Dai, M. and Cohen, B. (1992) Spatial orientation of the vestibular system. *Ann. NY Acad. Sci.*, **656**, 140–157.

Raphan, T. and Sturm, D. (1991) Modelling of the spatio-temporal organization of velocity storage in the vestibuloocular reflex by optokinetic studies. *J. Neurophysiol.*, **66**, 1410–1420.

Rey, C.G. and Galiana, H.L. (1993) Transient analysis of vestibular nystagmus. *Biol. Cybern.*, **69**, 395–405.

Robinson, D.A. (1981) The use of control systems analysis in the neurophysiology of eye movements. *Ann. Rev. Neurosci.*, **4**:463–503.

Robinson, D.A., Zee, D.S., Hain, T.C., Holmes, A. and Rosenberg, L.F. (1984). Alexander's Law: Its behavior and origin in the human vestibulo-ocular reflex. *Ann. Neurol.*, **16**, 714–722.

Seidman, S.H., Leigh, R.J., Tomsak, R.L., Grant, M.P. and Dell'Osso, L.F. (1995). Dynamic properties of the human vestibulo-ocular reflex during head rotations in roll. *Vis. Res.*, **35**, 679–689.

Smith, C.E. and Goldberg, J.M. (1986). A stochastic afterhyperpolarization model of repetitive activity in vestibular afferents. *Biol. Cybern.*, **54**, 41–51.

Suzuki, J-I., Cohen, B. and Bender, M.B. (1964). Compensatory eye move ments induced by vertical canal stimulation. *Exp. Neurol.*, **9**, 137–160.

Szentagothai J. (1950) The elementary vestibulo-ocular reflex. *J. Neurophysiol.*, **13**, 395–407.

Young, L.R. and Oman, C.M. (1969) Model for vestibular adaptation to horizontal rotation. *Aerosp. Med.*, **40**, 1076–1080.

The
Rela

S.H.

[1] *Depar*
[2] *Depar*
Univers

Visual
from t
moven
visual
a varie
Man
occur j
movem
subject
saccad
gaze-h
Ther
be diff
in the p
therefo
Cyclod
suggest
additio
present
mechar
A re
influen
to velo
0.5–0.7
respons
is abse
sinusoi
sponse
and pit
Torsi
vertical
In addi
eration