# CHARACTERIZATION OF HUMAN VERTICAL OPTOKINETIC NYSTAGMUS AND AFTER-NYSTAGMUS: A STUDY OF SYMMETRY AND ITS DEPENDENCE UPON HEAD ORIENTATION WITH RESPECT TO NORMAL GRAVITY, AND THE INFLUENCE OF VARIED GRAVITOINERTIAL FORCES

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GANG WEI

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# CHARACTERIZATION OF HUMAN VERTICAL OPTOKINETIC NYSTAGMUS AND AFTER-NYSTAGMUS: A STUDY OF SYMMETRY AND ITS DEPENDENCE UPON HEAD ORIENTATION WITH RESPECT TO NORMAL GRAVITY, AND THE INFLUENCE OF VARIED GRAVITOINERTIAL FORCES

BY

GANG WEI

A Thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

To
My Parents

**ABSTRACT**

Characteristics of human vertical optokinetic nystagmus (VOKN) and after-nystagmus (VOKAN) were examined by electro-oculography (EOG) and ISCAN imaging system on the ground and on board of a NASA's KC-135 aircraft in a parabolic flight study. The test device was a white plastic hemisphere onto which moving stripes, as visual stimulation, were projected from an internally illuminated slotted drum. Slow phase velocity (SPV) before extinguishing the stimulation was calculated. Single or double exponential regression of the OKAN decay curve after the stimulation was carried out and area under the regression curves was calculated. Three steps of experiments were carried out.

1) Stimulus velocity dependence study: VOKN and VOKAN were investigated using vertical optokinetic stimuli at velocities of 20, 40, 60 and 80 deg/s, respectively. 40 deg/s turned out to be the most appropriate stimulus velocity for inducing reliable VOKN and VOKAN. Stimulation at 20 deg/s in either upward or downward direction produced a decay with only a short time constant. VOKN-SPV and the area under VOKAN decay curve at 40 deg/s showed no significant difference from the corresponding values at 60 or 80 deg/s, indicating that eye following and the velocity storage mechanism had saturated at

40 deg/s. However, the gains at 60 and 80 deg/s became low and eye movement regularity was poor. It is proposed that, as in the horizontal case, two separate mechanisms are involved in the vertical eye movement: one predominantly in the low stimulus velocity range, presumably smooth pursuit mediated, and the other activated at high stimulus velocities, presumably mediated by the optokinetic system.

2) Asymmetry of VOKN/VOKAN and its gravity dependence: Under normal gravity, the subjects were tested in upright and ear down (90 deg roll) positions respectively. Analysis of the VOKN and VOKAN revealed a significant asymmetry of vertical eye movements in the subjects' sagittal plane, i.e. stronger upward SPV than downward in both VOKN and VOKAN decay. This asymmetry became even more prominent when the head was in the 90° roll position, while the HOKAN quantity decreased compared to head upright position. It is postulated that the asymmetry of VOKN and VOKAN in humans, as in animals, is due to the asymmetrical storage capability of the vertical velocity storage mechanism which mainly contributes to upward eye movements. In addition, the vertical storage mechanism is modified by the action of gravity on the otolith organs in such a way that it favours eye movements in an axis aligned with the spatial vertical. Only two out of 18 subjects, however, displayed cross-coupling, as in the monkey but weak, from the horizontal to the vertical mode of storage when the head was tilted away from the spatial vertical.

3) Parabolic flight study: The aircraft produced alternating periods of micro- (ca. $10^{-2}$ G) and hyper- (ca. 1.8 G) gravitoinertial forces. Each phase lasted approximately 20-25 sec. As compared to the baseline data on the ground, there was a significant increase of downward VOKN/VOKAN while the upward VOKN/VOKAN did not change significantly in both micro- and hyper-G. As a consequence, the asymmetry of VOKN/VOKAN, normally seen on the ground, was lost. It is postulated that the increase of downward VOKN/VOKAN in non-1 G conditions was governed by two different mechanisms. In micro-G, the normal inhibition effect in 1 G on the downward eye movement mediated by otolith organ activity to the vertical velocity storage was removed. In hyper-G, the downward VOKN/VOKAN was facilitated by augmented otolith-ocular reflex because of the increased gravitoinertial force, so as to produce enhanced compensatory downward eye movement.

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All procedures involving human subjects were approved by the Human Ethics Committee of the University of Manitoba.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ANOVA | = Analysis of Variance |
| AOS | = Accessory Optic System |
| ATD | = Ascending Tract of Deiters |
| CCD | = Charge-coupled Device |
| CNS | = Central Nervous System |
| COR | = Cervico-ocular Reflex |
| deg | = degree |
| DLPN | = Dorsolateral Pontine Nuclei |
| DVN | = Descending Vestibular Nuclei |
| ENG | = Electronystagmograph |
| EOG | = Electro-oculography |
| FEF | = Frontal Eye Field |
| FTN | = Floccular Target Neurons |
| HOKAN | = Horizontal OKAN |
| HP | = Hewlett-Packard |
| IN | = Inferior Vestibular Nerve |
| INC | = Interstitial Nucleus of Cajal |
| IR | = Infra Red |
| LGN | = Lateral Geniculate Nucleus |
| LR | = Lateral Rectus |
| LTN | = Lateral Terminal Nucleus |
| LVN | = Lateral Vestibular Nuclei |
| LVOR | = Linear VOR |
| MLF | = Medial Longitudinal Fasciculus |

MR = Medial Rectus

MST = Meddle Superior Temporal Visual Area

MT = Middle Temporal Visual Area

MVN = Medial Vestibular Nuclei

NI = Neural Integrator

NOT = Nucleus of the Optic Tract

NPH = Nucleus prepositus Hypoglossi

NRTP = Nucleus of the reticularis Tegmenti Pontis

OK = Optokinetic

OKAN = Optokinetic After-nystagmus

OKN = Optokinetic Nystagmus

OOR = Otolith-ocular Reflex

OVAR = Off-Vertical Axis Rotation

PAN = Pursuit Afternystagmus

PB = Pitch Backward

PF = Pitch Forward

PMT = Paramedian Tract

PRN = Post-rotatory Nystagmus

PVP = Position-vestibular-pause

RL = Roll Left

RR = Roll Right

SD = Standard Deviation

SE = Standard Error

SN = Superior Vestibular Nerve

SPD = Slow Phase Duration

SPV = Slow Phase Velocity

SVN = Superior Vestibular Nuclei

TVOR = Translational VOR

VN = Vestibular Nuclei

VOKAN = Vertical OKAN

VOKN = Vertical OKN

VOR = Vestibulo-ocular Reflex

## LIST OF FIGURES

# CHAPTER 1

# INTRODUCTION

For our view of the world to remain clear and stable, images of the seen world must be held relatively steady upon the retina. Under natural conditions, a variety of voluntary and involuntary head movements occur, ranging from the transmitted cardiac pulsations to the perturbations incurred during motion. Also, movement of the visual scene across the field of view causes blurring of images. In order to maintain images steady on the retina, compensatory eye movements are required to counteract the effect of motion of the head or visual scene. The brain uses a number of sensory signals to program compensatory eye movements, including inputs from the labyrinthine semicircular canals, the otoliths, vision, and the somatosensory system. In addition, the command signals for voluntary head movements also can be used to help control compensatory eye movements.

There are five basic types of eye movements and each has one particular function, which is controlled relatively independently through separate neural pathways. These pathways only converge at the level of the motoneurons that innervate the eye muscles.

I. Vestibulo-ocular reflex (VOR): The VOR serves to maintain stable vision during perturbations of the head by promptly producing following (slow phase) eye rotations to

compensate for high frequency movement of the head. The VOR includes otolith/ocular and canal/ocular reflexes.

II. Optokinetic (OK) responses: Movement of the visual scene across the field of view evokes an involuntary, conjugate to-and-fro movement of the eyes called optokinetic nystagmus (OKN). In natural circumstances, OKN is usually evoked by motion of the observer with respect to a stationary world rather than by motion of the visual scene, for example, the view from a moving train. OKN is particularly good at compensating for slow oscillations of the head or for movements of the head at a constant velocity, whereas the VOR is most effective for rapid oscillations of the head. Thus, OKN and VOR complement each other.

III. Saccades: These are fast conjugate eye movements which reset eye position. The circuitry can be triggered from the vestibular or optokinetic systems, producing the fast-phase of optokinetic or vestibular nystagmus to enable acquisition and pursuit of the oncoming visual target. The saccadic system can also be under voluntary control, in which case its purpose is to move the visual fixation point from one target of interest to another as quickly as possible.

IV. Smooth pursuit: Eye movements following a small moving visual target constitute pursuit. It is a voluntary task, thus requiring motivation and attention. Smooth pursuit eye movements are only found in species with a fovea, and enable the maintenance of a clear image of the moving object.

Visual fixation, which can be considered a stationary type of pursuit, holds the image of a stationary object on the fovea when the head is stationary.

V. Convergence: This consists of slow, disconjugate eye movements enabling frontal-eyed animals to foveate near objects and establish stereoscopic vision.

All these types of eye movement, except convergence, are intimately related to head movements. Each system alone is not sufficient for entire compensation of head and body motion. They must function cooperatively and interactively to produce fluent and accurate eye movements. Vestibular, optokinetic and visual fixation systems act to hold images of the seen world steady on the retina. Therefore, their function is to hold gaze steady. The saccade, smooth pursuit and vergence systems are to acquire and hold images of objects of interest on the fovea and thus their function is to shift gaze.

The optokinetic system is the main subject of this thesis.

Motion of the visual surround induces OKN, which is characterized by following eye movements (slow phase) interrupted by fast resetting movements (fast phase) in the opposite direction. When the stimulus is terminated, i.e. upon extinguishing the light, the nystagmus continues in the dark with diminishing slow phase velocity. This is known as

optokinetic after-nystagmus (OKAN) (figure 1). OKAN is thought to represent the discharge of stored neural activity related to retinal slip (stimulus velocity minus eye velocity in the space) in the brain stem which has been charged up during previous optokinetic stimulation. This phenomenon is called "velocity storage" (1). Although a precise role for the velocity storage has not yet been clearly delineated, it is thought that it acts to improve visual stabilization by prolonging the duration of compensatory eye movements or counteract unwanted responses.

When horizontal OKN (HOKN) and OKAN (HOKAN) are generated about the yaw (cranio-sacral) axis of an upright subject, they are symmetrical between leftward and rightward stimulus directions. When the stimulation is about the pitch (interaural) axis, vertical OKN (VOKN) and OKAN (VOKAN) are generated. It seems that VOKN and VOKAN are somewhat different from their horizontal counterparts. In monkeys, upward and downward VOKN & VOKAN are asymmetric, i.e. slow eye movement is stronger for upward-going than downward-going, in case the animals are in the upright position in the earth's gravity environment. The upward eye movement becomes stronger when the animals are placed in the lateral (ear down) position, whereas downward eye movement does not change correspondingly. The asymmetry, i.e. weaker downward VOKN and weak or absent downward VOKAN, is thought to indicate that stored activity related to slow phase eye velocity contributes little to the

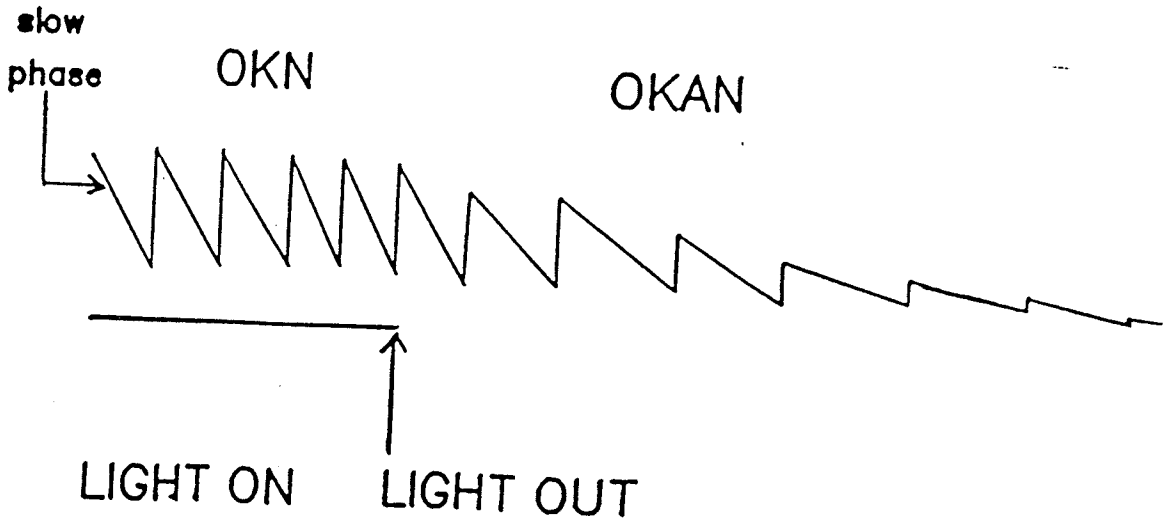


Figure 1. Schematic diagram of OKN and OKAN.

production of downward VOKN and VOKAN. Moreover, this asymmetry is more prominent when the head is tilted, presumably due to the enhancement of upward VOKN and VOKAN because of influence from otolith organ activity. These observations suggest that the velocity storage mechanism is modified by gravity, implicating the otolith organs as the sensors of gravity.

It has also been observed in animal studies that in an upright head position, horizontal OKAN is in the same direction as the horizontal OK stimulus and there are no vertical or roll OKAN components. However, if animals receive horizontal OK stimulation while they are in a static roll tilt position (i.e. ear down), their horizontal OKAN is suppressed. Meanwhile, a vertical OKAN emerges. This is referred to as "cross-coupling" from the horizontal to the vertical mode of storage. If animals are in the supine (on the back) position during horizontal OK stimulation, a roll OKAN emerges during the horizontal OKAN suppression, hence "cross-coupling" from the horizontal to the roll torsional storage. A three dimensional model for the velocity storage was proposed by Raphan et al. to explain these phenomena (2). They suggest that cross-coupling acts as a gyroscopic mechanism that tends to bring the plane of the nystagmus toward the spatial horizontal plane.

Space travel and parabolic flight can change gravitoinertial force impacting on the otolith organs which in

turn have effects on the optokinetic system. Recently, modifications of the optokinetic reflex have been noted both in the microgravity phase of parabolic flight and during spaceflight (3,4). Hence the environment of altered gravitoinertial force provides a useful experimental means for the study of otolith organ physiology.

Information about human VOKN and OKAN has been scanty and often inconsistent, even contradictory, although there have been some sporadic studies dealing with human VOKN and/or VOKAN.

In an attempt to systematically characterize vertical optokinetic system in humans, the purpose of the studies presented in this dissertation was to investigate the human vertical optokinetic reflex and its dependence upon head orientation with respect to normal gravity and the influence of varied gravitoinertial forces. The ultimate objective is a better understanding of otolith physiology.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Optokinetic Reflex

Motion of the visual surround induces optokinetic nystagmus or OKN, which is an involuntary, conjugate pursuit eye movement interrupted with saccadic movement in the opposite direction. Its purpose is to stabilize the retinal image as the subject moves about. With an effective stimulus, the velocity of the slow phase of OKN is approximately equal to stimulus velocity up to a range between 30 and 50 deg/s (for HOKN), beyond that it declines. When the stimulus is replaced by darkness, the nystagmus continues with diminishing slow phase velocity known as optokinetic after-nystagmus (OKAN). All of the early studies of the optokinetic reflex were carried out with stimulation about the yaw axis of the subject, referred to in this thesis as "horizontal" stimulation, generating HOKN/HOKAN. Vertical OKN/OKAN (VOKN/VOKAN) are generated with stimulation about the pitch axis of the subject.

## 2.2 Neural pathways of the Optokinetic System

There are two main neural pathways responsible for generation of OKN: a subcortical pathway and a cortical pathway; the former is primarily involved in processing of OKN signals in the nucleus of the optic tract (NOT) and the latter is related to voluntary smooth pursuit eye movements (1,5,6). The subcortical component of OKN has been referred to as "stare" nystagmus because it is evoked by passively staring at the stimulus. That is the slow, indirect and involuntary component which has attributes of long latency and the velocity storage, and consequently it continues as OKAN after removal of the stimulus. By contrast, the smooth pursuit component has been referred to as "look" nystagmus which is the fast, early, smooth pursuit, direct and voluntary component, evoked by actively looking at stimulus features (7).

Visual signals to subcortical nuclei controlling OKN are conveyed from each retina along the accessory optic tract that crosses and terminates in the contralateral accessory optic system (AOS). This system has three subnuclei: the lateral, medial, and dorsal terminal nuclei. The lateral and medial nuclei seem to be mostly concerned with vertical OKN, whereas the dorsal nucleus and the NOT in the pretectum are concerned with HOKN (8).

In most afoveate animals, such as the rabbit, HOKN is

controlled by signals relayed through the NOT with little or no input from higher visual centers. Thus, ablation of the NOT in the rabbit abolishes HOKN (9). In the rabbit, almost all cells in the NOT respond to visual stimuli at velocities of up to 20 deg/s over large areas of the central region of the contralateral retina. The cells in the right NOT respond only to nasally moving stimuli to the left eye, and the cells in the left NOT respond only to nasally moving stimuli to the right eye (10).

In cats, ablation of the NOT also abolishes HOKN (11), and large lesions in the visual cortex or cortical pathways have the same effect (12-14). About half of the cells in each NOT receive inputs from binocular cells in the visual cortex and have an upper velocity limit of over 100 deg/s. These cells, therefore, respond to stimuli presented to either eye but only to stimuli moving in the same direction in space. Thus, in a cat with one eye open, signals can reach both nuclei of the optic tract - the contralateral nucleus by the direct ascending pathway and the ipsilateral nucleus by the cortical pathway. Since the cells in the two nuclei have opposite directional preferences, HOKN occurs for both directions of stimulus motion, even when only one eye is exposed to the stimulus (15).

In primates, a lesion in one NOT in the monkey reduces the gain of HOKN toward the side of the lesion and reduces or abolishes afternystagmus in the same direction, but leaving

smooth pursuit and saccadic eye movements intact (16,17). Cells in each NOT of the monkey respond to stimuli presented to either eye moving ipsilaterally with velocities of between 0.1 and 400 deg/s. Most of those cells have large receptive fields that include the fovea (18,19). Electrical stimulation of cells in the NOT of the monkey only elicits slow rise of HOKN SPV and an afternystagmus in the ipsilateral direction (17,19). This phenomenon means that stimulation of the NOT only excites the subcortical visual pathway that projects to the vestibular nuclei, but does not affect the direct pathway function.

From the pretectum, visual motion signals are conveyed to the nucleus reticularis tegmentis pontis (NRTP) and the prepositus hypoglossi nucleus (NPH), also indirectly from the NRTP (20,11,21,22). In the monkey, the signals are relayed to the NPH through the neighbouring dorsomedial pontine nucleus (23) and the inferior olive (24). Projections from the NOT to NRTP are known to exist since NRTP neurons in the monkey have been found to respond to moving visual patterns (23). Bilateral lesions of the NRTP almost abolish optokinetic responses of VN units and HOKN in the rat (25) and the cat (11). Next, the NOT and NRTP both project to the NPH (21,26) and the NPH projects bilaterally to the vestibular nucleus (27,28). Lesions of the NPH abolish HOKN and HOKAN in the monkey (29) and in the cat (30).

The signals that reach the vestibular nucleus from the

NOT are conveyed to the same cells that receive inputs from the horizontal semicircular canals. These cells discharge at a rate proportional to the velocity of the slow phase of HOKN up to a velocity of 60 deg/s (31). Each cell also responds in the dark when the head is rotated in the opposite direction (32). Combined rotation of the visual surroundings and of the body within a certain range of velocities and accelerations results in neural activity proportional to the velocity of the visual stimulus relative to the body (33). Cells in the vestibular nucleus also respond during HOKAN and post-rotatory nystagmus (34). Therefore, HOKN and HOKAN are largely affected by lesions of the ventral vestibular nucleus (29). Bilateral labyrinthectomy in monkeys (35,36) or humans (37,38) abolishes or severely reduces OKAN. From the vestibular nucleus, signals responsible for VOR ascend to the oculomotor nuclei along the MLF and the tract of Deiters.

The slow build-up of HOKN and decay of HOKAN are thought to result from charging and discharging of a velocity storage mechanism somewhere in the neighbourhood of the MVN and NPH (39). This is thought to be the same velocity storage mechanism that contributes to the maintenance of the VOR (40-43).

The cortical component of HOKN produces a fast and high gain response of following at high stimulus velocities (44). The pathway is distinct from that conveying signals for the subcortical component of HOKN. Brainstem lesions in humans can

produce a selective loss of smooth pursuit eye movement in a particular direction and a low gain HOKN with the slow buildup and afternystagmus response of HOKN (45). Complete removal of the visual cortex in the monkey severely reduces the gain of HOKN due to the inability of animals to respond to high-velocity stimulation, but HOKAN is still left intact (46). Lesions in the MT and MST cortex of the monkey lead to a reduction in the gain of HOKN toward the side of the lesion and a reduction in the rapid onset of HOKN in both directions. Such lesions also result in an inability to match the velocity of pursuit eye movement to that of a moving target (47).

The cortical component of HOKN and the voluntary pursuit of single objects seem to share a common mechanism in the flocculus of the cerebellum. Some studies in the monkey demonstrate that some of the mossy fibers of the flocculus respond to retinal slip velocity and others to stimulus velocity, i.e. retinal slip velocity plus eye velocity (48,49). Some of the Purkinje cells show a modulation of their activity in response to changes in the velocity of voluntary pursuit and to changes in the velocity of the pursuit phase of HOKN at velocity above 40 to 60 deg/s. These cells only display a transient response to stimulus onset but are silent during HOKAN (36,50). Lesions of the flocculus reduce HOKN gain at stimulus velocities above 60 deg/s and abolish the rapid onset and decline of HOKN, leaving the slow buildup and afternystagmus of the subcortical component of HOKN intact

(51,52).

The midbrain reticular formation in the area of the interstitial nucleus of Cajal (INC) has close connections with the vestibular and oculomotor nuclei (53,54). Some neurons in the INC receive visual input (55), and an anatomical study revealed pathways that could relay a visual input to the INC (56). By means of single cell recording, it has been shown that the INC contains neurons whose activity is closely related with vertical optokinetic and otolith organ stimuli, i.e. the neurons that respond to linear acceleration in the dark also respond to optokinetic stimulation (57,58). These results suggest that those INC neurons receive a convergence of inputs from the otolithic and visual sources.

## 2.3 Dynamics of OKN and OKAN

There are two independent mechanisms governing optokinetic responses: one has a long time constant and generates OKAN; the other has a short time constant and generates no after-response (5). In our lab, it has been demonstrated that human HOKAN decay can be best described by a two component, exponential model: SPV = A exp (-Bt) + C exp (-Dt), where A and C are the initial values of the short time constant (1/B) decay and long time constant (1/D) decay, respectively (59).

In monkeys, OKN SPV increases rapidly during the initial 100 msec of exposure to OK stimulation, followed by a more gradual increase with a time constant of about 2.5 sec for a stimulus velocity of 45 deg/s, rising to 5 sec or more at stimulus velocities above 90 deg/s (1). It is believed that the initial rapid rise is mediated by the activation of the smooth pursuit pathways and that the gradual increase is due to the activation of the subcortical pathways with velocity storage. However, in humans, HOKN SPV reaches its full value in the first beat, which suggests that the time constant of the smooth pursuit component in humans is very short and dominates OKN (60,61).

It has been proposed that the buildup of SPV and gradual decay result from the charging and discharging of a neural velocity storage mechanism in the brainstem (62). In humans,

OKN has a rapid onset, but OKAN, as in monkeys, does not reach its maximum strength until the stimulus has been on for a certain period. According to one estimate, for a stimulus velocity of 60 deg/s, the time constant of the charging time for the velocity storage is about 20 sec, and the time constant of the decay of HOKAN is about 25 sec (63). According to another estimate, these time constant are in the range of 5 to 11 sec (64). The cause of this difference is uncertain. But using different stimulus paradigms may have an effect. The former used constant velocity optokinetic stimuli, while the latter used sinusoidal optokinetic stimuli with periodic, brief intervals of darkness to sample HOKAN during optokinetic stimulation. The frequent sampling along the test in the latter case might not give enough time for the velocity storage to be fully charged up. But in both studies, the maximum velocity of human OKAN was found to be 20 deg/s, whereas in the monkey, it reaches values of 90 to 120 deg/s (61).

In an initial period of positive HOKAN, known as HOKAN I, the nystagmus continues in the same direction as the preceding HOKN. This may be followed by a period of negative (reversed) HOKAN, OKAN II, which occurs in the opposite direction. A second positive period, OKAN III, has sometimes been observed. The successive positive and negative phases of OKAN and post-rotatory VOR reveal that the velocity storage mechanism involves the buildup of two opposing tonic processes with

different time constants (65). In the monkey, OKAN I decreases and OKAN II increases in duration with repeated exposure to optokinetic stimulation at 60 deg/s (66). Prolonged exposure of cats to stimulus velocities below 10 deg/sec selectively prolongs OKAN I (67). In humans, brief periods of fixation on stationary objects inhibit OKAN I but enhance OKAN II (68). There is a severe attenuation or total loss of OKAN I after bilateral labyrinthectomy in the monkey (69) and in human patients with bilateral labyrinthine lesions (70). However, OKAN II survives after labyrinthectomy (196). Maioli (71) proposed that there are two first-order storage elements interconnected by an inhibitory feedback loop, one responsible for OKAN I and the other for OKAN II.

The mechanism controlling OKN may be represented as a simple velocity servo system. There are several mathematic models to describe the optokinetic system in cooperation with the vestibular system (1,72-74). The stimulus moving at angular velocity $\omega$ relative to the head generates a motion signal in the visual system that is converted into a signal that moves the eyes at angular velocity G. The movements of the eyes create a feedback loop that reduces the retinal motion signal to a residual velocity error signal, $\dot{e} = \omega - G$. The gain of the system, g, is slow-phase eye velocity divided by the velocity of the moving visual display: $G/\omega$. For perfect foveal image stabilization, the gain is 1. In the cat, the gain of HOKN evoked by a display with spatial frequencies

(stripes per degree of visual angle) in the range 2.8 to 0.18 cycles per degree has been found to be nearly one up to a stimulus velocity of between 5 and 8 deg/s, beyond which it rapidly declines (75). In the monkey, the gain of HOKN in response to whole field motion of a striped pattern with one stripe every 45 degrees (spatial frequency ≈ 0.02 cycles/s) was found to be approximately 1 up to a stimulus velocity of about 180 deg/s (about 4 cycles/s), after which it levelled off and became irregular (62). In humans, HOKN gain in response to a moving display of dots subtending between 2 and 4 degrees has been found to be near one for stimulus velocities up to between 20 and 50 deg/s and to decline at stimulus velocities over 150 deg/s (76).

## 2.4 Stimulus Characteristics for OKN and OKAN

An extensive investigation has been carried out by Schor and Narayan to study the dependence of human HOKN on the spatio-temporal properties of the stimulus (77). They used a 45 degree-wide display of vertical stripes of various spatial frequencies moving horizontally at various velocities. At a spatial frequency of 0.5 cycles per degree, HOKN gain was near 1 for velocities up to about 24 deg/s. Thus, the velocity of the slow phase of OKN is nearly equal to stimulus velocity

over this range. The higher the spatial frequency, the lower the velocity at which the gain began to fall significantly below 1. Over a wide range of spatial frequencies, the temporal frequency of the stimulus at which the gain fell to zero was constant at about 24 Hz, which is not far below the frequency beyond which an intermittent stimulus perceptually fuses. Thus, the factor that determines the upper limit of velocity of HOKN is the temporal (or target) frequency of the stimulus, rather than its spatial frequency or velocity alone. The temporal frequency of a moving stimulus equals spatial frequency times its angular velocity.

In the case of VOKN, using a moving pattern composed of irregular spots of light, Thomson and Saunders (78) have found that, at high target velocities above 30 deg/s, the VOKN responses are less well sustained than the horizontal responses, in particular for upward-moving stimuli. It seems that VOKN has a lower upper limit of evoked velocity.

Under stroboscopic illumination, OKN can also be evoked by intermittently illuminated moving displays as long as the spatial displacement of the stimulus between flashes is not too great. The upper limit of spatial displacement required to keep HOKN gain at its maximum value has been found to be about 2.8 degrees, which is in the range of spatial displacements required for the perception of smooth movement when the eyes are stationary (79).

Systematic investigations of characteristics of HOKAN by

using different stimulus velocities and different stimulus times have been done in terms of the two-component exponential model for HOKAN decay in our laboratory (80,81). For the velocity study, results show two types of response: a low-level response at lower stimulus velocities (10-30 deg/s) and a high-level response at higher stimulus velocities (40-70 deg/s). The results fit the conclusion that HOKAN decay is a two-component process. The direct (pursuit) pathway is responsible for the low-level response while indirect (non-pursuit) pathway is responsible for high-level response. For the time exposure study, the results show the dependence of the long time constant integrator of HOKAN on stimulus exposure time. The short time constant integrator appeared to be independent of stimulus exposure time. It is concluded that these two pathways have different sensitivities to stimulus velocity and to exposure time and each component is distinct.

Another study in our lab demonstrates that full field stimulation is not essential for an adequate optokinetic response, but a suitable match between stimulus spatial frequency and stimulus velocity is necessary (199). In that study, a foveal band consisted of 5 deg high and 4 deg wide (visual angle) black rectangles, with and without the presence of peripheral stripes, was used to evoke HOKN and HOKAN. With a moderate stimulus velocity (40 or 60 deg/s) and 2 Hz stripe frequency, higher gains of HOKN and stronger HOKAN were induced, compared to higher stimulus velocities.

Disc-shaped central occluders can inhibit HOKN in response to a peripheral stimulus unless the subject concentrates on the moving stimulus (84,90). However, when the central occluder is a horizontal band, HOKN occurs whether or not the subject pays attention to the moving stimulus (87). Thus, the effects of attention must have been due to the edges of the disc-shaped occluders. Therefore, it is suggested that although the central retina is required for high-gain HOKN at high stimulus velocities, HOKN still can be evoked from the periphery area of the retina. The better gain with central stimuli could be due to the much higher density of ganglion cells in the central retina compared with the peripheral retina, or it could be due to the pursuit component of OKN being limited to the central retina (87).

In humans, the density of ganglion cells is greater in the upper half than in the lower half of the retina (91). The upper half of the retina (lower visual field) has a shorter reaction time (92) and better spatial and temporal resolution (93) and is more extensively represented in the MT cortex, an area of the brain containing many direction-selective cells (94). For this reason, Murasugi and Howard have found that higher gain of HOKN is evoked by stimuli confined to the lower visual field than that elicited from the upper visual field (95). The hemifield difference for HOKN does not depend on stimulus velocity and is greater when the stimuli do not include the foveal region. In one study for VOKN and VOKAN

(96), same authors stimulated different retinal areas by occluding either peripheral or central area of the retina. It has been found that in the periphery-only stimulation condition, their subjects showed up-down asymmetry at stimulus velocities above 30 deg/sec. In the central-strip stimulation condition, the VOKN gains were lower but not significantly different from the full-field responses. In the third condition, central-only stimulation, both upward and downward gains were attenuated and there was no up-down asymmetry. These results suggest that the upper-lower vision field difference is in the subcortical rather than in the cortical component of VOKN.

## 2.5 Interaction of the Optokinetic System with the Vestibular System

OKN and the VOR (including otolith-ocular reflex) are responsible for stabilizing the world images on the retina as animals move about. The two responses complement each other when the head rotates in the context of a stationary visual scene. OKN operates best at low frequencies of head rotation and is maintained when the head rotates at a constant velocity, while the VOR operates best at high frequencies of head rotation in the region where the gain of OKN falls off

(97). Therefore, acting together, the VOR and OKN have a larger dynamic range than either functioning alone.

Optokinetic afternystagmus (OKAN) is thought to represent the discharge of neural activity related to eye velocity from a velocity storage integrator in the brainstem which has been charged up during optokinetic stimulation (62,98). Velocity storage is also involved in the generation of post-rotatory nystagmus (PRN) and in the continuous slow phase velocity during off-vertical axis rotation (OVAR) (99,100).

It is now a well accepted concept that a velocity storage mechanism is common to both the optokinetic and vestibular systems in the horizontal plane (1,101). It has been shown that neurons in the vestibular nuclei can be driven by purely either visual or labyrinthine stimuli (102,103). As for location of the velocity storage, electrical microstimulation of some sites in VN of alert monkeys evoked nystagmus and after-nystagmus with the same characteristics as those induced by vestibular or optokinetic stimuli, indicating that velocity storage is represented in VN (104).

In the post-rotatory period, the aftereffects of optokinetic and rotatory responses in opposite directions cancel each other for stable image on the retina. The OVAR per-rotatory nystagmus is attributed to otolith organ activity because it is abolished by destruction of the otoliths (105), while plugging the canals has no effect (106,107). It has been proposed that tilt-induced otolith organ activity couples to

the velocity storage during OVAR thus generating continuous per-rotatory nystagmus (107-109). In our laboratory, the effect of active or passive head movements about the pitch, roll, and yaw axes on human HOKAN has been investigated (110-112). It has been found that tilt-dependent HOKAN suppression was produced by pitch or roll head movements, and not by yaw axis head movement. Those results support the notion that otolith organ mediated activity arising from pitch or roll head movements couples to the horizontal velocity storage, thereby suppressing HOKAN.

## 2.6 Vertical OKN/OKAN and Their Dependence on Gravity

HOKN/HOKAN are generated by stimulus motion about the yaw axis of a subject, and are symmetrical left and right. When this motion is about the pitch axis, VOKN/VOKAN are generated. In an upright head position, slow phases are in the same direction as OK stimulus, be it horizontal or vertical, and there is no eye movement component in any other direction.

It appears that VOKN/VOKAN are different from their horizontal counterparts. In monkeys, upward and downward OKN & OKAN are asymmetric, i.e. upward SPV is higher than downward SPV when the animals are in an upright position in the earth's gravity environment (2,113-117); besides, the upward SPV

becomes stronger when the animals are placed in the lateral position, whereas, downward SPV does not change (2,113). Similar asymmetry in cats is also observed (118-120). It is postulated that the asymmetry, i.e. weaker downward OKN and weak or absent downward OKAN, is thought to indicate that stored activity related to slow phase eye velocity contributes less to the production of the downward OKN/OKAN. This asymmetry is even more prominent due to the enhancement of the upward OKN/OKAN, when the animal's head is tilted, presumably, because of the influence from otolith organ activity indicating the velocity storage mechanism is modified by gravity mediated through the otolith organs (2,113,114,120).

After bilateral utriculo-sacculectomies in squirrel monkeys, a clear improvement of VOKN gain in both directions has been found in an upright position while the asymmetry of SPV (upward greater than downward) still remains; and the upward VOKAN is enhanced and its duration is prolonged postoperatively, whereas the downward VOKAN does not show any clear change (121). Bilateral sacculectomy alone causes a gain increase of downward OKN and a gain decrease of upward OKN (116). One study in microgravity has shown that the absence of tonic otolith organ input in microgravity produces a striking effect on the optokinetic nystagmus in a human subject: upon entering the space, the normal asymmetry of VOKN was reversed, i.e. downward VOKN was greater than upward VOKN, and this change was corrected three days later in space (3). These

findings support an otolith origin for modifications of VOKN/VOKAN and suggest that otolith activity affects the vertical velocity storage mechanism that stores activity related to vertical slow phase eye velocity and thereby modulates its output gain. This has been modelled in the three-dimensional models proposed by Raphan et al. (2,109) and Hain (122).

The otolith organ is a primary receptor of gravitational and linear acceleration and is not sensitive to angular acceleration (123). The utriculus is most sensitive to roll and pitch, and the sacculus is most sensitive to cephalo-caudal accelerations (124). The polarization vectors for SN (superior vestibular nerve) units are in or near the plane of the utricular macula, those for IN (inferior vestibular nerve) units in or near the plane of the saccular macula (125). Different neurons in the vestibular nuclei receiving sensory input from the vestibular labyrinth have also been shown to be responsive to static tilts around the cat's pitch or roll axes (126-129). Change of head position actually means changing the otolith organ activity, which modifies the activity state of the VN where the velocity storage integrator is accommodated (2,110-113).

In a monkey tilting study (2), it has been found that while animals are upright, the OKAN is horizontal (about the yaw axis) and there are no vertical (about the pitch axis) or torsional (about the roll axis) components (figure 2).

However, if the monkey is tilted in roll 90° from upright and receives yaw axis OK stimulation, its horizontal OKAN is suppressed. Meanwhile, a vertical OKAN emerges (figures 3 & 4). This was termed "cross-coupling" from the horizontal to the vertical mode of the storage by Raphan and Cohen (2). If animals are in supine position during horizontal OK stimulation, a roll OKAN emerges during the horizontal OKAN suppression (figure 5), hence "cross-coupling" from horizontal to torsional storage. A three-dimensional model for velocity storage has been proposed by Raphan et al. to illustrate this phenomenon (2,130) (figure 6). They suggest that cross-coupling acts like a gyroscopic mechanism that tends to maintain the principal axis of the storage along the spatial vertical axis, i.e. the time course of the storage should be longer about the axis closer to the spatial vertical. Similar observations have also been reported in cats (131).

According to Raphan's model (2), cross-coupling is mediated through the velocity storage mechanism. This postulate is supported by their subsequent experiments on monkeys. Electrical stimulation of the vestibular nuclei of alert monkeys evokes similar cross-coupling as from HOKAN or vestibular post-rotatory nystagmus elicited in tilted positions (104). Also, the velocity storage acts in a multi-dimensional manner, since lateral canal nerve section can abolish HOKAN, but VOKAN, recorded with animals on their sides, is preserved (132). In accordance with this phenomenon,

nystagmus with storage characteristics, induced from different parts of VN, has different directional components. Predominantly horizontal responses are elicited by stimulating more caudally in VN, whereas nystagmus from the region of SVN has more prominent vertical components (104). The latter is consistent with the prominent vertical canal input to SVN, and the presence of cells in SVN that project directly to vertical eye muscle subgroups in the oculomotor and trochlear nuclei (133,134). Another electrophysiological study (197) shows that the electrical stimulation of the nucleus of optic tract (NOT) only elicits the slow rise component of nystagmus and after-nystagmus, and does not affect the direct pathway function i.e. stimulation of NOT only excites pathways in the subcortical visual system that project to the vestibular nuclei. This means that stimulation of NOT only activates the velocity storage mechanism. When the animal was upright, stimulation of NOT induced pure horizontal nystagmus and OKAN. When the animal was tilted and stimulated, however, vertical components appeared both in the nystagmus and after-nystagmus. These vertical components tend to bring the plane of the nystagmus toward the spatial horizontal plane.

The above evidence indicates that the gravitational field is of fundamental importance in cross-coupling. In Raphan's model (2,130), illustrated in figure 6, the element H controls velocity integrator time constant with directionality. The authors have postulated that the element H codes the spatial

vertical and therefore is a key factor to determine if there would be cross-coupling and the direction of its vector as well. They termed this "reorganization" of the velocity storage. This reorganization is dependent on head position with respect to gravity, i.e. depending on the stimulation of the otolith organs.

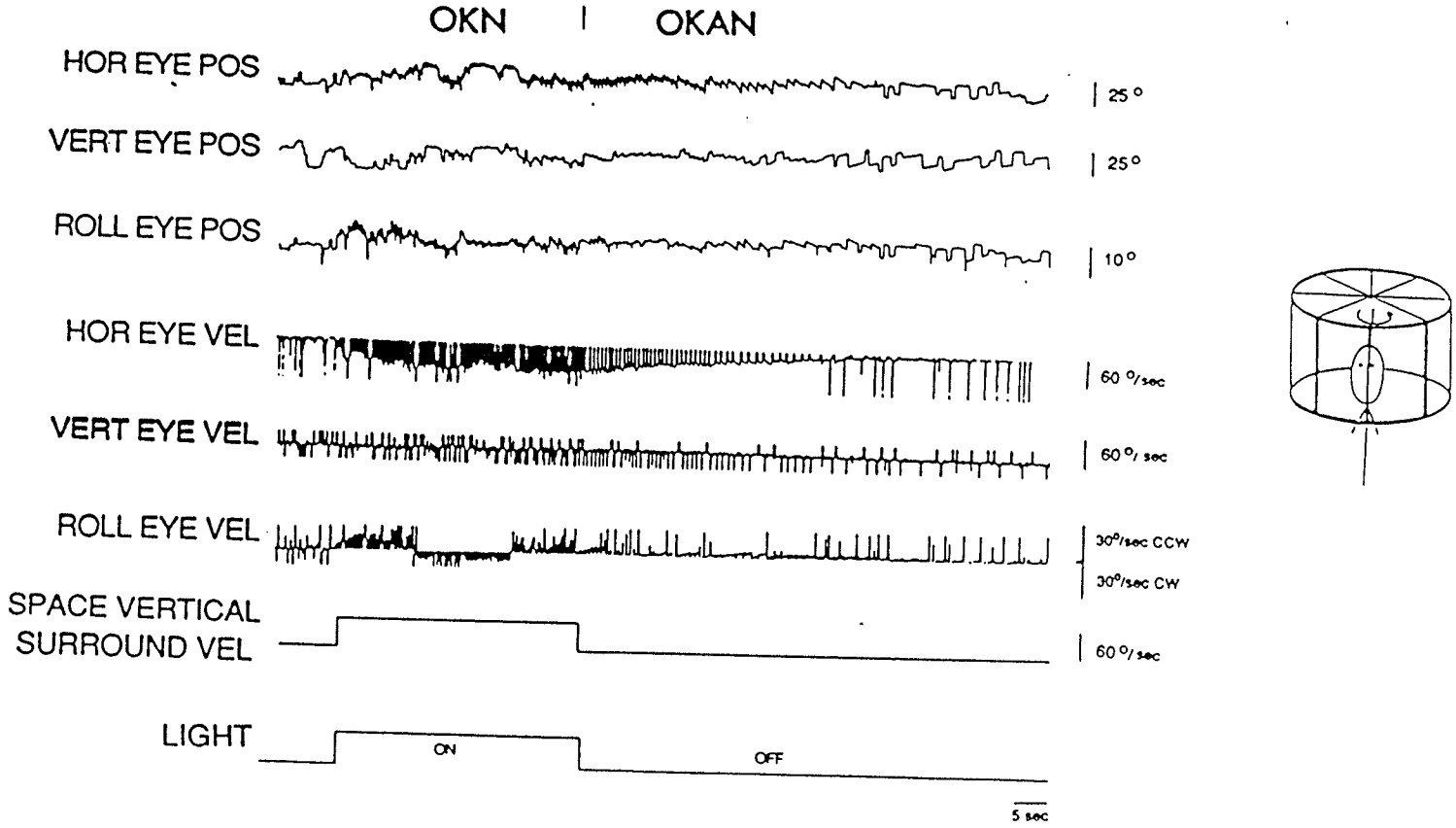


Figure 2. OKN and OKAN induced by surround movement to the left in the monkey's yaw or horizontal plane with the animal upright. The traces in this and subsequent figures are, from top to bottom, horizontal, vertical, and roll eye velocity; movement of the visual field about the animal's yaw axis (space vertical surround velocity); and the status of illumination (light). In the erect position the OKAN was horizontal, and the axis of eye rotation was coincident with gravity. (from (2))

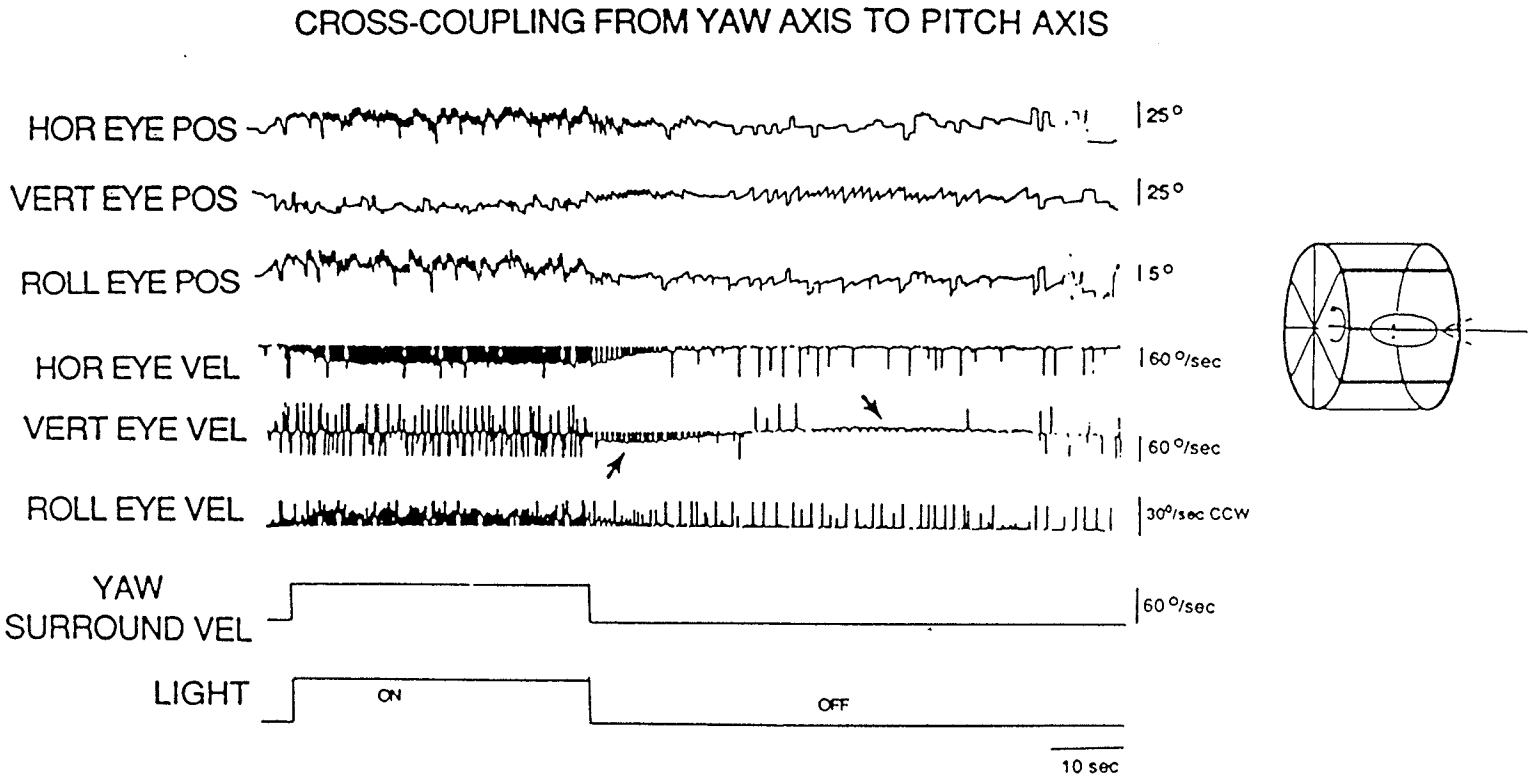


Figure 3. Cross-coupling from yaw axis to pitch axis. OKN and OKAN induced by rotation of the surround to the left in the animal's yaw axis with the animal in the 90-deg roll position, right side down. The horizontal component of the primary OKAN was brief in duration and was accompanied by downward slow phase velocity (upward arrow) that built to a maximum and then declined. This was followed by secondary OKAN (downward arrow) that was upward in the animal's frame of reference, that is, in its sagittal plane. (from (2))

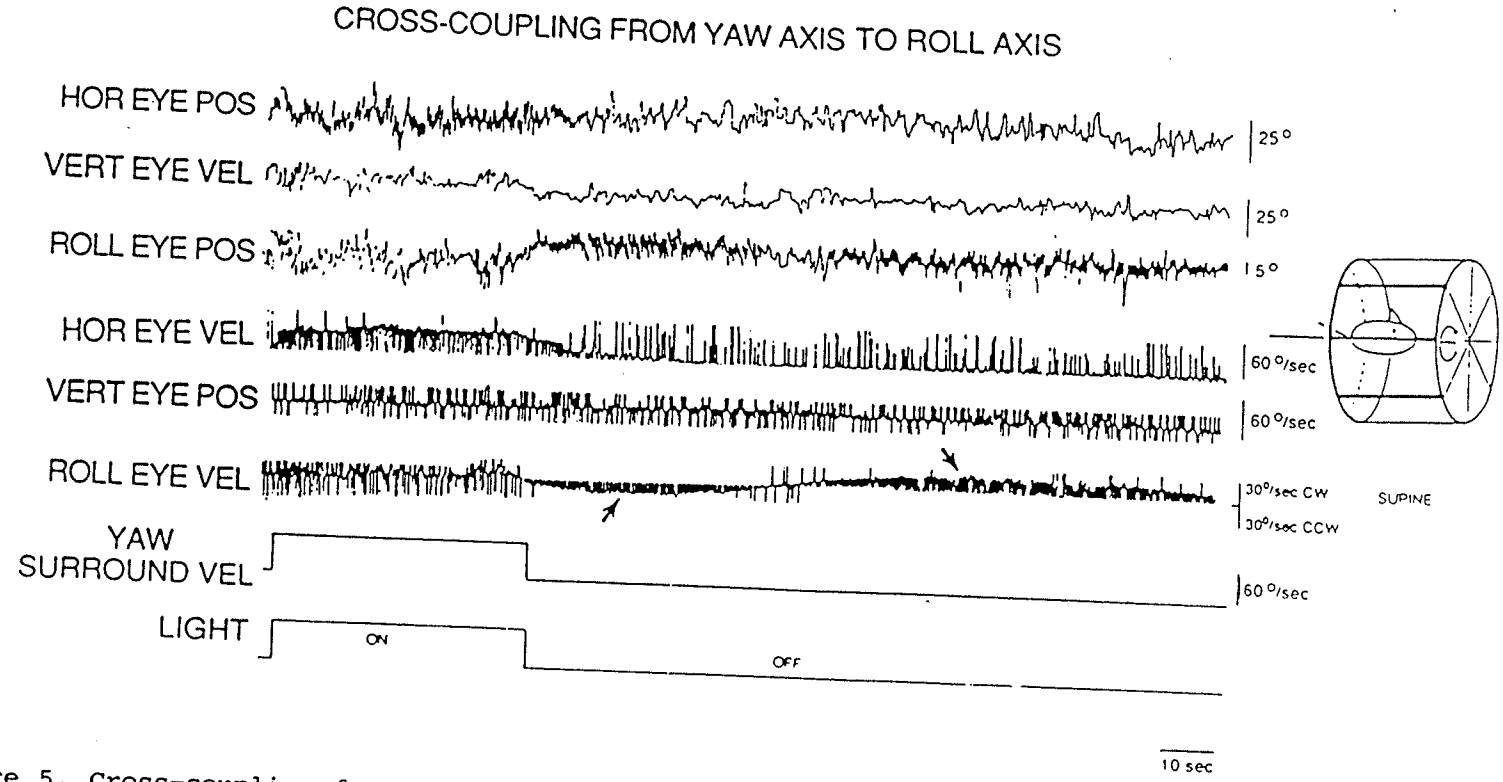


Figure 5. Cross-coupling from yaw axis to roll axis. OKN and OKAN induced by rotation of the visual surround to the right in the animal's yaw axis with the animal supine. The primary horizontal component of OKAN was brief, as in figures 3 and 4, and a counterclockwise roll component developed. This was followed by secondary OKAN that was purely clockwise. Note that during primary and secondary OKAN, the roll component increased at a time when the horizontal component was either declining or was absent. (from (2))

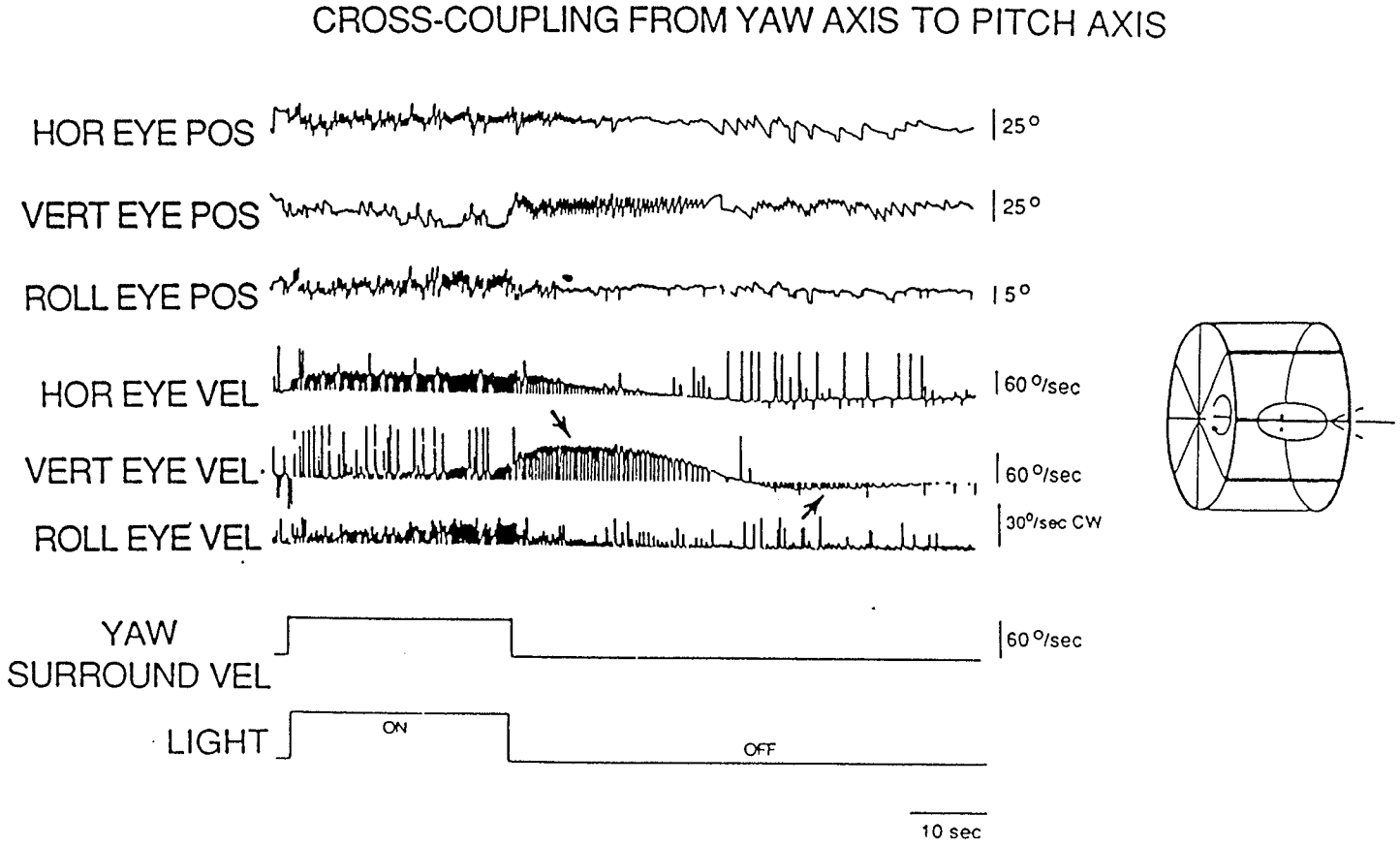


Figure 4. Cross-coupling from the yaw axis to pitch axis. OKN and OKAN induced by rotation of the visual surround to the right in the animal's yaw axis with the animal in the 90-deg roll position, right side down. There was a component of upward slow phase velocity during the OKN that increased during primary OKAN (downward arrow). The duration of the horizontal component was briefer than when the animal was upright (figure 2). The secondary OKAN (upward arrow) was downward in the animal's sagittal plane. Note that the upward component during the primary OKAN was stronger than the downward component in figure 13. (from (2))

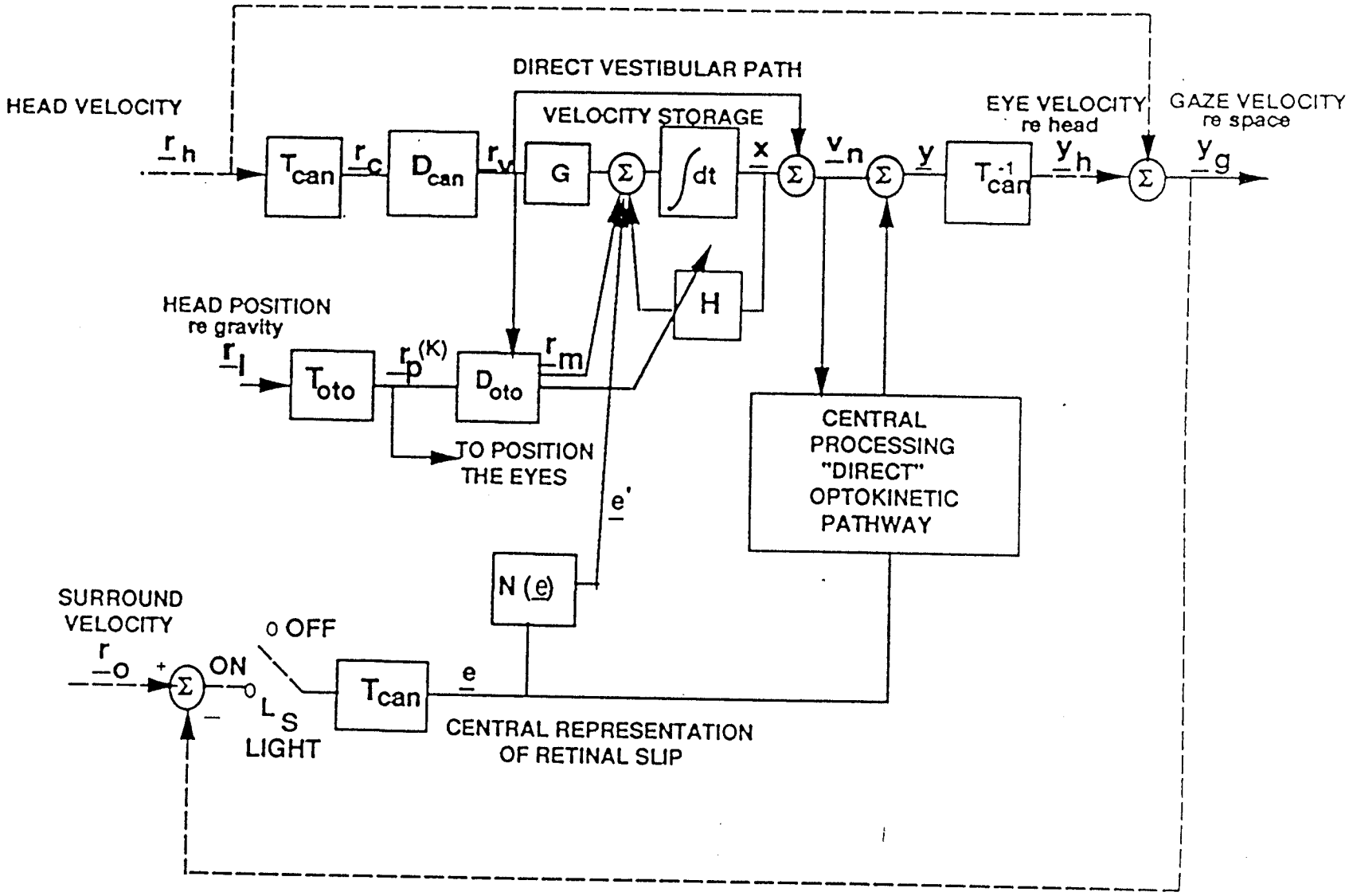


Figure 6. Three-dimensional model of visual vestibular interaction proposed by Raphan and Cohen. (from 130))

Information about human VOKN/VOKAN is scanty and inconsistent, and there are considerable variations in reports, though there have been some studies dealing with VOKN and/or VOKAN in man in head upright and/or tilted positions. Among these reports, some authors have detected up/down asymmetry of VOKN (96,135-137); others have not (119,138-140). Baloh et al. (140) even reported that the gain of downward OKN is greater than that of upward on average, though the difference for the two directions has not reached statistical significance. Nevertheless, upward OKAN has occurred in more than half (6 out of 10) of their subjects, while no downward OKAN has been seen in any subject. There are a few reports which also mentioned VOKAN and head position effects on VOKN/VOKAN (135,139), but those findings are inconsistent. The study by Calhoun et al. (139) has shown that the incidence of upward OKAN increases by changing head position from upright to lateral tilt position, while downward OKAN is not affected by head position change. LeLiever et al. (135), however, have found that upward OKAN itself is not affected by head position change (the VOKAN time constant is generally the same in either head position), and as for velocity sensitivity of OK stimulus, there is no best stripe velocity for VOKAN production. Cross-coupling in humans, claimed as in monkeys has been recently reported by Clément and Lathan (141), but has not been seen by Lafortune et al. (112).

To date, investigation of VOKN/VOKAN in short-term

(parabolic flight) or long-term (space flight) microgravity and hypergravity has not been systematically carried out.

Modifications of the optokinetic reflex have been noted by Vieville et al. (142), both in the microgravity phase of parabolic flight and during spaceflight. In space, there is a dramatic reversal of the normal asymmetry of the human VOKN due to the increase of downward VOKN slow phase velocity and decrease of upward VOKN slow phase velocity, which is consistent with the results from a parabolic flight study. However, this "misalignment" reverts after three days in space, probably because of the central adaptation. In the same space flight study, they also found that following the upward OK stimulation, there are increases of upward OKAN time constant on the first day, with the value returning gradually to the preflight level by day 3. All these modifications suggest that the absence of otolith input, or the reinterpretation by the CNS of the "new" otolithic input clearly has an effect on the optokinetic system, which may correlate with space adaptation and readaptation to the earth's gravitational force. According to the sensory reinterpretation hypothesis proposed by Young et al. (143), the physiological adaptation to weightlessness would involve a CNS reinterpretation of sensory input signals from otoliths as well as from visual and tactile cues in orientation perception and posture control. They suggest increased weighting of visual cues and reduced weighting of graviceptor

signals in weightlessness. It remains to be verified whether this hypothesis can explain the gradual disappearance of space motion sickness symptoms and return to normal sensory-motor interactions which indicate that adaptation has occurred.

It is also suggested by Clement et al. (142) that the reversal of the VOKN asymmetry and a downward shift in beating field on the first in-space day is due to the absence of saccular input which would normally (in 1 G) play an inhibitory role on the optokinetic system, mediated through the velocity storage mechanism. This hypothesis has been put forward on the basis of studies by Igarashi et al. (116,121,144), who have found that bilateral utriculo-sacculectomy of monkeys causes the enhancement of VOKN in both directions, the enhancement of the downward slow phase OKN being clearer than that of upward slow phase OKN. The upward VOKAN is enhanced and downward VOKAN does not show any clear change (121). In another study, after bilateral sacculectomy, the same authors have found that there is a gain increase of downward slow phase nystagmus and a gain decrease of upward slow phase nystagmus (116). These results agree with the findings on VOKN in man under microgravity and support an otolith origin for modifications of VOKN/VOKAN, suggesting that otolith activity is transmitted to velocity storage that stores activity related to vertical slow phase eye velocity and further modulates its output gain. It can be inferred that the increase in the velocity storage in microgravity as

measurable by VOKAN is due to the absence of inhibitory saccular and/or utricular input.

## CHAPTER 3

## PURPOSES OF STUDY

There are fragmentary studies on human VOKN/VOKAN scattered through the literature, but a systematic study has not been carried out. The study presented in this dissertation investigated the charging and discharging characteristics of the vertical velocity storage and effects with otolith organ activity under different gravitoinertial forces. The investigation was undertaken to verify the features of VOKN/VOKAN and cross-coupling in humans and to answer following questions:

1. What is the dependence of human VOKN/VOKAN on the velocity of the optokinetic stimulus?

2. Can a significant up/down asymmetry of human VOKN/VOKAN be revealed by a systematic study?

3. Does head orientation have any influence on VOKN/VOKAN?

4. How does a change in gravitoinertial force level affect human VOKN/VOKAN?

5. Does cross-coupling occur in humans?

6. Does the three dimensional model developed from monkey studies hold for humans?

A better understanding of the mechanisms of the interaction of otolith organ activity with velocity storage in three dimensional space in humans will lead to clarification of some aspects of vestibular/oculomotor physiology. This will aid in the development of more reliable diagnostic tests of vestibular disorders in clinic, and could help to provide a better understanding of space adaptation and motion sickness.

# CHAPTER 4

# MATERIALS AND METHODS

## 4.1 Test Equipment and Set-up

I. Hemisphere- A white plastic hemisphere (100 cm diameter - Servo Med, Stockholm; OK5), was placed in front of the subjects. Stripes were projected on the inside surface of the hemisphere by an internally illuminated slotted drum. The drum could be rotated to project either vertical or horizontal moving stripes of 2° width (at the eye), alternating with dark intervals of 18° width (figure 7).

A chair was used for our subjects to sit on, which could be adjusted to fit different heights of the subjects to have the nasion at the center point of the hemisphere. An adjustable bed was used when the subjects were tested in 90° roll position. The subjects were lying down on their left side by the edge of the bed, and the bed can be adjusted to a proper position horizontally and vertically to get the eyes at the center location of the hemisphere to ensure full field vision of the stimulation.

II. EOG- All the tests were recorded with standard D.C. electro-oculography (EOG). The pigmented layer of the retina maintains a negative potential with regard to the surrounding tissue. Because of the sclera's insulating properties the

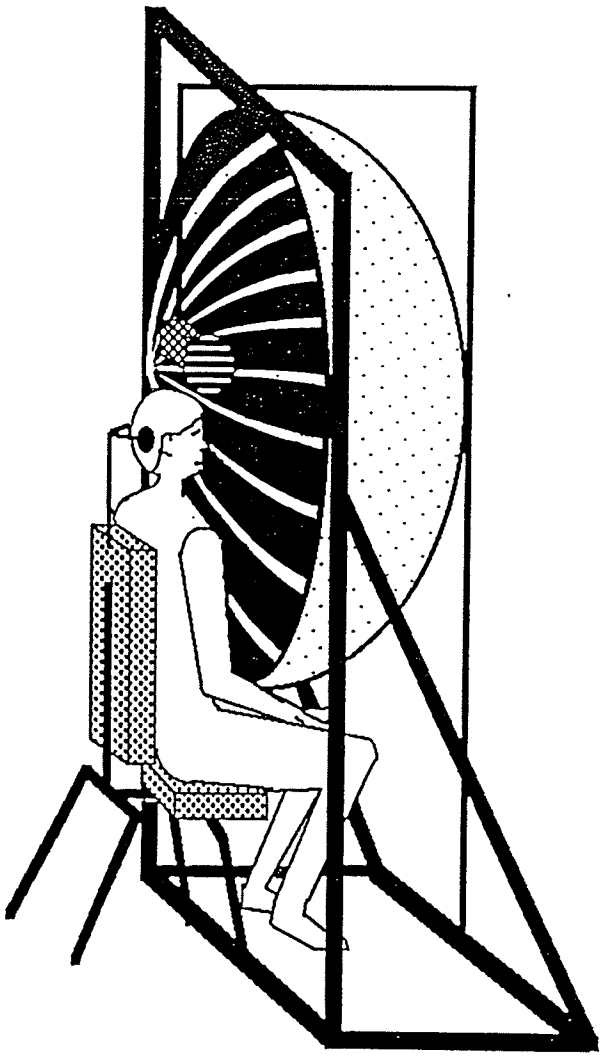

Figure 7. Schematic diagram of the optokinetic testing facility.

cornea becomes positive in relation to the retina. The potential difference between the cornea and retina, known as the corneoretinal potential, acts as an electric dipole. The potential difference between the two poles is normally at least 1mv (145). Movement of the eyeballs induces corresponding changes in potential between the electrodes placed around the eye because the orientation of the dipole changes (figure 8). The potential difference detected is very small, in the order of 15 to 80 $\mu$v/deg (146). The minute potential difference is amplified up to 20,000 times. As the upper most frequency of interest in the analog voltage signal induced in optokinetics is generated lower than 30 Hz, a 30 Hz low-pass analog filter was used to attenuate unwanted signals of higher frequency.

Changes occur in the corneal-retinal potential of the eye when the level of surround illumination is altered (147,148). Intensity of the potential is the same in either total darkness or in a red light environment. The corneal-retinal potential decreases to a minimum (about 80%) during the first 10 minutes and then returns to its original value over a similar time course on transition from normal room light to total darkness or red light environment, and the potential increases in the first 10 minutes, reaching a maximum value which is about 60% higher than in the darkness when there is transition from total darkness or red light environment to the light condition. However, during the first 60 to 80 seconds,

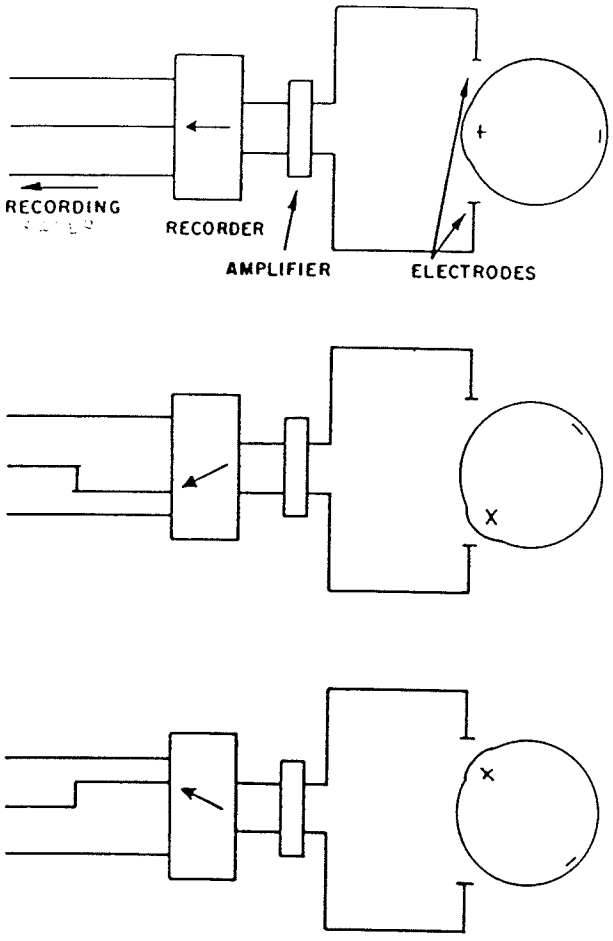


Figure 8. Principle of electronystagmography (ENG).(from (195))

the corneal-retinal potential actually decreases from darkness to light-on and increases from light-on to darkness in a course of damped oscillation. The peak change amplitude is about 0.05 mv, i.e. not more than 5% of the corneal-retinal potential (148). Our test protocol was 60 sec light-on and 60 sec light-off, which was the same for each subject and in each test condition. Since our interest was to compare VOKN/VOKAN in different test conditions rather than different light conditions, the variation of the corneal-retinal potential in our test paradigm did not significantly affect our results.

After cleaning the skin areas with alcohol prep, non-polarisable silver-silver chloride electrodes (Graphic Controls Medi-Trace, Gananoque, Ontario) for DC electro-oculography were applied at six locations: one electrode above and one below the left eye with a reference electrode on the back below the neck (C2) for vertical eye movements, and one beside each of the left and right outer canthi with a reference electrode placed above the nasion for horizontal eye movement recording.

III. ISCAN- A head mounted eye imaging system (RK-416 Pupil Tracking System manufactured by ISCAN, Inc.). The system consists of a miniature CCD monochrome camera (TM-540), a solid state infrared illuminator, a dichroic mirror and mechanical assembly, as shown in figure 9. Specifications for

A

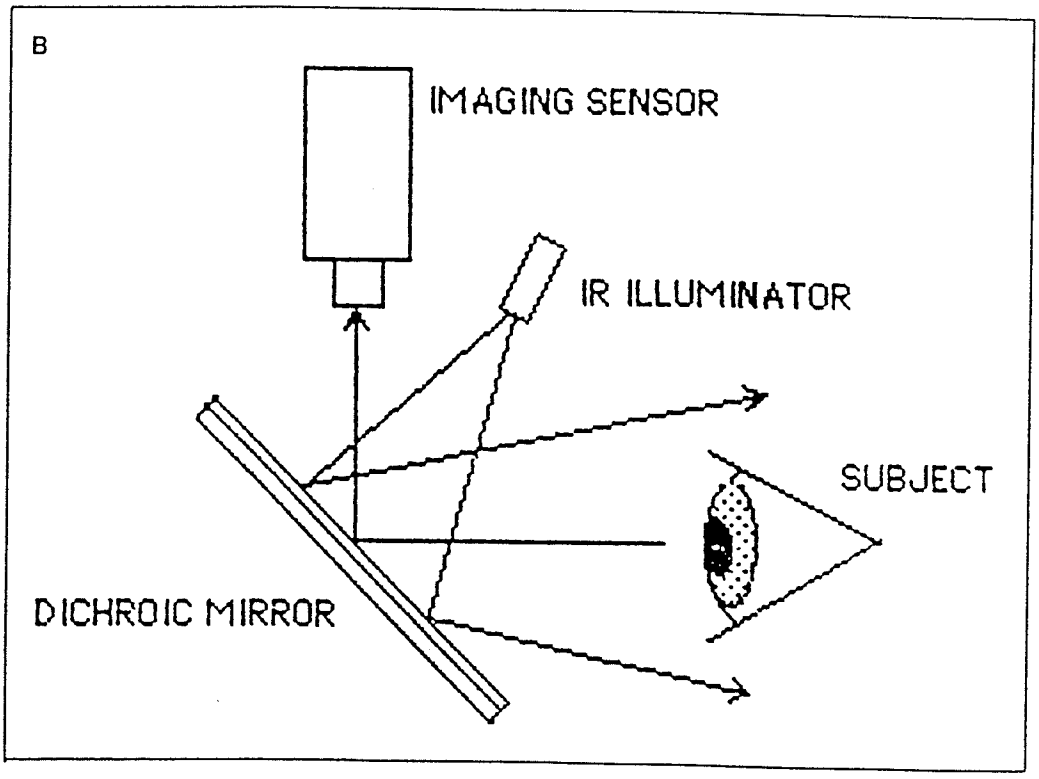


Figure 9. Diagram of the ISCAN head mounted imaging system for eye movement monitoring. A: Set-up. B: Schematic illustration.

the imaging sensor are: size = 1.6250" × 1.2500" × 1.0625"; spatial resolution = 512 (Horizontal) × 256 (Vertical) pixels. The temporal resolution of the camera is 30 Hz. Accuracy of the system is 0.5° of visual angle over ±40° field of view. The right eye, illuminated by low level (1mW/$cm^2$) infra red (IR) light (approximately 850 nm), was scanned by the IR-sensitive video camera. During testing, eye movements and event signals were recorded on 8 mm video tapes (Sony P6-120MP, Hi8) with a video recorder (Sony GV-500, Hi8). Video records were fed into computer for analysis later on. ISCAN being a relatively new technology was introduced later in the study and subsequently was only used in the parabolic flight study. ISCAN eliminates muscle artifacts, skin resistance, electronic baseline drift, electrode crosstalk and intrinsic nonlinearity of EOG.

### 4.2 Test Protocol

A previous study in our lab on stimulus exposure time on HOKN/HOKAN indicates that mean values of HOKAN saturated at 40 sec and 60 sec were not found to be significantly different (81). In order to produce reliable OKN/OKAN, a 60 sec stimulation was set up as standard stimulus time period in our lab. To make comparison with horizontal OKN/OKAN, 60 sec stimulus exposure time was also applied to the subjects.

Therefore, each OKN and OKAN trial consisted of 60 second unidirectional OK stimulation followed by a lights-out period of 60 seconds, which assured sufficient time for recording OKAN in the dark. During the stimulation, the subjects were instructed to: "look ahead and try to follow and count as many stripes as possible over the middle range of the hemisphere". When in the dark, "try not to concentrate on eye's position". In this way, possible vergence effects were also minimized and the subjects did not have a clear perception of the location of the hemisphere in relation to themselves. To prevent drowsiness in the dark, subjects were asked to do simple mental arithmetic, such as 400 minus 7 continuously. For the whole test, the subjects were asked to stay still and alert. Horizontal and vertical calibrations of ±10° were carried out by following red light dots (1° in diameter) projected from the back of the hemisphere before and after each trial. Signals from both vertical and horizontal channels were recorded simultaneously. In order to avoid possible cross-talk, care was taken to make sure the electrodes were in vertical and horizontal planes. Any cross-talk resulted in readjusting the electrodes around the eyes until there was no cross-talk detected during the calibration saccades. We were also concerned about vertical EOG linearity because it had been reported (78,149) that vertical EOG does not give linear recorded voltage versus vertical eye displacement when vertical gaze amplitude exceeds 20-25°. This has been

confirmed in our lab by depicting EOG linearity. It is shown in figure 10 that EOG gives approximately linear measurement (error within 5%) over the range of ±20°. Each value was a mean of three consecutive calibration trials on the left eye. Since most vertical optokinetic responses in our experiments were observed to remain within ±10° of the centre gaze position, calibration at ±10° was done based on the assumption that the VEOG is a linear function of vertical eye displacement within this range (78,150).

### 4.3 Study of Stimulus Velocity Dependence of VOKN/VOKAN

A total of 11 subjects, with no known history of hearing and vestibular disorders, participated in this study: 4 female and 7 male, ranging in age from 22 to 35 years. The subjects sat comfortably in front of the hemisphere with a distance of 50 cm from nasion to the centre of the hemisphere. In order to study the velocity sensitivity, stripe velocities of 20, 40, 60 and 80 deg/s were used respectively in both upward and downward directions. To minimize a possible habituation effect, subjects received stimulation at two velocities (20 and 60 deg/s) during one session and another two velocities (40 and 80 deg/s) during the other session (at least one week later). Stimulus direction sequences were randomized. A total of 8 trials was performed on each subject.

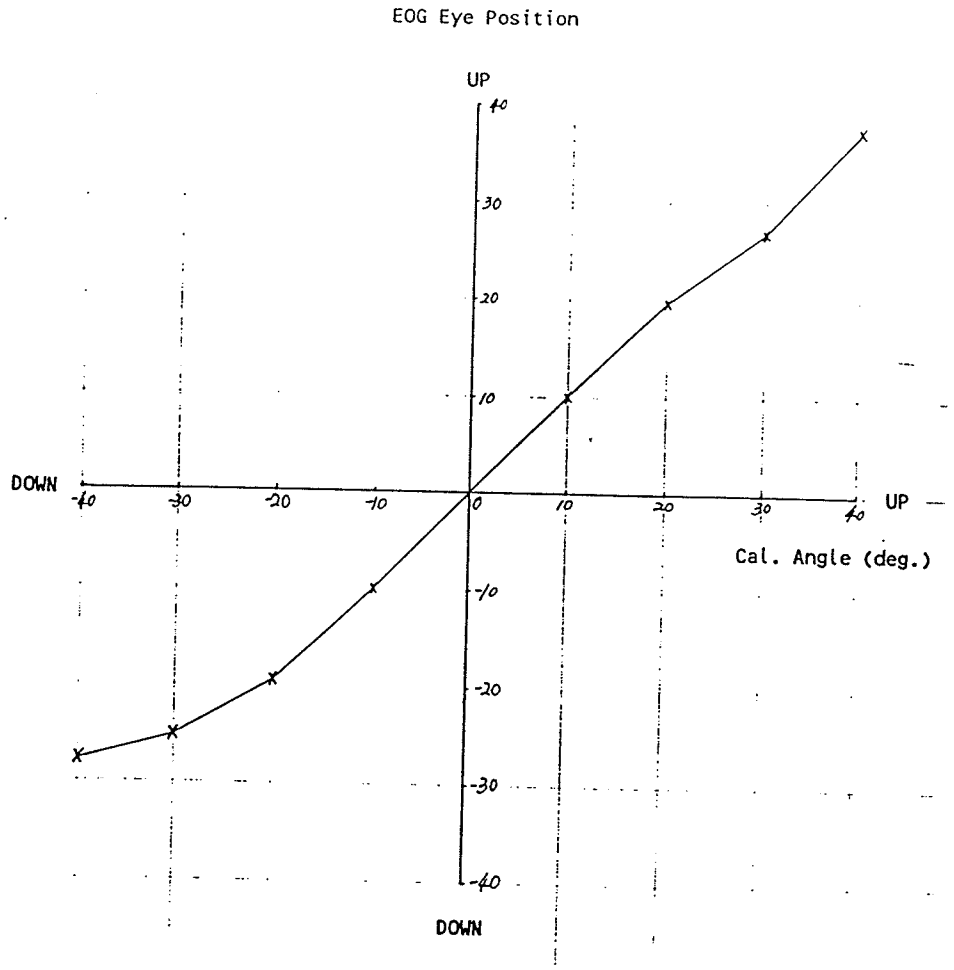


Figure 10. The graph depicting the EOG linearity vs eye calibration angle.

## 4.4 Study of VOKN/VOKAN and Their Dependence Upon Head Orientation

A total of 18 subjects, with no known history of hearing or vestibular disorders, participated in this study: 8 female and 10 male, ranging in age from 20 to 35 years. The subjects were tested in two head positions: upright (as described in the last section) and 90° roll (left ear down). In the 90° roll position, subjects were comfortably lying on their left side on an adjustable bed. Care was taken to support the head in an anatomically neutral position so the neck muscles were relaxed. In such way, possible cervical-ocular reflex (COR) effect was minimized, because the COR is elicited by rotating the torso or either a forward or backward inclination of the torso but a side way tilt of the torso does not evoke this reflex (200). Also, this reflex is more evident in infants and patients than in normal adult (201). Horizontal (leftward or rightward) and vertical (upward or downward) optokinetic stimuli at a speed of 40°/s were presented in both head positions. There were two testing sessions. In the first session, subjects were tested in one head position only. The second session was carried out in the other head position at least one week later. Head position and stripe direction were randomised. A total of 8 trials was thus performed on each subject, 4 per test session. The randomisation was weighted such that the same number of subjects commenced and completed

with each of the two different protocols. The above two studies were carried out in our lab in Winnipeg, Canada.

## 4.5 Study of VOKN/VOKAN During Parabolic Flight

The experiments were conducted aboard NASA's KC-135 aircraft, based at Ellington Field, Houston, Texas, which was flown in a parabolic path to generate alternating periods of micro-G (ca. $10^{-2}$ G) and hyper-G (ca. 1.8 G) (figure 11). Each phase lasted approximately 20 - 25s. On each test day, 40 parabolas were flown over a 90 minute period in 4 sets of 10, with periods of straight and level flight between them. Given the G vector definition within the aircraft's orthogonal reference frame as x-axis (fore-aft), y-axis (lateral) and z-axis (up-down), the resultant G vector during the flight was always aligned with the aircraft's z-axis.

A total of 14 subjects, with no known history of hearing or vestibular disorders, participated in this study: 4 female and 10 male, ranging in age from 22 to 42 years. The subjects were recruited among staff who were carrying out other projects but were free at the time of the test. 12 of the subjects were naive to our test.

Before the flight, habituation and 1 G control tests were carried out on the ground. To maintain darkness during the

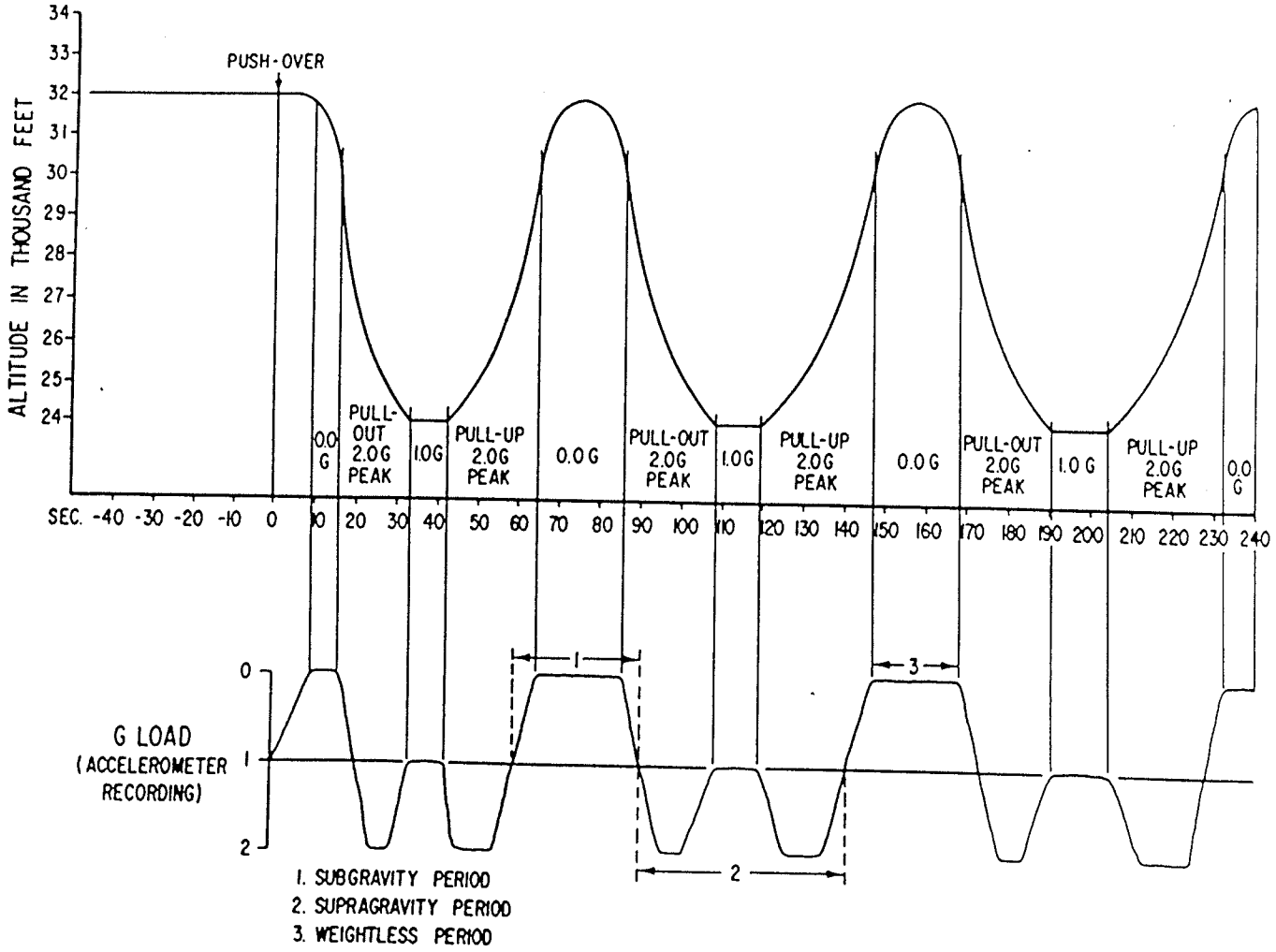


Figure 11. Schematic illustration of the flight profile of the Boeing KC-135 aircraft used to generate alternating periods of the free fall and high gravitoinertial acceleration level. (from (198))

lights-out period, a black cloth shroud was used to surround the hemisphere and the subjects.

As demonstrated earlier in our lab (151), repeated exposure to unidirectional OK stimulation resulted in reduction of HOKAN and there was no further significant decrement after three trials, and there was no recovery up to 8 weeks later. Therefore, the ground control test was always preceded by a habituation test, which consisted of three consecutive trials in each direction, either upward or downward. Standard test procedures as used for previous ground study were applied: each VOKN/VOKAN trial consisted of 60 second unidirectional OK stimulation at 40 deg/s, followed by a lights-out period of 60 seconds. After habituation runs, the 1 G control data were collected.

For the flight study, the testing equipment was mounted firmly on the floor of the aircraft. A cold air blower was also installed underneath the subjects to provide ventilation within the shroud during the test. The ISCAN helmet was snugly placed on subject's head to make sure the camera recorded the pupil image in the center of the frame. Left-right and up-down eye movements following calibration dots were used as a check of proper alignment of the camera to avoid a tilted image. The video recorder with a monitor screen on it was mounted on the computer equipment in front of the operators to provide on-line monitoring of the eye movements, eye position and possible camera slippage of the ISCAN helmet on the head so as

to secure good quality recordings. In the upright position, with his/her head supported by the head rest and strapped with velcro, the subject was strapped snugly in the testing chair to prevent him/her from moving during the flight. The subject's pitch axis was always aligned with the aircraft x-axis; the G vector was always aligned with the subject's yaw axis.

Stimulation protocols were as follows:

A. Following approximate 60 s period of OK stimulation at 40 deg/s, upward and downward respectively, the stimulus was removed at the onset of micro-G. The OKAN decay was then recorded throughout micro-G phase.

B. Same stimulation, except the stimulus was removed at the onset of hyper-G. The OKAN decay was then recorded throughout hyper-G phase.

One subject was tested in each flight. The first parabolas was usually skipped since sometimes it was not reliable. Three repeated trials were carried out for each test protocol respectively, and there were 2 different protocols in either A or B. Therefore, a total of 12 trials was normally carried out in each flight. In case the recording was not satisfactory, extra trials were added during the last few parabolas. There were two subjects who became sick in the

course of the test, and in these cases the test was either terminated or continued after a rest. These two subjects did not complete all 12 trials.

## 4.6 Analysis Procedure

Because of physical variations among the subjects, the actual distance between the eyes and the center of the hemisphere varied. Therefore calibration parameters were put in based on actual angle from the nasion to two calibration dots, at ± 10° for vertical and for horizontal, calculated by hand, measuring for each subject the actual distance between the nasion and the center of the hemisphere. Analysis software asked for the calculated angle between the calibration dots and calculated the calibration value by taking an average of the calibrations made before and after each trial.

I. EOG data analysis:

The amplified horizontal and vertical EOG signals and event signals (light/dark and gravity shift) were converted to digital data at 200 samples per second, and stored on floppy diskettes by a computer (Hewlett Packard 91538). As the upper most frequency of interest in the voltage signal induced in optokinetics is generally lower than 30 Hz, a 30 Hz low-pass frequency filter was used to attenuate unwanted signals of

higher frequency.

During analysis, the eye position trace was enlarged on a scrolling screen so as to be able to inspect the fast and slow phases as clearly as possible. The operator had discretion to avoid taking eye blinks and other noise and to chose valid eye position traces for calculating eye velocity. Eye blink traces were very distinctive from nystagmus, as shown on figures 12 and 15 (in the section of results). Beginning and ending points of the clear slow phases were taken and the program took those points to calculate SPV. The mean SPV of the last 5s of OKN from each trial was calculated. The analysis software calculated SPV based on the points the operator selected and it did not display velocity profile.

Nonlinear regression analysis by Marquardt's procedure (152) of each OKAN SPV decay was carried out to determine, from estimated initial values, the equation of the least-squares best fitting line. Marquardt's procedure was used to obtain the estimated parameters in each iteration until the best fitting line was achieved. The area under the regression curve, which is mathematically equivalent to cumulative eye movement, was determined by the Trapezoidal Rule integration (153).

Time constant values were not shown to be sensitive because of high intersubject variability of time constant. We have chosen to use area under the regression curve to define the response. Here we used the area under the regression curve

fit of the VOKAN decay as the value representing the amount of VOKAN storage. Values of area under the curve and area under the raw data points were very close although they were not necessarily the same. Larger values of area under the curve indicated a more fully charged integrator or a longer time constant, or both.

II. ISCAN data analysis:

The recorded eye movement video was played back to an IBM 386 PC, through a PK-416PC (pupil tracking circuit board designed by ISCAN INC.). By taking 2 pictures out of one frame by means of interlacing, the system automatically computed the instantaneous position of the pupil in two dimensions at 60 pictures/s, providing analog x and y output signals. These analog signals, and event signals from audio channels of the VCR were fed into a MAC II computer that had National 16 bit A/D converter, and converted into digital form at 60 Hz by DATA-4th (software designed by Krug Life Sciences CORP.). Subsequent calibration and interactive analysis were carried out using KRUG "Oculo 1" software, which was designed for space shuttle flight STS42 - International Microgravity Laboratory I.

Calibration files were set up as follows: First, calibration files were opened to get calibration traces on a scrolling screen. Then, calibration parameters were put in based on actual angle from the nasion to two calibration dots,

calculated by hand measuring actual distance between the nasion and the center of the hemisphere. Valid calibration levels were marked with a cursor by the operator and then every valid calibration was calculated. An average of calibration values before and after calibration was taken for the analysis.

The data was filtered digitally, using a 10 Hz Chebyshev low-pass filter to attenuate unwanted signals of higher frequency. Calibrations were applied to filtered VOKN/VOKAN data, which was then digitally differentiated to give the velocity profile. VOKN/VOKAN traces could be enlarged to ensure clear recognition of the data. The fast phase components of VOKN in the period 20 sec prior to the light-out and VOKAN were taken out interactively by the operator on the scrolling screen, followed by calculation by the program of mean SPV of the OKN component. The calculation of the mean SPV was accomplished with the 'Oculo 1' using a linear least square regression.

Single or double exponential regression of the VOKAN decay curve was carried out by Oculo 1 to get the best regression fit. The judgement of better curve fit is based on least-squared residuals, for which, the smaller the better. The area under the regression curve, which is mathematically equivalent to cumulative eye movement, was calculated. Statistical analysis was carried out with ANOVA, using a commercial software NCSS.

# CHAPTER 5

# RESULTS

## 5.1 Stimulus Velocity Dependence of Human Vertical Optokinetic Nystagmus and Afternystagmus

### 5.11 Effects of Stimulus Velocity on VOKN

Figure 12 shows raw VOKN at different stimulus velocities. Statistical results of VOKN at each stimulus velocity are presented in figures 13 and 14. In figure 13, the statistical analysis did not reveal significant difference between the SPV values at stimulus velocities from 40 to 80 deg/s for either upward or downward direction. There was a highly significant difference between 20 deg/s and other stimulus velocities. Figure 14 shows that gains at stimulus velocities greater than 40 deg/s became progressively poorer, even though the retinal slip increased. This indicates that VOKN function does not work efficiently at stimulus velocities greater than 40 deg/s. Gain asymmetry was maximal at 40 deg/s; it became smaller at 60 deg/s. At 80 deg/s, the asymmetry was further reduced and even slightly reversed. Most of the subjects found it difficult to follow the stripes at stimulus velocities greater than 40 deg/s. At 20 and 40 deg/s, standard errors were relatively small, indicating good regularity of following. When the stimulus velocity went up to 60 or 80

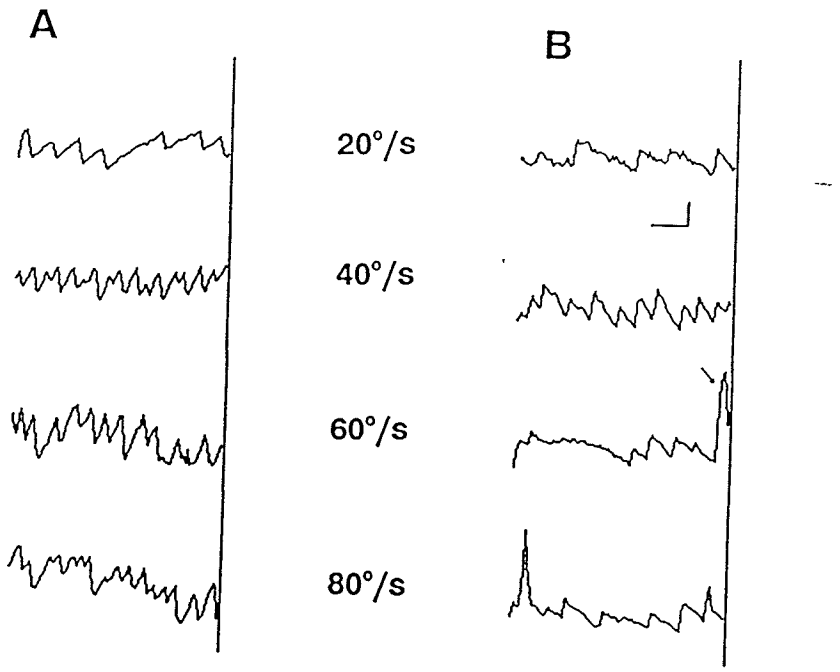


Figure 12. Examples of raw VOKN records obtained at stripe velocities of 20, 40, 60, and 80 deg/s, respectively. A. slow phase upward OKN; B: slow phase downward VOKN. The duration of each trace is 5 sec. Trace end at lights-out. The arrow indicates blink artifact. Calibration mark indicates 10 degrees and 1 sec.

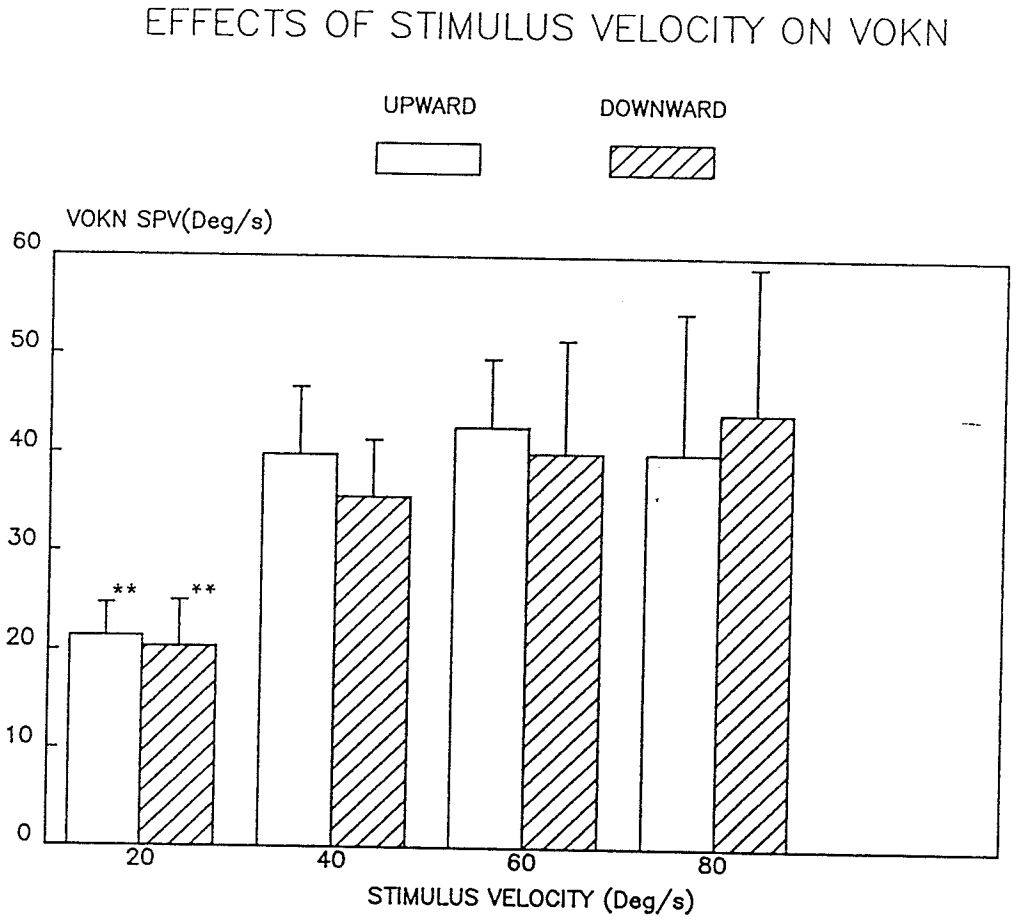


Figure 13. Values are represented as Mean ± SE of 11 subjects. Analysis was carried out to compare the SPV at the stimulation of 40 deg/s with other stimulus velocities. **p <0.01.

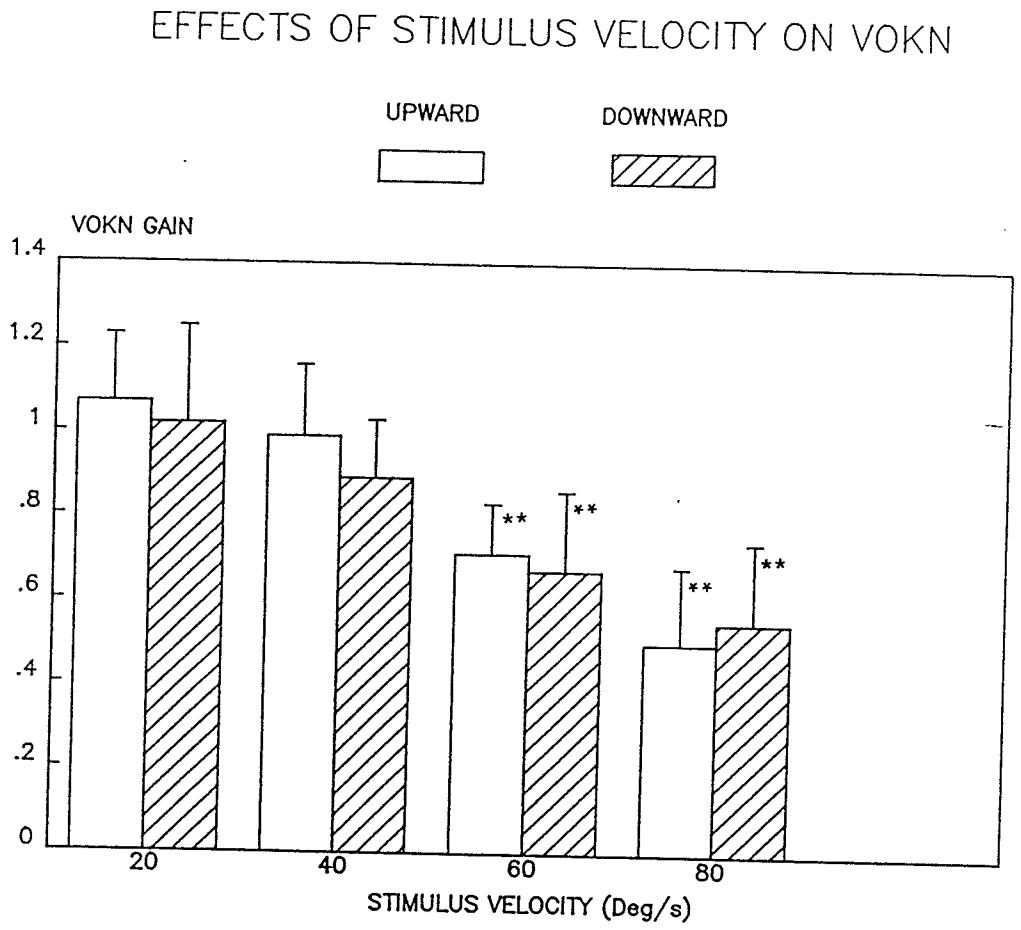


Figure 14. Values are represented as Mean ± SE of 11 subjects. Analysis was carried out to compare the gain at the stimulation of 40 deg/s with other stimulus velocities. **p <0.01.

deg/s, eye following speed did not increase compatibly. The variability of slow phase eye velocity among the subjects did, however, become increasingly large. Therefore, the effectiveness of VOKN following was saturated at 40 deg/s. In contrast, upward and downward gains were almost identical and unity gains were observed at 20 deg/s, which agrees with the findings reported by Calhoun et al. (139) and Collins et al. (119).

### 5.12 Effects of Stimulus Velocity on VOKAN

Figure 15 shows VOKAN decays for the four stimulus velocities. There was little VOKAN at 20 deg/s for both upward and downward stimuli, but VOKAN became stronger at stimulus velocities other than 20 deg/s. Statistical analysis, shown in figure 16, reveals a significant difference ($p < 0.05$) between 40 deg/s and 20 deg/s for both upward and downward VOKAN decay, whereas no difference was detected between 40 deg/s and 60 or 80 deg/s in either direction. Thus, the values of area under the decay curve indicate that velocity storage had saturated at 40 deg/s. A higher stimulus velocity did not produce significant changes of the values for either upward or downward VOKAN. All stimulus-downward decays were best fitted by the single exponential model, with mean short time constant being 1.6, 1.7, 0.7, and 0.6 s for stimulus at 20, 40, 60 and

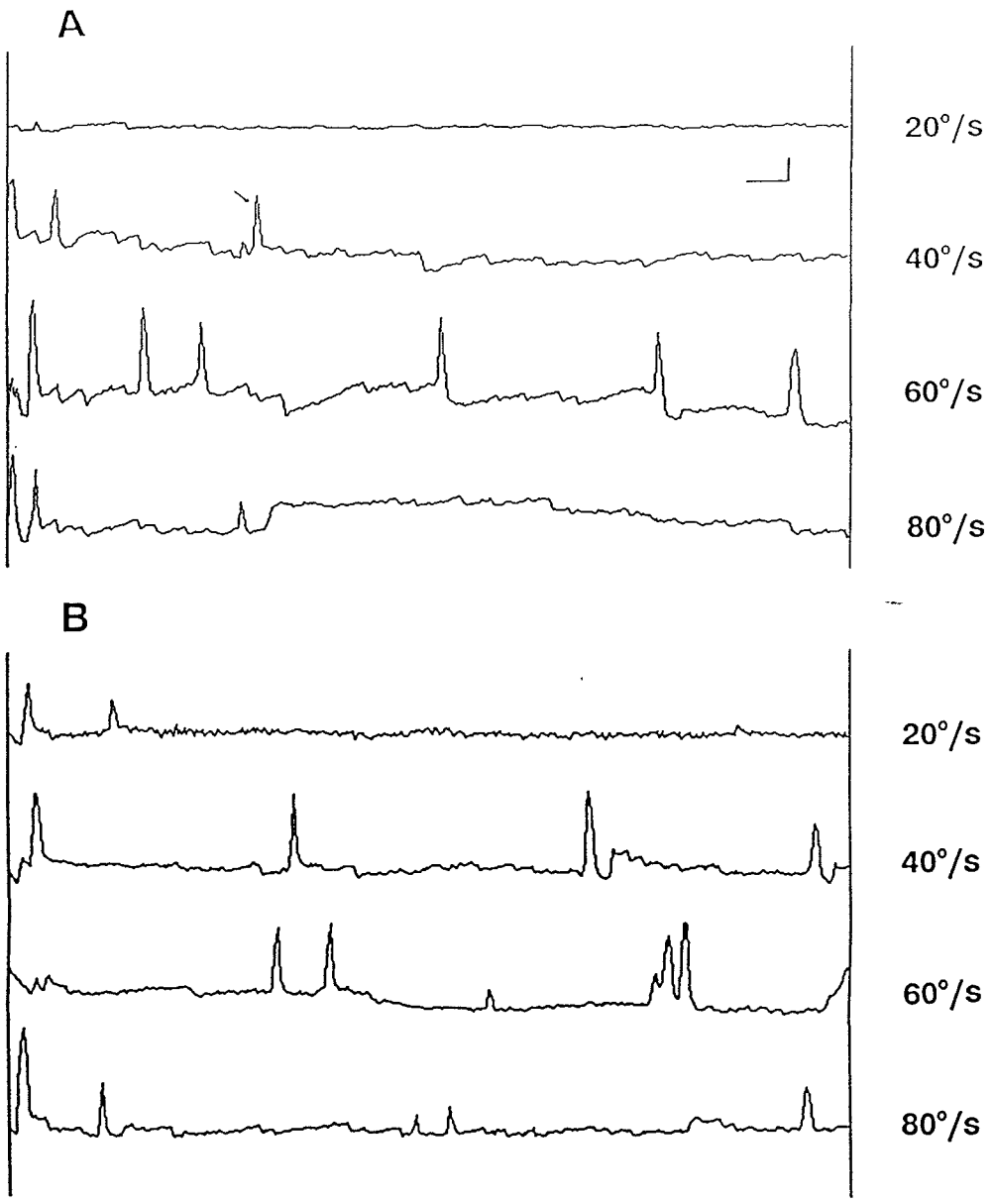


Figure 15. Examples of raw VOKAN records obtained in the dark after 60-sec stimulation at stripe velocities of 20, 40, 60 and 80 deg/s, respectively. The duration of each trace is 20 sec. Traces commence at lights-out. A: slow phase upward OKAN; B: slow phase downward VOKAN. The arrow indicates blink artifact. Calibration mark indicates 10 degree and 1 sec.

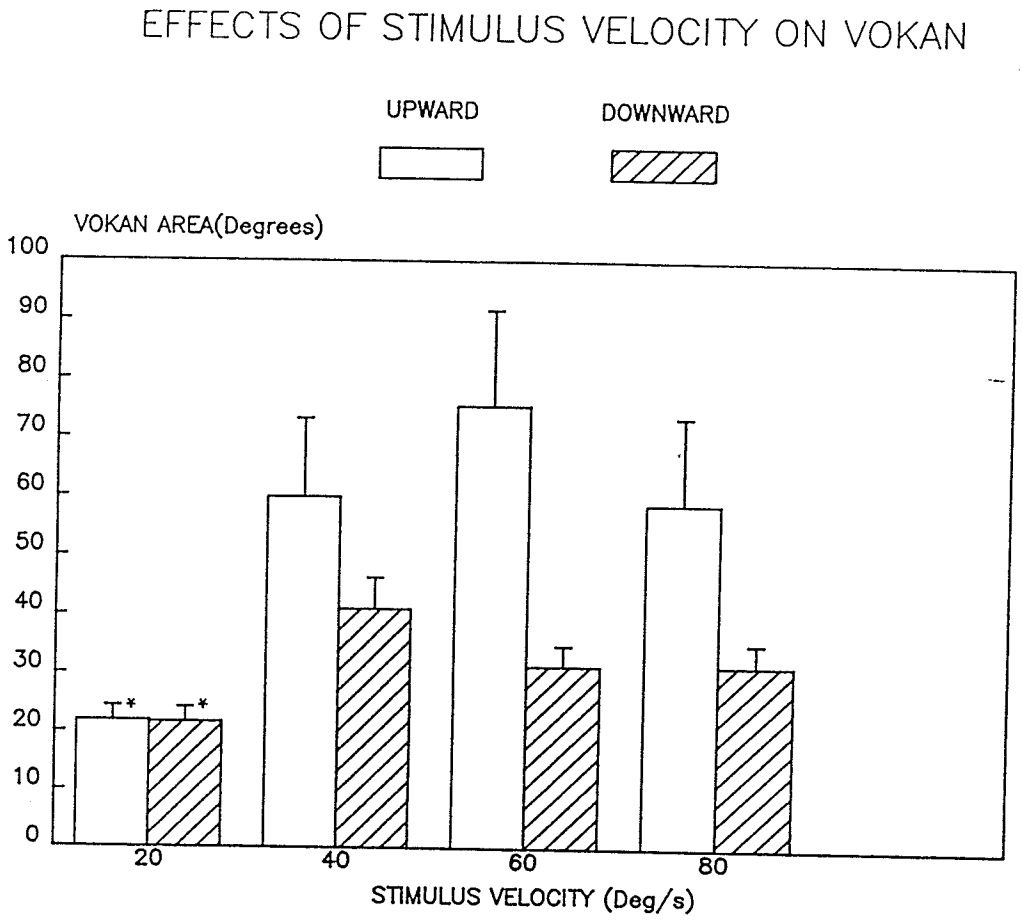


Figure 16. Values are represented as Mean ± SE of 11 subjects. Analysis was carried out to compare the VOKAN area at the stimulation of 40 deg/s with other stimulus velocities. *p <0.05.

80 deg/s, respectively. This suggests that the stimulus-downward after-response consisted only of a fast decay without a secondary slow decay. In contrast, upward stimulation of 40, 60 or 80 deg/s resulted in decays with time constants of 7s or longer in 5 subjects. The mean value of the short time constant was 1.0, 0.7 or 0.8 s, and that of the long time constant was 11, 15 or 9 s, for stimulation at 40, 60 or 80 deg/s, respectively. There is no significant difference between those time constant values from the statistics. Thus, it seems clear that vertical velocity storage was more activated during upward stimulation but not with downward stimulation.

## 5.2 VOKN and VOKAN, and Their Dependence Upon Head Orientation With Respect to Earth Gravity

### 5.21 VOKN Asymmetry

Values of the VOKN mean SPV with 40 deg/s stimulus in each of the two head positions are summarized in figure 17. When the subjects were in the upright position, there was a significant ($p < 0.05$) up/down difference, indicating stronger upward eye following than downward. In the 90° roll position, the p value was smaller ($p < 0.01$), indicating that there was a highly significant difference between upward and downward

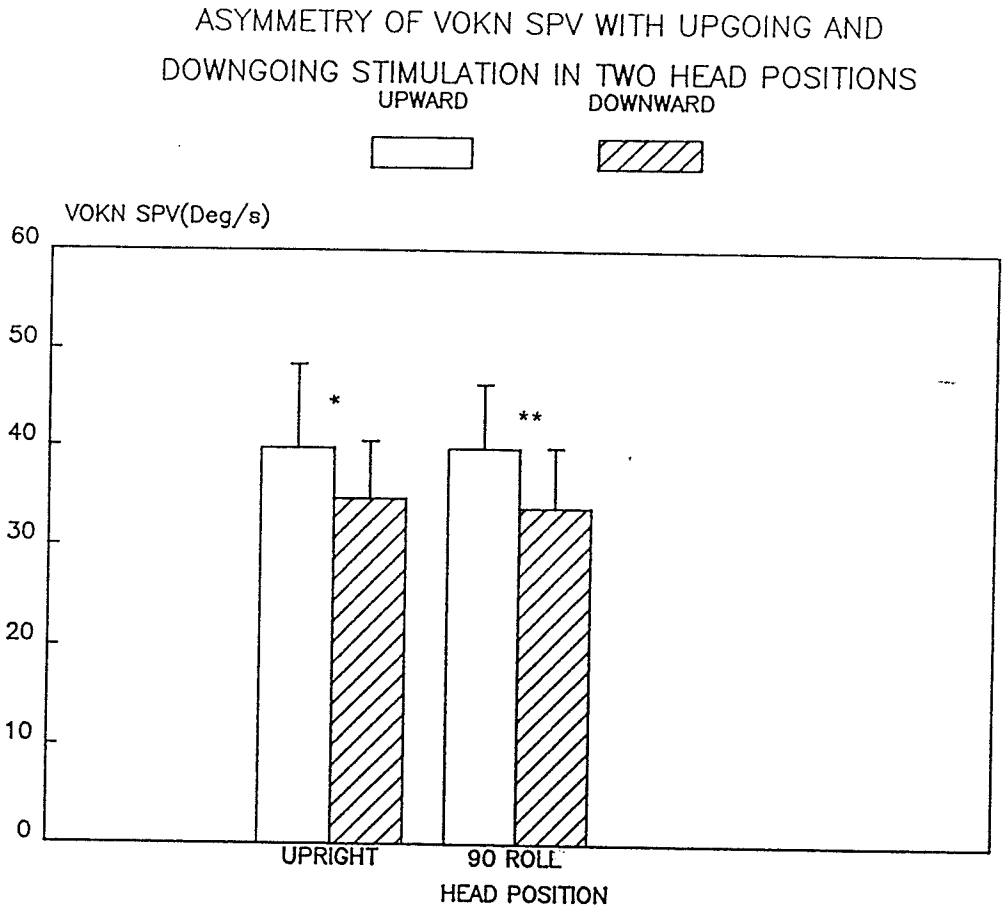


Figure 17. Values are represented as Mean ± SE of 18 subjects. Analysis was carried out to compare the asymmetry of VOKN SPV with upward and downward stimulation in two head positions. *p <0.05; **p <0.01.

eye following movements. On closer examination, the respective mean values for upward and downward SPV remained almost the same, but the variability (represented in SE) of values for upward SPV was reduced (from 8.6 to 6.6 deg/s) in the 90 degree roll position compared to that for the upright position, while the variability remained relatively unchanged for downward SPV in either position. Most of the subjects (12 out of 18) showed an up-greater-than-down asymmetry in both the upright and 90 degree roll positions; two subjects did not show clear asymmetry in either position. The other four subjects showed a down-greater-than-up asymmetry in the upright position. Two of these four also showed an up-greater-than-down asymmetry in 90 degree position. The other two remained the same as in the upright position.

### 5.22 VOKAN Decay

The area under the decay was the measurement parameter of interest since it has less variability and is a measurable response from most subjects (155,156). Figure 18 depicts the results from the examination of the VOKAN decay. In either head position, VOKAN was always significantly stronger for the upward stimulation than downward ($p < 0.05$ for upright,

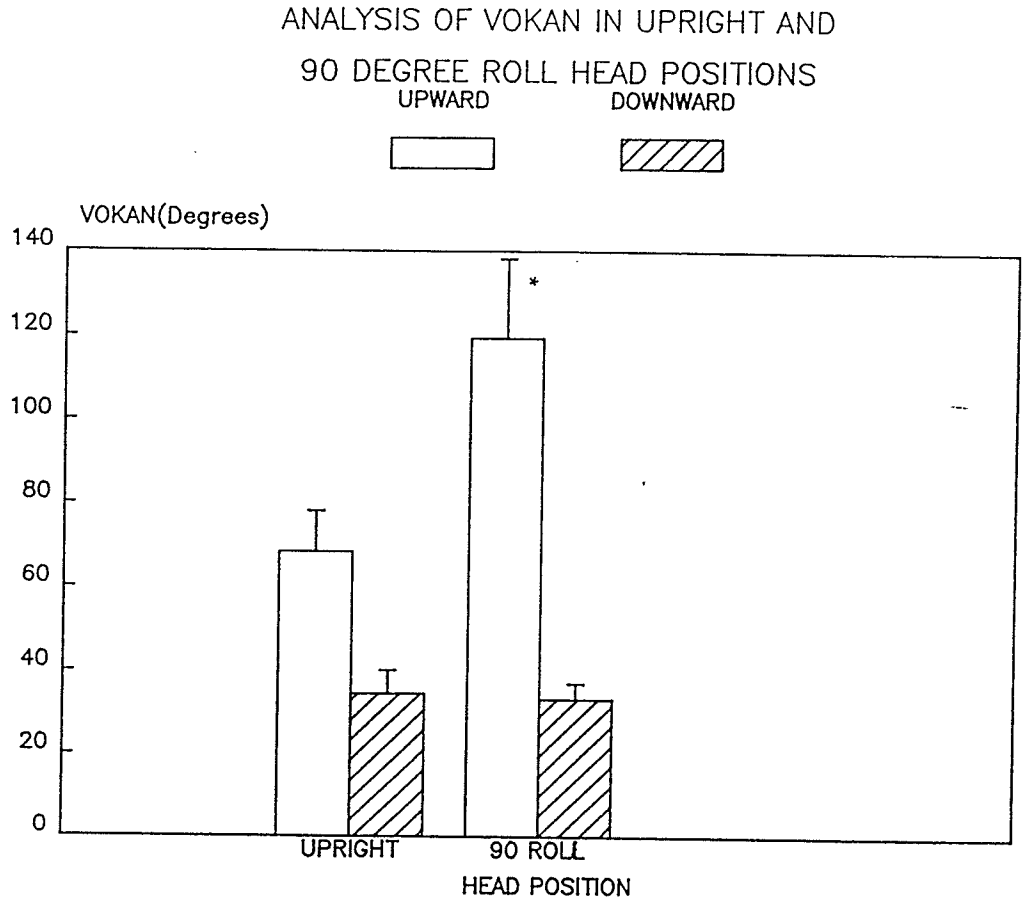


Figure 18. Values are represented as Mean ± SE of 18 subjects. Analysis was carried out to compare the VOKAN in two head positions, upward and downward respectively. *p <0.05.

$p < 0.01$ for 90 degree roll). The area value for upward VOKAN increased significantly as subjects changed from head upright to 90 degree roll, while the value for downward VOKAN remained almost the same in either head position. Figure 19 exhibits typical examples from one subject. Upward OKAN responses were generated in most of the subjects (15 out of 18 in upright, 16 out of 18 in 90 degree roll), while fewer downward OKAN responses occurred (6 out of 18 in upright, 10 out of 18 in 90 degree roll). In terms of the double exponential model (60), 8 cases fit this model best in the upright position, 10 cases in 90 degree roll position, only for upward OKAN. Compared to their horizontal counterpart, vertical eye movements have a higher degree of variation, and fewer subjects demonstrated double exponential decay. The long time constants (mean ± SE) of upward OKAN in the upright and 90 degree roll positions were 9 ± 1.7 s (N = 8) and 16 ± 2.5 s (N = 10) respectively. Downward OKAN, where measurable, could only be fitted with single exponential decay. The time constants of measurable downward OKAN in the upright and 90 degree roll positions were 1.3 ± 0.4 s (N = 6) and 0.8 ± 0.1 s (N = 10), respectively. The statistical analysis did not show a significant difference for these time constants because of large variability.

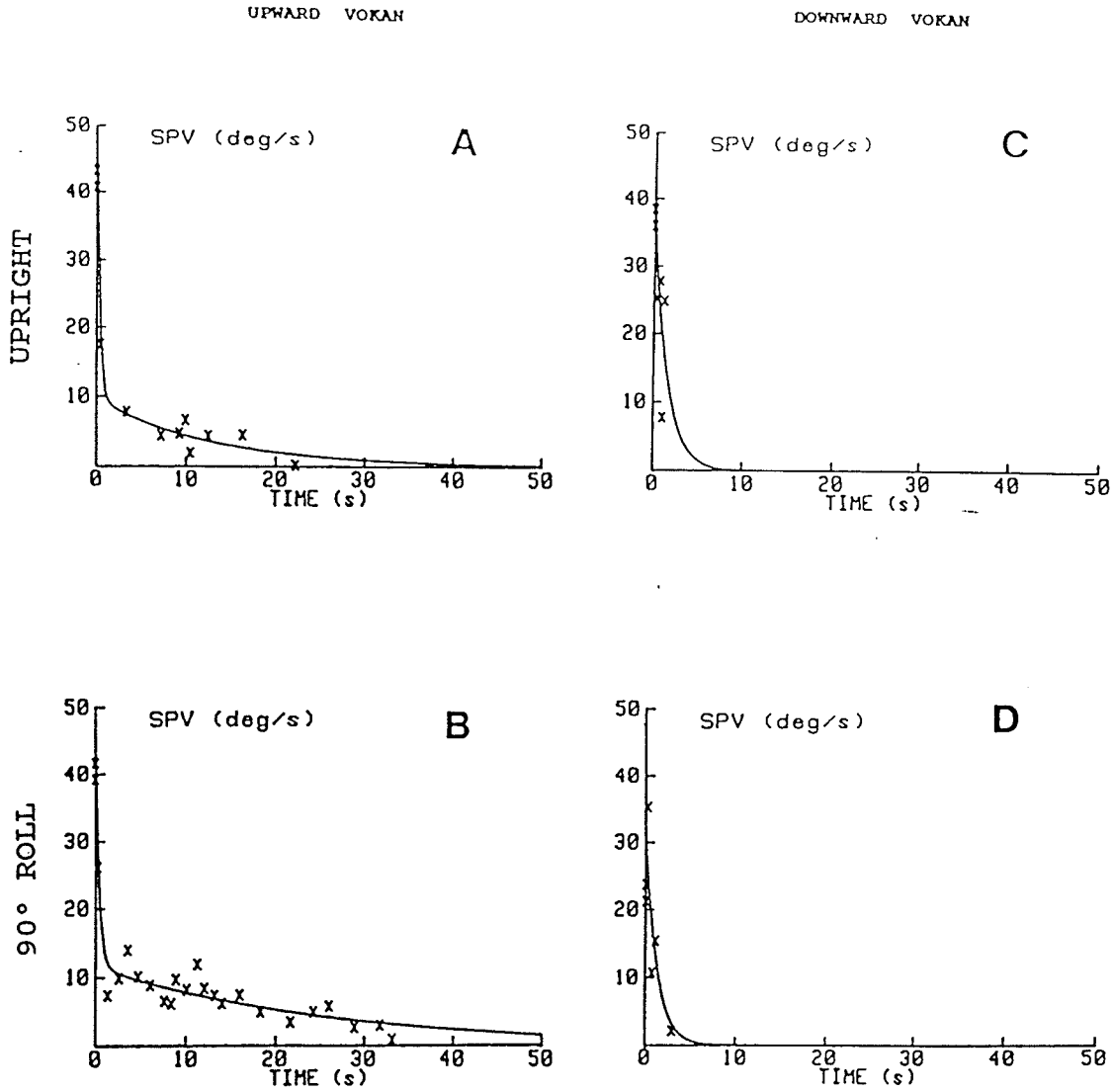


**Fig 19.** Regression curve fits for the VOKAN data from one subject following upward and downward stimulation. A and B show double exponential model decays; C and D show single exponential model decays. Head was upright in A and C, and in the 90° roll position in B and D.

### 5.23 Reversal of VOKAN

The direction of VOKAN is usually the same as its previous VOKN. However, similar to other reports (135,157), some of our subjects (4 out of 18) showed reversed VOKAN, i.e. VOKAN was in a direction opposite to that of the previous VOKN (inappropriate-directed VOKAN) without apparent appropriate-directed component. Following downward stimuli, two of those four showed upward VOKAN only in the head upright position, one other in 90° roll position, and the fourth showed reversed upward VOKAN in both head positions. Generally, the reversed VOKAN was weak in intensity. One subject showed a few clear beats (see figure 20). Following upward stimulation, three of those had appropriately directed upward VOKAN, but the other one did not show appropriate VOKAN.

### 5.24 Cross-coupling

Two of 18 subjects tested on the ground showed discernible cross-coupling from the horizontal to the vertical mode, i.e., from the yaw to pitch axis, following horizontal OK stimulation in one direction when the subjects were in 90° roll position (see figure 21). Absence of a vertical eye movement component in the first five seconds of OKN rules out the possibility of cross-talk. These two subjects exhibited


Fig 20. An example of the reversal of VOKAN in one subject after downward stimulation with the head in the upright position. The VOKN trace shows the first 5 s after lights on and the last 5 s before lights out. The lights out point was at the end of the upper tracing, and the lower tracing is continuous with it. Duration of VOKAN tracing is 20 s after lights out.

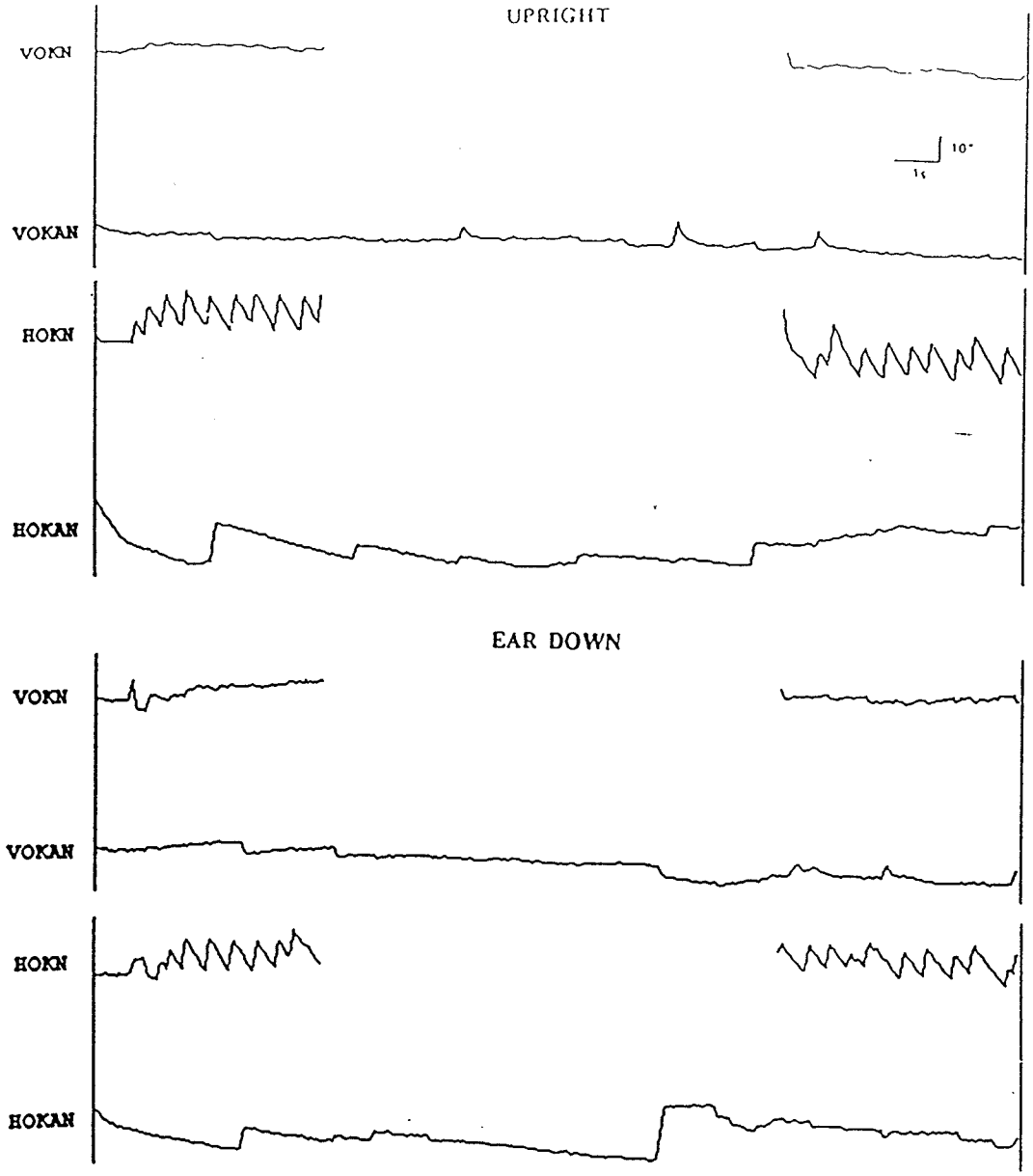


Fig 21. An example of cross-coupling, which appeared after horizontal stimulation leftward in the 90° roll position but not with head upright. The reduced HOKAN strength in the 90° roll position should also be noted. Duration of VOKN or HOKN traces is 5 s at the beginning of lights on and 5 s before lights out. Duration of VOKAN and HOKAN traces is 20 s after lights out.

cross-coupling following the horizontal OK stimulation in only one direction: leftward for one subject resulting in an upward component and rightward for the other resulting in a downward component. It seems that the cross-coupling started shortly before lights out since some VOKN components, though very weak, emerged before the horizontal OK stimulus was removed. No cross-coupling appeared following stimulation in the other direction. No recognizable cross-coupling occurred in other subjects following horizontal (the yaw axis) OK stimulation in either direction. Also, there was no cross-coupling from pitch to yaw axis following vertical stimulation in any head position.

### 5.25 HOKN and HOKAN

Mean values of area under the HOKAN decay curve decreased significantly from upright to 90° roll positions (see figure 22). HOKN remained the same in either head position. No statistical difference was found for other parameters between the two different head positions.

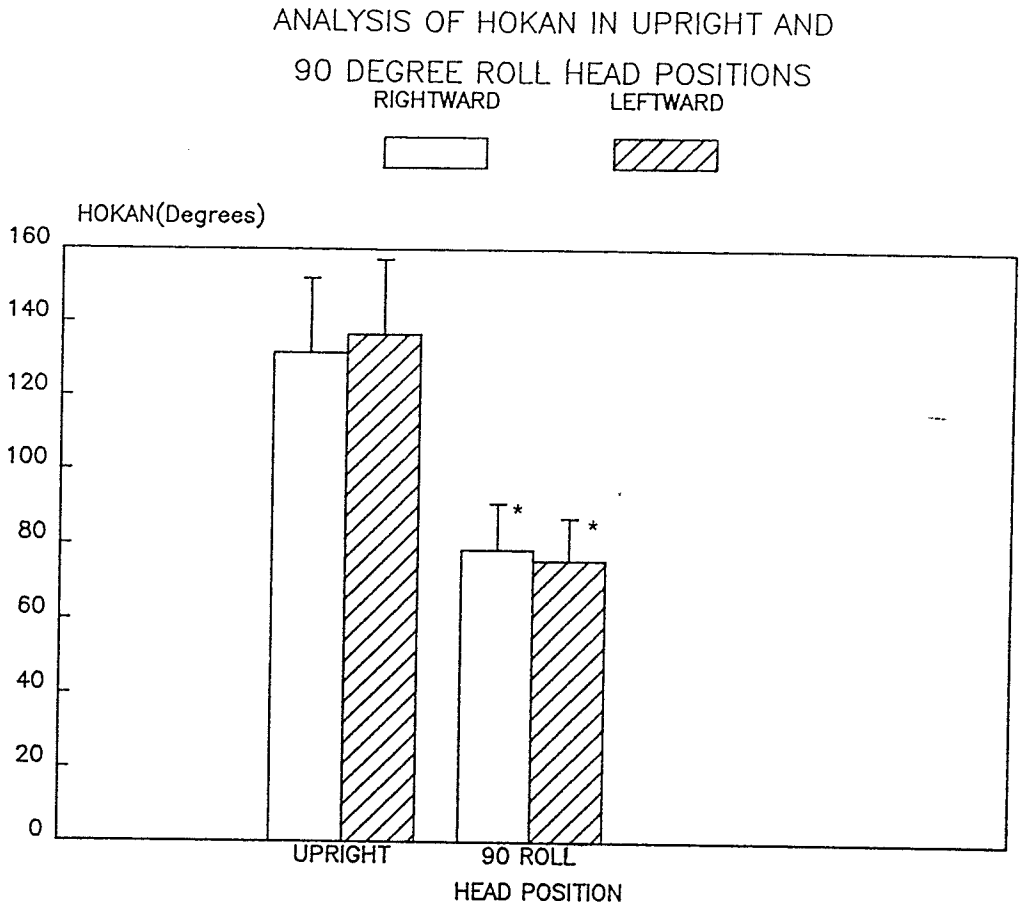


Figure 22. Values are represented as Mean ± SE of 18 subjects. Analysis was carried out to compare the HOKAN in two head positions, upright and ear-down respectively. *p <0.05.

## 5.3 VOKN and VOKAN During the Parabolic Flight

### 5.31 EOG Data

#### 5.311 VOKN During the Parabolic Flight

Mean values of upward and downward VOKN SPV in 1 G vs micro-G and hyper-G are depicted in figure 23. There was no significant difference for upward VOKN, while there was significant difference ($p < 0.01$) for downward VOKN. This indicates that downward VOKN was enhanced in micro-G and hyper-G. On the ground, there was stronger upward SPV than downward. However, in both micro- and hyper-G during parabolic flight, the downward VOKN SPV increased significantly while that of upward VOKN SPV remained approximately the same as on the ground.

#### 5.312 VOKAN During the Parabolic Flight

The results are shown in figure 24. The VOKAN quantity was measured by the area under the exponential decay curve. Basically, as compared to VOKN, VOKAN in both micro- and hyper-G levels showed the same modification profile against 1-G condition. The result indicates that velocity storage for

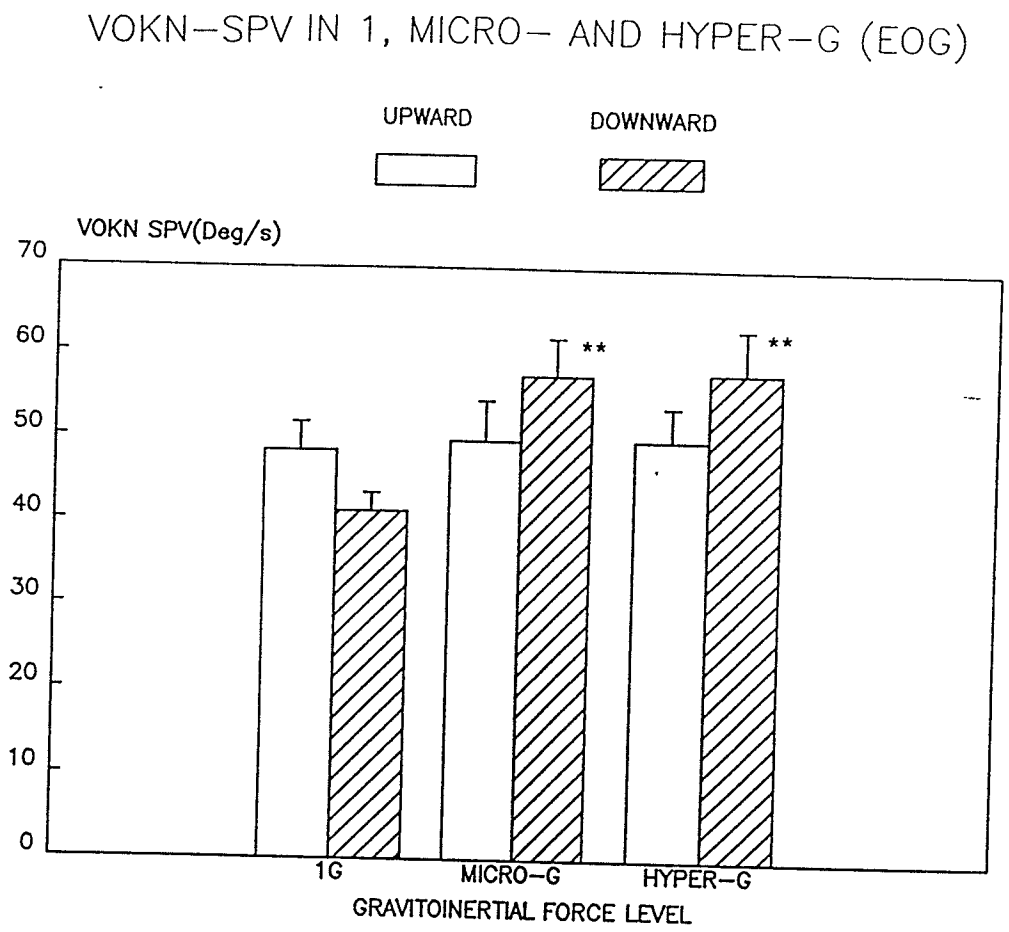


Figure 23. Values are represented as Mean ± SE of 14 subjects. Analysis was carried out to compare the VOKN in different gravitoinertial levels, upward and downward respectively.
**p <0.01.

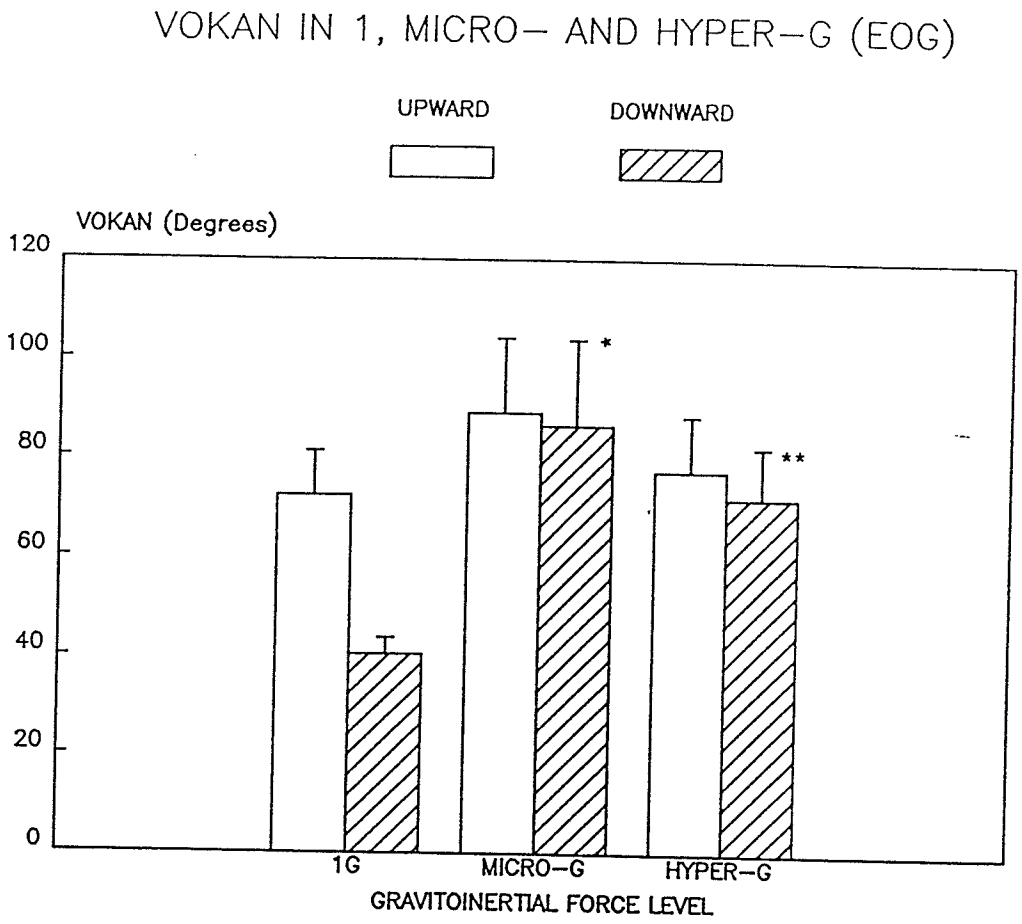


Figure 24. Values are represented as Mean ± SE of 14 subjects. Analysis was carried out to compare the VOKAN in different gravitoinertial levels, upward and downward respectively. (*p <0.05 in the comparison of downward VOKAN in micro-G with downward VOKAN in 1 G; **p <0.01 in the comparison of downward VOKAN in hyper-G with downward VOKAN in 1-G)

downward OKAN was enhanced in either micro- or hyper-G, which brought about the prolongation of the corresponding VOKAN decay, as compared to that on ground (see figure 25). Short time constants were between 1.1 - 1.4 sec for all conditions and there was no statistical difference among them. The long time constants of upward OKAN were 11 sec in 1 G (N = 9), 7 sec in micro-G (N = 7) and 9 sec in hyper-G (N = 6). For downward OKAN, a few subjects displayed long time constants of 11 sec (N = 2) in micro-G and 4 sec (N = 2) in hyper-G.

### 5.313 Reversal of VOKAN During the Parabolic Flight

It seems that there were more occurrences of VOKAN reversal in non-1 G conditions than on the ground. Six of 14 subjects showed reversed VOKAN, i.e. VOKAN was in a direction opposite to that of the previous VOKN, at least once in either micro- or hyper-G. Following downward stimuli, five of these subjects demonstrated upward VOKAN in either micro- or hyper-G; one of these five also showed downward VOKAN after an upward stimulus in micro-G. The last subject only demonstrated downward OKAN after the upward stimuli in micro- and hyper-G.

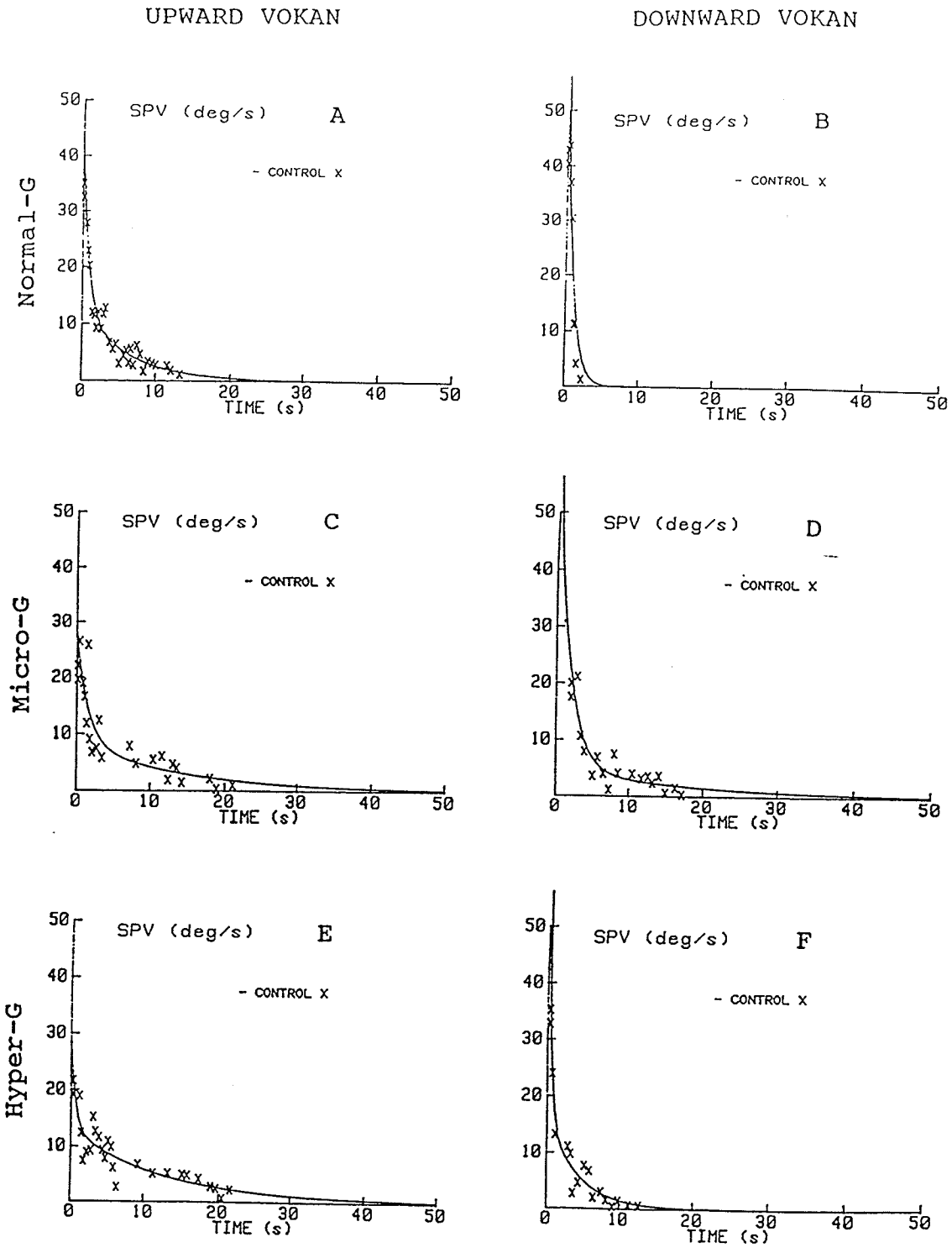


Figure 25. An example of regression curve fits for the VOKAN following upward and downward OK stimulation at three different gravitational levels. Note areas under the regression curves for downward VOKAN increased at micro- and hyper-G, while those for upward VOKAN remained virtually unchanged.

## 5.32 ISCAN Data

### 5.321 VOKN During Parabolic Flight

Mean values of upward and downward VOKN SPV in 1 G vs micro-G and hyper-G are depicted in figure 26. Basically, those ISCAN data demonstrate the same pattern of changes as EOG data in terms of VOKN SPV in different G levels, except that the gains of EOG data were higher than that of ISCAN. ISCAN data seems more realistic since the amplitude of the values, i.e. gains are reasonable. Nevertheless, the discrepancy between the absolute values obtained from the two systems did not interfere with the significance derived from this study, because our interest was to compare the responses between three different gravitoinertial force levels.

### 5.322 VOKAN During the Parabolic Flight

Results are shown in figure 27. As in VOKN data, the ISCAN data demonstrated the same profile of changes as EOG data in terms of VOKAN decay at different G levels. Thus, the implications are the same, i.e. the velocity storage mechanism for downward OKAN was enhanced in micro- and hyper-G, which brought about the stronger of VOKAN decay (see figures 28, 29 and 30). Short time constants were between 0.8 - 1.2 sec for

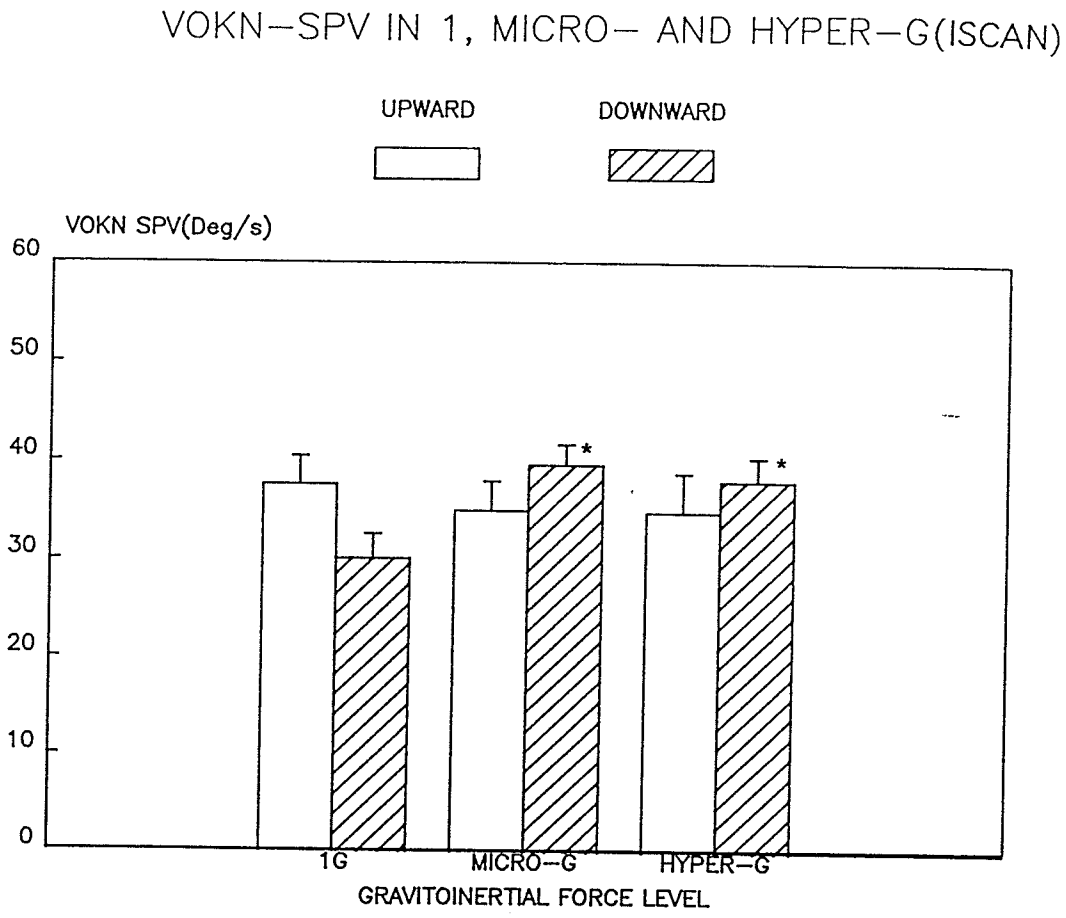


Figure 26. Values are represented as Mean ± SE of 14 subjects. Analysis was carried out to compare the VOKN in different gravitoinertial levels, upward and downward respectively.
*p <0.05.

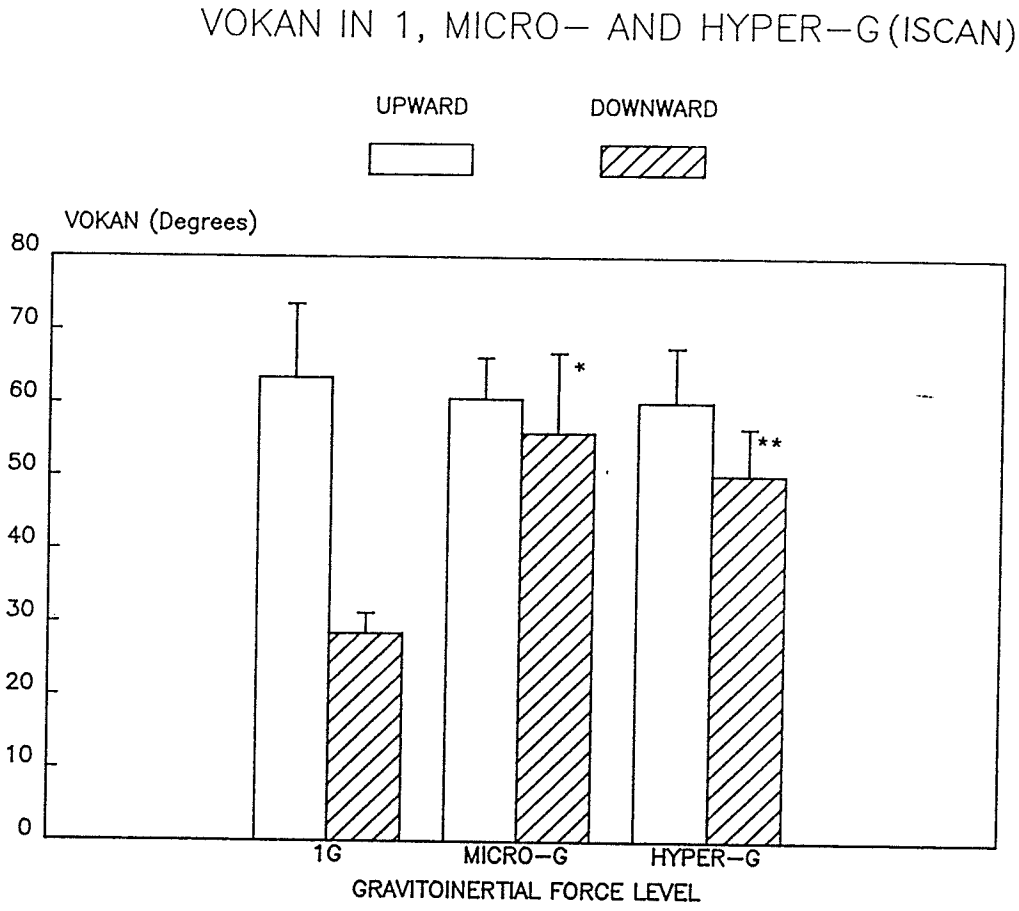


Figure 27. Values are represented as Mean ± SE of 14 subjects. Analysis was carried out to compare the VOKAN in different gravitoinertial levels, upward and downward respectively.
*p <0.05; **p <0.01.

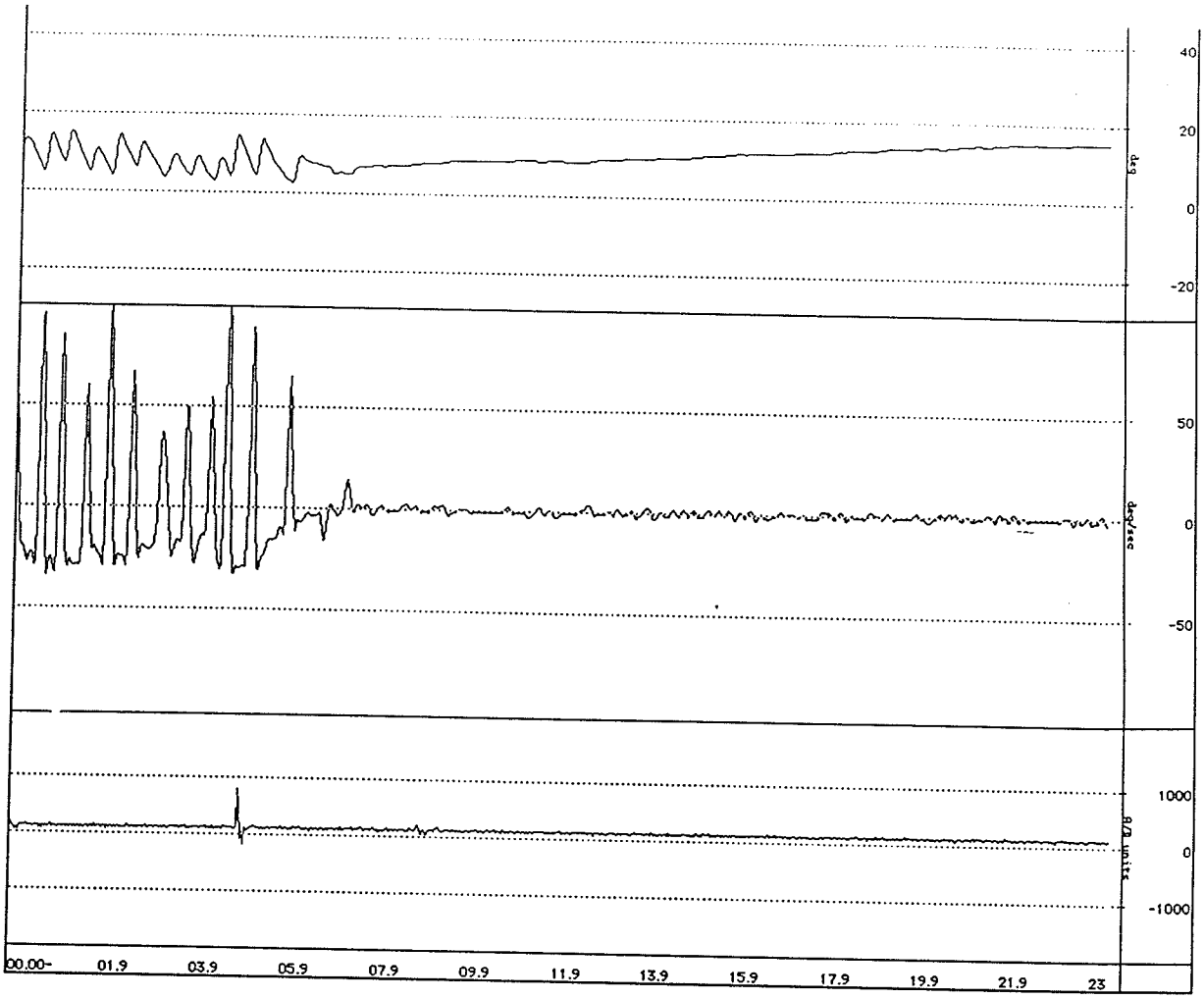


Figure 28. Downward VOKN/VOKAN on ground recorded by ISCAN with the subject upright. The traces in this and subsequent two figures are, from top to bottom, eye position, eye velocity and the status of illumination (the impulse indicates lights-out point). Time scale is in seconds.

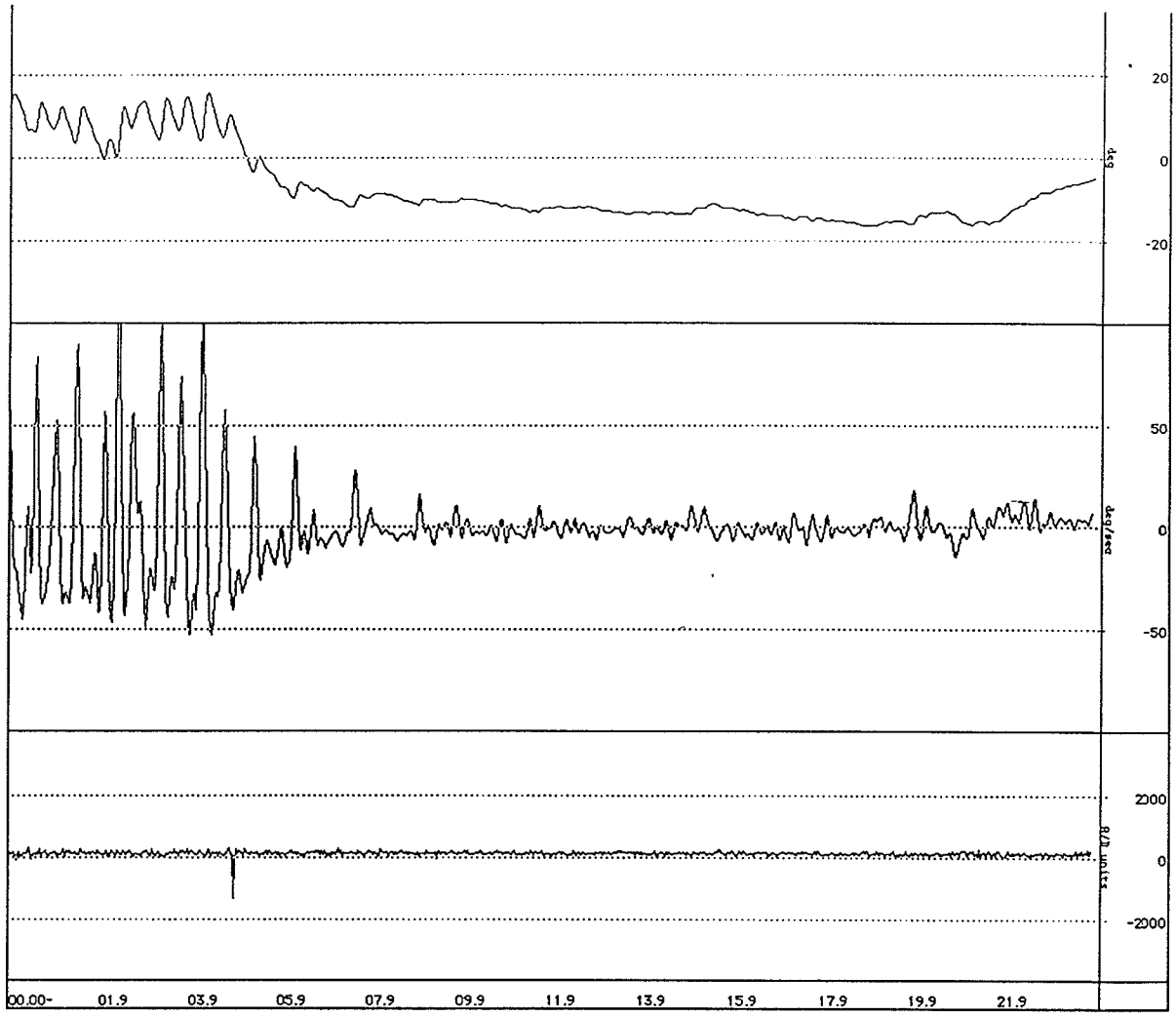


Figure 29. Downward VOKN/VOKAN in the micro-G phase were stronger than on ground.

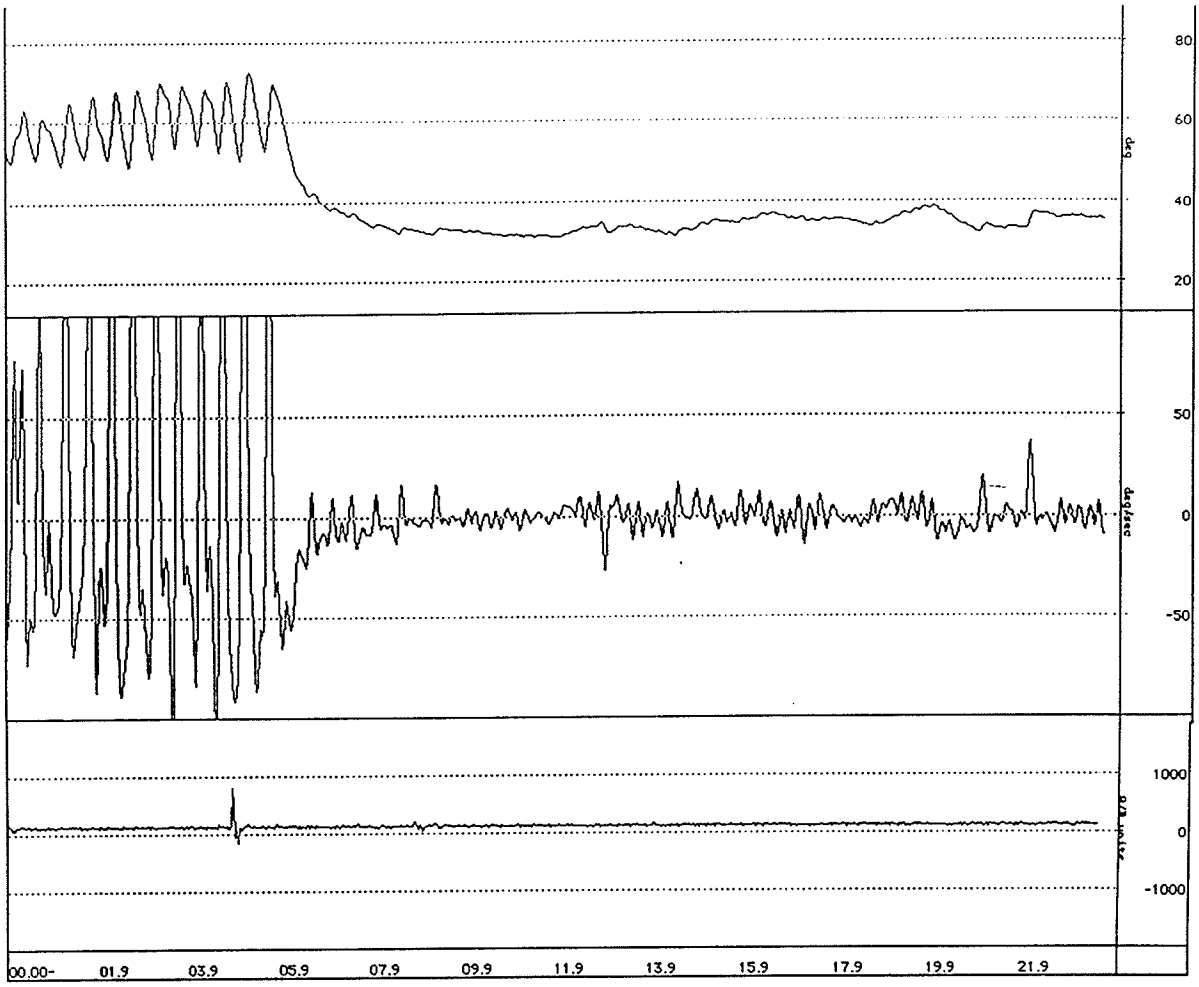


Figure 30. Downward VOKN/VOKAN in the hyper-G phase were stronger than on ground.

all conditions and there was no statistical difference among them. The long time constants of upward OKAN were 12 sec in 1 G (N = 10), 13 sec in micro-G (N = 8) and 11 sec in hyper-G (N = 7). For downward OKAN, there was no long component decay in 1 G while a few subjects displayed the long time constants of 16 sec (N = 5) in micro- and 6 sec (N = 3) in hyper-G.

### 5.323 Reversal of VOKAN During the Parabolic Flight

There was a higher occurrence of VOKAN reversal recorded with ISCAN system. Ten of 14 subjects demonstrated reversed VOKAN at least once in one trial either in micro- or hyper-G, not necessarily in every trial. Intensity of the reversal was usually in the range of 2 - 5 deg/s and it died away in a few seconds, which is similar to that on the ground. Following the downward stimuli, eight of these subjects demonstrated upward OKAN in either micro- or hyper-G; two of these eight also showed downward OKAN after an upward stimulus in micro- and hyper-G. The other two only demonstrated downward OKAN after the upward stimuli in micro- or hyper-G.

### 5.324 Gaze Shift in Micro- and Hyper-G

ISCAN has several advantages over EOG. One of those is that ISCAN does not have drifting artifacts as EOG may have due to drifts from the amplifier and electrode contact potentials. Therefore, it can be seen if there are real gaze shifts of the eyes. During parabolic flights, as reported by Clement et al. (142), there were gaze shifts dependent upon G levels. For example, gaze shifted downwards during transition from hypergravity to microgravity and vice versa during transition from microgravity to hypergravity. As shown in figure 31, the eye position was lower during micro-G period. After about 20 sec, when the transition from micro-G to hyper-G took place, the eye position was moving up to a higher level. Vice versa to the transition from hyper-G to micro-G. The magnitude of the transition was in the range of about 8 - 10 degrees per G.

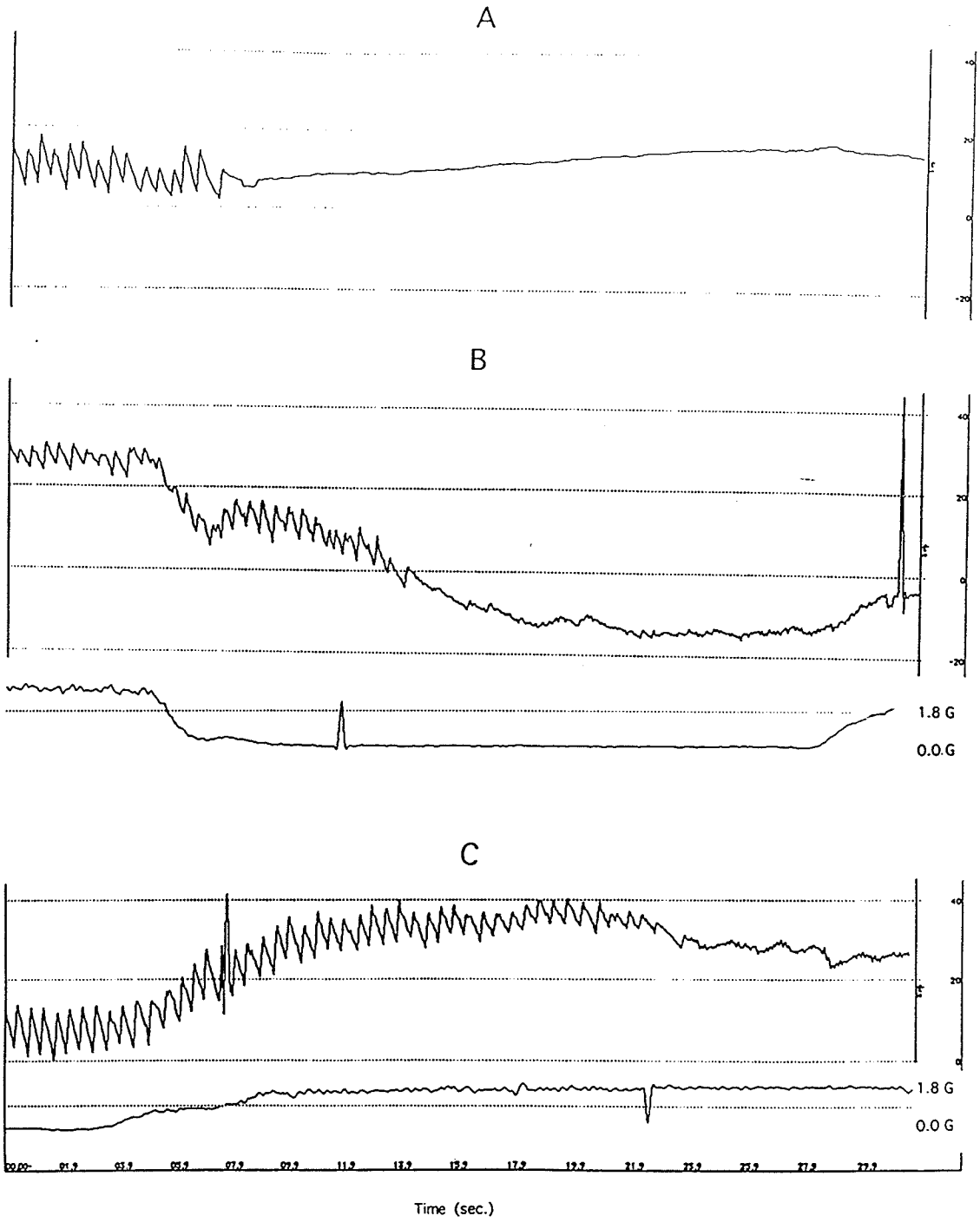


Figure 31. An example of gaze shifts dependent upon G levels.
A. No gaze shift on ground; B. Gaze shifted downwards during transition from hyper-G to micro-G; C. Vice versa during transition from micro-G to hyper-G.

# CHAPTER 6

# DISCUSSION

## 6.1 Stimulus Velocity Dependence of VOKN and VOKAN

In this study, vertical OKN and OKAN are shown to be dependent upon stimulus velocity. The relationship between the optokinetic responses and stimulus velocities tells us that an appropriate stimulus is necessary to generate reliable VOKN and VOKAN responses. Many factors, such as pattern shape, visual field, spatial frequency, contrast, duration etc, determine OK stimulus features. One of the most important factors is stimulus velocity (3,80,135,136,158).

Results reported by Clément and colleagues (3) showed that, in Earth orbit flight, OKN gain did not change significantly for a pattern velocity of 20 deg/s. By contrast, at 50 deg/s, the vertical and horizontal gains were changed upon first exposure to microgravity. Another example is from the reports of Calhoun and colleagues (139) and LeLiever and colleagues (135). They found that, at higher stimulus velocities (40, 50, 60 and 70 deg/s), more subjects displayed an up/down asymmetry. A study by Mizukoshi and colleagues (158) showed that horizontal OKN SPV decreased at stimulus velocities exceeding 60 deg/s. Nevertheless, using stimuli of 0-200 deg/s with 1 deg/s$^2$, Takahashi and colleagues (136) showed that horizontal OKN SPV saturated at velocities up to

120 deg/s.

Although different stimulus velocity profiles were applied, the difference in responsiveness between the maximal velocities in the above reports probably is also due, in part, to the spatial frequency difference. According to Holm-Jensen and Peitersen (159), a synchronous response (SPV gain close to unity) could be obtained at the target frequency below 3.0 Hz. Mizukoshi and colleagues (158) used a stimulus velocity of 60 deg/s with a target frequency close to 3.0 Hz, whereas in a study by Takahashi and colleagues (136), higher velocities were required to reach 3.0 Hz because their OK stimulus consisted only of 12 stripes/360 degrees.

As for human vertical eye movements, Takahashi and colleagues (136), using stimuli of 0-200 deg/s with 1 deg/s$^2$ of constant angular acceleration, showed that OKN SPV reached a maximum level at 70 deg/s with higher upward eye speed than downward (around 50 deg/s for upward; 40 deg/s for downward). Comparably, exposed to the same stimuli, monkeys could reach a maximum at 120 deg/s stimulus and displayed larger up/down asymmetry with an SPV around 65 deg/s for upward following and an SPV of less than 40 deg/s for downward following (115).

Our stimulation target frequency, at 20, 40, 60, or 80 deg/s, was 1.0, 2.0, 3.0, or 4.0 Hz, respectively. The stimulus velocity dependence of horizontal OKN/OKAN had previously been studied in our laboratory (80) where the same stripe spacing was used as in the present VOKN and VOKAN

study. The horizontal stimulus velocities were 10, 20, 30, 40, 60 and 70 deg/s, and the evoked horizontal OKN was saturated at 60 deg/s with SPV reaching 53.7 deg/s.

In the present study, vertical OKN-SPV and gains reached maximum at a stimulus velocity of 40 deg/s with decreased gains at 60 deg/s or 80 deg/s. A maximal asymmetry, upward greater than downward, among different stimulus velocities was also shown. This agrees with the results reported by LeLiever and Correia (135), where VOKN had the highest gain at 40 deg/s. The fact that vertical OKN saturated at a lower stimulus velocity and had lower maximal eye following speed compared to its horizontal counterpart, indicates that vertical optokinetic following ability is not as vigorous as horizontal, and also, it shows an up/down asymmetry, which agrees with findings in studies on monkeys (113,115). This asymmetry of VOKN SPV gains was greatest at 40 deg/s, and became much smaller at 60 deg/s and 80 deg/s. This was probably due to the poor following of moving stripes at high speeds, because the gains at 60 and 80 deg/s were significantly lower than at 40 deg/s. VOKN generally had larger variations among subjects and became progressively worse with reduced gains as stimulus velocities increased, a finding which is similar to results obtained by other authors (96,136,137).

It seems paradoxical that increased stimulus velocity beyond 40 deg/s results in reduced VOKN gain and substantially

the same level of OKAN, while retinal slip, i.e. stimulus velocity minus SPV, is increasing, since it is believed that OKN and the velocity storage are driven by retinal slip. However, processing of retinal slip information in the pretectal nuclei is non-linear, i.e. the neuron activity increases with retinal slip velocity in a certain range; beyond that point, the neural discharge actually decreases (10,24,160). A study by Fletcher and colleagues (76) addressed this non-linearity in human optokinetic responses. They found that HOKN and HOKAN were maximum at drum velocities of 100-150 deg/s, and for higher stimulus velocities up to 220 deg/s, HOKN and HOKAN fell or reached a plateau. Regarding VOKN, two studies have shown that, with random-dot stimulation, VOKN gain decreased progressively when the stimulus velocity increased from about 10 to 70 deg/s (96,137). In our case, the gain decreased progressively and VOKAN area remained almost the same at stimulus velocities above 40 deg/s, even though retinal slip increased, indicating that the vertical retinal slip is less effective in driving the eyes at a stimulus velocity above 40 deg/s.

Our results show that the vertical velocity storage was saturated at a stimulus velocity of 40 deg/s. Like VOKN, human VOKAN also has a much lower saturation level than in the monkey, which saturates at about 100 deg/s (113). The strength of VOKAN, as represented by the values of area under the regression curve, was significantly lower at 20 deg/s. In

contrast, it did not increase significantly as stimulus velocity increased from 40 to 80 deg/s. In comparison, the previous study in our laboratory on horizontal OKAN showed that there was a significant difference between stimulus velocities of 10-30 deg/s and 40-70 deg/s for OKAN cumulative displacement, with no statistical difference from 10-30 deg/s or 40-70 deg/s (80). At 20 deg/s which, presumably, activated mainly pursuit mechanisms, OKN SPV, its gain and area under the VOKAN decay curves for both up and down directions were actually the same and also significantly lower than at other stimulus velocities. This indicates that little velocity storage was involved and pursuit was predominant for this behaviour.

In vertical smooth pursuit dynamic studies, using multiple sinusoidal frequency stimuli, it was shown that there was no consistent up or down pursuit preponderance (161,162). Other vertical eye movement studies also provide further evidence that no distinct up/down asymmetry was observed at stimulus velocity below 30 deg/s (96,137). Some horizontal eye movement investigations may also lend support to this conclusion. Horizontal smooth pursuit in the human reached maximal accuracy at about 30 deg/s (163-165). Higher speed stimuli probably produced weaker pursuit and stronger OK involvement (80,166). For example, a 50 deg/s "smooth pursuit" stimulus actually generated the same time constant as OKAN decay in a study by Muratore and Zee (167). This would

indicate that their pursuit target velocity of 50 deg/s did not represent an absolutely pure pursuit stimulus and it introduced more OK storage than pursuit storage. Therefore, low-velocity stimulation, as 20 deg/s in the present experiment, could have produced mainly the pursuit effect, whereas the optokinetic system and its velocity storage were significantly activated by stimulation in the higher velocity range, 40-80 deg/s.

Therefore, it may be proposed that, analogous to their horizontal counterpart, there are two separate mechanisms involved in vertical following eye movements: one predominant in the low stimulus velocity range, presumably pursuit mediated, and the other activated nonlinearly in only a higher stimulus velocity range, presumably mediated by the optokinetic system. However, the difference from their horizontal counterpart is that there is an independent vertical eye movement mechanism in the brain stem (168), a lesion of which causes major defects of upward slow phase OKN/OKAN with only little influence on downward OKN/OKAN and intact horizontal eye movements (169). Therefore, it is suggested that the human vertical velocity storage mechanism, which is only activated at higher stimulus velocities, contributes mainly to upward following eye movements with much less effect on downward following eye movements, thereby producing an up/down asymmetry. The findings from monkey studies support this concept (113,114,117).

## 6.2 Asymmetry of VOKN/VOKAN and Its Dependence Upon Head Orientation With Respect to Gravity on Earth

Unlike HOKN and HOKAN in man, which have been extensively investigated (59,111,112,154,170), human VOKN/VOKAN appear to have some peculiarities. Information about the characteristics of, and the mechanisms underlying human VOKN and VOKAN is lacking or inconsistent, although there are scattered reports concerning various aspects of vertical eye movements (3,96,135,137,139,171). Animal studies have shown some fairly consistent evidence of up/down asymmetry of VOKN and/or VOKAN, i.e. stronger upward component than downward (2,115,116). Moreover, this asymmetry has been shown to be modified by different head positions, presumably a consequence of otolith organ stimulation (2). There is also a graded increase in the strength and duration of upward VOKAN as monkeys are tilted away from the spatial vertical. Thus, upward VOKN and VOKAN are maximal around the pitch axis when it is aligned with gravity (2). It has been proposed that a storage mechanism is utilized in generating stronger upward OKN and that the observed asymmetry in vertical nystagmus reflects an asymmetrical storage capability for eye movements in the upward and downward directions (2).

In the present study, subjects were tested in each of two

different head positions: upright and 90° roll. As seen in animals, a significant asymmetry ($p < 0.05$) between upward and downward VOKN, i.e. upward SPV > downward SPV, was found in humans. When the subjects were in the 90° roll position, the asymmetry became more obvious ($p < 0.01$). Statistically, the absolute values of both upward and downward SPV remained almost the same either in the upright or 90° roll position. However, from figure 17, we can see that variability of the upward SPV became smaller in 90° roll position (6.6 deg/s) than in the upright position (8.6 deg/s). Thus, in 90° roll position, the asymmetry was more consistent and prominent between upward and downward VOKN.

The vertical OKAN, represented in this study by area under the regression curve, showed the same changing profile as VOKN. For the upward OKAN decay, there was a significant difference for areas ($p < 0.05$) between the upright and 90° roll positions, i.e. when the subjects changed their head position from upright to 90° roll, the area value increased prominently. In contrast, the change of head position had little influence on downward OKAN, i.e. the mean area value remained almost the same in both head positions although more subjects showed measurable downward OKAN from upright to 90° roll positions (see figures 18 and 19). This phenomenon reflects the asymmetric feature of the vertical dimension of the velocity storage mechanism and gravity vector effect on it by way of otolith organ activity. The underlying mechanism

seems to be that the velocity storage integrator acts more efficiently when the SPV in pitch is directed around the axis of the spatial vertical. It, then, contributes more to the upward eye movement component to help stabilize upward SPV, hence, less variability. This is supported by studies on monkeys (2,173). For the same mechanism, our result shows that the values of area under the decay curve for horizontal OKAN, which reflects velocity storage for horizontal SPV, decreased significantly from head upright to 90° roll positions due to the change of eye movement axis with respect to the gravity axis.

In this experiment, the subjects were receiving identical optokinetic stimuli in different head positions. Clearly, the only variable was the change of head position with respect to gravity. The otolith organ is a primary receptor of the gravitational and linear acceleration (174). The response of otolith neurons to static tilts, at least in the squirrel monkey, is such that the sacculus is most sensitive to roll tilt and the utriculus most sensitive to pitch tilt (125). Different neurons in cat vestibular nucleus receiving sensory input from the vestibular labyrinth have also been shown to be preferentially responsive to static tilts about the pitch (128) or roll (126,175) axis, respectively. A change in head position means a change in otolith organ activity (125,128,175), which modifies integrator output (2).

Some studies have indicated that otolith-mediated

activity, due to a change in head position with respect to gravity, couples to the velocity storage mechanism in the yaw axis, thereby producing continuous horizontal nystagmus during off vertical axis rotation (OVAR) (132) and suppression of nystagmus following OVAR (108). The study by Correia et al. (106), which supports these findings, showed that after the blocking of all six semicircular canal ducts, horizontal and vertical nystagmus in response to angular acceleration about an earth-vertical axis were abolished. In contrast, nystagmus during constant velocity rotation around an earth-horizontal axis remained. Igarashi et al. (176) reported that bilateral macular ablation in monkeys prevented the observed nystagmus suppression following rotation around an axis tilted from the vertical.

Our present study provides evidence that gravity can also affect vertical velocity storage in humans through activity mediated by the otolith organs. This has been supported by previous studies in the monkey (2,116) and other studies in man (3,139). These studies reported that after bilateral utriculo-sacculectomy in squirrel monkeys, a clear improvement of VOKN SPV in both directions was found in the upright position while the asymmetry (upward SPV greater than downward) remained. Furthermore, upward VOKAN was enhanced and its duration was prolonged post-operatively, whereas downward VOKAN did not show any clear change. Bilateral sacculectomy also caused a gain increase of downward VOKN and a decrease of

upward VOKN (116). A microgravity study found that this modified gravity state had a striking effect on optokinetic nystagmus, which was presumably due to the change of otolith activity (3). However, other animal experiments with various lesions, such as semicircular canal plug and its nerve section in rhesus monkeys (132) did not produce a significant change in vertical OKN. These findings support an otolith origin for modifications of VOKN and VOKAN and suggest that otolith activity is transmitted to the vertical velocity storage mechanism that stores activity related to vertical slow phase eye velocity, and further modulates its output gain. This is in agreement with the three-dimensional models proposed by Raphan et al. (2,177) and Hain (122).

Böhmer and Baloh (178) found no consistent up-down asymmetry in VOKN, although VOKAN was found to be asymmetric. Their result contrasts with ours in terms of VOKN asymmetry. Two factors may explain this difference between the two results. First, Böhmer & Baloh used 90° × 90° field of vision rather than full field stimulation, as used in our study. Second, by our calculation based on available information in their article, the stimulus stripe frequencies they used were estimated as 1.0 and 1.3 Hz for 45 and 60 deg/s, respectively. According to Holm-Jensen and Peitersen (159) and our study (156), stimulus stripe frequencies between 2 and 3 Hz as well as proper stimulus velocity are necessary for provoking reliable optokinetic response and velocity storage. Any target

frequency below 2 Hz would tend to produce more pursuit eye movements than optokinetic. Therefore, in the study by Böhmer & Baloh (178), it seems that upward velocity storage was not charged up sufficiently to produce significant asymmetry of OKN because of low target frequencies and a narrower stimulus field. Thus, a significant proportion of the response could be mediated by a pursuit effect.

We suggest that the asymmetry between upward and downward OKN/OKAN was due to the velocity storage mechanism, because the velocity storage responsible for upward OKN/OKAN is charged up during stimulation, whereas there is much less or no velocity storage for downward eye movements. A possible physiological explanation for this phenomenon is, based on what Murasugi and Howard argued (96), that the asymmetry is due to an inhibition effect on downward following eye movements. The lower section of the human visual field is larger than the upper section and therefore contains more information. Since it is impossible to track motion in all depth planes simultaneously, for a better stabilization of the visual field ahead during forward locomotion, humans have a preference for upper vision field over lower one, i.e. the influence of predominant downward optic information has to be inhibited to let the upper vision field track better. Another study which may lend additional support to this explanation, found that vertical OKN asymmetry tended to be reversed in an upside-down body position (157). In this situation, the point

of interest ahead is in the lower rather than the upper section of the vision field with respect to the subject, since the seen world is inverted when the subject is upside down.

Cross-coupling in monkeys is thought to be mediated through the velocity storage mechanism (177). There is evidence to support this postulate. Electrical stimulation of the vestibular nuclei of alert monkeys revealed responses similar to cross-coupling for horizontal OKAN or for vestibular post-rotatory nystagmus elicited in tilted positions (104). Another electrophysiological study (197) showed that electrical stimulation of the nucleus of optic tract (NOT) elicited a slow rise of SPV, but did not affect the direct pathway function, i.e. stimulation of NOT only excited pathways in the subcortical visual system that projects to the vestibular nuclei. Stimulation of NOT thus appears to activate the velocity storage mechanism. If the animal was upright, stimulation of NOT induced pure horizontal SPV. If the animal was tilted while stimulated, however, vertical components appeared both in the nystagmus and after-nystagmus. These vertical components tended to bring the plane of the nystagmus toward the spatial horizontal plane. In other words, the resultant OKAN tends to be aligned with the spatial vertical.

Regarding cross-coupling in humans, our data did not show such dramatic results as in the monkey (2,179). Only two out of 18 subjects expressed cross-coupling. This was of low

intensity, from the horizontal to the vertical mode after horizontal OK stimulation in only one direction, and only when the subjects were in 90° roll position. There was no discernible cross-coupling for the rest of our subjects. It seems that cross-coupling between vertical and horizontal velocity storage modes does not express itself in the afternystagmus tracing in most human subjects (at least under our laboratory conditions). Even the two subjects with cross-coupling displayed only a few beats of low intensity vertical components. It is not clear whether the cross-coupling nystagmus shown by two of our subjects was due to variation among normal humans, or whether in the others it was not expressed somehow. Also, human OKAN might be too weak to reveal the cross-coupling seen in monkeys.

Close comparison of the data from all subjects in figures 18 and 22 reveals that the VOKAN (upward slow phases only) increased while the HOKAN decreased as the head position changed from upright to 90° roll. This is consistent with the findings in monkey studies (2,173), that velocity storage along the Earth-vertical axis is preferred. In other words, there was indeed "cross-coupling" of the SPV from the yaw to the pitch axis, albeit there was no discernible cross-coupled afternystagmus for most of the subjects. Therefore, it still makes sense if we argue that human velocity storage also holds the characteristics of multi-dimensional dynamics.

Clement and Lathan (141) reported that their subjects

showed cross-coupling similar to that shown in the monkey, but there were a few inconsistencies in their study. First, the velocities, duration and visual field of their stimulus appeared to be less than ideal to induce reliable OKN and OKAN. Secondly, their data showed the same direction (upward slow phase) of the crossed vertical component regardless of the horizontal stimulus directions. According to the model of Raphan and Cohen (2,173), cross-axis effects should obey the right-hand rule, which would mean that the directions for crossed vertical components for horizontal stimulation in opposite directions should be mirror-like. Thirdly, their data showed that the crossed vertical component appeared vigorously, long (at least more than five seconds from what could be seen in the figure presented in their article) before lights out. In comparison, our data displayed obvious cross-coupling only after the stimulation was removed. Our result was similar to that in monkeys (2,173), which displayed that there was only a weak vertical component for very short time before lights out, if any. During the stimulation, the SPV was dominantly along the stimulus direction, i.e., along the subject's yaw axis, suggesting that the SPV about the pitch axis was suppressed by the direct optokinetic pathway to maintain eye velocity about the yaw axis in the compensatory direction. Therefore, it should not have a vigorous vertical component during the horizontal stimulation. Hence, the so-called cross-coupling described by Clément and Lathan (141)

may be due to a cross-talk or a spontaneous nystagmus effect. In another study, Gizzi et al. showed robust cross-coupling during the stimulation rather than in afternystagmus components (180). Compared to our results, theirs were different in several respects. In their study, a limited visual field stimulus was presented to the subjects, which was 88° (horizontal) × 72° (vertical). Consequently, it probably did not generate a fully evoked OKN, and therefore lower gains were produced: 0.77 for horizontal OKN, 0.72 for upward OKN and 0.84 for downward VOKN with the head upright. In contrast, our data showed a close to unity gain for horizontal and upward OKN, with lower gain (0.87) for downward OKN. Also, their subjects had no significant circular vection during or after stimulation. While our subjects frequently reported circular vection during the stimulation, and some even felt short circular vection after the stimulation. Instead of the finding in our study that shows the upward SPV greater than the downward, their data shows downward SPV being greater than upward. With the head tilted, gain of upward SPV actually did not increase while there was a gain increase in downward SPV.

The occurrence of reversed VOKAN, i.e. "inappropriate-direction" VOKAN observed in humans (135,157,178) has not been reported in animal studies. In the present study, 4 out of 18 human subjects demonstrated the reversal of VOKAN only following downward stimulation. This did not appear to be dependent on head position. The mechanism underlying the

reversal of VOKAN remains to be verified, although Böhmer and Baloh (178) postulated that reversed OKAN, defined as OKAN II by them, is due to expression of the secondary velocity storage which is oppositely directed to the primary velocity storage.

## 6.3 VOKN/VOKAN During the Parabolic Flight

Parabolic flight provides us with a simple way to generate alternating periods of gravitoinertial force level, microgravity and hypergravity. Taking advantage of this, we had a chance to test the effects of different gravitoinertial force on VOKN and VOKAN.

### 6.31 Loss of Asymmetry of VOKN/VOKAN During the Parabolic Flight

Figures 23 through 27 show the results of VOKN/VOKAN data analysis from EOG and ISCAN on the ground and in parabolic flight. There was an increase of downward VOKN/VOKAN but unchanged upward VOKN/OKAN in both micro- and hyper-G. This outcome seems paradoxical because one may expect that hypogravity and hypergravity would have opposite effects, i.e.

hyper-G impact on the otoliths induces augmented otolith ocular reflex (OOR) that facilitates downward eye movement (our subjects were sitting upright relative to the floor of the airplane, thus the body's yaw axis was aligned with aircraft's z axis), whereas micro-G would produce an opposite effect.

Gravity has a direct effect on the otolith organs, and thus gravity information is delivered to the CNS. But the output, which is the drive to the oculomotor system, is dependent upon integrated processing, by the CNS, of information from a variety of sensing systems, including other peripheral sensing inputs (e.g. visual, acoustic, somatosensory) and central cortical inputs (e.g. cognitive factors). As a consequence, the CNS plays an important role in the control of reactions of the oculomotor system. Under normal gravitation conditions, the oculomotor system acts in a way that it is adapted to normal gravity, as discussed in the last section. Conceivably, it behaves differently under exposure to an unusual situation - changed gravitoinertial force level environment.

Experiments on monkeys have shown that bilateral ablations of the utricular and saccular maculae induced an increase of VOKN in both upward and downward directions (121), and that bilateral sacculectomy caused an increase of downward VOKN and a decrease of upward VOKN (116). The latter is similar to phenomena during early exposure to microgravity in

orbital (3) or parabolic (4) flight. In both situations, the asymmetry of VOKN was reversed, i.e. downward SPV became greater than upward SPV. Microgravity creates a functional equivalence to ablation of gravity receptors. All those experiments have one thing in common, that is, removal of the normal gravity sensing function of the otoliths (particularly the sacculus), which resulted in the above changes of the asymmetry. However, other animal experiments with various lesions not involving the otolith system, such as semicircular canal plug and nerve section in monkeys (132), did not cause a significant change in vertical OKN. It has been suggested that, in earth gravity, the asymmetry between upward and downward VOKN/VOKAN is due to asymmetric function of the vertical velocity storage integrator, i.e. the velocity storage responsible for upward VOKN/VOKAN is charged up, whereas there is much less velocity storage for downward eye movements (2,113,114), because of the inhibition effect on downward eye movement, mediated through the otolith organs.

It is proposed that the loss of the asymmetry in micro-G was due to a disinhibition effect initiated by the graviceptors, primarily the otoliths, on the optokinetic system for downward eye movements via the velocity storage mechanism, while the loss of the asymmetry in hyper-G was due to an enhanced compensation effect by augmented otolith-ocular reflex, which facilitated downward VOKN/VOKAN.

In microgravity, the otoliths are released from the

constant pull of gravity. As a consequence, the signals from the otoliths are equivalent to the body accelerating downward along its yaw axis. The fact that increased responses of downward OKN/OKAN, as well as the downward shift of the beating field were observed, means that the effect was not a simple vestibular compensatory event, because the eyes were not driven in a direction opposite to the acceleration.

The CNS is able to integrate multiple sensory information, such as vestibular, visual and somatosensory inputs, so as to stabilize gaze by generating compensatory eye movements. Neural structures such as the INC (181), Group y (182), flocculus, parafloculus (74), uvula and nodulus (183), relay otolith inputs and are known to influence vertical eye movement. The midbrain reticular formation, within and in vicinity of the INC, has close connections with the vestibular and oculomotor nuclei (53,54). Some neurons in the INC receive visual input (55). An anatomical study reveals pathways that could relay a visual input to the INC (56). Single cell recordings reveal that this region contains neurons whose activity is closely related to vertical optokinetic and otolith organ stimuli, i.e., the neurons that respond to vertical linear acceleration in the dark also respond to optokinetic stimulation (57,58). Otolith inputs activated by vertical linear acceleration could reach the INC region through the lateral vestibular nucleus (184-186) or the dorsal part of the group y nucleus (187,188). These results suggest

that those INC neurons receive a convergence of otolith and visual inputs and may constitute part of the vertical velocity storage integrator. The uvula and nodulus are also important for multisensory convergence (189). An electrical stimulation study reveals that the uvula and nodulus are also involved in the vertical oculomotor system and are related to the velocity storage. It was found that stimulation evoked vertical nystagmus and afternystagmus, with stronger upward components in the dorsal uvula and ventral nodulus than downward components evoked in the ventral uvula and dorsal nodulus (190).

Therefore, the vertical asymmetry of VOKN/OKAN may reflect a central neural function that exerts asymmetrical drive on the vertical velocity storage to regulate its output in response to the tonic afferent input from the otoliths. Moreover, the asymmetry is modified by different head orientations, presumably a consequence of the changed static otolith activity (2).

Obviously, in our experimental environment, the most significant variable was the change of gravitoinertial force level, which had a direct effect on the otolith organs. It seems that the otolith response to changed gravitoinertial force was primarily responsible for the modified behaviour of the velocity storage mechanism. Notwithstanding this, we are not certain about effects of other factors encountered in non-1 G, such as redistribution of the liquid media of body

constitution and altered somatosensory input. In the phase of microgravity, the otolith organs were unloaded and thus the static inhibition effect on downward VOKN/VOKAN had been removed and at the same time visual scene information had become more dominant, which resulted in allowing the velocity storage to act symmetrically in both directions. In our study, an efficient stimulus velocity- 40 deg/s was used, which could produce saturated response of VOKN/VOKAN on the ground (156). Being exposed to the same intensity of visual stimulus in both directions in micro-G, downward VOKN/VOKAN could function more effectively because of the disinhibition effect due to the unloading of the otolith organs.

But, possible mechanisms underlying the phenomenon in the micro-G phase during parabolic flight can not be an adaptation effect in the conventional sense, because central adaptation can only take place during long-term exposure to microgravity, and the brief microgravity phase during parabolic flight did not provide enough time to allow it to happen.

By analogy, studies on arm pointing during parabolic flight demonstrated similar phenomena: compared to the normal gravity baseline data, their subjects pointed consistently higher than the target level under changed gravitoinertial levels, no matter in hyper-G or micro-G conditions (191). On the ground, arm movements are executed by "playing back" established motor programs based on normal gravity (192). Thus, adding a mass to the pointing arm on the ground did not

impair the accuracy and movement kinematics of the arm pointing (193), but the changed-G force impaired arm pointing either with or without adding a mass to the arm (191,194).

The results from those studies imply to us that the information, indicating gravity influence, from the otoliths, rather than the input from the proprioceptors in the arm, plays a crucial role for the motor programs to function properly. Since the proprioceptors provide the sense of static and dynamic position of limbs and body, the subject should have pointed correctly if the arm movement is soly programed based on the input from proprioception. The observed overshoot in micro-G was attributed to inappropriate motor programs in execution mainly because of losing the previously appropriate suitable otolith inputs, and this resulted in uncalibration of the arm proprioception. However, in the hyper-G situation, the overshoot was simply a consequence of augmented antigravity reflex, initiated by the impact upon the otoliths. The ocular and spinal vestibular reflexes are similar in a sense of functional organization (195,196). Therefore, it can be inferred that what happens to the vestibulospinal reflex could happen to the vestibulo-ocular reflex.

### 6.32 Reversal of VOKAN During Parabolic Flight

There was a higher occurrence rate of reversal of VOKAN

following downward stimulation in non-1 G conditions than on the ground. It was similar to that in 1 G, except there was reversed downward VOKAN following upward stimulation as well. It appears that the reversal occurred in an unpredictable manner, since it did not happen to every subject nor did it happen in every trial on the individuals who displayed a reversal. It was not long lasting and died away in a few seconds. Therefore it was not like spontaneous nystagmus, which could last long and have no apparent decay. Although the mechanism underlying this phenomenon remains to be verified, it may imply that vertical velocity storage becomes unstable in non-1 G environment because of the loss of useful normal gravity input from the otolith organs. Without proper spatial reference provided by the otolith organs, velocity storage is confused. In other words, velocity storage becomes uncalibrated when exposed to a novel gravitational environment.

## CHAPTER 7

## CONCLUSIONS

In this thesis, three steps of investigation of the human VOKN/VOKAN have been presented, from which some conclusions can be drawn as follows:

1) Vertical stimulus velocity study: In order to produce reliable vertical OKN and OKAN, appropriate velocity and proper spatial frequency of the stimulation must be employed. Under the conditions reported here, a 40 deg/s stimulus has been found to be capable of generating reliable VOKN and VOKAN in humans.

As in the horizontal case, two separate mechanisms are involved in the vertical eye movement: one predominantly in the low stimulus velocity range, presumably smooth pursuit mediated, and the other predominantly activated at higher stimulus velocities, presumably mediated by optokinetic system.

2) Asymmetry of VOKN/VOKAN and its gravity dependence: Our study supports the conclusion that the human velocity storage mechanism is vertically asymmetric with higher upward SPV than downward in both VOKN and VOKAN. This is consistent with the studies in monkeys and cats. Velocity storage is also modified by changing head orientation with respect to gravity, an effect which is probably mediated through the otolith organs. The existing asymmetry would become even greater by an

increase in upward SPV when the head orientation is tilted away from the spatial vertical.

Consistent with monkey data, human velocity storage appears optimum when the axis of stimulation is aligned with the gravity. However, unlike in monkeys, identical cross-coupling from the yaw axis to the pitch axis is not expressed in most human subjects.

3) Parabolic flight study: As compared to the baseline data on the ground, there was a significant increase of downward VOKN/VOKAN but virtually unchanged upward VOKN/VOKAN in both micro- and hyper-G. As a consequence, the asymmetry of VOKN/VOKAN, normally seen on the ground, was lost.

It is postulated that the increase of downward VOKN/VOKAN in non-1 G conditions was governed by two different mechanisms. In micro-G, the normal inhibition effect in 1 G on the downward eye movement mediated by otolith organ activity to the vertical velocity storage is removed. While in hyper-G, the downward VOKN/VOKAN are facilitated by the otolith-ocular reflex because of the increased gravitoinertial force, so as to produce enhanced compensatory downward eye movement.

In short, in terms of the velocity storage in the three-dimensional organization, human vertical optokinetic reflex is dependent upon head orientation with respect to gravity and also is influenced by gravitoinertial force level.

# CHAPTER 8

# IMPLICATIONS AND IDEAS FOR FUTURE RESEARCH

## 8.1 Clinical Implications of the Study

Clinical testing of vestibular function has improved greatly since the era of Bárány. Technological innovations have allowed us to employ stimuli precisely and to accurately measure the vestibularly driven eye movements generated by the VOR. In spite of these advances, most currently available tests, e.g., caloric and rotation tests, are only useful to measure canal function, which has been extensively studied. But what of the otoliths and their interactions with other systems for body balance and gaze stability through the velocity storage? Until now, not much has been known about otolith function and pathology in terms of clinical significance. It is not even clear whether isolated otolith dysfunction exists as a clinical entity. The reason for this lack of knowledge is that there have been no simple tests that could accurately and readily measure otolith function and detect its pathology in clinical settings.

There are several methods to test otolith function, which include the parallel swing, the linear sled, and vertical oscillation. All of these tests provide strictly otolith stimulation, however, none have been used in routine clinical testing. Most testing of otolith function in basic science

laboratories has been done using either the linear sled or parallel swings. But, such equipment is too expensive and often occupies too much space to be practically suitable for use in a clinical testing laboratory. But, examination of corresponding modifications of OKN/OKAN in response to head orientation could become useful in assessing otolith organ function.

Optokinetic nystagmus could be used as a tool for measuring otolith responses, because optokinetic stimulation might provide a tool for obtaining a more sensitive indicator of dynamic otolith function. Vertical and horizontal OKN/OKAN are influenced by gravity effect in terms of head position or changed gravitoinertial force levels. This gravity effect is mediated through the otolith organs, which can be reflected with the interaction between optokinetic and otolith systems.

A clinical OKN/OKAN test could be a potentially useful tool in the diagnosis of disorders in the vestibular system centrally and peripherally. Testing OKAN is an easy way to measure the velocity storage mechanism in the brainstem, which reflects central nervous system function, as well as to measure peripheral vestibular function. For example, HOKAN has been shown to be abolished by unilateral or bilateral labyrinthine deficits both in monkey and man. In unilateral deficits, HOKAN with slow phase directed toward the side of opposite to the lesion is severely reduced or abolished. Thus the HOKAN has lateralizing value in the diagnosis of

unilateral peripheral vestibular diseases. The observed loss of HOKAN is accompanied by a corresponding change in the caloric test. Furthermore, the HOKAN test can be useful in distinguishing a peripheral deficit from a central lesion since HOKAN is absent bilaterally in unilateral brain stem disorders, (e.g. Wallenburg's syndrome) or diffuse central diseases, (e.g. multiple sclerosis) even though caloric responses on both sides can still be symmetrical. Therefore, loss of HOKAN bilaterally with retention of caloric responses suggests a brainstem disease rather than a peripheral lesion.

Charging and discharging characteristics of the vertical velocity storage in patients with vestibular deficits now remain to be investigated and compared to known characteristics of normal velocity storage. It is known that downbeat or upbeat vertical nystagmus is one of the major features of central vestibular dysfunctions signifying disorders of the cerebellum or brainstem. Examination of stimulus velocity, asymmetry of VOKN/VOKAN and head orientation dependence in patients may yield more information in the well-known difficult task of diagnosing vestibular deficits.

## 8.2 Future Studies in Conditions of Altered Gravitoinertial Forces

Evidence for the gravity-dependence of the velocity storage has already been presented in both monkeys and humans. A three dimensional structure for velocity storage has been proposed by Cohen & Raphan (2). Further experiments are necessary to explore the velocity storage mechanism in more depth and consequently help to solve practical problems encountered in clinic and space adventure.

The gravity-dependence characteristics of vertical velocity storage can be further examined by changing head orientation while testing OKN/OKAN during parabolic flight. In this condition, it will be interesting to see if there is typical cross-coupling in humans, similar to the cross-coupling shown in monkeys. Head movements in pitch are apparently most effective in eliciting motion sickness in micro- or hyper-gravity. Results from the present studies have shown that visually induced vertical eye movement (in the pitch axis) governed by the velocity storage is gravity-dependent.

A few questions need to be answered by future studies. Could velocity storage activity be related to space motion sickness susceptibility? What is the significance of the time-course of the VOKN/VOKAN asymmetry reversal and later-on recovery with relation to space adaptation? Further

investigations of these questions could reveal some correlations with space adaptation and space motion sickness.

Changes in the role of otolithic cues in spatial orientation are expected in changed gravitoinertial force environment. However, it is not known how the change of excitability of the otoliths and consequent effect on the velocity storage occurs in micro- or hyper-G. Interesting studies may involve the recording of neural activity of the otolith afferent, VN neurons, and cerebellar cells, under changed gravitoinertial conditions. Also, in space, it is interesting to see the effect of exposure to long-term microgravity on the otolith afferent, VN neurons and the cerebellum. These experiments may tell us about modification, or reinterpretation, within the central nervous system in the processing of neural signals from the otoliths.

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