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INDEXED IN Cam. Sci. Abstr., CABS

ISSN 0957-4271
(936)
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PATHOGENESIS OF MENIERE’S DISEASE

Michael M. Paparella, MD, and Barry P. Kimberley, MD FRCS(C)
Department of Otolaryngology, University of Minnesota
Reprint address: Dr. Michael M. Paparella, Minnesota Ear, Head and Neck Clinic, 701 25th Avenue So, Minneapolis MN 55454

Introduction

Meniere’s disease, a disorder of inner ear function that is commonly encountered in otolaryngologic practice, can cause devastating hearing and vestibular symptoms. Successful treatment of this disorder depends upon understanding its mode of origin and natural development, its pathogenesis. Because current understanding of the pathogenesis of Meniere’s disease is imprecise, treatment is significantly influenced by empiric principles. This review will show, however, that anatomic variations in temporal bone, malabsorption in the endolymphatic sac, and genetic factors each play major roles in the pathogenesis of Meniere’s disease. Knowledge of these factors can be helpful in the design of methods of treatment.

Classification of Meniere’s Disease

Rather than distinguishing Meniere’s disease (of “idiopathic,” ie, as yet unknown, etiologic origin) from Meniere’s syndrome (of known etiologic origin), we prefer to use the term Meniere’s disease for all cases demonstrating the symptom-complex characteristic of Meniere’s. Cases can then be divided into those of known and of unknown etiologic origins, as listed in Table 1. Among our patients, approximately 25% can be associated with one of the known causes listed in Table 1.

Natural History

In a review of over 500 patients with Meniere’s disease (1), we found an equal distribution between the sexes. The disease was by far the most common among adults, although there are many instances of children as young as 6 years of age with classical Meniere’s disease (2). Roughly 15% of patients with Meniere’s disease can identify blood-relatives with the same disease. This suggests the significance of genetic factors in its etiology. The reported incidence of bilaterality of involvement ranges between 33% and 50% (1,3). Certainly the probability of bilaterality increases as the patient ages.

Pathogenesis: Functional Factors Resulting in Hydrops

A phenomenon fundamental to the development of Meniere’s disease is endolymphatic hydrops. The development of hydrops is generally a function of dysfunctional malabsorption of endolymph. Absorption of endolymph is believed to occur rather exclusively in the endolymphatic duct and sac (4). Malabsorption may itself be a result of 1) disturbed function of components comprising the endolymphatic duct and sac, 2) mechanical obstruction of the endolymphatic duct and sac, or 3) altered anatomy in the temporal bone. The first two issues are discussed below, while anatomic factors are discussed in the next section.

Received 16 January 1990; Accepted 19 January 1990.
Endolymph is produced primarily by the stria vascularis. A small amount comes from the planum semilunatum and dark vestibular cells. Endolymphatic flow is both longitudinal (along the axis of the endolymphatic duct toward the endolymphatic sac) and radial (across the membrane of the endolymphatic space into the perilymphatic system) (5). Meniere's disease is generally a consequence of altered longitudinal flow. Typically, a causative pathologic condition leading towards symptomatic Meniere's disease and hydrops evolves over a long course of time (years).

Studies in temporal bones provide insights into some of the many different pathologic mechanisms that may result in hydrops. For example, perisaccular fibrosis (6), atrophy of the sac (7), and narrowing of the lumen in the endolymphatic duct (8) have been observed in human temporal bones that also demonstrated hydrops. Kimura (9) and Paparella (2) have reported on the common coincidence of otitis media and hydrops. Otosclerotic foci enveloping the vestibular aqueduct and resulting in malfunction of the endolymphatic duct and sac have been reported (10,11,12).

Ikeda and Sando (8) studied vascularity near the endolymphatic sac in temporal bones that exhibited hydrops, and in normal bones. They found poor vascularity surrounding the endolymphatic sac in ears with Meniere's disease and hypothesized that the normally rich vascular system of the endolymphatic sac has an important function in absorption of endolymph and that the lack of vascularity associated with hydropic ears may be a factor in the pathogenesis of endolymphatic hydrops. Other lesions in the temporal bone that have been associated with development of hydrops include syphilitic osteitis of the otic capsule (13,15) and leukemic infiltrate (14,15). Type II collagen autoimmunity toward the endolymphatic sac has been suggested as a mechanism (16) but has not been proven in a human temporal bone. It has been known for some time that experimental obstruction of the endolymphatic duct will routinely result in endolymphatic hydrops in many animal models (9).

### Pathogenesis: Anatomic Factors

Many anatomic studies have found significant differences between hydropic and normal temporal bones. Rumbaugh et al (17) observed, using radiography, a smaller vestibular aqueduct in ears affected by Meniere's disease. Stahle and Wilbrand (18) reported results from radiographic evaluations of 86 ears with Meniere's disease. They found 1) decreased or absent pneumatization of the petrous portion of the temporal bone, 2) lack of periaqueductal pneumatization, 3) short vestibular aqueducts, and 4) reduction in the size of the mastoid air-cell system. Sando and Ikeda (19) compared the area near the vestibular aqueduct in 27 temporal bones and found the area in hydropic bones to be significantly less (9.2 mm² versus 14.6 mm²).

We reported on the relationship of the position of the lateral sinus as well as the size of

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Pathogenesis of Meniere's Disease

Figure 1. a: An artist's depiction of a "normal" mastoid. Note the large distance from the posterior semicircular canal (p.c.) to the lateral sinus inferiorly, and a sizable Trautmann's triangle between the lateral sinus and semicircular canal. b: An artistic rendition of abnormal anatomy in a patient with Meniere's disease. Note the shorter measurement B and very short distance between the posterior canal and the lateral sinus, and the markedly reduced Trautmann's triangle.

Trautmann's triangle to the occurrence of Meniere's disease (20). In 23 patients undergoing endolymphatic sac enhancement surgery for Meniere's disease, measurements of the position of the lateral sinus and the area of Trautmann's triangle were obtained intraoperatively. Figures 1 and 2 illustrate the dimensions ("A, B, and C") that were measured. These measurements were compared with those obtained through dissection of 15 normal (pneumatized) temporal bones (Table 2 summarizes these comparisons). Comparison between ears with Meniere's disease and normal ears showed statistically significant differences in each of the measured dimensions. This study showed that the lateral sinus is displaced a) anteriorly and b) medially. This displacement results in a Trautmann's triangle diminished in size.

Arenberg's (21)-studies also described anatomical variations of the endolymphatic sac and the vestibular aqueduct. He showed that ears affected by Meniere's disease were associated with smaller endolymphatic sacs and anteriorly displaced lateral sinuses. He hypothesized that an anteriorly located lateral sinus could lead to incomplete posterior migration of the developing sac and duct.

Taken together, these studies suggest that ears affected by Meniere's disease are likely to demonstrate hypodevelopment of the endolymphatic duct and sac, the periaqueductal cells, and the mastoid air cells. It is perhaps not surprising that these particular anatomic alterations are associated with endolymphatic hydrops. One can postulate a cause-and-effect relationship between constricted anatomy in the temporal bone and malabsorption of endolymph.

Mechanisms (Pathophysiology)
Underlying Clinical Symptoms

Any explanation of the clinical symptoms of Meniere's disease should account for all of
the symptoms, including rapid or prolonged attacks of vertigo, disequilibrium, positional vertigo during and between attacks, fluctuating progressive sensorineural hearing loss, tinnitus, aural pressure, inability to tolerate loudness, and diplacusis. The attacks of Meniere's disease (vertigo, hearing loss, aural pressure) have been explained on the basis of both physical and chemical mechanisms. Schuknecht (4) has proposed membranous ruptures as the cause of all attacks of Meniere's disease. A recent review, however, of temporal bones that both demonstrated endolymphatic hydrops and were associated with well-documented Meniere's disease (5) has demonstrated cases with no evidence of membranous rupture. The theory of rupture would predict that in a typical attack of Meniere's disease, there would be simultaneous ruptures in the cochlear duct and the sacculae in order for both cochlear deafness and vertigo to occur together. Studies in temporal bone, however, have demonstrated that when membranous ruptures are present they are not necessarily seen in the scala media and in the sacculae or utricles simultaneously. It seems more likely, in fact, that membranous ruptures are temporally associated with resolution of the symptoms of aural pressure and vertigo or sudden "drop" attacks of Meniere's disease.

Other mechanisms beside membranous rupture are needed to account for all the symptoms associated with attacks of Meniere's. Physical and chemical mechanisms are most likely both operational. Physical factors can tamponade the cochlear duct, contributing to fluctuating progressive sensorineural hearing loss and other cochlear symptoms, while distension of the otothilic organs can physically affect the crista ampullaris, resulting in vestibular symptoms. Chemical factors can also affect the pars inferior and/or the pars superior through the occasional membranous rupture or through leaks in the membrane (1).

In typical Meniere's disease, cochlear and vestibular structures are similarly involved due to a dysfunctional endolymphatic duct and sac. In atypical Meniere's disease, secondary obstructive sites can occur in addition. In cochlear Meniere's disease, for example, it is possible that obstruction occurs at the ductus reuniens. In vestibular Meniere's disease on the other hand, the endolymphatic valve may be deficient, leading to utricular hydrops to the exclusion of the pars inferior (22).

Summary and Conclusions

While endolymphatic hydrops is a characteristic pathologic feature of Meniere's disease, there are exceptions to this rule. There is evidence that hydrops develops as a result of malabsorption of endolymph. This implies dysfunction of the endolymphatic sac and duct, which normally absorb endolymph.

In approximately 20% of cases of Meniere's disease, a specific pathologic condition in the temporal bone can be associated as a cause of endolymphatic hydrops. Syphilis, fractures of the temporal bone, otosclerosis, and preceding chronic otitis media are some of the more commonly encountered pathologic conditions so associated. Hypoplasia of the mastoid air-cell system and of periaqueductal air cells, and especially displacement medially but also anteriorly of the sigmoid (lateral) sinus are commonly observed in patients with Meniere's disease. Evidence is available to substantiate the etiologic bases of Meniere's disease as including multifactorial inheritance (1).

The clinical symptoms and findings result from both chemical and physical mechanisms. Pathogenesis appears to be due to malabsorption of endolymph in the environment of the endolymphatic sac, primarily affecting longitudinal flow. The possible role of such processes as autoimmune reactions and viral inflammation, especially in the endolymphatic sac, should be further investigated in the future.

Acknowledgment—This research was supported, in part, by NIH Grant #P50 NS4538 09A1, and by the International Hearing Foundation.
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ADAPTIVE MECHANISMS OF VOR COMPENSATION AFTER UNILATERAL PERIPHERAL VESTIBULAR LESIONS IN HUMANS

M. Fetter and J. Dichgans
Eberhard-Karls University, Department of Neurology, Tübingen, Federal Republic of Germany
Reprint address: M. Fetter, Department of Neurology, Hoppe-Seyler Str. 3, D-7400 Tübingen, Federal Republic of Germany

Abstract — To further elucidate possible central plastic adaptive processes during the recovery from a unilateral peripheral vestibular lesion, we investigated vestibular functions in humans over a period of 2 months after an acute unilateral labyrinthine lesion. A unilateral peripheral vestibular lesion creates both a tonic imbalance that causes spontaneous nystagmus and a decrease and directional asymmetry of dynamic vestibular responses. We establish that the tonic imbalance expressed by the spontaneous nystagmus rapidly decreased (similar to other species), whether the lesion remained complete or not. This rebalancing, in the case of complete lesions, is at least partly due to restoration of central vestibular tone on the lesioned side. This restoration of tone also explains, in the case of a complete lesion, the recovery of dynamic vestibular responses for high-velocity inhibitory stimulation of the remaining labyrinth. A clear recovery of the dynamic response for excitatory stimulation of the remaining labyrinth cannot be proven, as has been shown in monkeys during the first 4 days after a unilateral vestibular lesion. This is probably due to the fact that in our patients the first recording could not be performed before day 3 after the onset of symptoms. Therefore, any fast dynamic recovery may have been missed.

Keywords — VOR compensation; unilateral labyrinthine lesion; vestibular system, human.

Introduction

Recovery from a unilateral peripheral vestibular lesion has been used extensively as a model for studying the adaptive mechanisms by which the central nervous system assures accurate dynamic vestibular responses when the head is moving and static vestibular balance when the head is at rest (1-5). While extensive data have been collected on vestibular compensation in a variety of animal species, much less information is available in man. It has been shown recently (2) that in patients who have had an acute unilateral vestibular lesion, the horizontal vestibulo-ocular reflex (VOR) gain was asymmetric postdeficit, averaging 50 and 75% of normal for rotations toward and away from the lesioned side with a recovery within normal limits when tested 1-3 mo later, but with no recovery of the VOR time constant (2). However, no sufficient data are available on the immediate recovery processes during the first few days and weeks after a unilateral vestibular lesion.

A unilateral peripheral vestibular lesion leads to a complicated problem for adaptive mechanisms to solve because such a lesion not only creates a decrease and directional asymmetry in the gain of the VOR but also a tonic imbalance that causes spontaneous nystagmus. Recently, more thorough studies in primates have been performed that were designed to elucidate both aspects of vestibular compensation (6,7). It can be demonstrated that the recovery of static and dynamic vestibular asymmetries are quite distinct processes with respect to the time course of recovery and, therefore, presumed plastic neuronal changes in vestibular nuclei. Stimulated by these find-
ings, we performed the present study to investigate the time course of vestibular compensation in humans. The data were compared to the results found in rhesus monkeys.

**Methods**

We investigated 9 subjects (1 male, 8 females, mean age 36.8 ± 14.2) with an acute unilateral vestibular lesion due to suspected vestibular neuritis in 8 cases and after surgical removal of a small acoustic neuroma in 1 case during the first 2 mo after the onset of symptoms. Four of the patients had left-sided lesions and five had right-sided lesions.

Horizontal and vertical open-eye movements were recorded by DC-electrooculography in complete darkness using silver-silver chloride electrodes. All recordings were done while the subjects performed mental arithmetic to increase the state of alertness. Frequent calibrations were performed to reduce the influence of gain changes due to changes in the corneo-retinal potential. Data were written on a strip chart and analyzed manually.

The degree of the unilateral vestibular hypofunction was evaluated by caloric testing in the supine position with the head elevated 30°. Each external auditory canal was irrigated with water of 44°C and ice water for 30 s with intermissions of 5 to 10 min. A canal paresis score (CaP) was defined as the difference of the combined warm and cold caloric responses between the two ears divided by the sum of the responses (absolute values) in percent.

Static vestibulo-ocular disturbances were assessed in three ways: (1) by the average slow phase velocity (SPV) of spontaneous nystagmus (SPN) during a 1 min period; (2) by the maximum amount of SPV of nystagmus (average of 10 s during peak elicitation) that could be induced by ice water caloric to the intact side (slow phase toward the intact side), and (3) the maximum SPV of nystagmus (slow phase toward the intact side) that could be elicited by high velocity rotation toward the lesioned side. The latter two assessments represent a measure of restoration of tonic activity in the vestibular nuclei on the lesioned side, since both high velocity rotations toward the lesioned side and ice water caloric to the intact side reduce the activity on the intact side to close to zero. Therefore, any nystagmus occurring with the slow phase toward the intact side is produced by the vestibular nuclei on the lesioned side, as long as there is no dynamic input from the lesioned side (as is the case in complete lesions).

Dynamic vestibulo-ocular disturbances were quantified by measuring the maximum SPV and calculating the VOR gain (maximum eye velocity/maximum head velocity) in percent as well as the dominant vestibular time constant (t0) of postrotatory nystagmus after constant velocity rotations about the earth vertical axis of 60 and 180°/s in both directions. In some instances (see Results), the vestibular responses were corrected for spontaneous nystagmus. This was accomplished by subtracting the average SPV of the last few beats of spontaneous nystagmus immediately before any change in rotational stimulus. As a measure of the dynamic imbalance, VOR preponderance was calculated in percent as the quotient of the difference of the two responses (right and left rotation) divided by the sum of the two responses. The vestibular time constant was estimated using the time it took for SPV of postrotatory nystagmus to decline to 37% of the maximum velocity with the spontaneous nystagmus as baseline.

The criteria for patients to be included in the study were: (1) onset of symptoms less than 14 days before the initial measurement; (2) absent or greatly reduced caloric response on one side; (3) ability to sit in a rotatable chair for about 1 ½ h without too much discomfort. This procedure, unfortunately, led to different time intervals between onset of symptoms and the first recording session. Therefore, in most instances, individual time courses of recovery are shown.

Statistical comparison was performed using the t test for independent samples; P < 0.05 was chosen to denote significant differences.
Results

Patients were tested first between day 3 and day 13, then between day 7 and day 25, and finally between day 43 and day 68 after the onset of symptoms. Table 1 shows the recording days for each patient and indicates whether the lesion was complete (C), initially complete (IC) or incomplete (NC). (In 1 patient [3] only the initial two recording sessions could be performed.)

Caloric Stimulation

On the first recording day, 6 of the 9 subjects (1,3,4,7,8,9) had complete unilateral peripheral vestibular lesions with no caloric response (including ice-water caloric) on one side. The other 3 patients (2,5,6) had a marked canal paresis on one side with an average CalP for these 3 subjects of 64.7 ± 5.1°/s. While in 2 patients (4,8) the lesion remained complete (including the patient who underwent removal of an acoustic neuroma [8]) all other patients regained function of the lesioned labyrinth. In 4 cases (including the 3 patients with initially incomplete lesions [2,5,6,7]) the formerly lesioned labyrinth showed an even better caloric response than the intact labyrinth on the final recording day. The individual time courses of CalP are shown in Figure 1.

Tonic Imbalance

Spontaneous nystagmus. When first tested (3–13 days after the onset of symptoms), all patients exhibited horizontal SPN in the dark, beating toward the side of better caloric excitability with an average SPV of SPN of 19.1 ± 9.8°/s (range: 10–36°/s). Patients with a complete lesion averaged insignificantly higher amounts of SPN (22.9 ± 10.0°/s) than patients with incomplete lesions (11.3 ± 1.2°/s) (P > 0.09). At the second measurement (7–25 days after the onset of symptoms) the SPN was largely reduced in all subjects (whether the lesioned labyrinth had regained function or not) to an average SPV of 5.9 ± 4.6°/s. At the final measurement approximately 2 mo after the lesion, most of the 8 subjects had further decreased SPN to a level not much different from small drifts that can be found in normals (average SPN: 2.6 ± 1.6°/s). The individual time courses for each patient are shown in Figure 2.

Maximum Slow Phase Velocity toward the Intact Side

Ice-water caloric. Within 10 days after the lesion (data points of 6 patients) only 3 (4,6,9) produced a nystagmus oppositely directed to the SPN (2 of the 3 patients had a complete lesion). Between day 10 and day 20 after the lesion, the 7 patients without enduring complete lesions, had increased the ability to produce caloric-induced nystagmus opposite to SPN to nearly the final level. The two patients with complete lesions were slower in regaining the ability to turn around SPN by ice-water caloric on the intact. On the final recording day (day 43 and 68), however, these two patients had reached values comparable to those of patients who had regained bilateral labyrinthine function. The individual time courses are shown in Figure 3A.
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Figure 1. The time course of the canal paresis score (CaP) [%] for each patient is shown (normal value in our laboratory: <20%). While six patients had initially a complete unilateral labyrinthine lesion (indicated by filled squares), in only two patients this lesion remained complete (for better readability the scores for the two patients with complete lesions were set at two slightly different values just below 100%). All other subjects readily reduced their CaP with overcompensation in four subjects. In the following graphs complete lesions will be denoted by either filled squares or filled arrows. The change from filled to unfilled symbol indicates the change from complete lesion to incomplete lesion.

High-Velocity Rotational Excitation of the Lesioned Side

At the first recording session, a stop from high-velocity rotation (180°/s) toward the intact side (excitation of the lesioned side, inhibition of the intact side) elicited in all patients a nystagmus toward the lesioned side, with an average SPV toward the intact side of 49.6 ± 22.7°/s (range: 22–79°/s). In the 6 patients with initially complete lesions, the average SPV was significantly lower (38.6 ± 18.7°/s) than in the 3 patients with incomplete lesions (71.6 ± 10.1°/s) (P < 0.03). To various degrees, all patients recovered the ability to produce slow phases toward the intact side. While the patient with a complete lesion after removal of an acoustic neuroma had the lowest values throughout the observation period, the other patient with a complete unilateral lesion behaved like the patients who regained function of their labyrinth. The individual time courses of recovery are shown in Figure 3B.

Dynamic Imbalance

Maximum slow phase velocity (VOR gain).

At the first recording session the average value of the gain of the VOR, when the lesioned side was excited, was low for both 60 and 180°/s stimulation. For 60°/s stimulation the average gain for excitation of the lesioned side was 25% ± 11% (range: 7%–45%; 50% ± 16%, when corrected for spontaneous nystagmus) and for excitation of the intact side 103% ± 16% (range: 70%–127%; 80 ± 13%, when corrected for spontaneous nystagmus). For 180°/s stimulation the average gain for excitation of the lesioned side was 27% ±
Adaptive Mechanisms of VOR Compensation

Figure 2. The time course of spontaneous nystagmus is shown for the 5 subjects with right-sided lesions (slow phase of nystagmus toward the right, R) and for the 4 subjects with left-sided lesions (slow phase velocity toward the left, L). Patients with incomplete and complete lesions showed a similar fast decrease of spontaneous nystagmus (normal value: <3°/s).

13% (range: 12%-44%; 35% ± 12%, corrected) and for excitation of the intact side 83% ± 17% (range: 50%-101%; 74% ± 17%, corrected). While no consistent changes over time of the VOR gain toward the intact side could be detected (Figures 4A and B), the VOR gain toward the lesioned side showed a fast recovery within about 25 days after the lesion to values close to the final values in about half of the patients, plus a further increase in the other half of the patients. There was no clear difference between the patients with enduring complete lesions and the patients who regained bilateral function. The final average gain for 60°/s rotation for excitation of the intact side was 85% ± 22% and for excitation of the initially lesioned side 69% ± 11% (being significantly lower for the lesioned side, P < 0.03) and for 180°/s 76% ± 16% and 63% ± 17%, respectively, (with no significant difference for the two directions, P > 0.09). Individual time courses for VOR-gain recovery are shown in Figure 4.

Side Differences of VOR Gain (VOR Preponderance)

The initial VOR preponderance for rotations with 60°/s was 63 ± 12% (25 ± 13%, when corrected for SPN) and with 180°/s was 51 ± 16% (37 ± 15%, corrected). The recovery of dynamic imbalance remained incomplete for high velocity rotations in more than half of the subjects. With the 60°/s stimulus all patients had reduced their VOR preponderance at the last recording session to less than 15% (with an average of 8 ± 5%, when corrected for SPN). With the 180°/s stimulus this was only the case in three patients (with an average value of 14% ± 8%). Individual results are shown in Figure 5.

VOR Time Constant

When first measured after the lesion, the average time constant of postrotatory nystag-
Figure 3. Slow phase velocity induced by ice-water caloric reactions on the intact side (A) and by high-velocity excitation (180°/s) of the lesioned side (B) is shown during the time course of recovery. While initially with ice-water caloric reactions only 3 patients could produce slow phases opposite to the spontaneous nystagmus, this was the case in all patients when the lesioned side was excited with a high-velocity stimulus, even in patients with complete lesions. This indicates a very fast restoration of tonic activity in the vestibular nucleus on the lesioned side despite various degrees of deafferentation (certainly complete in one patient with an VIIIth nerve section during removal of an acoustic neuroma). (In a normal control group, ice-water caloric reactions induced SPVs ranging from 24 to 70°/s with an average of 39 ± 24°/s. Rotations with 180°/s induced SPVs ranging from 100 to 180°/s with an average of 139 ± 29°/s).
Figure 4. The time course of recovery of VOR gain for 60°/s (A) and for 180°/s (B) is shown with correction for spontaneous nystagmus. Rotation toward the intact side is denoted with squares, rotation toward the lesioned side is denoted with arrows and crosses (the change from arrow to cross indicates the change from complete to incomplete lesion). While no significant changes appeared for excitation of the intact side, there was clear recovery of the VOR gain, at least for high-velocity rotations, for excitation of the lesioned side mostly reaching the final value within ~25 days. (Normal VOR gain values in our laboratory: for 60°/s rotation >88% and for 180°/s rotation >45%.)
Figure 5. The time course of recovery of VOR preponderance for 60°/s (A, B) and for 180°/s (C, D) is shown with (B, D) and without (A, C) correction for spontaneous nystagmus. While with 60°/s rotation VOR preponderance was reduced to values below 15% by the end of the observation period, this was only the case in about half of the patients with 180°/s rotation, indicating incomplete rebalancing of the dynamic asymmetry at least for high-velocity stimuli. (Normal VOR preponderance values (corrected for spontaneous nystagmus) in our laboratory: for 60°/s rotation <8% and for 180°/s rotation <16%). (Figure continued on facing page.)
mus for 60°/s rotation with excitation of the lesioned side was 4.7 ± 1.1 s, for excitation of the intact side 6.6 ± 2.2 s, and for 180°/s was 6.2 ± 2.3 s and 7.8 ± 2.1 s, respectively.

There was a significant difference between the two directions of rotation for 60°/s stimulation ($P < 0.009$) but not for 180°/s stimulation ($P > 0.07$). Most of the patients who
regained function of their lesioned labyrinth showed a fast but incomplete recovery of the VOR time constant within about 25 days for both directions and both velocities without much further increase. The 2 patients with persistent complete lesions only marginally improved their VOR time constant, to approximately 8 to 10 s for excitation of the intact side and 6 to 9 s for excitation of the lesioned side (see Figures 6A and B). The VOR time constant remained below normal for more than half of the patients within the observation period. The final average value for rotations with 60°/s was 9.4 ± 3.2 s for excitation of the intact side and 9.3 ± 2.1 s for excitation of the initially lesioned side, and for 180°/s stimulation was 10.1 ± 2.4 s and 9.8 ± 2.0 s, respectively, with no significant differences between the two directions of rotation for both stimulus velocities.

Discussion

The vestibular system is organized bilaterally. Both sides are connected via the vestibular commissures in an inhibitory manner. Two major classes of central vestibular neurons participate in this arrangement: type I, which increase their discharge rate for ipsilateral rotations of the head and type II, which increase their discharge rate for contralateral rotations of the head. Type I cells are excitatory and project both to ocular motor neurons and, through the vestibular commissure, to type II neurons located in the contralateral vestibular nuclei. Type II cells are inhibitory and project to type I neurons on the same side. This arrangement allows afferent inputs from one labyrinth to influence vestibular neurons on both sides of the brain stem and makes possible a push-pull organization between the two vestibular nuclei, even when peripheral inputs from one labyrinth are missing (8-10). After a unilateral vestibular lesion, to reestablish accurate dynamic vestibular responses when the head is moving and static vestibular balance when the head is at rest, plastic adaptive processes must not only correct for the imbalance of vestibular tone, leading to spontaneous nystagmus and contributing to the asymmetry of dynamic vestibular responses, but must also increase synaptic efficacy to improve accurate dynamic vestibular responses (11). In this study we evaluated the changes in static and dynamic vestibular responses during vestibular compensation after a unilateral vestibular lesion in humans. We will discuss the results in humans by comparing them with the results described in primates after a unilateral vestibular lesion (6).

Compensation for Static Vestibular Imbalance

Static vestibular imbalance of the vestibular system induced by deafferentation of one vestibular nucleus leads to spontaneous nystagmus and contributes to the preponderance of dynamic vestibular responses. The static imbalance can be measured using the spontaneous nystagmus. Reduction of spontaneous nystagmus can be due either to reduction of vestibular tone on the intact side or due to restoration of tone on the lesioned side. The latter (in the case of a complete lesion) can be evaluated by the amount of slow phase velocity of nystagmus that can be elicited toward the intact side, remembering that in the horizontal plane a vestibular nucleus can only produce slow phases contralaterally. While reduction of vestibular tone on the intact side may be a first line of defense against an acute unilateral vestibular lesion to restore tonic vestibular balance (12), the ultimate goal of the vestibular system, in the case of an enduring complete unilateral lesion, must be to restore vestibular tone on the deafferented side to equal that on the intact side, since tone on the intact side is needed by the vestibular system to be able to respond to rotations in both directions. If the vestibular system merely eliminated tone on the intact side to balance the system it could only respond to rotations toward the intact side (excitatory stimulation for the remaining labyrinth).

Spontaneous nystagmus rapidly decreased in our patients, as in primates and other species, no matter whether the lesion was com-
Figure 6: The time course of recovery of the velocity storage mechanism as expressed by the vestibular time constant is shown for 60°/s rotation (A) and 180°/s rotation (B). Rotation toward the intact side is denoted with squares; rotation toward the lesioned side is denoted with arrows and crosses. Recovery of velocity storage was marginally possible in the two patients with remaining complete lesions. However, most of the patients did not regain normal function of velocity storage during the observation period. (Normal time constant values in our laboratory: for 60°/s rotation 13.4 ± 2.2 s and for 180°/s rotation 12.1 ± 1.7 s.)
plete or incomplete or whether the lesioned labyrinth regained function or not (7,13–18). Within 10 days after the lesion in 3 out of 6 patients, ice-water caloric stimulation on the intact side produced nystagmus opposite to spontaneous nystagmus, indicating that tone on the lesioned side had already been restored in these cases, since ice-water caloric stimulation induces a reduction of afferent vestibular activity on the irrigated side, mimicking a transient loss or severe reduction of function of the lateral canal. What remains and is responsible for the caloric-induced nystagmus toward the lesioned side is the tonic activity on the lesioned side. Of the 3 patients who initially could turn around their spontaneous nystagmus, 2 showed only low slow phase velocities opposite to their spontaneous nystagmus (4 and 6°/s); both of these patients had complete lesions at that time. The third patient had an incomplete lesion and showed a strong (30°/s) caloric-induced nystagmus opposite to spontaneous nystagmus, indicating that there was considerable tone on the lesioned side, probably coming from the partly lesioned labyrinth, which is the main if not the only source of tone for the vestibular nuclei in the intact situation (12,19).

Over time all patients increased their ability to turn around spontaneous nystagmus with ice-water caloric stimulation on the intact side, indicating more and more restoration of tone on the lesioned side. This was the case both for the patients who regained function of their formerly lesioned labyrinth and for the patients who retained a complete lesion. This finding supports our notion that restoration of tone on the lesioned side is at least partly responsible for the diminution of static vestibular asymmetry. Possible sources of tone could be a development of intrinsic activity in the vestibular nuclei itself or increased activity of afferents from the spinal cord or the cerebrum. Likewise a disinhibition of cerebellar afferents could contribute to the restoration of tone (5).

Another way of inducing slow phases toward the intact side is high-velocity rotation toward the lesioned side, which reduces the activity of the intact side toward zero. If the lesioned side is completely deafferented, the nystagmus that occurs in this situation is driven entirely by the tonic firing of type I vestibular neurons on the deafferented side. Since this is true only in the cases with complete lesions, we will further discuss only the patients in whom the lesion seemed to be complete. With a high-velocity rotation toward the lesioned side, all 6 patients with initially complete lesions produced slow phases toward the intact side ranging from 22 to 72°/s on the first recording day. These values were considerably higher than with ice-water caloric stimulation. This indicates that ice-water caloric stimulation does not completely inhibit a labyrinth or, more precisely, a lateral canal. More importantly, even in the cases with enduring complete lesions, a continuous increase of the amount of slow phase velocity toward the intact side induced by rotation toward the lesioned side could be observed, again indicating an increase in tone on the deafferented side.

Compensation of VOR Gain

Unlike monkeys, who show a fast recovery of VOR gain for rotations toward the intact side and a much slower recovery for rotations toward the lesioned side (6), most patients did not show a consistent change of the VOR gain for rotations toward the intact side (being $80 \pm 13\%$ at the first and $85 \pm 22\%$ at the last recording session for $60^\circ/s$ stimulation and $74 \pm 17\%$ and $76 \pm 16\%$ for $180^\circ/s$ stimulation, respectively, all values being in the normal range even at the first recording session). The initial fast recovery of VOR gain for excitation of the intact side known from primate studies, with most of the recovery completed within 3 to 4 days (6), has probably been missed due to the fact that the patients entered the study 3 to 13 days after the onset of symptoms. For rotations toward the lesioned side, most subjects showed a substantial VOR gain increase within about 25 days to close to final values. This was also the case for the two patients with enduring complete lesions. VOR preponderance decreased in parallel with the gain changes. This decrease was only partly due to the reduction of spontaneous nystagmus and could still be
Adaptive Mechanisms of VOR Compensation

seen after correction for spontaneous nystagmus. While about half of the patients could reduce VOR preponderance to close to zero for high-velocity rotations or even "overcompensated," including one of the patients with enduring complete lesions, the other half retained a substantial VOR preponderance for high velocity rotations even after 2 mo of recovery. Our results indicate that a VOR gain recovery is possible in humans, even in the case of a complete unilateral vestibular lesion, as was seen in primates, which contrasts with the findings in lower animals, where VOR gain compensation is much less complete (20,21).

The mechanisms for the increase of the VOR gain are still widely unknown. Using simulations with a bilateral model of the VOR we could show that there are several possibilities to increase the VOR gain (6). They all involve changes in synaptic efficacy. The increase of the VOR gain for rotations in the working range of the remaining labyrinth (in the case of a complete lesion) can be accomplished by increase of the synaptic sensitivity to which type I vestibular neurons on the intact side respond to primary afferent activity. The same result would be produced by adjustments of the synaptic sensitivity at a level closer to the ocular motoneurons or in a pathway parallel to the direct vestibulo-ocular reflex arc. Also adjustments of commissural synaptic sensitivities could be used to change the gain of the VOR. Precise electrophysiological measurements (unit recordings) during the recovery phase after a unilateral vestibular lesion in higher animals, which could help in resolving these questions, are still lacking for technical problems.

Changes in Velocity Storage

The central velocity-storage mechanism normally functions to prolong the VOR time constant above the value predicted by cupula-endolymph mechanics alone (22). In our patients, the time constant of the VOR was clearly subnormal, with average values between 4.7 and 7.8 s, depending on direction of rotation and velocity, reflecting a disabling of the velocity-storage mechanism, as has been reported previously in monkeys and in human patients (1,2,6,17,18,23). Some patients, especially those with incomplete lesions, showed a rapid and nearly complete restoration of the VOR time constant, paralleling the recovery of the lesioned labyrinth. Other patients, including the two with enduring complete lesions, only marginally increased their time constants, as did monkeys after a unilateral labyrinthectomy (6). It remains unclear why recovery of velocity storage seems to be prevented in the case of complete peripheral vestibular lesions, despite the fact that even in these cases the tonic activity in the vestibular nuclei is restored.

In summary, humans, like monkeys, have the ability to rapidly restore tonic vestibular symmetry within a few weeks after a unilateral vestibular lesion. Our results indicate that restoration of tone in the deafferented vestibular nucleus plays an important role in this rebalancing, being also responsible for the VOR gain recovery for high-velocity rotations toward the lesioned side. In as few as 3 days after the lesion, close to normal VOR gain values were found for rotations toward the intact side, indicating that most of the dynamic recovery in the working range of the intact labyrinth has already taken place by that time. This notion is supported by the results in monkeys, in whom most of the VOR gain recovery for rotations toward the intact side is achieved in the first 4 to 5 days, even though we were not able to really monitor this initial recovery, due to the fact that right after the lesion the patients are too sick to be recorded. And finally, while there is substantial recovery of static and dynamic vestibular function, no recovery takes place in the velocity-storage mechanism in the cases with complete unilateral vestibular lesions, which again parallels the findings in hemilabyrinthectomized monkeys.

Acknowledgments—The authors thank Mrs. G. Schönwälder for technical assistance with EOG recording. This research was supported by the Deutsche Forschungsgemeinschaft, SFB 307, A2.
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DYNAMICS OF ADAPTIVE CHANGE IN HUMAN VESTIBULO-OCULAR REFLEX DIRECTION

T.T. Khater, J.F. Baker, B.W. Peterson

Department of Physiology, Northwestern University School of Medicine, Chicago, IL 60611

Reprint address: T.T. Khater, Department of Physiology, Northwestern University School of Medicine, 303 E. Chicago Ave., Chicago, IL 60611

Abstract — Adaptive modification of vestibulo-ocular reflex (VOR) direction was characterized in humans by recording vertical and horizontal VOR eye movements during horizontal rotations in darkness at frequencies of 0.05 to 1 Hz before and after exposure to a VOR direction adaptation procedure. This procedure paired yaw horizontal vestibular rotation at 0.25 Hz with synchronous pitch vertical optokinetic motion. Saccades were removed from eye position records and VOR gain and phase were recorded. With an onset time constant of 36 min, the VOR measured during horizontal rotation in complete darkness acquired a vertical component in phase with the optokinetic stimulus presented during adaptation. The amplitude of this newly acquired vertical VOR component was maximal during rotation at the frequency of adaptation; at other frequencies, the amplitude was lower, but still significant. Unlike VOR direction adaptation in cats, the phase of the adaptive VOR component in humans did not show significant leads or lags at test frequencies below or above the adaptation frequency. These data suggest that, like the cat, the human VOR can be directionally adapted, and the pathways involving the adaptive component of the VOR are frequency specific.

Keywords — vestibulo-ocular reflex; adaptation; vestibulo-ocular reflex plasticity; optokinetic reflex.

Introduction

The vestibulo-ocular reflex (VOR) helps maintain a stable image on the retina by sensing head rotation of a certain direction and amplitude and producing a compensatory eye rotation of equal and opposite angular displacement. If the VOR did not have a gain close to unity, the resulting retinal slip of an image would cause that image to be blurred. Developmental change, calibration errors in neural circuitry, or damage to the vestibular or oculomotor apparatus can all alter the VOR output and precipitate retinal slip. This retinal slip provides a neural signal that is used to modify the VOR output and recalibrate the VOR gain (6,7,16). Once adaptation is complete, clear vision is restored, in either the short term (4,8,12) or the long term (5,9,14–16).

Errors in VOR direction can be caused by changes in the direction of visual field motion with respect to the direction of head motion. For example, the VOR direction will be erroneous if the visual field moves vertically every time the subject's head moves horizontally. VOR direction adaptation has been clearly shown to exist in cats, and can change the direction of eye movement produced by activation of the horizontal (10) or vertical semicircular canals, or the otolith organs (1). Study of the directional adaptive component of the human VOR has included the torsional VOR (2) or the vertical VOR (3), but adaptive change in human VOR direction has never been characterized across time and frequency as in cats (10). The experiments reported here are a description of an adaptive component of the human VOR. We show that this reflex dem-
onstrates frequency selectivity and time course response similar to the corresponding reflex of the cat.

**Methods**

Surface electro-oculographic (EOG) recordings were taken from 4 human males (ages 19-35) in 6 separate experimental sessions. Subjects were seated in a chair connected to a computer-controlled servomotor apparatus that could produce sinusoidal oscillations about the earth vertical axis, as illustrated in Figure 1. Their heads were fixed to the headrest of the chair, using a clamping device whose pads were placed securely on the subjects' temporal bones. The apparatus was enclosed in a light-proof room, which had a featureless screen 1.7 m in the front of the subject, upon which an optokinetic stimulus could be projected. Subjects were dark-adapted for a minimum of 30 min prior to each experiment in order to stabilize EOG.

![Figure 1. A schematic representation of our experimental setup during adaptation. As the arrows indicate, the subject was rotated around a vertical (yaw) axis, while viewing a pattern of spots projected on a screen in front of the subject. The spots moved vertically, rotating about an axis parallel to the subject's interaural axis (when the subject was facing directly ahead), and were synchronized to the yaw rotations of the chair. The subject's face shows the placement of the EOG electrodes.](image-url)
Dynamics of Change in Human VOR Direction

gain and minimize EOG drift. EOG electrodes were placed as illustrated in Figure 1 so that each eye's pair recorded approximately equal proportions of both horizontal and vertical components of eye movement. An electronic circuit was used to make a weighted sum and difference of the signals from the electrode pairs in order to produce pure vertical signals during optokinetic rotation, and pure horizontal signals during chair rotation with a stationary optokinetic stimulus. On the assumption that pure horizontal chair rotation resulted in no vertical eye motion, and that pure vertical optokinetic stimulation caused no horizontal eye motion, EOG crosstalk was minimized. The horizontal EOG signal was calibrated by instructing the subject to fixate on a stationary object on the screen while the chair was oscillated at a known amplitude in the horizontal plane. The vertical EOG signal was calibrated by instructing the subject to fixate on an object that was vertically oscillated on the screen at a known amplitude. After all EOG data had been collected, saccades were removed by computer-assisted manual editing of EOG records. The remaining slow phase velocities were fitted to sine waves in order to obtain a gain and phase value for each trial. Vertical gain was defined as vertical eye velocity divided by optokinetic stimulus velocity.

The subjects were adapted by exposing them to a visuo-vestibular stimulus which consisted of sinusoidal horizontal oscillation about an earth vertical axis at 0.25 Hz with a peak velocity of 19°/s, combined with a phase synchronized sinusoidal vertical optokinetic stimulus with a 26°/s peak velocity. The optokinetic stimulus was a full field (180° of visual angle) pattern of projected small spots. The axis of rotation of the spherical projection system was aligned parallel to the subject's interaural axis when the chair was centered at rest.

As a control, we measured the baseline horizontal and vertical VOR eye movements in an unadapted state by rotating the subjects horizontally in complete darkness at 0.05 Hz, 0.1 Hz, 0.25 Hz, 0.5 Hz, and 1.0 Hz. There were 4 trials at each frequency (8 trials at 1.0 Hz), and each trial consisted of 5 sinusoidal cycles (one cycle at 0.05 Hz). The data acquisition system sampled 1024 points of data for each trial, resulting in sample rates of 51.2 Hz, 20.5 Hz, 51.2 Hz, 102.4 Hz, and 204.8 Hz for the 5 respective rotation frequencies. The inputs to the data acquisition system were all filtered with 8 pole Bessel filters set to cut off at 10 Hz. Rotations had a constant peak velocity of 19°/s at all frequencies. Subjects were instructed to fixate on an imaginary object 1.7 m in front of them in order to elicit robust VOR responses. After a 2-h adaptation period, interrupted every 15 min by shutting off the optokinetic projector and measuring the horizontal and vertical VOR at the adaptation frequency, the subject underwent a series of tests identical to those in the unadapted state, again in complete darkness. Three of our subjects were subsequently “de-adapted” by rotating them in a stationary visual field; the optokinetic projector was turned on but remained immobile. Every 5 min throughout this “de-adaptation” period, the VOR was measured at 0.25 Hz in complete darkness, again while the subject was attempting to fixate on an imaginary object. Alertness was maintained by talking to the subject during the testing sessions. During the training sessions, different diversions such as music, murder mystery recordings, or humorous recordings were used to maintain alertness. Horizontal and vertical VOR gains and phases measured in the unadapted or adapted state were vectorially averaged together across multiple runs at the same test frequency. The preadaptation vertical VOR averages were then vectorially subtracted from the postadaptation vertical VOR averages to obtain the gain and phase of the adaptively generated changes in the VOR.

Results

Figures 2A and 2B depict the preadaptation and postadaptation vertical VOR induced by horizontal rotation at 0.25 Hz. After adaptation, when the subject was exposed to a horizontal vestibular stimulus in
A: Before Training  B: After adaptation  C: After "de-adaptation"

Figure 2. Horizontal head position and vertical eye position during yaw rotation before adaptation (A), after adaptation (B), and after "de-adaptation" (C). Vertical eye velocity and vertical eye velocity fit were computed for each trial taken, after saccades were removed. There is little vertical VOR during yaw before adaptation and after "de-adaptation," but vertical eye movement is clearly evident 2 h after adaptation. (The small vertical VOR responses in columns (A) and (C) are due to the limitations of the horizontal and vertical calibration procedure, and the expanded scale of the velocity fit records.) All data sets were taken from the same experiment.

complete darkness, the VOR showed a vertical component that was not seen prior to adaptation. The phase of the acquired response was the same as that of the adapting optokinetic stimulus. This additional component of the VOR was present throughout the post-adaptation testing period. Figure 2C shows the vertical VOR response in complete darkness 10 min after "de-adaptation" by rotation in a stationary visual field for a period of 20 min. Clearly, the response that was present throughout the postadaptation test interval diminished back to baseline.

Figure 3 shows the time course of adaptation of the vertical VOR. Adaptation initially occurs rapidly, first appearing after about 15-30 min, but the increase in vertical VOR gain rapidly tapers off. When modeled by a simple exponential, the time constant obtained by fitting the average of all six sets of time course data was 36 min, which is remarkably close to the value of 35 min obtained for the cat (10). When the subjects were rotated in a stationary visual environment after adaptation, all reported a sensation of visual field movement which was in the opposite direction of spot motion during training. In other words, when leftward vestibular stimulation had been coupled with upward optokinetic stimulation, the subjects reported a downward movement of the visual field when they were rotating leftward, even though the visual field was stationary. No subject, however, reported a sensation of body axis tilt. "De-
adaptation" time course was measured in 3 of the 6 cases. In each of these cases, the acquired vertical VOR response in complete darkness had clearly diminished in amplitude within 5 to 10 min, and had returned completely to baseline within 15 to 25 min.

As shown in Figure 4A, the greatest post-adaptation vertical VOR response to yaw movements occurred at the 0.25 Hz training frequency. At test frequencies lower and higher than the training frequency, the response was smaller, but still significantly greater than in the pretraining condition. This effect is similar to what happens in the cat. Surprisingly, the phase of the acquired response across all frequencies, showed little deviation from 0°. This is in contrast to VOR direction adaptation in the cat, which shows a significant phase lag at high frequencies, and a phase lead at the lower frequencies.

There was no consistent difference in the horizontal VOR after the adaptation period, as shown in Figure 4B. Some of our subjects showed an increase in gain, and some showed a decrease in gain. (A gain was assigned a negative value if its corresponding phase value was >90°, or <−90°.)

Discussion

Several studies in recent years have demonstrated a broad range of adaptive capability of the VOR. The gain, phase, and direction of the VOR have been shown to be modifiable in animals from goldfish (19,20) to rabbits (11) to monkeys (15) to humans (2,3,8,9). Adaptation of the VOR has been induced by altering visual input during vestibular stimulation produced by passive head rotation (12,17). Passive sinusoidal rotation has been used to study the frequency selectivity of VOR adaptation. All animals tested have shown selectively greater adaptation gain near the training frequency (6,10), with the broadest tuning reported in monkeys (13). Our results suggest that human VOR adaptation to sinusoidal rotation produces even broader frequency tuning than found in monkeys.

The time constant of 36 min that we obtained was very similar to the time constant obtained in comparable studies on the cat. Previous human studies have also shown that human time course of adaptation can have a short time constant, on the order of minutes (4,8), in addition to intermediate and long
Figure 4. Dynamics of induced vertical eye movement at a training frequency of 0.25 Hz. (A) Differential band-pass characteristics of vertical eye movements in the dark. Data in this plot display the postadaptation responses with the preadaptation responses vectorially subtracted from them. Vertical gain was defined as the ratio of eye velocity to optokinetic stimulus velocity. (B) Differential characteristics of horizontal eye movements in the dark. As above, the preadaptation horizontal eye responses were vectorially subtracted from the postadaptation responses and displayed. Note that vertical data show a stereotypically shaped curve, but horizontal data are not reproducible from subject to subject. Each symbol type represents data from a single experiment. Symbols connected by solid lines indicate the vectorial mean of all data at each particular frequency.

Time constants that can be as long as a few days (9). This evidence supports the idea that there may be more than one adaptive process going on in the brain: one that may react quickly, but not have a very strong effect, and others that may have a slower onset, but a more robust impact on VOR gain. Other possibilities that may account for different
Dynamics of Change in Human VOR Direction

Time constants include strength of the adaptation stimuli, both visual and vestibular, and state of awareness of the subject.

The broad frequency response we observed, with nearly constant phase across the spectrum from 0.05 to 1.0 Hz, could be attributed to either a species difference or to our use of a VOR direction adaptation paradigm. A comparison of cat and human VOR studies pairing yaw vestibular rotation to pitch optokinetic stimulation supports the idea of a species difference. Using the same bandpass filter model that we applied to our cat VOR direction adaptation data, we obtained time constants of 0.11 and 2.9 s for the human data, as compared to 0.14 and 1.1 s in cats (10). The more widely spaced time constants for the human data indicate that the human curve has a much broader tuning than the similarly shaped cat curve. The bandpass filter model provided a good fit to the adaptive VOR phases in the cat, but does not predict the nearly constant phase of adaptive human VOR (see Figure 2B). This apparent species difference suggests that human VOR modification involves more complex mechanisms than in lower animals.

Acknowledgment—This work was supported by NIH grants EY05289, EY06485, EY07342. Special thanks to Sharon K. Coles, Emily A. Keshner, Kevin A. Khater, John A. Miyano, Keith D. Powell, Kevin J. Quinn, and Steven A. Rude.

REFERENCES

DYSCALCULIA IN PATIENTS WITH VERTIGO

John Risey* and Wayne Briner†

Departments of *Otolaryngology and †Pharmacology,
Tulane University School of Medicine, New Orleans, LA 70112
Reprint address: John Risey, Department of Otolaryngology,
Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112

Abstract — This paper reports a hitherto undescribed relationship between vertigo of central origin and dyscalculia. Subjects with vertigo skipped and displaced decades when counting backwards by two. The error is not recognized when presented visually. The subjects also display decrements in ability to do mental arithmetic and in central auditory processing. The results are discussed in light of the relationship between the central vestibular/auditory system and structures involved in higher cognitive function. The relationship between balance disorders and children with learning disabilities is also examined.

Keywords — dyscalculia; vertigo.

Introduction

A direct correlation between vertigo and dyscalculia has not been previously reported. Dyscalculia is a symptom associated with a number of neurologic entities (1). The exact form varies with the size and localization of the lesion (2,3,4). Vertigo, on the other hand, is a classic symptom of peripheral vestibular dysfunction (5,6) but can be associated with central lesions (7,8).

For these reasons we became intrigued by the observation that several persons undergoing routine electronystagmographic (ENG) evaluation of vertigo produced specific and identical counting errors. The errors consisted of skipped and displaced decades when asked to count backwards by two's (i.e., 94, 92, 80, 88, 86, 84, 82, 70, 78...). The error occurred at each decade except the transition from 12 to 8. Simple repetition of the task by the patient neither eliminated nor materially changed the details of the counting errors. If questioned, the patient admitted difficulty but expressed confidence that the task was performed correctly. Although other errors may be present, the specific pattern of skipped and displaced decades was repeated on separate occasions. Although similar types of errors have been discussed by others (9), they have not been associated with vertigo.

We investigated this type of dyscalculia in 14 patients who presented to the otolaryngology clinic with the primary complaint of vertigo.

Methods

Fourteen patients presenting with a primary complaint of vertigo and demonstrating the counting error (i.e., 64, 62, 50, 58, 56, ...) were obtained for testing. As one control group seven patients complaining of vertigo who did not produce the counting error were also evaluated. As another control group eight additional patients were recruited. The patients making up the second control group entered the clinic with a primary complaint of tinnitus and did not complain of vertigo. Tinnitus patients were selected as the second control group because it is a common otologic complaint that involves the same end organ (inner ear) often involved in vertigo.

Dr. Briner's current address is; House Ear Institute, 256 S. Lake St., Los Angeles, CA 90057.

Received 15 Nov 1989; Revised 26 March 1990; Accepted 26 March 1990.
Cognitive Testing

Backward counting. All subjects were asked to count backward from 100 to 0 by 2's as quickly and as correctly as possible. The time for the subject to complete the task was recorded in seconds. The total number of errors made, of any type, was recorded. The subjects were classified as having the specific error if and only if they skipped and displaced decades, as described above.

Visual presentation. Each subject was shown a series of flash cards, one per second. Printed on the cards was a sequence of numbers representing the error (ie, 100, 98, 96, ..., 92, 80, 88, ..., 6, 4, 2, 0). The subjects were instructed to tell the investigator if they noticed anything unusual about the numbers. The number of cards on which the error was identified was recorded (maximum score 9). A higher score indicates better performance (ie, more errors detected).

Arithmetic skills. Each subject was given the math subtests of the Wechsler Adult Intelligence Scale (WAIS) (10). These tests involved mental arithmetic and the forward and backward recall of verbally presented digits. The scaled scores (Mean = 10, Standard Deviation = 3) were recorded for all tests as well as the raw scores for the digit recall portions.

Peripheral Audiologic Testing

Hearing tests. Every subject was tested for pure tone air and bone conduction thresholds, speech reception thresholds, and word discrimination tests for each ear. These procedures were carried out to rule out peripheral auditory pathology which might influence the findings.

Central Auditory Testing

Pitch Pattern Sequence (PPS) test. This test consists of a series of three tones, one of which differs in pitch from the other two (11). The subject was asked to verbally repeat the order of tone presentation in their correct sequence (ie, high, high, low). The tones are presented 50 dB above the 1 kHz threshold for hearing. Each ear was tested separately. Results are recorded as the percentage threshold for each ear. The results between the ears were also averaged to obtain a total score.

Staggered Spondaic Word (SSW) test. All subjects were given this test in which one spondaic word (eg, two syllable word with equal stress on each syllable) is presented to each ear. The presentation of the words is staggered with the second half of the first spondee overlapping the first half of the second spondee. The SSW produces a single numeric score. The larger and more positive the score the greater the central auditory impairment (12,13). The SSW is self-correcting for peripheral hearing loss (14) and is not significantly affected by age (15).

Evaluation of the Vestibular System

Electronystagmogram (ENG). The ENG is a standard clinical test for the evaluation of vertigo and was performed on all subjects who presented with a complaint of vertigo. This test was usually the last one to be performed. The ENG was a dependent variable and subjects were not preselected on the basis of this test. Subjects were classified as having vertigo of peripheral origin if they met the following criteria: spontaneous or positional nystagmus behind closed eyes only and unilateral weakness (as determined by Jongkees formula) of greater than 20% on caloric testing (16). Those subjects with vertigo who did not meet these criteria were classified as having vertigo of central origin.

Results

Conventional audiometric results (eg, pure tone and speech tests) were within normal limits for all three groups. There were no significant age or educational differences between the groups (Table 1). We were unable to obtain ENGs on two subjects with vertigo
Dyscalculia in Patients with Vertigo

Table 1. Patient Demographics
(N = 29; 15 male patients, 14 female patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SEM†</th>
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<tr>
<td>Age</td>
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Control, no vertigo, 8; with vertigo, 7; dyscalculia with vertigo, 14; central vertigo, 13; peripheral vertigo, 6. Two patients did not have electronystagmographies (ENGs) available.

(one who had the error, and the other one without it).

Subjects with the counting error consistently had a greater number of total errors in backward counting and took longer to complete the task than either of the two control groups. The dyscalculia group also performed the worst at visually recognizing errors on cards (Table 2).

The errors produced by the target group were not confined to simple counting. The target group also had the lowest scores for the arithmetic and digit span portions of the WAIS, and had greater difficulty in the backward digit span recall than either of the other two groups (Table 2).

SSW scores were significantly larger (indicating poorer performance) for the dyscalculia group when compared to the other two. Also, the SSW correlated significantly with all cognitive tests except forward counting.

The digit scaled score formed the strongest relationship. While there were no differences between groups for the PPS, the PPS did correlate with counting time and the digit scaled score. The right ear correlations demonstrated all of the averaged correlations. The PPS score for the left ear correlated only with the digit backward test (Table 3).

No subject with a peripheral (vestibular end organ involvement) cause of vertigo (as determined by ENG results) was found to have dyscalculia. Conversely, all subjects with dyscalculia were found to have central vestibular abnormalities (Table 4). It is important to note that the patients were not preselected for the type of vertigo. Rather, they were simply classified according to the presence or absence of counting error, and the ENG test was administered as the last test.

When patients with vertigo were considered separately and classified by type (peripheral or central), the group with central vertigo did significantly poorer on the SSW and on all cognitive tests, except digit forward (Table 5).

Discussion

It is clear that the error described is associated with central vertigo. We have found that about 20% of patients presenting with a
complaint of vertigo will produce the error (unpublished data). Additionally, the error does not appear to be an isolated phenomenon or artifact. Patients with the disorder display a general impairment in their ability to do mental arithmetic. Longer counting times are present and, in fact, the patients were unable to recognize the error when it was presented to them visually.

A central site of lesion is indicated by the poorer (larger) SSW scores for those with the error. The dyscalculia group made approximately 9 times as many errors on the SSW as the control subjects. This indicates that the error is not due to a dysfunction of the vestibular system alone, but is associated with a disorder common to both the vestibular and higher cognitive systems, and is detectable using audiometrics (ie, via testing of the auditory system). Another indication that the source of the described error is of central origin comes from correlations of cognitive tests with the SSW and PPS. We do not feel that these findings are the result of attention deficits specific to central vertigo for two reasons: 1) it is highly improbable that an attentional deficit would result in a specific pattern of dyscalculia such as the type reported here; and 2) the central vertigo group did not demonstrate difficulty with peripheral auditory tests that require a high level of attention. We do not believe that this phenomenon is the result of vertigo interfering with normal intellectual functioning. If this were the case, that vertigo causes poorer performance due to a general distracting or interfering property of the symptom on intellectual function, then poor performance would be present for all patients with vertigo (central and peripheral) and not just those with central vertigo.

The central vestibular system can be considered on at least three levels, the brainstem, thalamus, and cortex. The brainstem represents the initial level of central integration (17). From the level of the brainstem the ascending vestibular system projects to a number of thalamic nuclei including nucleus ventralis intermedius, medial geniculate body, nucleus ventralis posterior lateralis, nucleus magnocellularis, nucleus ventralis posterior-medius, and the medial nucleus of the thalamus (18,19,20). Because of the diffuse nature of vestibular projections it is suggested by Liedgren et al (18) that there is no specific thalamic vestibular nuclei. Also, it is important to note that the ascending vestibular system and the ascending auditory system are anatomically parallel to each other (17,20). Also, the auditory system projects to the medial geniculate body, as does the vestibular system (20).

Dyscalculia has been associated with thalamic lesions (21) and localized to lesions of the anterior dorsomedial, anterior, and anteriomedial thalamic nuclear groups and the mammillothalamic tract (22). In addition,

### Table 3. Correlation Coefficients: Audiometric Tests of Central Function and Cognitive Performance

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<td>-.265</td>
</tr>
<tr>
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</tr>
<tr>
<td>Errors recognized visual</td>
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</tr>
<tr>
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<tr>
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<td></td>
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<tr>
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<td>.110</td>
</tr>
<tr>
<td>Backward</td>
<td>.347*</td>
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<tr>
<td>Scale score</td>
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<table>
<thead>
<tr>
<th></th>
<th>Right ear</th>
<th>Left ear</th>
<th>Average</th>
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<tr>
<td>Errors verbal counting</td>
<td>-.265</td>
<td>-.295</td>
<td>-.290</td>
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<tr>
<td>Counting time</td>
<td>-.524*</td>
<td>-.315</td>
<td>-.429*</td>
</tr>
<tr>
<td>Errors recognized visual</td>
<td>.221</td>
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<tr>
<td>Arithmetic scale score</td>
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<td>.229</td>
<td>.254</td>
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<td>Digit</td>
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<td></td>
<td></td>
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<tr>
<td>Forward</td>
<td>.110</td>
<td>.067</td>
<td>.090</td>
</tr>
<tr>
<td>Backward</td>
<td>.347*</td>
<td>.393*</td>
<td>.384*</td>
</tr>
<tr>
<td>Scale score</td>
<td>.342*</td>
<td>.297</td>
<td>.330*</td>
</tr>
</tbody>
</table>

*P < 0.05.

### Table 4. Chi-square Analysis: Dyscalculia and Source of Vertigo

<table>
<thead>
<tr>
<th>Source of vertigo</th>
<th>Peripheral</th>
<th>Central</th>
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</thead>
<tbody>
<tr>
<td>Dyscalculia</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Controls</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

χ²(1) = 19.0, P < 0.001.
Ojemann (23) was able to produce errors and rate changes in backward counting by stimulating the anterior and interlaminar thalamic nuclei. Because of the diffuse nature of vestibular projections, the majority of the thalamic nuclei involved probably received input from the central vestibular system.

The vestibular cortex has been localized to several areas including the superior temporal gyrus (24), posterior postcentral gyrus at the base of the intraparietal sulcus between the first and second somatosensory fields, juxtaposed between the somatosensory and acoustic areas, the sensorimotor cortex and pre- and post-central gyrus, parietal-temporal cortex, and as being adjacent to the auditory cortex (25,19,17,8). The vestibular, auditory, and association cortices are probably heavily interconnected (26,27,24) and have extensive connections with the thalamus (24).

Cortical lesions that produce dyscalculia have been localized to either hemisphere. Specific cortical lesions causing dyscalculia have been attributed to the medial temporal lobe (22), left parietal lobe (28), left posterior hemisphere and right hemisphere (29), left angular gyrus (3,30), left temporal-occipital lesion or right parieto-temporo-occipital area (31). Because the vestibular cortex is represented bilaterally, a large number of cerebral lesions directly insult either the vestibular cortex and/or the association cortex to which it projects.

The vestibular system was shown to influence higher cognitive function by Cappa et al (32) who temporarily reversed neglect phenomenon and agnosia by stimulating the vestibular system with caloric irrigation. Additionally, children with learning disabilities have been found to have disorders of the vestibular and/or the proprioceptive systems (33,34,35,36).

We find it reasonable to hypothesize that the error in counting found in patients with central vertigo has its origin in an anatomic or physiologic impairment at the level of the thalamus or, more probably, the temporo-parietal cortex. Reasons include that the disorder is 1) reflected in poor performance on tests of central (cortical) auditory dysfunction including the SSW and PPS (12,13,11), and 2) because the error is not detected by the subjects even when presented visually. We suggest that the most likely site of lesion is the high level association cortex.

A correlation between the clinical complaint of vertigo and the inability to correctly process numbers has not been previously reported. Additional research needs to be conducted to extend these observations and possibly correlate them with indices of neurologic deficit for both adults and children. Particularly, work needs to be performed in the area of children with learning disorders because the existence of balance problems among such children is reported to be high (34). One of the typical characteristics of the learning disabled is difficulty performing mathematical computations (37). The ability to positively correlate these two components

---

**Table 5. ANOVA Central vs. Peripheral Vertigo (mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Central (N = 13)</th>
<th>Peripheral (N = 6)</th>
<th>F(1,16)</th>
</tr>
</thead>
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<tr>
<td>Error backward verbal counting</td>
<td>10.7 (4.6)</td>
<td>0 (0)</td>
<td>31.3*</td>
</tr>
<tr>
<td>Counting time</td>
<td>64.2 (9.2)</td>
<td>47.5 (5.1)</td>
<td>6.7*</td>
</tr>
<tr>
<td>Number recognized visual errors</td>
<td>3.0 (3.5)</td>
<td>9 (0)</td>
<td>16.7*</td>
</tr>
<tr>
<td>Arithmetic scale score</td>
<td>7.6 (0.7)</td>
<td>12.2 (0.9)</td>
<td>15.1*</td>
</tr>
<tr>
<td>Digit span</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>5.7 (0.3)</td>
<td>6.0 (1.0)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Backward</td>
<td>3.8 (0.3)</td>
<td>5.5 (0.6)</td>
<td>10.6*</td>
</tr>
<tr>
<td>Scale score</td>
<td>7.8 (0.6)</td>
<td>11.7 (1.5)</td>
<td>8.7*</td>
</tr>
<tr>
<td>SSW†</td>
<td>9.8 (2.6)</td>
<td>0.8 (0.7)</td>
<td>5.7*</td>
</tr>
<tr>
<td>PPS† (average left and right ears)</td>
<td>68.6 (8.8)</td>
<td>85.2 (6.5)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*P < 0.05.
†See Table 2, footnote †.
Acknowledgment—We would like to thank Dr. Ed O’Neal and Dr. Cornelia Koniditsiotis for supplying some of the materials used as well as providing advice. Dr. Briner is supported by NIH training grant NSO-7058 to the Kresge Hearing Research Group of the South (via Dr. Charles Berlin and Dr. Paul Guth). We would like to thank Dr. Robert Miller for his support of this research by allowing access to clinical facilities. Thanks to Dr. Paul Guth and Dr. Jack Katz for critically reading the manuscript.

REFERENCES

SUPPRESSION OF OPTOKINETIC VELOCITY STORAGE 
IN HUMANS BY STATIC TILT IN PITCH

S.H. Lafortune, * D.J. Ireland,† and R.M. Jell* †

Departments of *Physiology and †Otalaryngology, University of Manitoba, Winnipeg, Manitoba, Canada
Reprint address: R.M. Jell, Ph.D., Department of Physiology, University of Manitoba, Winnipeg, MB, Canada, R3E 0W3

Abstract — The effects of static tilts about the pitch axis on human horizontal optokinetic afternystagmus OKAN (HOKAN) were examined. Static tilts in pitch produced tilt-dependent HOKAN suppression. The slow decay (indirect pathway) component (coefficient C and long time constant 1/D) of the two-component model for OKAN was significantly reduced, while the short decay (direct pathway) component (coefficient A and short time constant 1/B) remained invariant as angle of tilt was increased. These results provide further evidence that otolith organ activity can couple to horizontal velocity storage in humans; in accordance with models proposed in the literature.

Keywords — velocity storage; integrator; vestibular; man; oculomotor; otolith organs.

Introduction

A common velocity storage integrator is thought to be involved in the generation of horizontal optokinetic afternystagmus (OKAN) and postrotatory nystagmus (PRN). Characteristics of the horizontal velocity storage mechanism have been studied extensively in monkeys (1,2,3,4,5), cats (6,7) and humans (8,9,10,11,12,13,14,15). We have shown in an earlier paper (13) that human horizontal OKAN (HOKAN) slow phase velocity (SPV) decay can be described by a 2-component double exponential model of the form: \( SPV = A \exp(-Bt) + C \exp(-Dt) \). The velocity storage associated with HOKAN or PRN can be modulated by off-vertical axis rotation (OVAR) (3,16,17,18). In monkeys, as in humans, OVAR generates a continuous horizontal nystagmus which lasts as long as the stimulus persists (16,17,18,19,20). This continuous slow phase eye velocity has been attributed to activity arising mainly in the otolith organs (21,22) because plugging all six semicircular canals does not abolish the OVAR response (18 [monkeys], 21 [cats]), while ablating the otolith organs does (22 [rabbits]). On the other hand, it has been demonstrated that the PRN following OVAR about any axis other than the vertical is always significantly less than that following vertical axis rotation (16,23,24,25,26). To account for the continuous nystagmus during OVAR, Cohen et al (18) proposed that otolith-mediated activity, due to a change in head position with respect to gravity, coupled to the velocity storage mechanism thereby prolonging the nystagmus. To explain PRN suppression after OVAR, it was suggested that this otolith-induced slow phase activity, being oppositely directed to the postrotatory response, then cancelled the latter. That the otoliths were also responsible for the PRN suppression following OVAR was verified by Igarashi et al. (27), who showed that bilateral macular ablation in monkeys prevented the observed PRN suppression following rotation about an axis tilted laterally at 9° and 18° from the vertical.

Tilt-induced suppression of PRN can also be produced if animals are passively tilted during the PRN following rotation, or during the HOKAN obtained following optokinetic stimulation about the vertical axis (5,16). This
The effect was shown to be dependent upon the integrity of the cerebellar nodulus and uvula since nodulo-uvulectomy abolished tilt suppression of both PRN and HOKAN in monkeys (5). Passively tilting humans during PRN after vertical axis rotation has also been shown to induce PRN suppression (24). If PRN and HOKAN share the same velocity storage mechanism, then passive or static tilts in pitch should also result in suppression of HOKAN. In fact, this has been demonstrated in the monkey (16,28).

In a recent study (29), we found that active head tilts about the pitch (left-right) axis resulted in HOKAN suppression, with pitch forward tilts exerting the most significant effect. These results were in agreement with studies on PRN suppression induced by active head tilts (30,31,32) in humans. However, active head movement raised questions of specificity of the effect because of the possible contribution of nonvestibular input to velocity storage. It therefore became necessary to examine the effect of static head tilts on the HOKAN. Active yaw movements were included as a control in our study (29) because they were expected to generate a similar nonvestibular input without otolith stimulation.

It has been proposed that velocity storage has a three-dimensional gravity-dependent organization, permitting storage of eye velocity information in each of the three canal planes (28,33) and cross-coupling from any of the three “modes” of storage (horizontal, vertical, or torsional) to another.

In the present study, we have attempted to examine the effects of static tilt about the pitch axis on two-component human HOKAN. Some of the results have already been presented in a preliminary report (34). Vertical eye movements were recorded during the HOKAN in order to determine whether cross-coupling from the horizontal mode of storage to the vertical mode had occurred.

**Methods**

A total of 10 normal subjects, 4 male and 6 female, ranging in age from 18 to 35 years and with no known history of vestibular or visuomotor disorder, participated in this study. Subjects, head restrained against a headrest by a velcro strap, were seated in a tilting chair upon which was mounted a plastic optokinetic sphere of diameter 85 cm. The sphere was attached at the top to the shaft of a motor, and was open at the bottom. The optokinetic sphere (white) was lined internally with 2-deg.-wide vertical black stripes spaced at 20 deg. intervals, and could be lowered to completely encircle the subject's head and shoulders. Both chair and sphere together could be tilted backward from the vertical. Static tilt angles examined were 10°, 20°, 30°, 40°, 60° and 70° from the vertical and were determined by plumb line on the chair. The position of the sphere with respect to the chair and subject was kept constant at all angles of tilt. The distance from the inside surface of the sphere to the subject's nasion was 38 cm.

One OKN/OKAN trial consisted of 60 s of horizontal optokinetic (OK) stimulation at a constant velocity of 40°/s. At the end of this interval, the lights were extinguished and the DKAN recorded.

Horizontal and vertical eye movement signals were detected using DC-coupled standard electro-oculography (EOG) with 3M Red Dot infant EOG electrodes. Horizontal electrodes were placed at the outer canthi of each eye, with reference at the nasion. Vertical electrodes were placed above and below the left eye, with reference at the second cervical vertebra. The detected voltage signals were relayed to a computer model 9836 Hewlett-Packard for display, digital storage (sampling rate 200/s) and subsequent analysis.

The angle (20°) between the centers of 2 stripes was used for horizontal calibrations. Colored dots (8 mm diameter) placed 20° above and below the center of the sphere were used for vertical calibrations. Because it had previously been established that response decrements in OKAN measurement parameters occur during the initial three horizontal OKN/OKAN trials of naive subjects (35), a “habituating” session consisting
of 3 trials with leftward sphere rotation followed by 3 trials with rightward sphere rotation, was carried out before the first test session.

One test session consisted of one control (upright) OKN/OKAN trial and 3 tilt trials in which the chair was in a tilted position during horizontal optokinetic stimulation. These trials were repeated in the opposite sphere direction within the same session. A total of 2 test sessions (8 trials/session) per subject was carried out in order to examine all 6 angles of tilt in both sphere directions. The order of control and tilt trials in each session was completely randomized.

Data analysis

Data analysis was carried out as described in earlier papers (13,35), except for minor changes. The raw HOKAN decay obtained in each trial was displayed on a computer screen. Digitization of beginning and end points of each slow phase displayed was performed interactively by means of a cursor, yielding plots of slow phase velocity (SPV) decay after lights out. Measurement parameters for each HOKAN decay included total area under the decay curve, and coefficients of the double exponential model for human OKAN of the form: \[ SPV = A \exp(-Bt) + C \exp(-Dt) \] (13). Coefficient A is the initial SPV of the fast decay or direct pathway component while coefficient C is the initial SPV of the slow decay or indirect pathway component. The short time constant of the fast decay is represented by the term \(1/B\) and the long time constant of the slow decay is represented by \(1/D\). Estimates of the coefficients and time constants of the double exponential equation were obtained using nonlinear regression analysis according to Marquardt’s procedure (36). Area under the decay curve was determined by Simpson’s Rule integration.

Effects of tilt angles on the area under the OKAN decay curve, on the coefficients, on the time constants, and on OKN gain were tested statistically by means of analysis of variance (ANOVA) (37), using the 3-way split plot design (based on Hicks (38)). In order to identify the source of the significant differences revealed by the ANOVA, the planned multiple comparisons test, using the least significant difference t test (37), was included in the analysis.

Results

An example of one subject’s raw HOKAN obtained in the control (upright) and static tilt positions is presented in Figure 1. The associated vertical eye movements, obtained at each angle of tilt for the same subject, are shown in Figure 2. Vertical eye movements in the control position during HOKAN were either nonexistent or consisted of blink artefacts, notwithstanding the presence in some records of cross-talk during OKN. The pattern of vertical eye movement activity varied considerably between subjects. For 9 out of 10 subjects, no distinct vertical nystagmus pattern was observed, either in the control position or at any tilt angle. In one subject, a clear vertical nystagmus, slow phases downward, appeared immediately upon extinguishing the lights following 60 s of horizontal OKN while tilted in pitch. The response, which was present for all tilt trials but not for control trials, resembled a spontaneous nystagmus in that the SPV did not decay appreciably during the 60-minute interval in the dark. In addition, the nystagmus became stronger with every tilt trial as the test session progressed. However, at 30° of tilt after rightward stripe rotation and at 60° of tilt after leftward stripe rotation, a slight lowering of the downward SPV values was apparent over the course of the HOKAN.

The significance of the effects of static tilt angle about the pitch axis on HOKAN parameters and OKN gain is summarized in Table 1. As shown in Figure 3 and Table 1, no significant effect of static tilt angle in pitch on the parameters of the short time constant component of HOKAN (A and 1/B) could be demonstrated. (Control values from both test sessions were pooled.) Multiple comparisons did reveal, however, a slight trend towards a
Figure 1. Examples of raw horizontal OKN/OKAN records obtained for one subject at each static tilt angle in pitch: 10°, 20°, 30°, 40°, 60°, and 70° from the vertical. Direction of stripes was rightwards. Controls 1 and 2 are the OKN/OKAN records obtained in the vertical position for test sessions 1 and 2. (All trials were randomized within both sessions.) In the top trace of each record are presented 20 s of steady state OKN. Lights-out occurred at end of each upper trace. Each bottom trace shows 20 s of HOKAN immediately following lights out. Calibrations are 1 s and 10°.

tilt angle dependent lowering of coefficient $A$ values, with significantly lower values ($P < 0.05$) observed at 70° tilts than at 10° or 30° tilts. A significant asymmetry ($P < 0.01$) was observed between coefficient $A$ values obtained with leftward sphere rotations and values obtained with rightward sphere rotations.

Compared to control values, tilt induced a significant reduction ($P < 0.01$) in coefficient $C$ values of the long time constant component of HOKAN (Figure 4). No asymmetries in responses to leftward or rightward sphere rotations could be detected.

A highly significant decrease ($P < 0.001$) in the long time constant ($1/D$) was obtained at all angles of tilt examined (Figure 4, Table 1). No asymmetries were apparent between responses to leftward and rightward sphere directions. The time constant was reduced to 20.8 s at 10° of tilt and remained at that level up to 40° of tilt. At 60° of tilt, its value decreased to half of the control value (14.7 s) and at 70° it was reduced to approximately one quarter of the control value (7.8 s).

The total area under the decay curve was also significantly reduced ($P < 0.001$) at all angles of tilt (Figure 5, Table 1). A linear relationship between angle of tilt and area under the curve was observed. A slight asymmetry ($P < 0.05$) was found between the mean values obtained from leftward and rightward sphere rotations.

Mean OKN gain varied between 1.0 and 1.2 (Figure 5). The ANOVA showed that the OKN gain was tilt-dependent, but multiple comparisons revealed that this was due to a significant drop ($P < 0.01$) at 60° and 70° of tilt. OKN gains below 60° of tilt were not tilt-dependent ($P > 0.05$). There was no left-right asymmetry in this effect.
Figure 2. Vertical eye movements recorded for each horizontal OKN/OKAN record presented in Figure 1. Top trace of each record shows the 20 s interval of vertical eye movements measured during the corresponding OKN interval shown in Figure 1. Lights out occurred at end of each upper trace. Bottom trace shows the vertical eye movements during the first 20 s of HOKAN. Calibrations are 1 s and 10°.

Table 1. Effects of Static Tilt Angle About the Pitch Axis on OKAN Parameters and OKN Gain

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Static tilt angle</th>
<th>Probability (P) values (i)</th>
<th>Probability (P) values (ii)</th>
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<tr>
<td>OKAN:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>NS</td>
<td>p &lt; 0.01</td>
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</tr>
<tr>
<td>1/B</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>p &lt; 0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>1/D</td>
<td>p &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>OKN: Gain</td>
<td>p &lt; 0.001</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Levels of significance were determined by analysis of variance. NS = not significant. A significant P value for a parameter implies that the parameter is dependent upon (i) tilt angle, or (ii) stimulus direction.

Discussion

In this study, we have demonstrated that static whole body tilts about the pitch axis during horizontal optokinetic stimulation result in suppression of human horizontal OKAN (HOKAN). Static tilts about the pitch axis (backwards from the vertical) were found to induce a highly significant reduction in the long time constant component of the two-component model for HOKAN. A tilt-dependent decrease was demonstrated in coefficient C, the long time constant 1/D and total area under the decay curve. These results are in agreement with findings on suppression of HOKAN following static tilts during horizontal optokinetic stimulation in monkeys (28). Of interest is the observation that the decline in 1/D was steepest at 60° and 70° of tilt, which are closest to the supine position, in accordance with the observation by Fernandez et al (39) that utricular afferents are most sensitive to small tilts when the animals are near the prone or supine positions. On the other hand, the relationship between tilt angle and total area under the decay curve was clearly linear.
Figure 3. Effect of static tilt about the pitch axis (backwards from the vertical [0°] on coefficient A and short time constant $1/B$ of the short time constant component of human HOKAN. Values are means + SE of 10 subjects. Left and right indicate stripe direction.

Figure 4. Effect of static tilt about the pitch axis on coefficient C and long time constant $1/D$ of the long time constant component of human HOKAN. Values are means + SE of 10 subjects. Left and right indicate stripe direction.

Figure 5. Effect of static tilt about the pitch axis on OKN gain and area under the HOKAN decay. Values are means + SE of 10 subjects. Left and right indicate stripe direction.
There was no evidence of any significant interaction between the short time constant components of HOKAN and otolithic input arising from static tilt in pitch. However, a slight trend towards a tilt angle dependent lowering of coefficient $A$ was revealed, suggesting that interaction of otolith-organ-mediated activity with the direct pathway (pursuit-mediated?) integrator responsible for the short time constant decay (14) was a possibility. A study by Buizza et al (40) demonstrating an effect on smooth pursuit gain by otolith-organ-mediated activity might lend support to this idea, if indeed smooth pursuit pathways are involved in generating the fast component of HOKAN.

In our study, there was no detectable asymmetry in the observed suppressive effect of static tilt in pitch on HOKAN long time constant parameters $C$ and $1/D$, in contrast to the asymmetries observed in the suppressive effects of active head tilts on HOKAN recently described (29). The lack of asymmetry in the long time constant component parameters with static tilt in pitch may indicate that the asymmetric responses observed in the effects of active head movements could have been, in part, the result of activation of neck muscles. The convergence of neck muscle activity (or efference copy) onto vestibular nuclei (VN) neurons exhibiting different sensitivities to pitch or roll, ipsilateral or contralateral tilts, as shown in the cat (41), could have been responsible for some of the asymmetries. The significant asymmetry in coefficient $A$ values is difficult to explain since static tilt in pitch does not have any major effect on the short time constant component. Also, the asymmetry between leftward and rightward mean values for the area under the decay curve is surprising since no asymmetry was observed for coefficient $C$ and $1/D$. The unmasking of an inherent asymmetry in human otolithic function by alterations in $g$ levels was recently reported (42). This inherent asymmetry could be indirectly responsible for the observed asymmetry in coefficient $A$ and total area values. In any case, these observations do not affect our conclusion that otolith-organ-mediated activity induced by static tilts in pitch interacts with the indirect pathway responsible for the long time constant component of human HOKAN.

In agreement with data obtained from monkeys (28), we found no evidence of cross-coupling from the horizontal to the vertical mode of storage during HOKAN suppression induced by static tilt in pitch.

In this study, OKN gains were greater than unity at most tilt angles examined. A possible reason for this observation would be that the surround may have been closer to the subjects than in previously reported conditions where the gain obtained was unity. This has been inferred from a recent study (43) in which we examined HOKAN produced with different optokinetic stimuli. In conditions where HOKAN was produced by means of a stationary surround at approximately 80 cm from the subjects' nasion during rotation at 60°/s, the gain was exactly 1.0. A report by Viirre et al (44), which showed a VOR gain decrease with target distance in monkeys, provides support for this conclusion.

An effect of tilt-induced otolith organ activity on OKN was indicated by a small but significant drop in gain at pitch angles of 60° and 70°. The observed tilt-dependent decrease in OKN gain probably reflects the otolith-organ-mediated suppression of the indirect pathway velocity storage, which was revealed by the significant lowering of parameters describing the long time constant component of HOKAN. Horizontal OKN gain has been found to be decreased in microgravity (45). This finding suggests that the absence of otolith organ input in microgravity has an effect on the optokinetic system which could be mediated by the velocity storage.

Our findings are compatible with the concept of otolith-organ mediated activity interacting with the velocity storage in humans, according to the models of Raphan and Cohen (28,33), Hain (46) and Hain et al (32). The continuous nystagmus during OVAR, the PRN cancellation following OVAR, and the HOKAN suppression following optokinetic stimulation during static tilt are thus accounted for by the same mechanism, namely interaction of otolith-organ-mediated activity...
with the horizontal velocity storage. Igarasahi et al (27) have shown that the otoliths are responsible for lateral tilt-induced PRN suppression in monkeys, and Cohen et al (18) have shown that the OVAR response is also dependent upon the otolith organs since plugging the semicircular canals in monkeys does not abolish it, although nonvestibular inputs cannot be ruled out. The fact that utricular and saccular primary afferents respond to static tilts about the pitch or roll axes, as documented by Fernandez et al (39) and Fernandez and Goldberg (47), indicates that they probably are responsible for the effects observed on PRN and OKAN. However, some evidence has been presented in the gerbil (48) which suggests a possible involvement of the semicircular canals in the static tilt induced effects. These authors showed that lateral canal afferents as well as otolith afferents respond to static tilts about the pitch axis. Convergence of optokinetic, macular, and canal inputs on VN units during OVAR has been proposed by Reisine et al (49). It is conceivable that optokinetic signals, macular signals, and even canal signals arising from static tilts could converge on these VN units during optokinetic stimulation about an axis tilted from the vertical. Units in the VN which respond to electrical stimulation of the utricle appear to be highly sensitive to static pitch (50) so that the effects of static tilt in pitch during optokinetic stimulation on HOKAN could conceivably result from stimulation of utricular afferents converging onto optokinetically responsive VN cells.

Both unidimensional models proposed by Cohen et al (51) and Hain et al (32) for otolith activity coupling to human horizontal velocity storage could account for both the active and static tilt-induced HOKAN suppression that we have observed in our studies. In both models, otolith activity must first reach the nodulus and/or uvula.

In summary, we have demonstrated HOKAN suppression by static tilts in pitch. Mainly the parameters describing the slow decay (indirect) component (C and/or 1/D) of HOKAN were found to be significantly reduced by static tilts although there appeared to be a trend towards a tilt-dependent lowering of coefficient \( A \), which represents the initial SPV of the fast (direct) decay component. The suppression was mostly apparent in the total area under the tilt trial decays. A left-right asymmetry in the effects of static tilt in pitch on coefficient \( A \) and area under the decay was revealed. Based on the studies summarized in the introduction, it was concluded that these effects were otolith-organ specific. Our results thus provide further evidence that otolith-mediated activity can couple to the horizontal velocity storage in humans.

Acknowledgments - This research was supported by the Medical Research Council of Canada and the Winnipeg Health Sciences Centre Research Foundation. We gratefully acknowledge the participation of our subjects and the technical assistance of Susan Kenny and David Wong. Preliminary data have been presented at the Barany Society meeting, Uppsala, 1988.

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AGE-RELATED CHANGES IN HUMAN VESTIBULO-OCULAR REFLEXES: SINUSOIDAL ROTATION AND CALORIC TESTS

R.J. Peterka, PhD,* F.O. Black, MD, and M.B. Schoenhoff, BS

Good Samaritan Hospital and Medical Center, R. S. Dow Neurological Sciences Institute, and Department of Neuro-otology, Portland, OR

Reprint address: Robert J. Peterka, Dept of Neuro-otology, N010, Good Samaritan Hospital & Medical Center, 1040 N.W. 22nd Avenue, Portland, OR 97210

Abstract — The dynamic response properties of horizontal vestibulo-ocular reflex (VOR) were characterized in 216 human subjects ranging in age from 7 to 81 y. The effects of aging on VOR dynamics and parameter distributions that describe VOR responses to caloric and to sinusoidal rotational stimuli were determined in a putatively normal population. Caloric test parameters showed no consistent trend with age. Rotation test parameters showed declining response amplitude and slightly less compensatory response phase with increasing age. The magnitudes of these changes were not large relative to the variability within the population. The age-related trends in VOR were not consistent with the anatomic changes in the periphery reported by others that showed an increasing rate of peripheral hair cell and nerve fiber loss in subjects over 55 y. The poor correlation between physiological and anatomical data suggest that adaptive mechanisms in the central nervous system are important in maintaining the VOR.

Keywords — vestibular; eye movements; rotation testing.

Introduction

Age-related changes in the peripheral vestibular organs include loss of hair cells (16), vestibular nerve fibers (4), and Scarpa’s ganglion cells (15). The rate of loss of these peripheral vestibular anatomical structures increases in subjects older than about 55 y. If reflex function depends directly on intact peripheral vestibular structures, then we might expect a decline in vestibulo-ocular reflex (VOR) function paralleling anatomical deterioration. Alternatively, if the central adaptive mechanisms remain intact in older subjects, then VOR function may remain relatively stable regardless of peripheral anatomical deterioration.

Literature on age-related changes in vestibular function is limited. Experiments on humans are usually performed on a small number of subjects, and these subjects are typically young adults. The exceptions to this occur in the clinical literature on caloric testing of the VOR (5,11). The results of these studies are rather ambiguous and include increased, decreased, and unchanged responses with increasing age. Caloric test results are therefore not consistent with the known age-dependent anatomical changes in peripheral vestibular receptors and nerve fibers. Studies on age-related changes in VOR identified using rotation testing are less complete either because the age range of subjects was limited (20,18), or because older analysis methods did not permit detailed characterization of responses to rotation (19). However, small age-related declines have been identified in these studies. Since normal VOR function has not been studied in the same subjects using both caloric and rotation tests, it is possible that the source of this difference between caloric and rotation tests is simply related to the choice of sample test populations.

*Dr. Peterka is presently the Scientific Systems Manager at Department of Neuro-otology and Assistant Scientist at R. S. Dow Neurological Sciences Institute.

Received 9 February 1990; Accepted 12 March 1990.
The present experiments were designed to characterize the dynamic response properties of human horizontal VOR in a normal population using passive rotational and caloric stimuli. The population was selected to provide results related to the effects of the aging process on these reflexes, and to determine if physiological changes were consistent with anatomic changes which occur with age. Optokinetic reflex and postural control function were also tested in the same subjects on the same day, and are reported in companion papers (12-14).

Methods

Vestibular reflexes were tested in 216 human subjects (90 male and 126 female) aged 7 to 81 y. Ages were approximately uniformly distributed over the entire range. Subjects were required to meet the following criteria:

1. normal age-corrected auditory pure tone responses
2. middle ear reflexes present bilaterally
3. normal middle ear impedance
4. no history of head blows of sufficient magnitude to cause loss of consciousness
5. normal neurologic and otologic physical exams
6. normal corrected vision
7. no history of ototoxic drug use
8. no history of dizziness or disequilibrium
9. moderate or absent use of alcohol with instructions to abstain from alcohol and caffeine 24 h prior to testing
10. no use of psychotropic drugs
11. no history of meningitis, encephalitis, stroke, seizure disorders, diabetes, hypertension, heart disease, or other systemic diseases.

We did not reject subjects based on the results of any of the vestibular, optokinetic, or posture tests performed.

Rotation Tests

Subjects sat in a chair mounted on a 108 N·m velocity servo-controlled motor (Contraves Goerz Corp, Pittsburgh, PA, Model 824) which rotated them about an earth vertical axis. Subjects performed tests of VOR function with eyes closed in a darkened room. Horizontal and vertical eye movements were recorded by electrooculographic (EOG) techniques (bandwidth DC to 80 Hz) using silver/silver chloride electrodes. Horizontal EOG was recorded using bitemporal electrodes, and vertical EOG was recorded by electrodes placed above and below one eye. Stimulus delivery and data collection were controlled by computer (DEC LSI 11/73). Chair tachometer signals as well as horizontal and vertical EOG were digitized and stored for later analysis. Digitizing rates were 200/s for the horizontal EOG and 50/s for vertical EOG and stimulus velocity. Calibrations of the EOG were performed before and after each rotation test.

Rotational stimuli for VOR tests included both a pseudorandom stimulus (14) and single frequency sinusoidal stimuli. Sinusoidal stimuli included 0.05, 0.2, and 0.8 Hz rotations with peak velocities of 60°/s. The duration of sine tests were 100 s (5 cycles) for 0.05 Hz, 45 s (9 cycles) for 0.2 Hz, and 26.25 s (21 cycles) for 0.8 Hz. The first cycle in each data record was considered a transient response and was ignored in the data analysis.

Subjects were given verbal tasks throughout testing to maintain a constant level of alertness. The tasks consisted of alphabetically naming such things as names, places, and foods.

Rotation Test Data Analysis. Eye position data were differentiated to calculate eye velocity. Fast phases of the nystagmus were identified using a method similar to Barnes (3). Curve fits to the remaining slow phase eye velocity data allowed the estimation of VOR response parameters. Curve fits were made to each period of the response. Periods that contained corrupted data were rejected before the final averaging of response parameter values from the remaining periods.

The curve fits to sinusoidal responses were of the form:

\[ r(t) = B_r + A_r \sin(2\pi f + P_r) \]
where \( B \) is bias in \( \text{°}/\text{s} \), \( A \) is response amplitude in \( \text{°}/\text{s} \), \( P \) is response phase in degrees, and \( f \) is the stimulus frequency. The recorded chair velocity data were separately analyzed to calculate stimulus velocity amplitude, \( A_s \), and phase, \( P_s \). The VOR gain of the reflex is defined as the ratio \( A_r/A_s \), and the phase of the reflex as \( P_r - P_s \). Since the VOR is a compensatory reflex, the values of \( P_r - P_s \) were close to \(-180^\circ\). For the convenience of working with smaller numbers, a value of \( 180^\circ \) was added to \( P_r - P_s \) for the VOR test. This is equivalent to inverting the horizontal eye position data.

In order to quantify nonlinear responses, the horizontal eye velocity data was shifted in time by an amount determined by the calculated phase of each period of the response. The time shift was in a direction that brought the response into phase with the stimulus. Slow phase eye velocity was then plotted against stimulus velocity to yield a scatter of points that generally lie along a negatively sloping line. An example is shown in Figure 1. The slope of the line is equal to VOR gain.

A linear VOR response is consistent with equal VOR gains for rotations in opposite directions. One type of nonlinear VOR response, sometimes seen in abnormal subjects, has unequal gains for rotations to the right and left. This type of nonlinearity was quantified by separately calculating the slopes of the eye velocity versus stimulus velocity data for chair rotations to the right and to the left. The slopes were calculated by a least squares fit of a two-segment line to the data. One line segment was for positive and the other for negative stimulus velocities. The two line segments were constrained to intersect one another at zero stimulus velocity.

The two-part linear curve fit yields three parameters: 1) the reflex gain for slow phase eye movements to the right, \( G_R \); 2) the gain for slow phase eye movements to the left, \( G_L \); and 3) the bias.

**Figure 1.** Example of VOR rotation test data. Upper trace shows slow phase eye velocity response to a 0.05 Hz, 60°/s peak velocity sinusoidal rotational stimulus. Solid curve through the data is the curve fit to each cycle. Response gain, phase, and bias are obtained from these curve fits. Lower left trace shows horizontal eye movements evoked by one period of the rotational stimulus. Solid vertical bars under the horizontal EOG trace show the location of fast phase portions of the nystagmus identified in the analysis. Lower right plot shows slow phase eye velocity plotted against stimulus velocity. The two part linear fit is used to measure response symmetry of VOR gain.
Caloric Tests

Four irrigations of the external ear canals were made using a Brookler-Grams closed loop caloric irrigator. Subjects were in a supine position with head elevated about 30° above horizontal to assure maximal stimulation of the horizontal semicircular canals. The caloric test was not performed on subjects under 12 y, and complete data were not obtained on other subjects who became nauseated or simply chose not to continue the irrigations because of discomfort. Each ear was alternately irrigated for 45 s at 30 and 44 °C. Horizontal and vertical eye movements were recorded with EOG techniques identical to those described for rotation tests. Eye movements were recorded during and after each irrigation for a total of 3 min. Horizontal eye movements were analyzed to calculate peak slow phase eye velocity. Caloric responses were quantified by labyrinthine asymmetry (LA), directional preponderance (DP), and average response (AR) measures defined by:

\[
LA = \frac{(RW + RC) - (LW + LC)}{RW + RC + LW + LC} \times 100
\]

[2]

\[
DP = \frac{(RW + LC) - (RC + LW)}{RW + RC + LW + LC} \times 100
\]

[3]

\[
AR = \frac{(RW + RC + LW + LC)}{4}
\]

[4]

where \(RW, RC, LW, LC\) are the absolute values of peak slow phase eye velocities recorded during right warm, right cold, left warm, and left cold irrigations, respectively. Subjects were tasked throughout caloric testing to maintain alertness.

Visualization of Trends

In order to visualize trends in scatterplots, a robust locally weighted regression analysis (lowess fit) was used to smooth the scatterplots (6). This smoothing is similar to a moving average filter, but is less sensitive to outlying points and allows variable amounts of smoothing. A lowess smoothing parameter of 0.5 and iteration parameter of 2 were used on all data sets.

Data Quality

The overall quality of each rotation and caloric test for each subject was subjectively given a rating of good, fair, or poor. Only good and fair quality data are included in the data summaries in the results section. Quality judgments were based on the standard deviation of response parameters (such as gain, phase, and bias from rotation tests), on the consistency of the responses throughout the duration of the stimulus, and on the accuracy of the eye movement analysis in the separation of slow and fast phases of nystagmus. The actual values of response parameters were not used in judgment of data quality. The test results from about 4% of subjects were rated poor for each test. Poor quality data for one subject on a given test were not used to disqualify data from the same subject on other tests.

Results

The subjects showed a wide range of responses on all measures of VOR function. Age-related changes were identified in many rotation test response measures, but the magnitude of these changes was not large relative to the variability of the data. Most changes indicated a decline in function. In contrast,
no obvious or consistent changes as a function of age were found in caloric test responses. There were no significant differences in reflexes between males and females.

**VOR Responses to Rotation**

Typical VOR rotation test results are shown in Figure 1. Population statistics for gain, phase, bias, offset, and asymmetry are given in Table 1. The small differences in Ns are due to data eliminated because of poor quality. The distributions of all parameters were fairly symmetric about their means. Gain increased with increasing frequency and had lower variance at 0.8 Hz as compared to 0.2 and 0.05 Hz. The phase variance also decreased with increasing frequency. The variances of the offset distributions were somewhat less than the variances of the bias distributions at 0.05 and 0.2 Hz, and greater at 0.8 Hz.

Neither bias, offset, nor asymmetry were highly correlated across the three test frequencies. The largest correlation coefficient was 0.71 between bias at 0.2 and 0.8 Hz. Correlations comparing bias at 0.05 and 0.2 Hz, and at 0.05 and 0.8 Hz were 0.56 and 0.52, respectively. The correlation coefficients comparing response offset at the three test frequencies ranged from 0.43 to 0.57. Asymmetry correlations across test frequencies were the lowest of all symmetry measures (range 0.10–0.37).

There were small changes in rotation test gain and phase responses with age (Figure 2). In particular, all gains decreased with increasing age. The gain trend was more consistent at 0.05 Hz than at 0.2 and 0.8 Hz. Phases increased with increasing age at all frequencies tested, although the effect was more pronounced at 0.2 and 0.8 Hz than at 0.05 Hz. The age-related changes in gain and phase were both roughly linear. Linear regression slopes, intercepts, and correlation coefficients are summarized in Table 2. Rotation test measures of response symmetry (the absolute values of bias, offset, and asymmetry) showed no age-related trends.

**VOR Responses to Caloric Stimuli**

Caloric test results were generally in agreement with those of others who reported normal ranges of LA of about 15 to 25%. Our results were consistent with a 25% upper limit of normal since 95% of our subjects had LA measures below this value. The distribution of AR had a mean of 17.0°/s (±9.0 SD, range 4.5–63.2) and was skewed toward larger values.

Age-related effects on caloric test results

---

**Table 1. VOR Response Parameters for Single Sine Stimuli: Mean, SD,* and Percentile Values on Parameter Distributions**

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Gain Mean</th>
<th>Gain SD</th>
<th>Phase Mean</th>
<th>Phase SD</th>
<th>Bias Mean</th>
<th>Bias SD</th>
<th>Offset Mean</th>
<th>Offset SD</th>
<th>Asymmetry Mean</th>
<th>Asymmetry SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.68</td>
<td>0.15</td>
<td>10.5</td>
<td>4.85</td>
<td>-0.44</td>
<td>3.56</td>
<td>2.90</td>
<td>7.5</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.75</td>
<td>0.16</td>
<td>1.62</td>
<td>3.17</td>
<td>-0.62</td>
<td>2.91</td>
<td>2.32</td>
<td>6.6</td>
<td>-1.5</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>0.84</td>
<td>0.13</td>
<td>0.79</td>
<td>2.59</td>
<td>-0.28</td>
<td>2.76</td>
<td>3.13</td>
<td>5.9</td>
<td>-1.4</td>
<td></td>
</tr>
</tbody>
</table>

*SD = standard deviation. Units are VOR phase in degrees, bias in °/s, offset in °/s, and asymmetry in percent.
Figure 2. VOR gain and phase as a function of subject age. Data were obtained from sinusoidal rotational stimulation at 0.05, 0.2, and 0.8 Hz. Solid curves are lowess fits.

were ambiguous. A linear regression curve fit to AR versus age (Figure 3A) showed an average decrease with increasing age. The linear regression had an associated correlation coefficient of $-0.15$, which was significantly different from zero ($P < 0.05$). However, the lowess fit shown in Figure 3A indicated that a linear regression was probably not an appropriate description of the data. AR decreased for subjects up to about 40 y, and then increased at a low rate for older subjects.

Figure 3B shows the absolute value of LA versus age. The lowess fit shows essentially no change over the first 6 age decades, and a slight increase in older subjects. Due to the large variance in the data, a much larger sample would be required to determine if the small increase in older subjects was significant.
Table 2. Age Effects on VOR Rotation Test Gain and Phase Measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope (change/y)</th>
<th>Intercept at 0 years</th>
<th>Correlation coefficient</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05 Hz</td>
<td>-0.0030</td>
<td>0.80</td>
<td>-0.39*</td>
<td>208</td>
</tr>
<tr>
<td>0.2 Hz</td>
<td>-0.0026</td>
<td>0.85</td>
<td>-0.34*</td>
<td>208</td>
</tr>
<tr>
<td>0.8 Hz</td>
<td>-0.0022</td>
<td>0.93</td>
<td>-0.33*</td>
<td>204</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05 Hz</td>
<td>0.029</td>
<td>9.3</td>
<td>0.12</td>
<td>208</td>
</tr>
<tr>
<td>0.2 Hz</td>
<td>0.042</td>
<td>0.0</td>
<td>0.27*</td>
<td>208</td>
</tr>
<tr>
<td>0.8 Hz</td>
<td>0.050</td>
<td>-1.2</td>
<td>0.39*</td>
<td>204</td>
</tr>
</tbody>
</table>

*Significantly different from zero (P < 0.05).

Correlations among Rotation and Caloric Parameters

Table 3 summarizes correlations among various caloric and rotation test measures. Among rotation test response symmetry measures, bias and offset were highly correlated at all test frequencies. Bias and asymmetry showed moderate correlations (about 0.6) at 0.05 and 0.2 Hz, but no correlation at 0.8 Hz. There was a small positive correlation between offset and asymmetry at 0.05 Hz, no correlation at 0.2 Hz, and a larger negative correlation at 0.8 Hz.

The correlations between response bias at all test frequencies and caloric DP were about -0.4. Offset and DP showed a similar pattern but with slightly less negative correlations. Asymmetry and DP showed small negative correlations (about -0.2) at 0.05 and 0.2 Hz, but no correlation at 0.8 Hz. There was no correlation between LA and DP, or between LA and any of the rotation test symmetry measures.

Caloric AR and rotation test gain and phase measures are known to covary in some vestibular abnormalities (2). Within our putatively normal population, there were only small correlations between these parameters. Correlations between AR and gain at the three test frequencies ranged from 0.22 to 0.31. The correlation between AR and phase was only -0.12 at 0.05 Hz, and less at the other two test frequencies.

Discussion

VOR Parameter Correlations

The pattern of correlation between caloric and rotation test parameters, and among the rotation test parameters themselves apparently depends on rotation test frequency. The asymmetry parameter, which measures the differ-

Figure 3. Caloric test AR (A) and LA (B) as a function of subject age. Solid curves are lowess fits.
Table 3. Correlations among Caloric and Rotation Test Response Parameters*

<table>
<thead>
<tr>
<th>Frequency = 0.05 Hz</th>
<th>DP</th>
<th>Bias</th>
<th>Offset</th>
<th>Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>-0.07</td>
<td>0.08</td>
<td>0.12</td>
<td>-0.01</td>
</tr>
<tr>
<td>DP</td>
<td>-0.41</td>
<td>-0.37</td>
<td>-0.25</td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>0.92</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offset</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency = 0.2 Hz</th>
<th>DP</th>
<th>Bias</th>
<th>Offset</th>
<th>Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>-0.07</td>
<td>0.14</td>
<td>0.13</td>
<td>0.07</td>
</tr>
<tr>
<td>DP</td>
<td>-0.39</td>
<td>-0.33</td>
<td>-0.21</td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>0.83</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offset</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency = 0.8 Hz</th>
<th>DP</th>
<th>Bias</th>
<th>Offset</th>
<th>Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>-0.07</td>
<td>0.13</td>
<td>0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>DP</td>
<td>-0.42</td>
<td>-0.41</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>0.85</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offset</td>
<td>-0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are from the 153 subjects who completed all tests with good or fair quality data.

ence in VOR gain for rotations to the right and left, showed the most complex frequency-dependent pattern. For example, the correlations between bias and asymmetry were about 0.6 at 0.05 and 0.2 Hz, but less than 0.1 at 0.8 Hz. The correlation between caloric DP and asymmetry was also higher at 0.05 and 0.2 Hz compared to 0.8 Hz. In addition, there was a shift in the correlations between offset and asymmetry from a positive value at 0.05 Hz, to a near zero value at 0.2 Hz, and then to a negative value at 0.8 Hz. Finally, the correlations between asymmetry measures made at different test frequencies were poorer than either the bias or offset parameter correlations across frequency. The poor correlation of asymmetry measures at different test frequencies and the changing relationship of asymmetry to the other caloric and rotation test symmetry measures suggests that the physiological mechanisms which control symmetry are either frequency dependent or that separate physiological factors dominate at different frequencies of head motion.

**VOR Changes with Age**

We were able to identify small age effects on some VOR response measures. The direction of change of VOR gains was expected. Other age-related changes were not expected. These include increased VOR phase leads with increasing age, and the fact that VOR function measured using the caloric test did not show the same trend as VOR function measured using rotation tests.

Age-related changes in VOR function identified in this study do not follow the same time course as age-related peripheral vestibular anatomical changes identified by others. Figure 4 shows the lowess curve fit to 0.8 Hz VOR gain versus age plotted along with curve fits to data on human crista hair cell counts (16), vestibular nerve fibers (4), and Scarpa’s ganglion cells (15) as a function of age. The ordinate scales are linear and are normalized to their values at a subject age of 30 y. For ages up to about 50 y, there is a gradual decline in both VOR gain and the various measures of peripheral vestibular anatomic components. For the VOR gain this gradual decline continues at about the same rate through the higher age decades. However, the rate of decline of all anatomic measures greatly increases after about age 60, resulting in a sharper decline than the VOR gain.

![Figure 4. Comparison of age-related changes in VOR gain and peripheral vestibular anatomical data. The 0.8 Hz VOR gain fit is the same as in Figure 2. All curve fits to anatomic data are lowess fits to published data. All fits are plotted on a linear scale normalized to 1.0 at age 30 y. The normalization factors are 0.87 for 0.8 Hz VOR gain, 6940 crista hair cells, 17450 vestibular nerve fibers, and 18135 Scarpa’s ganglion cells.](image-url)
in a divergence between the anatomical and physiological data, with the VOR functioning better in older subjects than would be predicted based on changes in peripheral vestibular anatomy.

Because the subjects of this study were volunteers, it could be argued that the sample of older subjects would be biased in favor of exceptionally healthy elderly individuals who do not reflect the physiological function of a randomly selected population. Several results argue against a strong bias toward exceptionally healthy elderly subjects. First, the auditory pure tone threshold functions of our subjects were consistent with the expected age-related changes (17). Second, extended frequency audiometry (8–20 KHz) was performed on most subjects and showed consistent monotonically declining function with increasing age. Third, the optokinetic reflex time delay showed monotonic increases with age (14). Finally, posture test results (13) in the same subjects showed clear age effects. It seems unlikely that the peripheral vestibular system of these subjects would escape distributed aging processes when other systems did not.

The increases in VOR phase leads at higher frequencies with increasing age were not anticipated. On the surface they would seem to represent a degradation of function since increased phase leads take the system response away from the goal of perfect compensatory eye movements (unity gain and zero phase). Perhaps the phase advance is an artifact of an adaptation that improves overall VOR function. For example, studies of peripheral semicircular canal function in the squirrel monkey have shown that higher gain peripheral nerve fibers have dynamic properties which include phase advances at higher frequencies (7). Phase advances indicate a sensitivity to the velocity of cupula deflection in addition to the cupula position. In contrast, lower gain canal fibers show cupula position sensitivity and therefore, due to the integrating accelerometer characteristics of canal biophysics, the nerve responses are in phase with head velocity at higher frequencies of rotational movements.

On the basis of our results, we might postulate that in young people, low gain tonic canal fibers provide the major contribution to the VOR. As the subject ages and there is a gradual loss of peripheral canal input due to cell death, adaptive mechanisms in the central nervous system may be able to selectively increase the contribution of high gain canal nerve input. The net effect would be to maintain the gain of the VOR at a reasonable level allowing for the generation of adequate compensatory eye movements. However, this mechanism of gain enhancement would be accompanied by the possibly undesirable phase leads associated with the dynamics of the high gain canal fibers. A trade-off may be occurring in favor of maintaining the desirable feature of high response amplitude at the expense of the timing of compensatory eye movements.

This hypothesis may be consistent with the multichannel model of the VOR (9) developed to explain the dynamic properties of VOR adaptation. However, assuming that human and monkey VOR adaptation occurs by similar mechanisms, there are other studies that are not consistent with this hypothesis. Minor and Goldberg (10) have shown that phasic canal fibers do not appear to contribute at all to the VOR of the squirrel monkey. If phasic fibers do not contribute to the VOR, they cannot participate in alterations in VOR dynamics. One might argue that these phasic fibers only contribute to the VOR when they are needed for the adaptive enhancement of the reflex. However, this would be inconsistent with other results that suggest it is an enhancement of the contribution of the tonic fibers that mediates adaptive increases in VOR gain (8).

Finally, a hypothesis calling for an increased phasic fiber contribution to the VOR of older subjects may also be inconsistent with anatomical aging results that showed relatively greater hair cell loss on the crest of the crista (16), and the greatest losses of the thick fibers innervating the canal cristas (4). Since the higher gain afferent fibers, at least in the chinchilla, tend to be larger in diameter and to originate from the crest of the crista (1), the selective loss of these cells with increasing
age would preclude their participation in VOR gain enhancement.

Current understanding of the mechanisms of VOR adaptation and of anatomical changes in peripheral vestibular receptors does not provide a good explanation of our VOR data. Studies of VOR adaptation, often performed in younger animals, may not adequately characterize changes that occur with age since the aging process may also affect the functionality of the central neural networks involved in adaptation. An aging adaptive neural network could contribute its own dynamic component to the VOR that differs from the dynamic properties observed in younger animals.

Clinical Significance

The presence of age-related changes in VOR function identified using rotation tests has implications for the assessment of normal function. Part of the variability of VOR response parameters is caused by this age effect. The square of the correlation coefficient gives an estimate of the proportion of variance related to changes with age. The VOR gain versus age measures had correlation coefficients between 0.3 and 0.4. Therefore, approximately 10% to 15% of the variance of gain data is accounted for by the effect of age. Measures of normal vestibular function should account for these age effects.

Since the majority of the observed response variability is independent of age, it is clear that the functional characteristics vary widely within any given age group in a putatively normal population. To the extent that aging effects are deleterious and that our reflex measures accurately characterize the general decline in function, a significant proportion of subjects within any age group look "older" than their chronological ages and may be less functional with regard to their orientation control abilities. One could hypothesize that these subjects would be more susceptible to the development of balance and orientation control problems as their vestibular function further declines with age. Perhaps there is some threshold beyond which the brain's adaptive mechanisms are not able to compensate for the declining function. After this point is reached, subjects may develop dizziness and equilibrium control complaints, or perhaps individuals will restrict their activities so as to avoid situations that stress their remaining capabilities. A longitudinal rather than a cross-sectional study would be required to test this hypothesis.

Although we did not observe large age-related trends in VOR function, it is apparent that central adaptive mechanisms cannot sustain VOR function indefinitely in the face of increasing losses of peripheral receptors and neural substrate. It will be important to extend the age limit of our study to the eighth and ninth decades, and to explore larger amplitude and higher frequency stimuli that more nearly resemble natural head motion. The point at which physiological function begins to follow the anatomical decline will define the effective functional reserve of the central adaptive mechanisms.

Acknowledgment—We wish to thank Christopher Newell, Patrick Shea, and Martha Benolken for their assistance. This research was supported by NASA research grants NCC9-8 and NAG 9-117.

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AGE-RELATED CHANGES IN HUMAN VESTIBULO-OCULAR AND OPTOKINETIC REFLEXES: PSEUDORANDOM ROTATION TESTS

R.J. Peterka, PhD,* F.O. Black, MD, and M.B. Schoenhoff, BS

Good Samaritan Hospital and Medical Center, R. S. Dow Neurological Sciences Institute, and Department of Neuro-otology, Portland, OR
Reprint address: Robert J. Peterka, Dept of Neuro-otology, N010, Good Samaritan Hospital & Medical Center, 1040 N.W. 22nd Avenue, Portland, OR 97210

Abstract — The dynamic response properties of horizontal vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR) were characterized in 216 human subjects ranging in age from 7 to 81 y. The object of this cross-sectional study was to determine the effects of aging on VOR and OKR reflex dynamics, and to identify the distributions of parameters that describe VOR and OKR responses to pseudorandom stimuli in a putatively normal population. In general, VOR and OKR response parameters changed in a manner consistent with declining function with increasing age. For the VOR this was reflected in declining response amplitudes, although the magnitude of the decline was small relative to the variability of the data. For the OKR the lag time of the response, probably associated with the time required for visual information processing, increased linearly with age at a rate of about 1 ms per year.

Keywords — vestibular; visual-vestibular; eye movements.

Introduction

A great deal is known about age-related performance declines in various visual perception tasks (7). These tasks are usually studied in controlled settings in which oculomotor performance is assumed not to play an important role. However, in natural settings it is obvious that changes in oculomotor performance with age could have a deleterious effect on many aspects of visual perception. In particular, vestibulo-ocular reflex (VOR) and optokinetic reflex (OKR) normally function together to provide clear vision by generating compensatory eye movements that minimize image motion on the surface of the retina during head movements. It is important to know how the VOR and OKR change with age, since a degradation in these reflexes could impair the acquisition of visual information during active and passive head movements.

During horizontal head rotations in the light with earth-fixed visual surrounds, the VOR and visual motion information through optokinetic and pursuit tracking systems combine to produce compensatory eye movements that facilitate clear vision by maintaining a fixed gaze direction. The combined VOR and visual tracking reflexes are effective over a bandwidth from DC to several Hertz (9).

Literature on age-related changes in vestibular and oculomotor function is limited. Experiments on humans are usually performed on a small number of subjects, and these subjects are typically young adults. The exceptions to this occur in the clinical literature on caloric testing of the VOR (3), in some work on age-related changes in pursuit tracking ability (16,17), and in responses to constant velocity optokinetic stimuli (10,18).

The present experiments were designed to characterize horizontal VOR and OKR dynamic response properties, and the variability of those responses in normal humans. The
population was selected to provide results related to the effects of the aging process on these reflexes. Tests of VOR function using caloric and sinusoidal rotational stimuli, and tests of posture control were also made in the same subjects and are reported in companion papers (12–14).

**Methods**

Vestibular and oculomotor reflexes were tested in 216 human subjects (90 male and 126 female) aged 7 to 81 y. Ages were approximately uniformly distributed over the entire range. Details of subject selection are given in a previous paper (13). We did not reject subjects based on the results of any of the vestibular, optokinetic, or posture tests performed.

**Rotation Tests**

Test conditions for the VOR were identical to those described earlier (13). Additionally, for the OKR the subject was surrounded by a circular cloth cylinder 1.8 m in diameter. The cylinder acted as a projection screen for an optokinetic stimulus. A full field optokinetic stimulus was provided by a pin hole type projector mounted on a 6.8 N·m servo motor (Genisco Technology Corp, Rancho Dominguez, CA, Model 1100(5) attached to the ceiling directly above the subject’s head. The projector produced randomly placed vertical stripes of light against a mostly dark background.

Rotational stimuli for VOR tests included both single frequency sinusoidal stimuli [results reported in (13)] and a pseudorandom stimulus. The pseudorandom stimulus consisted of the summation of 8 discrete sinusoidal frequencies. The frequency components were selected to minimize corruption of the results of the data analysis due to possible nonlinear responses of the VOR system (19). The 8 frequencies were 0.0092, 0.021, 0.046, 0.095, 0.180, 0.388, 0.766, and 1.535 Hz. The nominal amplitudes of these components were all 15.6°/s, except the highest frequency component, which was 7.8°/s. The peak instantaneous velocity was about 40°/s. The total stimulus duration was about 220 s. Transient responses were avoided by recording only the final 163.84 s of data. Complete OKR data were not obtained on all subjects since the stimulus induced motion sickness symptoms in some subjects, requiring the early termination of the test.

Subjects were given verbal tasks throughout the VOR and OKR rotation tests to maintain a constant level of alertness. The tasks consisted of alphabetically naming such things as names, places, or foods.

**Data Analysis**

Eye position data were differentiated to calculate eye velocity. Fast phases of the nystagmus were identified and eliminated (11). The Fourier analysis of the remaining slow phase eye movements provided estimates of the response parameters given by the following equation:

\[
r(t) = B + \sum_{i=1}^{N} A_i \sin(2\pi f_i + P_i)
\]

where \(B\) is bias or average slow phase velocity, with units of °/s, \(N\) is the number of sinusoidal components in the pseudorandom stimulus, \(A_i\) is the response amplitude at the \(i\)th frequency \(f_i\), and \(P_i\) is the response phase at the \(i\)th frequency. A Fourier analysis of the stimulus velocity was performed to calculate the amplitudes and phases of the stimulus waveform. The reflex gains and phases at the \(N\) stimulus frequencies were computed as the
The algorithms for gain and phase calculations were verified by simulating reflex responses with known electronic circuits. Before analysis, segments of the simulated responses were eliminated to simulate the patterns of missing data caused by the elimination of nystagmus fast phases from real eye movement data.

The gain and phase values of the VOR reflex were fitted with a transfer function equation of the following form:

$$H_{\text{vor}}(s) = \frac{K_v T_v s}{T_v s + 1}$$  \[2\]

where $T_v$ is an estimate of the VOR time constant (units of seconds), $K_v$ is the VOR gain constant, and $s$ is the Laplace transform variable.

OKR gain and phase data for all subjects were well fit by a 3 parameter transfer function of the form

$$H_{\text{okr}}(s) = \frac{K_o \exp(-T_d s)}{T_o s + 1}$$  \[3\]

where $T_o$ is a time constant with units of seconds, $K_o$ is the OKR gain constant relating slow phase eye velocity to stimulus velocity, and $T_d$ is a time delay parameter with units of seconds describing the lag between visual field movement and eye movement. The $T_o s + 1$ factor represents a lowpass filter which accounts for the declining gain with increasing frequency observed in some subjects. Larger values of $T_o$ are consistent with gain declines beginning at lower frequencies. A value of zero for $T_o$ [i.e., the transfer function reduces to $H_{\text{okr}}(s) = K_o \exp(-T_d s)$] accounts for subjects whose gain did not decline with increasing frequency. $T_o$ is not the time constant associated with velocity storage and optokinetic after-nystagmus (5).

**Visualization of Trends**

In order to visualize trends in scatterplots, a robust locally weighted regression analysis (lowess fit) was used to smooth the scatterplots (4). This smoothing is similar to a moving average filter, but is less sensitive to outlying points and allows variable amounts of smoothing. A lowess smoothing parameter of 0.5 and iteration parameter of 2 were used on all data sets.

**Data Quality**

The overall quality of each rotation test for each subject was subjectively given a rating of good, fair, or poor. Only good and fair quality data are included in the data summaries in the results section. Quality judgments were based on the consistency of the responses throughout the duration of the stimulus, and on the accuracy of the eye movement analysis in the separation of slow and fast phases of nystagmus. The actual values of response parameters were not used in judgment of data quality. The test results from about 4% of subjects were rated poor for each test. Poor quality data for one subject on a given test was not used to disqualify data from the same subject on other tests.

**Results**

The subjects showed a wide range of responses on all measures of VOR and OKR function. Age-related changes were identified in almost all rotation test response measures, but the magnitude of these changes was not large relative to the variability of the data. Most changes indicated a decline in function. There were no significant differences in reflexes between males and females.

**VOR Responses**

A sample of a typical response to a pseudorandom VOR stimulus is shown in Fig-
Figure 1. The pseudorandom stimulus evokes a complex eye movement pattern (Figure 1C). However, separation of slow and fast components, and calculation of slow phase eye velocity reveals the underlying compensatory motion (Figure 1B). A spectral analysis of slow phase eye velocity and the recorded stimulus velocity provides measures of response gain and phase as a function of stimulus frequency. Examples of gain and phase data from 3 subjects are shown in Figure 2. Typically the gain is lower at the lowest test frequency and increases with increasing frequency. In some subjects the gain monotonically increases over the frequency range tested and in others it appears to reach an asymptote. The solid lines through the data points represent curve fits of a 2 parameter transfer function (eqn 2) to the data of each subject.

The pattern of VOR gain and phase data of most subjects was similar in form to the data in Figure 2A, and was well characterized by the 2 parameter transfer function model (eqn 2). There were deviations from this pattern which are exemplified by the data from 2 other subjects in Figures 2B and 2C. The low frequency data in 2B were fit well by the 2-parameter model but the higher frequency data showed increasing phase leads with increasing frequency. The phases of VOR responses to 0.05, 0.2, and 0.8 Hz sinusoidal rotations were 10.7°, 2.0°, and 6.9°, respectively, for this subject, and therefore confirmed the general pattern. A more accurate curve fit to this data would require a higher frequency lead term in the transfer function.

A transfer function of this form would be similar to the one used to describe the dynamic responses of phasic canal afferents in the squirrel monkey (6).

The VOR phase data in Figure 2C were fairly flat and greater than zero across all test frequencies. The phase of responses to sinusoidal stimuli were 3.7°, -2.8°, and 2.1° at 0.05, 0.2, and 0.8 Hz, again confirming the general pattern but with less phase lead than the pseudorandom data. The curve fit identified a long VOR time constant of 44.9 s. However, the two parameter model does not
describe either the low or high frequency phase data well. A transfer function fit with an \( s^k \) Laplace operator is better able to describe this type of data (1).

VOR gain and phase data from pseudorandom stimulus test results are summarized in Table 1. As with single frequency sinusoidal results, the variance of gain data was similar across all frequencies. The variance of phases data was larger at low frequencies than at high, probably reflecting the variance of the VOR time constant among individuals. The variance of the phase data at 1.535 Hz was larger than the variance at adjacent lower frequencies. This probably resulted from the fact that the stimulus amplitude of the highest frequency component was half that of the lower frequencies, resulting in a lower signal-to-noise ratio at the 1.535 Hz test frequency.

The distributions of the VOR gain constants and time constants for the pseudorandom stimulus are summarized in Table 2. The gain constant distribution was symmetric with an average value of 0.72. The VOR time constant distribution was skewed toward longer time constants. Mean value was 24.4 s and median value was 23.0 s. Only two subjects had time constants below 10 s. One of these subjects (time constant = 8.2 s) had a partial unilateral loss of vestibular function as judged by caloric testing. A short time constant is consistent with a unilateral loss of vestibular function (8). However, the other subject (time constant = 7.0 s) had normal caloric test results.

Table 1. VOR Gain and Phase (mean ± 1 SD*)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Gain</th>
<th>Phase (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0092</td>
<td>0.58 ± 0.14</td>
<td>34.0 ± 8.6</td>
</tr>
<tr>
<td>0.021</td>
<td>0.64 ± 0.15</td>
<td>19.4 ± 5.6</td>
</tr>
<tr>
<td>0.046</td>
<td>0.69 ± 0.15</td>
<td>11.4 ± 3.8</td>
</tr>
<tr>
<td>0.095</td>
<td>0.71 ± 0.16</td>
<td>6.6 ± 2.9</td>
</tr>
<tr>
<td>0.180</td>
<td>0.73 ± 0.16</td>
<td>5.1 ± 2.7</td>
</tr>
<tr>
<td>0.388</td>
<td>0.75 ± 0.16</td>
<td>3.8 ± 2.7</td>
</tr>
<tr>
<td>0.766</td>
<td>0.75 ± 0.16</td>
<td>4.1 ± 3.5</td>
</tr>
<tr>
<td>1.535</td>
<td>0.74 ± 0.17</td>
<td>4.4 ± 6.2</td>
</tr>
</tbody>
</table>

*SD = standard deviation.
Table 2. VOR Response Parameters for Pseudorandom Stimulus: Mean, SD, and Percentile Values from Parameter Distributions (N = 207)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>2.5%</th>
<th>5%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain constant</td>
<td>0.72</td>
<td>0.16</td>
<td>0.42</td>
<td>0.48</td>
<td>0.61</td>
<td>0.73</td>
<td>0.81</td>
<td>0.97</td>
<td>1.02</td>
</tr>
<tr>
<td>Time constant (s)</td>
<td>24.5</td>
<td>8.6</td>
<td>13.6</td>
<td>14.2</td>
<td>18.4</td>
<td>23.1</td>
<td>28.1</td>
<td>43.6</td>
<td>47.4</td>
</tr>
<tr>
<td>Bias (°/s)</td>
<td>-0.1</td>
<td>2.1</td>
<td>-5.0</td>
<td>-3.8</td>
<td>-1.3</td>
<td>-0.0</td>
<td>1.3</td>
<td>3.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Comparison of VOR Measured by Single Frequency and Pseudorandom Stimuli

If the VOR were a linear system, then gain and phase data obtained from single frequency sinusoidal and pseudorandom stimulation should be identical within the random variability introduced by measurement errors. Statistical comparisons were made between the single frequency (13) and pseudorandom gains and phases and are shown in Table 3. Single sine and pseudorandom results were not significantly different at the lowest frequency (0.05 Hz). Small but consistent differences were evident at higher frequencies. In particular, the single frequency gain was higher at 0.8 Hz than the pseudorandom derived gain, and the pseudorandom phase values at 0.2 and 0.8 Hz were phase advanced by about 3° compared to single frequency sine results. The improved phase response from sine tests may represent a small predictive effect; however, this effect apparently did not carry over to the 0.05 Hz data.

The gain value from the 0.8 Hz test was higher than the pseudorandom test result. This might also be due to a predictive effect. However, in this case it seems likely that the data analysis methods could have contributed to this higher value. During the analysis of the single frequency sine tests, the experimenter had the ability to reject data from stimulus cycles that were obviously corrupted. These corrupted data cycles could easily be identified based on gain, phase, and/or bias values that deviated greatly from the values for other cycles. There were several causes for poor data cycles, including transient EMG interference, excessive blinking, gaze deviations from the horizontal plane, inattentiveness to tasking, and failure of the fast phase eye movement detection algorithm. With experience, it became a simple task to detect and correct these problems by rejecting the affected cycles. The net effect usually increased the average gain measure. Eye movement recordings were also transiently corrupted during pseudorandom testing, but we did not have a means of correcting or eliminating these problems, and they were therefore aver-

Table 3. Comparison of Single Sine and Pseudorandom Gain and Phase Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single sine (Hz)</th>
<th>Pseudorandom (Hz)</th>
<th>Average difference</th>
<th>N †</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain</td>
<td>0.05</td>
<td>0.046</td>
<td>-0.011</td>
<td>199</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.180</td>
<td>0.019</td>
<td>199</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.766</td>
<td>0.095</td>
<td>195</td>
<td>†</td>
</tr>
<tr>
<td>Phase</td>
<td>0.05</td>
<td>0.046</td>
<td>-0.3</td>
<td>199</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.180</td>
<td>-3.2</td>
<td>199</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.766</td>
<td>-3.4</td>
<td>195</td>
<td>†</td>
</tr>
</tbody>
</table>

*Positive differences indicate that the average single sine parameter value was larger than the average pseudorandom parameter value. The average differences listed are corrected for the difference in test frequencies between the single sine and pseudorandom stimuli. Gain and phase corrections were based on the VOR transfer function in eqn 2 with average time constant of 24.5 s and gain constant of 0.72.

†Ns are smaller than those in Table 2 because comparisons were not made if either test had poor quality data.

‡Significant difference (P < 0.05, paired t test).
aged into the final result. The rejection of corrupted portions of single sine results, but not pseudorandom results, could account for the higher gains measured during sinusoidal rotations.

**OKR Responses**

Typical OKR test results from pseudorandom stimulation for two subjects are shown in Figure 3. Response gain was less than unity in all subjects. The gains of most subjects were approximately flat across the bandwidth of frequencies tested (0.02 to 1.5 Hz) as in Figure 3A. Phases were near 0° at the lowest frequencies and showed monotonic increasing phase lags as frequency increased. Since perfect tracking of the visual stimulus is represented by unity gain and zero phase at all frequencies, subjects demonstrated imperfect tracking in terms of both amplitude (gain) and timing (phase). The major variation on the typical OKR result was the presence of declining gain with increasing frequency in some subjects. Figure 3B shows the OKR transfer function data from one such subject.

The means, standard deviations, and ranges of OKR gain constant, time constant, time delay, and bias are given in Table 4. OKR response bias was near zero for all subjects. Both the gain constant and time delay had approximately symmetric distributions. In contrast, the OKR time constant had a highly skewed and possibly bimodal distribution with about 40% of the values near zero. OKR time constants near zero reflect the fact that OKR gains for these subjects were approximately constant over the frequency range tested.

The OKR pseudorandom stimulus was quite provocative in the initiation of motion sickness symptoms. Twenty subjects requested the termination of testing as a result of the onset of motion sickness symptoms. Approximately an equal number experienced motion sickness symptoms but were able to complete the 220 s duration OKR stimulus. It was not possible to calculate OKR gains and phases from incomplete trials using our current analysis methods. Therefore, it was not possible to test the hypothesis that abnormal OKR responses were related to motion sickness sensitivity in these highly susceptible subjects. However, OKR gains and phases from subjects who reported the onset of motion sickness symptoms but were able to complete the test did not show any obvious differences compared with subjects who did not report symptoms. Also, comparisons of VOR rotation test results of OKR motion-sickness susceptible subjects with nonsusceptible subjects did not reveal any differences.

![Figure 3](image-url). Examples of OKR gain and phase data from two individuals derived from responses to pseudorandom optokinetic stimulation. Solid lines show transfer function curve fits to data. Equations of the curve fits are inset. Gain and frequency scales are logarithmic.
Age-Related Changes in VOR and OKR

Several VOR and OKR response parameters changed with age (Figures 4 and 5), while the absolute values of VOR and OKR bias did not. Many of the age-related changes showed roughly linear trends. Linear regression slope, intercept, and correlation coefficients are summarized in Table 5. Both VOR time constant (Figure 4B) and OKR gain constant (Figure 5A) increased slightly in subjects up to about 30 y and then decreased with increasing age. The OKR time delay parameter increased with increasing age and showed the clearest age-related trend (r = 0.53 and slope = 1.2 ms/y) of all VOR and OKR parameters.

The age-related change in the OKR time constant was clearly not linear. Data in Figure 5B show that a large proportion of subjects between about 20 and 60 y had OKR time constants close to zero, indicating that their OKR gains were constant across frequency. In contrast, there were very few subjects under 20 y of age and proportionally fewer subjects over 60 who had zero OKR time constants, indicating that on average their OKR gains declined with increasing frequency. The lowess curve fit indicates that age-related trends were minimal for subjects between 20 and 60 y. Subjects under 20 showed an age-related decline in their OKR time constant with increasing age. Subjects over 60 showed an age-related increase in their OKR time constant with increasing age.

Discussion

Pseudorandom Testing

There are both advantages and disadvantages to the use of pseudorandom stimuli for VOR and OKR testing. An advantage is the concurrent testing of response dynamics over a large frequency bandwidth. The total test

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### Table 4. OKR Response Parameters for Pseudorandom Stimulus: Mean, SD, and Percentile Values from Parameter Distributions* (N = 179 subjects)

<table>
<thead>
<tr>
<th></th>
<th>Gain constant</th>
<th>Time constant (s)</th>
<th>Time delay (s)</th>
<th>Bias (°/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.65</td>
<td>0.080</td>
<td>0.180</td>
<td>-0.1</td>
</tr>
<tr>
<td>SD</td>
<td>0.12</td>
<td>0.080</td>
<td>0.043</td>
<td>0.8</td>
</tr>
<tr>
<td>2.5%</td>
<td>0.40</td>
<td>0.002</td>
<td>0.099</td>
<td>-1.7</td>
</tr>
<tr>
<td>5%</td>
<td>0.47</td>
<td>0.003</td>
<td>0.114</td>
<td>-1.5</td>
</tr>
<tr>
<td>25%</td>
<td>0.59</td>
<td>0.008</td>
<td>0.147</td>
<td>-0.7</td>
</tr>
<tr>
<td>50%</td>
<td>0.66</td>
<td>0.06</td>
<td>0.187</td>
<td>-0.1</td>
</tr>
<tr>
<td>75%</td>
<td>0.72</td>
<td>0.12</td>
<td>0.216</td>
<td>0.3</td>
</tr>
<tr>
<td>95%</td>
<td>0.77</td>
<td>0.23</td>
<td>3.2±3</td>
<td>...</td>
</tr>
<tr>
<td>97.5%</td>
<td>0.87</td>
<td>0.25</td>
<td>0.253</td>
<td>1.4</td>
</tr>
</tbody>
</table>

---

**Figure 4.** VOR gain constant (A) and time constant (B) parameters as a function of subject age. Parameter values were estimated from transfer function curve fits to gain and phase data obtained from pseudorandom rotation test results. Solid curves are lowess fits.
time is reduced compared to the equivalent testing using single frequency sinusoidal stimuli. In addition, all gain and phase measures obtained from pseudorandom responses are obtained at the same average level of subject arousal. Therefore, a subject's reflex gains, which depend on subject alertness, can be compared across test frequencies without worry of possible alertness changes as in sequential testing at individual frequencies. A wide bandwidth stimulus can therefore reveal patterns of gain and phase changes over a range of test frequencies that are not as evident or as reliable when single frequency sinusoids are used. These detailed patterns of gain and phase changes with frequency may contain more clinically useful information than the simple summaries of response dynamics in terms of derived gain constants and time constants. In addition, a pseudorandom stimulus may provide a more "realistic" or "natural" stimulus than more predictable ones, and therefore test the dynamics of the components under conditions similar to everyday conditions.

Pseudorandom testing has the disadvantage that the complexity of the eye movement responses makes it difficult to judge the quality of the responses. The failure to maintain subject alertness throughout the test coupled with the failure to recognize the lack of alertness would bias the gain and phase measures of reflex dynamics.

The similarity between pseudorandom and sinusoidal VOR test results suggests that information from the two test techniques is relatively interchangeable. The most significant difference between VOR responses was the small 3° phase lead of pseudorandom results relative to sines at higher stimulus frequencies. However, others have shown large differences in OKR dynamics when gain and phase data derived from single frequency sinusoidal tests are compared to pseudorandom results (20). In particular, OKR gains from sinusoidal tests are generally higher and show less phase lags at any particular test frequency than pseudorandom results. The simplest interpretation of these differences is that prediction plays an important role in visually-driven eye movements. The mechanisms involved in this prediction are poorly understood, but it is known that the brain's predictive mechanisms influence the overall dynamic responses of pursuit eye movements even when pseudorandom visual stimuli are used (2).
Table 5. Age Effects on VOR and OKR Response Parameters*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope (change/yr)</th>
<th>Intercept at 0 years</th>
<th>Correlation coefficient</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOR gain constant</td>
<td>-0.0019</td>
<td>0.79</td>
<td>-0.24</td>
<td>207</td>
</tr>
<tr>
<td>VOR time constant (s)</td>
<td>-0.62</td>
<td>27.0</td>
<td>-0.15</td>
<td>207</td>
</tr>
<tr>
<td>OKR gain constant</td>
<td>-0.0015</td>
<td>0.71</td>
<td>-0.26</td>
<td>179</td>
</tr>
<tr>
<td>OKR time delay (s)</td>
<td>0.0012</td>
<td>0.13</td>
<td>0.53</td>
<td>179</td>
</tr>
</tbody>
</table>

* All parameter values that showed significant or nearly significant linear trends with age are listed.

ular, the predictive mechanism apparently favors the highest frequency component of the stimulus at the expense of lower frequency components causing the gains of lower frequency components of pursuit eye movements to be depressed while the gain of the highest frequency is enhanced. Although there are differences between pursuit and optokinetic response dynamics to pseudorandom stimulation (20), similar mechanisms to those which occur in pursuit tracking may influence optokinetic responses to full field visual stimuli.

The presence of a predictive mechanism as well as other nonlinear properties of visually-guided eye movements does not necessarily disqualify the use of pseudorandom stimuli for OKR testing. Rather, pseudorandom stimuli may prove to be useful in quantifying the functionality of the predictive mechanism which is likely an important contributor to the control of gaze. Perhaps the larger proportion of young and old subjects with declining OKR gains at higher stimulus frequencies (larger $T_o$'s) may indicate a less functional predictive mechanism for visually-guided eye movements in these age groups.

VOR and OKR Changes with Age

We were able to identify small age effects on VOR and larger age effects on OKR reflexes. The direction of change of some reflex parameters were expected, such as declining VOR gains, declining OKR gains, and increased time delays in the OKR with increasing age. However, the decreased high frequency OKR gain of the youngest and oldest subjects as compared to middle-aged subjects was not expected.

The rate at which the OKR time delay increased with age was quite large and is similar to the changes found in pursuit latency with increasing age (16,17). If this increased time delay is representative of general changes in the speed of visual system motion processing associated with visuomotor tasks, this could affect tasks such as posture control, which use vision for feedback control. Longer feedback time delays generally contribute to decreased stability and poorer overall performance.

The interpretation of age-related changes in OKR time delay is complicated by the fact that the OKR time constant and time delay parameters are probably not independent. This is because the lag term $T_o s + 1$ in eqn 3 which accounts for the declining gain at higher stimulus frequencies also accounts for some of the phase lag. The larger the OKR time constant, $T_o$, the more phase accounted for by the lag term, and therefore the smaller the value of the OKR time delay parameter, $T_d$, required to explain the remaining phase lag. Since the youngest subjects had the largest $T_o$'s, this would tend to bias their $T_d$'s toward lower values. The oldest subjects also tended to have larger $T_o$'s, which should also bias their $T_d$'s toward lower values. However, Figure 5C shows that, despite this possible bias toward lower values, older subjects still had the largest $T_d$'s in the population. Therefore, although the exact time course of the age-related change in time delay in Figure 5C may be distorted by the interaction with $T_o$, it is apparent that the oldest subjects did have the largest response delays.
Both younger (<15 y) and older (>65 y) subjects were relatively less responsive to the higher frequency components of the stimulus. The lower OKR responsiveness at higher frequencies could have functional consequences, particularly for older subjects. While it is generally appreciated that visual tracking reflexes improve visual-vestibular generated compensatory eye movements during low frequency head movements, visual motion information is apparently used to improve the dynamics of compensatory eye movements at higher stimulus frequencies associated with natural head movements (15). This would be particularly important for individuals who had VOR phase leads at higher frequencies (Figure 2B).

Since older individuals had larger VOR phase leads on average than younger subjects (13), we might expect that the older subjects would need more help from their visual tracking reflexes to correct their imperfect VOR dynamics. However, the sensitivity to optokinetic motion at higher frequencies declined in many older subjects making it less likely that visual tracking reflexes could correct for imperfect VOR dynamics.

Acknowledgment—We wish to thank Christopher Newell, Patrick Shea, and Martha Benolken for their assistance. This research was supported by NASA research grants NCC9-8 and NAG 9-117.

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AGE-RELATED CHANGES IN HUMAN POSTURE CONTROL: SENSORY ORGANIZATION TESTS

R.J. Peterka, PhD,* and F.O. Black, MD

Good Samaritan Hospital and Medical Center, R. S. Dow Neurological Sciences Institute, and Department of Neuro-otology, Portland, OR

Reprint address: Robert J. Peterka, Dept of Neuro-otology, N010, Good Samaritan Hospital & Medical Center, 1040 N.W. 22nd Ave., Portland, OR 97210

Abstract—Postural control was measured in 214 human subjects ranging in age from 7 to 81 y. Sensory organization tests measured the magnitude of anterior-posterior body sway during six 21 s trials in which visual and somatosensory orientation cues were normal, altered (by rotating the visual surround and support surface in proportion to the subject's sway), or vision eliminated (eyes closed). No age-related increase in postural sway was found for subjects standing on a fixed support surface with eyes open or closed. However, age-related increases in sway were found for conditions involving altered visual or somatosensory cues. Subjects older than about 55 y showed the largest sway increases. Subjects younger than about 15 y were also sensitive to alteration of sensory cues. On average, the older subjects were more affected by altered visual cues, whereas younger subjects had more difficulty with altered somatosensory cues.

Keywords—posturography, vestibular, somatosensory, vision, equilibrium, development.

Introduction

The automatic control of upright stance is an active sensorimotor process that maintains the body's center of gravity over the base of support (the feet). This process requires that deviations of body position from upright be sensed and processed to initiate motor commands that oppose the initial deviation and return the body to an upright position. The vestibular, somatosensory, and visual systems are the main sources of sensory information on body motion. However, situations commonly arise in which information from the various sensory systems is absent or altered even in individuals with physiologically normal sensory function. For example, somatosensory cues from compliant surfaces can be misleading, and visual cues are eliminated when the eyes are closed. In order to maintain postural control under a variety of environmental conditions, motion information from sensory systems must be organized by the central nervous system so that inappropriate or inadequate sensory inputs can be ignored when necessary.

One method for testing postural control, which we will call sensory organization tests, involves postural responses that occur over tens of seconds to minutes when subjects attempt to stand quietly in various sensory conditions. The simplest sensory organization tests are the clinical standard Romberg tests, which characterize spontaneous postural sway when the subject's eyes are open and closed (3,10). The standard Romberg tests can be extended by altering somatosensory and/or visual motion cues. The alteration of somatosensory and/or visual cues by rotating the subject's visual field and/or support surface in equal proportion to the subject's own sway (11) tests the subject's ability to maintain
equilibrium when various combinations of sensory cues are inappropriate or inadequate for orientation to earth vertical. Postural control under these altered conditions may be more difficult than when information is missing, as with eyes closed.

The increased incidence of falls in the older population (18) suggests that one or more of the components required for accurate postural control degenerates with age. Studies that have looked for differences in postural control between young and old adults have generally found these differences (10,19), including increased sway or falls in various sensory organization tests. In addition children show developmental changes in postural control that converge to adult patterns at about age 10 y (6,15). However, the limited scope of these studies with their small sample sizes and restricted test paradigms have not clarified either the time course or the mechanism involved in the changes in use of sensory information for postural control with increasing age. We tested a putatively normal population with a wide age distribution using both postural motor coordination (12) and sensory organization tests. In addition, vestibulo-ocular (VOR) and optokinetic reflexes (OKR) were independently tested in the same individuals (13,14) for comparison to postural responses.

Methods

Postural sway under various sensory conditions was measured in 214 human subjects (90 male and 124 female) aged 7 to 81 y. Ages were approximately uniformly distributed over the entire range. Details of subject selection are given in a previous paper (14). No subjects were excluded from the population based on any vestibular, optokinetic, or posture test results.

Body Sway Measurements

The anterior–posterior (AP) sway angle ($\theta_{\text{ap}}$, see Figure 1) of each subject was recorded using a rod attached to a potentiometer. The potentiometer was mounted on a post next to the subject. The end of the rod rested in a V-shaped holder centered on the subject’s back at hip level. A voltage proportional to the angular displacement of the potentiometer was recorded and later transformed using appropriate trigonometric conversions to $\theta_{\text{ap}}$. A second potentiometer mounted at shoulder level recorded AP displacements at the shoulder in the last 65 subjects tested. A measure of hip angle ($\theta_h$, Figure 1) was calculated from AP angles measured at the hip and shoulder. An approximate center-of-gravity AP sway angle ($\theta_{\text{cg}}$) was calculated using the following formula:

$$\theta_{\text{cg}} = \tan^{-1} \left[ \frac{0.860 \sin \theta_{\text{ap}} + 0.242 \sin (\theta_{\text{ap}} + \theta_h)}{0.860 \cos \theta_{\text{ap}} + 0.242 \cos (\theta_{\text{ap}} + \theta_h)} \right].$$

This formula was derived assuming the subjects had average body mass distribution and average proportional lengths of various body segments (5). To the extent that the various subjects deviated from average body configurations, the measurement of $\theta_{\text{cg}}$ would be in error. This error was probably not more than 10% in this population. Sway angles were sampled at 50 Hz.

Test Conditions

Subjects stood with feet separated by about 20 cm on a movable support surface surrounded in front and on two sides by a movable visual surround. The visual surround was a box with randomly placed 2 cm black dots on a white surface. The average spacing between the dots was about 20 cm, and the distance from the subject to the box was about 50 cm. Support surface motion was controlled by a hydraulic position servo system that could produce toe up and toe down rotations about an axis collinear with the subject’s ankle joints. Visual surround motion was controlled by a separate hydraulic servo system that rotated the box about the ankle joint axis. Subjects wore a harness attached to the ceiling to prevent injury in
case of a fall. The harness did not impede body motions even during large amplitude sways.

Each subject performed 6 tests, which provided a functional evaluation of the ability of the subject to effectively use vestibular, somatosensory, and visual information in the control of upright posture (11). The subject's task was to maintain an upright stance for 21 s during each of the six conditions with as little postural sway as possible and without moving the feet. The test was rated a fall if the subject required the assistance of the harness to maintain upright stance or if a step was taken in order to prevent a fall into the harness. The 6 test conditions generally were performed once. In later subjects, a test condition was immediately repeated if the subject fell in that condition. Tabulated results on falls and sway are based on the performance in the first test of each condition.

Conditions 1 and 2 required the subject to stand on a stable surface for 21 s facing an earth-fixed visual field with eyes open and then with eyes closed. The remaining four conditions placed the subject in more demanding sensory environments. These environments were created by rotating the visual field and/or the support surface in equal proportion to $\theta_{ap}$. For example, as the subject swayed forward, the visual field rotated forward about an axis through the ankle joint. Under this condition the normal relationship between body motion and retinal image motion is altered. This is referred to as sway-referenced vision as opposed to the earth-referenced vision in condition 1. The precise relation between the retina and the box depended on the movement patterns that subjects used during sway. The same technique was applied to the support surface by rotating it about the ankle joint in proportion to $\theta_{ap}$. This sway-referenced support condition greatly reduced the change in ankle joint angle as the subject swayed back and forth and therefore altered the somatosensory cues contributing to postural control. The entire sensory test sequence included all 6 combinations of eyes closed, sway-referenced, and earth-referenced vision and support surface conditions given in Table 1.
Table 1. Sensory Organization Test Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensory conflict</th>
<th>Visual reference</th>
<th>Support surface reference</th>
<th>Earth-referenced (accurate)</th>
<th>Sway-referenced (altered)</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no earth</td>
<td>earth</td>
<td>earth</td>
<td>visual, vestibular, somatosensory</td>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>no eyes closed</td>
<td>earth</td>
<td>earth</td>
<td>visual, vestibular, somatosensory</td>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>yes sway</td>
<td>earth</td>
<td>earth</td>
<td>vestibular, visual, somatosensory</td>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>yes earth</td>
<td>sway</td>
<td>earth</td>
<td>vestibular, visual</td>
<td>somatosensory</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>yes eyes closed</td>
<td>sway</td>
<td>sway</td>
<td>somatosensory</td>
<td>visual</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>yes sway</td>
<td>sway</td>
<td>sway</td>
<td>somatosensory, visual</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Body Sway Analysis**

Sway data were summarized by two measures: average rectified sway (ARS) and peak-to-peak sway. Both measures were calculated over the final 20 s of the 21 s trials (the visual field and support surface were always earth-referenced during the first second of each trial). For ARS calculations, sway data was normalized by subtracting the average sway values recorded in the first second from the entire sway record. Sway data samples less than zero were then rectified (inverted), and the new sway trace was averaged over the final 20 s. ARS often did not reflect how close a given individual was to a fall since, for example, a subject who leaned forward by a few degrees and stayed in that position throughout the remainder of the trial could score the same as a subject who oscillated back and forth during the trial with the peak of the oscillations close to the threshold of a fall. The peak-to-peak sway measure was more indicative of the closeness of sway to fall thresholds.

**Movement Strategies**

Subjects typically use one of two body motion strategies to maintain upright stance without moving the feet (7). A hip strategy consists of $\theta_h$ and $\theta_{ap}$ motions that are out of phase. Subjects can be forced to use a hip strategy by asking them to stand on a narrow beam that limits the amount of torque that can be exerted at the ankle. A pure ankle strategy occurs when all motion is about the ankle joint (AP sway angles measured at the hip and shoulder are equal and $\theta_h$ is zero). A less pure ankle strategy occurs when there is some motion about the hip joint, but $\theta_{ap}$ and $\theta_h$ are in phase with each other. In order to quantify the type of body motion, a strategy measure was calculated according to the following formula:

$$\text{strategy score} = \frac{1}{2} ((\overline{\theta_{ap}} - \overline{\theta_{ap}})(\overline{\theta_h} - \overline{\theta_h}))$$

where the bars over the various terms indicate the average values over time, that is, the strategy score is the average product of zero-meaned $\theta_{ap}$ and $\theta_h$ calculated over the duration of the trial. The strategy score is negative if $\theta_h$ and $\theta_{ap}$ are out of phase indicating that the trunk and legs move in opposite directions, positive if they are in phase and the body moves like a whip, and zero when the body moves like an inverted pendulum with no bending at the waist. Since this measure is an average over the entire trial, changes in strategy during the trial would not be correctly characterized by this single measure. In practice, this was not a problem since this putatively normal population did not show marked strategy changes within trials.

**Visualization of Trends**

In order to visualize trends in scatterplots, a robust locally weighted regression analysis (lowess fit) was used to smooth the scatter-
Age-Related Changes in Posture

Table 2. AP Sway Measures in Completed Sensory Test Conditions (mean ± 1 SD*)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Average rectified sway (degrees)</th>
<th>Peak-to-peak sway (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214</td>
<td>0.26 ± 0.21</td>
<td>0.82 ± 0.44</td>
</tr>
<tr>
<td>2</td>
<td>214</td>
<td>0.42 ± 0.33</td>
<td>1.26 ± 0.58</td>
</tr>
<tr>
<td>3</td>
<td>189</td>
<td>0.68 ± 0.57</td>
<td>2.78 ± 2.00</td>
</tr>
<tr>
<td>4</td>
<td>213</td>
<td>0.74 ± 0.49</td>
<td>2.96 ± 1.97</td>
</tr>
<tr>
<td>5</td>
<td>192</td>
<td>1.20 ± 0.48</td>
<td>5.54 ± 2.23</td>
</tr>
<tr>
<td>6</td>
<td>155</td>
<td>1.32 ± 0.53</td>
<td>5.75 ± 2.12</td>
</tr>
</tbody>
</table>

* SD = standard deviation.

plots (4). This smoothing is similar to a moving average filter, but is less sensitive to outlying points and allows variable amounts of smoothing. A loweress smoothing parameter of 0.5 and iteration parameter of 2 were used on all data sets.

Results

As visual and somatosensory sensory information were removed and/or altered during the various sensory test conditions, subjects became less stable (Table 2) and falls became more likely. Most subjects did not fall in any condition, but their sway amplitudes increased as they were deprived of orientationally accurate sensory reference information. Some subjects, particularly older subjects, did fall. The pattern of falls was not random, but rather was restricted to certain conditions and combinations of conditions.

Sway Responses

All subjects had minimal sway standing with eyes open or eyes closed on a stable surface (conditions 1 and 2, see Figure 2). No subjects fell in conditions 1 or 2. Postural sway increased in condition 3 when the visual surround rotation was referenced to the subject’s sway. The median of the condition 3 sway distribution in Figure 2 was only about one degree higher than condition 2, indicating that most subjects had only slightly more difficulty controlling their posture under the sway-referenced vision condition than with eyes closed. However, the condition 3 distribution is highly skewed toward larger sway amplitudes indicating that a significant fraction of the population had difficulty maintaining their upright posture when visual orientation information was present but sway-referenced. In addition, 30 of 214 subjects (14%) fell in condition 3.

Condition 4 provided earth-referenced visual cues but sway-referenced somatosensory cues. This distribution was skewed toward larger sway angles in a similar manner to the condition 3 distribution. On average, subjects were more stable in condition 4 than in condition 3 since only three subjects out of 214 (1.4%) fell in condition 4.

Visual cues in condition 5 were absent (eyes closed) and somatosensory cues were altered by the sway-referenced support surface. This condition presumably forced a greater reliance on vestibular cues for postural control. Average sway was larger than in any of the previous conditions and was also skewed toward larger values. Twenty-eight of 214 subjects (13.1%) fell in this condition.

Condition 6 was the most difficult of the 6 conditions. Under this condition, both the visual surround and the support surface were sway referenced. As with condition 5, this condition forced a greater reliance on vestibular cues for postural control. However, the presence of altered visual orientation cues in condition 6 (as opposed to absent vision in condition 5) apparently increased the difficulty of the task. The average sway for subjects who completed condition 6 was larger than in any other conditions, and 70 of 214 subjects (32.7%) fell.

The amount of sway in one condition was generally a poor predictor of the amount of sway in another condition. Linear correlation coefficients relating peak-to-peak sway in various combinations of conditions were calculated for the 125 subjects who did not fall in any condition. The largest correlation coefficients (ranging from 0.42–0.54) were between conditions 1 and 4, 2 and 4, and among conditions 4, 5, and 6. Correlation coefficients comparing sway in conditions 1 and 4, and 2 and 4 were
Figure 2. Histograms of peak-to-peak $\theta_{ap}$ under the six different sensory test conditions. Gray bars to the right of each histogram indicate the number of subjects who fell in that condition. One subject in condition 3, and 5 subjects in condition 5 had sways greater than 12° but did not fall, and are not included in those respective histograms.

about 0.3. The correlations coefficients for all other paired comparisons were <0.2.

Movement Strategy

The use of an ankle strategy was by far the most common mode of postural sway in these subjects. The 65 subjects whose body motions were measured at both the hip and shoulder were the older portion of the entire population with a mean age of 56.2 y (12.5 SD, range 27 to 81 y). Their mean strategy scores were close to zero, and the variances of the scores were small in all six conditions (Table 3). This was confirmed by plotting peak-to-peak $\theta_{cg}$ versus peak-to-peak $\theta_{ap}$. For pure hip strategies $\theta_{cg}$ and $\theta_{ap}$ should be relatively unrelated, whereas a pure ankle strategy would have equal $\theta_{cg}$ and $\theta_{ap}$, and correlations of close to 1.0. Correlation coefficients between peak-to-peak $\theta_{cg}$ and $\theta_{ap}$ data ranged from 0.93 to 0.98 for the six conditions. Data points were tightly clustered around the line of equal $\theta_{cg}$ and $\theta_{ap}$. 
Table 3. AP Sway Measures for Subjects Who Completed the Sensory Tests, Sway Measured at Shoulder and Hip (mean ± 1 SD)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Peak-to-peak $\delta_{ap}$ sway (degrees)</th>
<th>Peak-to-peak $\delta_{cg}$ sway (degrees)</th>
<th>Peak-to-peak $\delta_{hp}$ sway (degrees)</th>
<th>Strategy score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>0.75 ± 0.32</td>
<td>0.72 ± 0.34</td>
<td>1.41 ± 0.56</td>
<td>-0.01 ± 0.05</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>1.21 ± 0.54</td>
<td>1.33 ± 0.59</td>
<td>1.78 ± 0.81</td>
<td>0.04 ± 0.07</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>3.01 ± 2.16</td>
<td>3.28 ± 2.18</td>
<td>3.56 ± 2.09</td>
<td>0.24 ± 0.56</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>2.41 ± 1.20</td>
<td>2.22 ± 1.15</td>
<td>2.96 ± 2.10</td>
<td>-0.14 ± 0.46</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>5.31 ± 2.45</td>
<td>5.50 ± 2.37</td>
<td>5.53 ± 3.44</td>
<td>0.21 ± 1.38</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>5.27 ± 1.86</td>
<td>5.58 ± 2.12</td>
<td>6.08 ± 4.91</td>
<td>0.49 ± 0.95</td>
</tr>
</tbody>
</table>

Fall Patterns

Table 4 summarizes the data on subjects who fell during one or more of the 6 conditions. Falls during sensory test conditions were not random occurrences, but rather were associated with the inability of some subjects to obtain and/or coordinate the sensory information available for the control of posture. Consider subjects who fell in two of the four conditions that presented them with sensory conflict situations. There are six possible combinations of paired falls within the grouping of the four more difficult conditions. If paired falls occurred randomly, they would be evenly distributed across the six possible combinations. This was clearly not the case since four of the six combinations of paired falls either were not observed or were rare. That is, no subjects fell in 3-4 and 4-5 paired conditions, and only two subjects fell in the 3-5 and one in the 4-6 combination of conditions. Therefore, paired falls were primarily limited to only two of the six possible paired combinations, with 12 subjects falling in 5-6 conditions, and 15 falling in 3-6 conditions.

The six subjects who fell in three conditions were also not randomly distributed among the four possible combinations. Rather all six subjects fell in the same set of three conditions; which was the 3-5-6 combination. This combination combines the features of the two most common paired condition falls, 3-6 and 5-6 as reported previously (1,2,11). Most of these subjects were older (aged 45, 48, 60, 66, 69, and 70 y).

There was a clear learning effect when sensory tests were repeated immediately following a fall. Thirty-three of the 131 first test falls were repeated. Only 6 of the 33 subjects (18%) fell in the repeated test. The number of repeat test falls for the four sensory conditions where falls occurred were 1 of 8 for condition 3, 0 of 2 for condition 4, 2 of 8 for condition 5, and 3 of 15 for condition 6.

Age-Related Changes

Figure 3 shows peak-to-peak sway and falls as a function of age. Generally, the number of falls increased with increasing age (Table 5). The incidence of falls was lowest for subjects aged 20-40 y. Subjects aged 13-19 y had a high incidence of single condition falls (33%) but low multiple condition falls (11%).
The lowess fits to peak-to-peak sway data in Figure 3 suggest that younger subjects swayed more than subjects in the middle of the age range. A comparison of peak-to-peak sway of 7 to 15 y olds with 30 to 39 y olds showed significant differences for conditions 1, 4, 5, and 6 ($P < 0.02$, Mann–Whitney non-parametric test). The larger sway of younger subjects was most evident in sensory conditions 4, 5, and 6, suggesting that younger subjects...
were sensitive to alterations in somatosensory cues.

The occurrence of single condition falls increased rapidly for subjects older than about 45 y, although the incidence of multiple condition falls remained quite stable through the 50s before showing an increase in the 60 to 70 y olds. A possible anomalous result was obtained in the over-70 age group for multiple falls. Their multiple fall rate was less than the fall rate for 60 to 70 y olds and approximately the same as for 40 to 60 y olds. This may be a result of the small sample size of the over-70 age group; an exceptionally healthy condition of this group, or an exceptionally high fall rate for subjects in the 60 to 70 age group.

Surprisingly, the increased incidence of falls in older subjects in conditions 3 and 5 was not accompanied by a trend toward increasing peak-to-peak \( \theta_{ap} \) among nonfallers (Figure 3). This is in contrast to condition 6 where both sway and falls increased with age. Since it is not possible to maintain stance with the body's center of gravity outside of its base of support, the theoretical limit of peak-to-peak sway is dependent on foot size and body mass distribution. Since most subjects have a 10° to 12° range of stable AP sway, and peak-to-peak \( \theta_{ap} \) average 3° and 5.3° for conditions 3 and 5, respectively, it seems that there was some room for the nonfalling population to shift toward larger sways in conditions 3 and 5, and that this shift would be accompanied by an increased number of falls. Although the falls increased, the peak-to-peak sway amplitude of nonfallers did not.

### Discussion

Age-related changes in postural control performance were not present in subjects older than about 15 y when they were tested under "normal" operating conditions during sensory test conditions 1 and 2. That is, when subjects stood on an earth-fixed support surface with eyes open or closed, their sway was small and the oldest subjects performed as well as the younger ones. Since the first two sensory tests are characterized by the presence of multiple sensory system inputs that converge and cooperate in the generation of appropriate postural control responses, it is apparent that subjects are well adapted to an environment without conflicting sensory cues. However, it is also clear from the other sensory test conditions that the "parts" that make up the "whole" of postural control are not equally functional in all individuals. The prevalence of falls and the wide range of postural sway amplitudes in sensory test conditions 3–6 demonstrate this functional inequality.

### Analysis of Fall Patterns

The pattern of falls among subjects who fell in two or more conditions can be logically associated with specific types of peripheral sensory or sensory integration problems. The 15 subjects who fell in the 3-6 conditions were highly sensitive to visual cues which were altered by sway-referencing the visual field. These subjects behaved paradoxically. The fact that they did not fall in condition 5 indicates that they were presumably able to use vestibular cues to properly maintain stable stance since no visual and only altered somatosensory cues were otherwise available. However, when visual cues were present in 3 and 6, they chose to ignore earth-referenced vestibular and somatosensory cues in condi-

### Table 5. Sensory Test Falls Sorted by Subject Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of subjects</th>
<th>Single falls</th>
<th>N</th>
<th>%</th>
<th>Multiple falls</th>
<th>N</th>
<th>%</th>
<th>Total falls</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12</td>
<td>21</td>
<td>3</td>
<td>14.3</td>
<td>2</td>
<td>9.5</td>
<td>5</td>
<td>23.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>27</td>
<td>9</td>
<td>33.3</td>
<td>3</td>
<td>11.1</td>
<td>12</td>
<td>44.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>28</td>
<td>4</td>
<td>14.3</td>
<td>2</td>
<td>7.1</td>
<td>6</td>
<td>21.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>32</td>
<td>4</td>
<td>12.5</td>
<td>2</td>
<td>6.3</td>
<td>6</td>
<td>18.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>32</td>
<td>9</td>
<td>28.1</td>
<td>6</td>
<td>18.8</td>
<td>15</td>
<td>46.9</td>
<td></td>
<td></td>
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<td>36</td>
<td>16.8</td>
<td>89</td>
<td>41.6</td>
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The occurrence of single condition falls increased rapidly for subjects older than about 45 y, although the incidence of multiple condition falls remained quite stable through the 50s before showing an increase in the 60 to 70 y olds. A possible anomalous result was obtained in the over-70 age group for multiple falls. Their multiple fall rate was less than the fall rate for 60 to 70 y olds and approximately the same as for 40 to 60 y olds. This may be a result of the small sample size of the over-70 age group; an exceptionally healthy condition of this group, or an exceptionally high fall rate for subjects in the 60 to 70 age group.

Surprisingly, the increased incidence of falls in older subjects in conditions 3 and 5 was not accompanied by a trend toward increasing peak-to-peak \( \theta_{ap} \) among nonfallers (Figure 3). This is in contrast to condition 6 where both sway and falls increased with age. Since it is not possible to maintain stance with the body's center of gravity outside of its base of support, the theoretical limit of peak-to-peak sway is dependent on foot size and body mass distribution. Since most subjects have a 10° to 12° range of stable AP sway, and peak-to-peak \( \theta_{ap} \) average 3° and 5.3° for conditions 3 and 5, respectively, it seems that there was some room for the nonfalling population to shift toward larger sways in conditions 3 and 5, and that this shift would be accompanied by an increased number of falls. Although the falls increased, the peak-to-peak sway amplitude of nonfallers did not.

### Discussion

Age-related changes in postural control performance were not present in subjects older than about 15 y when they were tested under "normal" operating conditions during sensory test conditions 1 and 2. That is, when subjects stood on an earth-fixed support surface with eyes open or closed, their sway was small and the oldest subjects performed as well as the younger ones. Since the first two sensory tests are characterized by the presence of multiple sensory system inputs that converge and cooperate in the generation of appropriate postural control responses, it is apparent that subjects are well adapted to an environment without conflicting sensory cues. However, it is also clear from the other sensory test conditions that the "parts" that make up the "whole" of postural control are not equally functional in all individuals. The prevalence of falls and the wide range of postural sway amplitudes in sensory test conditions 3–6 demonstrate this functional inequality.

### Analysis of Fall Patterns

The pattern of falls among subjects who fell in two or more conditions can be logically associated with specific types of peripheral sensory or sensory integration problems. The 15 subjects who fell in the 3-6 conditions were highly sensitive to visual cues which were altered by sway-referencing the visual field. These subjects behaved paradoxically. The fact that they did not fall in condition 5 indicates that they were presumably able to use vestibular cues to properly maintain stable stance since no visual and only altered somatosensory cues were otherwise available. However, when visual cues were present in 3 and 6, they chose to ignore earth-referenced vestibular and somatosensory cues in condi-
tion 3 and earth-referenced vestibular cues in condition 6 in favor of the altered visual reference. Although the mechanisms that cause and sustain this preference for a visual reference are not known, it seems likely to be a sensory selection problem rather than a motor coordination problem (11).

The second most common paired falls occurred in conditions 5 and 6, which force subjects to rely primarily on their vestibular systems for postural control since somatosensory and/or visual cues are either absent or altered. This pattern of falls is found frequently in subjects who have peripheral vestibular deficits (8,11). A subject with total bilateral peripheral loss of vestibular function is the extreme form of vestibular deficiency. Patients with bilateral loss as judged from absent caloric and rotation responses invariably fall in conditions 5 and 6 (2,11).

Falls in both conditions 5 and 6 could theoretically also arise from central mechanisms. The central postural control mechanisms perform complex tasks that include both the generation of the correct motor commands to the muscles and the selection of an appropriate orientation reference based on information from several sensory systems that at times may be conflicting. It is possible that peripheral vestibular signals may be normal, but the central mechanisms that make use of this information are faulty. The "fault" may have more than one source. For example, the processing of the sensory information may simply be too slow, in which case the appropriate motor commands never arrive at the muscles or arrive too late to prevent a fall. Alternatively, the central processing that must deal with conflicting sensory information may produce inappropriate responses based on the available sensory signals. These inappropriate responses could drive the system into instability with a resulting fall. A possible example of this may be learning-disabled children with normal VOR function who often fall in conditions 5 and 6 (8,16). Finally, motor coordination deficits and muscle weakness could also play a role in 5-6 fallers since these conditions evoke relatively large sway amplitudes in most subjects.

Developmental Postural Changes in Children

Subjects aged 7 to 15 y had increased peak-to-peak sway amplitudes in all sensory test conditions except conditions 2 and 3. This is consistent with previous results in children aged 2 to 15 y (15) and 1½ to 10 y (6,17). Both studies show increased AP sway in sensory condition 1 in the youngest children with a convergence toward adult performance at about age 3 to 10 y. One of these studies (6) also used sway-referenced tests identical to conditions 3-6 and again found the poorest performance in the youngest children but with incomplete convergence to adult values by age 10 y for all 4 conditions. Sway-referenced vision (condition 3) results presented here differ from this previous study (6) since the average peak-to-peak sway of the youngest subjects did not differ from adult sway values. However, condition 4, 5, and 6 results presented here agree with the previous findings (6) and extend those results to show that adult performance is not fully attained until about 20 y of age under these sensory conditions.

In all conditions with altered somatosensory inputs (conditions 4, 5, and 6), subjects younger than about 15 y showed more sway, on average, than middle-aged adults. This suggests that younger subjects rely more heavily on somatosensory cues than do middle-aged and many older adults even when accurate, earth-referenced visual and vestibular cues are available. Many children had sway results compatible with adult sways, while others swayed considerably more than middle-aged adults. This wider range of postural sway for children compared to adults may be associated with differing rates of development of postural control abilities in different children.

Postural Control Changes in the Elderly

Sensory test results showed that most falls occurred in subjects older than about 50 y. In
Age-Related Changes in Posture

condition 6, the increased number of falls was accompanied by increased sway among nonfallers. However, older nonfallers performed about the same as younger subjects in conditions 3 and 5 even though there were increased falls in the elderly group.

The finding that there is no general increase in sway with age in conditions 3 and 5, but there is an increase in falls suggests that the elderly fallers form one or more subgroups within the elderly population. These elderly fallers apparently either lack information required for postural control or have adopted postural control schemes that are distinct from the remainder of the population and that place them at increased risk for falls in particular sensory environments. However, when redundant sensory cues are available (conditions 1 and 2) and sway amplitudes are greatly reduced, these fallers cannot be distinguished from the remainder of the population.

A simple explanation for these results could be that the average body alignment of these subjects places their center of gravity near a stability limit so that relatively small increases in sway produce a fall. If this explanation were correct, then subjects who fell in condition 3 should also have fallen in other conditions (4, 5, and 6) that increased their sway above the levels in conditions 1 and 2. In general, this pattern of falls did not occur.

Impairments in either sensory system inputs, central nervous system processing, or motor system output could potentially initiate or facilitate the development of postural control schemes that are generally adaptive (judging from the good performance in conditions 1 and 2) but inadequate or nonadaptive in other sensory environments. These impairments might include reduced or altered sensory information; reduced, delayed or absent motor responses; or incorrect patterns of muscle activation resulting in inappropriate and noncompensatory responses. Comparisons of sensory organization test results with postural motor coordination results, and VOR and OKR responses give some insight into the factors that contribute to the age-related decline in postural control in this putatively normal population.

Comparison with Motor Coordination Tests

Neither the amplitude nor the timing of postural motor responses to forward and backward platform translations were correlated with the level of sway during sensory tests. In addition, the motor response parameters of subjects who fell during sensory tests were not distinguishable from nonfallers. This would tend to support a hypothesis that sensory system deficits and/or inappropriate central nervous system organization of sensory information are responsible for the increased likelihood of falls, independent of motor coordination problems.

However, the amplitude of platform translations used in the motor coordination tests did not produce body sways near fall thresholds, and thus did not require subjects to exert maximal muscular responses. A larger perturbation might have revealed relative muscle weaknesses as well as response timing problems within the subpopulation of fallers. Muscular strength relative to body mass and precise timing of responses might contribute to falls in conditions 5 and 6 where the average level of sway is closer to fall thresholds than in the other four conditions.

Comparison with VOR and OKR Function

There was evidence of VOR and OKR abnormalities in some subjects who fell in two or more conditions. Of the three subjects with the shortest VOR time constants one was a 5-6 faller and two were 3-5-6 fallers. The 5-6 faller with a short VOR time constant also had a significant partial unilateral loss of vestibular function in the caloric test. The subject who had the largest OKR time delay (average delay to the onset of eye movement following visual field movement) of any subject tested (268 ms) was also a 5-6 faller. Among subjects over 50 y, two of the three subjects with the lowest OKR gain constants were 3-5-6 fallers, and the other was a 3-6 faller. Finally, the two older subjects with the
largest OKR time constants, indicating decreased sensitivity to higher frequency visual field motions, were both 3-6 fallers.

With the exceptions mentioned above, VOR and OKR parameters of most subjects who fell in two or more conditions were not distinguishable from those of subjects who did not fall or fell in only one condition. A comparison of the overall incidence of extreme VOR and OKR parameters (>97.5 or <2.5 percentile points) among subjects who fell in two or more conditions were not distinguishable from those of subjects who fell in no more than one condition showed no significant difference between the groups.

There are at least three possible explanations for the weak correlation between VOR and OKR abnormalities and poor postural control. First, our VOR tests measured primarily horizontal canal function, whereas head movements during postural sway primarily stimulate vertical canals and otoliths. To the extent that a vestibular abnormality may only affect one or a limited number of the vestibular receptors in each ear, horizontal VOR and posture results could differ. Second, our OKR tests used horizontal plane visual motion stimuli while the visual system contribution to postural control during sensory tests is associated with the detection of pitch plane movement and with depth cues from the disparity of images on the retina of each eye. There might be a higher correlation of abnormal pitch plane OKR and vergence control responses with postural control deficits than with horizontal plane OKR. Third, differences between our VOR and posture test results could relate to central nervous system problems in the organization of sensory system interactions. Abnormalities in the central nervous system pathways involved in the organization of posture might be specific to the postural control system and therefore would not affect VOR responses.

In conclusion, it is apparent that some equilibrium control deficits exist in a putatively normal population. These deficits are more common in children and subjects older than about 50 y, but are normally masked by the presence of redundant sources of sensory orientation cues. In susceptible subjects, the loss of redundant information can unmask their deficit and cause a sudden loss of postural control.

Acknowledgment—We wish to thank Monika Schoenhoff, Christopher Newell, Patrick Shea, and Martha Benolken for their assistance, and Drs. Charlotte Shupert, Fay Horak, and Alar Mirka for insightful comments. This research was supported by NASA grants NCC9-8 and NAG 9-117, and NIH grant NS-19222.

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AGE-RELATED CHANGES IN HUMAN POSTURE CONTROL:
MOTOR COORDINATION TESTS

R.J. Peterka, PhD,* and F.O. Black, MD

Good Samaritan Hospital and Medical Center, R. S. Dow Neurological Sciences Institute, and Department of Neuro-otology, Portland, OR
Reprint address: Robert J. Peterka, Dept of Neuro-otology, N010, Good Samaritan Hospital & Medical Center, 1040 N.W. 22nd Ave., Portland, OR 97210

Abstract—Postural responses to support surface displacements were measured in 214 normal human subjects ranging in age from 7 to 81 y. Motor tests measured leg muscle electromyographic (EMG) latencies, body sway, and the amplitude and timing of changes in center of pressure displacements in response to sudden forward and backward horizontal translations of the support surface upon which the subjects stood. There were small increases in both EMG latencies and the time to reach the peak amplitude of center of pressure responses with increasing age. The amplitude of center of pressure responses showed no change with age if the amplitude measures were normalized by a factor related to subject height. In general, postural responses to sudden translations showed minimal changes with age, and all age-related trends that were identified were small relative to the variability within the population.

Keywords—posturography, EMG, coordination, equilibrium.

Introduction

If the posture of a quietly standing individual is suddenly perturbed by the application of an external force, rapid automatic responses are initiated to maintain postural equilibrium (2). These postural responses produce compensatory muscle contractions beginning about 100 ms following the start of the perturbation. Experimental tests of postural motor coordination typically measure postural reactions to short duration translations or rotations of the support surface under the subject (1,4,7,10). A consistent finding has been a coordinated synergy in which muscle contraction proceeds from distal to proximal leg and trunk muscles following a support surface perturbation.

Various factors associated with the visual, vestibular, and somatosensory systems have been shown to influence or modulate these responses. These factors include support surface condition (8), initial body position (4,9), stimulus velocity and displacement amplitudes (6), galvanic stimulation to the inner ear (12), and availability of visual (11) and proprioceptive cues (5).

The complexity of maintaining upright stance suggests that there would be a great deal of functional variability within a normal population as a result of individual variations in sensory system, central nervous system, and biomechanical function. Systematic changes may also occur as a result of childhood development and degeneration associated with aging. In order to define the range of normal function, and to identify the nature of any age-related changes in postural motor coordination, we tested a putatively normal population with a wide age distribution.

*Dr. Peterka is presently the Scientific Systems Manager at Department of Neuro-otology and Assistant Scientist at R. S. Dow Neurological Sciences Institute.

Received 9 February 1990; Accepted 12 March 1990.
Methods

Posture coordination function was tested in 214 human subjects (90 male and 124 female) aged 7 to 81 y. Ages were approximately uniformly distributed over the entire range. Rotation tests of horizontal vestibulocular and optokinetic reflex function, caloric tests, and sensory interaction tests of postural control were measured in these same subjects on the same day, and are reported in companion papers (13-15). Details of subject selection are given in previous papers (14, 15). Subjects were not excluded from the population based on any vestibular, optokinetic, or posture test results.

Subjects stood on a movable support surface surrounded in front and on two sides by a visual surround that was stationary during motor tests. The visual surround was a box with randomly placed 2 cm black dots on a flat white surface. The average spacing between the dots was about 20 cm, and the distance from the subject to the box was about 50 cm. Support surface motion was controlled by a hydraulic position servo system that could produce forward and backward translations and toe up and toe down rotations. The subject's ankle joints were aligned with the rotation axis located 7.4 cm above the center of the support surface. Force transducers in the support surface recorded vertical forces applied by each of the subject's legs. The anterior-posterior (AP) sway angle ($\theta_{ap}$) of each subject was recorded using a rod attached to a potentiometer. The potentiometer was mounted on a post next to the subject. The end of the rod rested in a V-shaped holder centered on the subject's back at hip level. A voltage proportional to the rotation of the potentiometer was recorded and later transformed using appropriate trigonometric conversions to $\theta_{ap}$.

Tests consisted of five each of forward platform translations, toe down rotations, backward translations, and toe up rotations of the subject's support surface. The subject stood with eyes open viewing the stationary visual surround. Only responses to translations are reported in this paper. Ramp translations were 3 cm in 0.25 s. The support surface returned slowly to the center position following each motion, and there was a variable delay averaging 4 s between stimuli. Four EMGs were recorded from the left leg using surface electrodes over the gastrocnemius (G), tibialis anterior (T), hamstring (H), and quadriceps (Q) muscles. EMGs were rectified, low pass filtered at 20 Hz, and sampled at 500 Hz. The latencies to the onset of the reflex EMG bursts were estimated from average EMG traces. Latencies were recorded from averaged traces only if the EMG onset times could unambiguously be separated from background activity. Consequently the number of subjects contributing to the data sets in the figures and tables varies.

AP displacement of each subject's center of pressure ($CP$ with units of cm) was calculated for each leg by the following formula:

$$CP = \frac{L(F_t - F_b)}{F_t + F_b}$$  \[1\]

where $L$, the length from the ankle joint to the front and to the back force transducers in the platform, was equal to 27.3 cm, and $F_t$ and $F_b$ were the vertical forces recorded by the front and back force transducers during the trial. The center of pressure velocity ($CPV$ in cm/s) was computed from $CP$ by a 2-point central difference formula. The $CP$ and $CPV$ traces from 5 trials were averaged, and various peak amplitude and time parameters were measured for each subject (Figure 1). All EMG, $CP$, $CPV$, and $\theta_{ap}$ times were referenced to the start of platform motion as determined by the earliest deviation of the average $CP$ trace from its baseline.

In order to visualize trends in various scatterplots, a robust locally weighted regression analysis (loess fit) was used to smooth the scatterplots (3). Lowess smoothing is similar to a moving average but is less influenced by values far from the central tendency of the data. The degree of smoothing is specified by a smoothing parameter ($f$) between 0 and 1. Larger $f$ values give more smoothing.

When a loess fit indicated an approximately linear trend, a linear regression anal-
analysis was performed along with the calculation of a linear correlation coefficient.

Results

General Response Pattern

Figure 1 shows typical EMG, CP, CPV, and $\theta_{ap}$ response patterns for one subject during a 3-cm backward translation. The backward support surface translation results in forward body sway with respect to the platform. In the first 100 ms, the CP movement away from baseline is probably the result of passive properties of body biomechanics combined with artifacts of the platform force recording system. Approximately 110 ms following the start of the translation, the distal leg muscles (gastrocnemius) which oppose the forward body sway begin to contract, as evidenced by EMG recordings. The proximal leg muscles (hamstrings) begin to contract about 20 to 30 ms following the distal muscles. The dorsal leg muscle contractions generate torque about the ankle joint that causes a forward displacement of $CP$. The onset of the active torque generation ($CPo$) begins about 130 ms after the start of platform translation. CP reaches a peak displacement amplitude ($CPa$) at about 230 ms ($CPt$). Sway ($\theta_{ap}$) reaches a peak ($\theta_a$) at about 260 ms ($\theta_t$) and then returns toward an upright position. The time ($CPVt$) of the CPV peak amplitude ($CPVa$) occurs between $CPo$ and $CPt$.

Forward support surface translations causing backward sway with respect to the platform initiate contractions of the T and Q muscles. The patterns of sway and changes in CP are similar to those for backward translations, but have opposite sign.

The population statistics describing EMG onset times, $CPo$, $CPt$, $CPVt$, $\theta_1$, $CPa$, $CPVa$, and $\theta_a$ are given in Table 1. The values of all EMG onsets, $CPo$, and $CPVa$ were symmetrically distributed about their means. $CPa$ and $CPVa$ distributions were slightly skewed toward larger values. Most values of $\theta_t$ for both forward and backward translations were tightly grouped around 260 ms, but about 15% of the population had values of $\theta_t$ of about 375 ms. $\theta_t$ for forward translations also included a scattering of times shorter than 260 ms.

$CPt$ for both forward and backward translations showed bimodal distributions. For backward translations, 82% of the subjects had both right and left leg $CPt$s centered about a mean of 245 ms, 11% had both right and left $CPt$s centered about 360 ms, and the remainder of the population had one leg’s $CPt$ less than 300 ms and the other leg’s $CPt$ greater than 300 ms. For forward translations, 49% of the subjects had both right and left leg $CPt$s centered about a mean of 260 ms, 34% had both right and left $CPt$s centered about 350 ms, and the remainder of the population had one leg’s $CPt$ less than 300 ms and the other leg’s $CPt$ greater than 300 ms.

For both forward and backward translations, subjects with shorter $CPt$s (<300 ms)
had larger mean values of $CPV_a$ and smaller mean values of $CP_o$ and $CPV_i$ (all significant at $P < 0.01$) than subjects with longer $CP_t$s (>300 ms). For backward but not forward translations, mean $CP_a$ were also significantly larger for the short $CP_t$ group. There was no clear relation between the bimodality of the $\theta_t$ and $CP_t$ distributions. That is, many subjects with larger $ept$s had smaller $B_{ts}$, and other subjects with smaller $CP_t$s had larger $B_{ts}$.

The response pattern from three subjects during backward translation and two subjects during forward translation did not allow for accurate estimation of the various center of pressure and sway parameters. In all these cases there appeared to be little or no active torque generated by the subjects.

**Age-Related Changes in EMG Onsets**

With the exception of the quadriceps, EMG onset times generally increased with increasing subject age (Figure 2A–D). Linear fits to the data (Table 2) showed that the rate of change of EMG onset times with age were $0.21 \text{ ms/y}$ for $Go$, $0.30$ for $Ho$, $0.10$ for $To$, and $-0.07$ for $Qo$ with linear correlation coefficients of $0.335$, $0.267$, $0.158$, and $-0.075$, respectively. However, the lowess fits to $Go$, $To$, and $Ho$ suggested that there may be an inflection point at about age 55 with a larger rate of change for subjects older than 55 y. To compare the rates for younger and older subjects, 2-part linear fits were made to $Go$, $Ho$, and $To$ for subjects younger and older than 55 y with the constraint that the two linear fits intersect at age 55 y. The slopes for younger versus older subjects were $0.17$ versus $0.40$, $0.14$ versus $0.83$, and $0.02$ versus $0.45 \text{ ms/y}$ for $Go$, $Ho$, and $To$, respectively. The slowing of motor responses in the older age group was most evident in the $Tr$ responses since there was a transition from essentially no trend with age for subjects younger than 55 y to a slope comparable to the $Go$ and $Ho$ data.

The difference between the EMG onset times for the $H$ and $G$ muscles ($Ho - Go$) during backward translations, and between $Q$ and $T$ muscles ($Qo - To$) during forward translations is plotted as a function of subject age in Figure 2E and F. There was a small increase in the $Ho - Go$ delay with increasing age ($0.17 \text{ ms/y}$ with $r = 0.185$). For the $Qo - To$ delay, subjects younger than 20 y tended to have larger $Qo - To$ delays (mean $22.2 \text{ ms} \pm 22.0 \text{ SD}$) than subjects older than 20 y (mean $9.6 \text{ ms} \pm 18.0 \text{ SD}$). The difference in mean $Qo - To$ between these two groups is significant $P < 0.01$). The larger $Qo - To$ delays for younger compared to older subjects is the result of: (1) later $Qo$ values for youn-

### Table 1. EMG, CP, CPV, and $\theta_{sp}$ Parameters (mean ± 1 SD)

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<td>$CP_a/\theta_{sp}^2$</td>
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<tr>
<td>$\theta_{sp}$</td>
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*SD, standard deviation.
Age-Related Changes in Posture

Figure 2. EMG onset times (A, B, C, D) from support surface translations as a function of subject age, and the difference between proximal and distal EMG onset times (E, F) as a function of age. Plots are based on recordings from 182, 168, 206, and 147 subjects for $G_o$, $H_o$, $T_o$, and $Q_o$, and 145 and 147 for $H_o - G_o$ and $Q_o - T_o$, respectively. Solid lines through data are lowess fits with $f = 0.5$.

(1) The upward trend in $T_o$ with age, particularly for older subjects, coupled with essentially no age trend for $Q_o$ in subjects older than 20 y.

Age-Related Changes in CP and CPV

Figure 3 shows $CP_a$, $CP_t$, $CPV_a$, $CPV_t$, and $CP_o$ as a function of age from backward translations recorded from the right leg. In addition, $CP_a$ normalized by dividing by the square of subject height in meters is also plotted. Table 2 summarizes linear regression fits to $CP_t$, $CPV_t$, and $CP_o$ data versus age. Linear regressions to $CP_t$, which had a bimodal distribution, were restricted to the larger group of subjects whose $CP_t$s were <300 ms. $CP_t$, $CPV_t$, and $CP_o$ for backward translations, and $CP_t$ for forward translations showed small (0.2 ms/y), approximately linear increases with increasing age. $CPV_t$ and $CP_o$ for forward translations did not change significantly with age.

Values of $CP_a$ and $CPV_a$ for subjects older than about 20 y did not show any consistent trend. However, $CP_a$ and $CPV_a$ for subjects younger than 20 y showed large increases with increasing age in both forward and backward translations (Table 2). Normalizing $CP_a$ and
Table 2. Linear Regression and Correlation Coefficients for EMG, CP, CPV, and $\theta_v$ Parameters versus Age*

<table>
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<tr>
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<tr>
<td>$\theta_v$</td>
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</table>

* Units are the same as in Table 1.
† Correlation coefficients significantly different from zero ($P < 0.05$).
‡ Only includes values with both right and left CP, a < 300 ms.
§ Only includes $\theta_v$ < 300 ms.

$CP_V_a$, by the square of the individual subjects’ heights ($h^2$) removed most of the age-related trends in $CP_a$ and $CP_V_a$ in the younger subjects, indicating that the source of this trend was probably related to changes in body dimensions with growth. Normalization by $h^2$ also reduced the entire population’s variability of $CP_a$ relative to the mean value. For example, the coefficient of variation ($CV = SD/mean$) of $CP_a$ from right leg backward translations was 0.98 while the $CV$ of $CP_a/h^2$ was 0.29. The normalization only slightly reduced the $CV$ of $CP_V_a$ from 0.44 to 0.41. Normalization of $CP_a$ by $h^2$ theoretically provides a value proportional to the peak rotational acceleration of the body about the ankle joint (see Discussion).

**Right-Left Asymmetry**

Table 3 summarizes comparisons between measures of $CP_a$, $CP_t$, $CP_V_a$, $CP_V_t$, and $\theta_v$ recorded from the right and left legs during forward and backward translations. The $CP_a$ and $CP_V_a$ responses from the left leg were significantly larger than the right during backward, but not forward translations. With the exception of forward translation $CP_t$, in which right side responses were longer than left, there were no significant timing differences between right and left leg responses.

**Comparison of EMG and CP Timing**

Table 4 summarizes the correlations between EMG onset times and the various measures of CP and sway times including $CP_o$, $CP_a$, $CP_t$, $CP_V_t$, and $\theta_v$. The average of right and left leg responses of $CP_o$, $CP_a$, and $CP_V_t$ were used in the calculations. The bi-modal distributions of $CP_t$ and $\theta_v$ distorted the correlation analysis when data from all subjects were included; therefore, the analysis was restricted to the larger portion of the population with shorter $CP_t$ and $\theta_v$ responses.

In general, there were moderate, positive correlations between the various response timing measures. For both forward and back-
ward translations, the largest correlations were between \( CP_o \) and \( CP_V \). The largest correlation between any EMG and CP parameters was between \( T_0 \) and \( CP_o \) for forward translations. \( \theta_t \) correlations with other response time parameters were smaller than most other comparisons.

The interpretation of this correlation analysis is potentially problematic since different subsets of the population contributed to different correlation measures. However, a correlation analysis that included only subjects with no missing values gave similar results.

**Forward-Backward Translation Comparison**

Table 1 shows that \( CP_o, CP_t, CP_V \), and \( \theta_t \) response times were larger for forward than backward translations, even though \( T_0 \) and \( Q_o \) times were similar, and even slightly shorter than \( G_o \) and \( H_o \) times. In addition, the timing difference between forward and backward translations increases for parameters that occur later in the normal sequence of motion. That is, EMG timing is similar, \( CP_o \) is 10 ms later, \( CP_V \) is 13 ms later, and \( CP_t \) and \( \theta_t \) are about 30 ms later for forward compared to backward translations.

Response amplitude measures also differed between forward and backward translations. Both \( CP_a \) and \( CP_V a \) were significantly larger for backward translations, and \( \theta_t \) was larger for forward translations (all \( P < 0.0001 \), paired \( t \) test). This pattern is consistent with the generation of less corrective torque on forward translations compared to backward, resulting in larger peak body sway from forward platform motions.

**Discussion**

Most of the results of motor tests of postural control showed a wide range of what must be considered normal function. In spite of the large variances, age-related changes in function were identified in some response parameters. Although these changes were statistically significant, they were small in magnitude. In particular, the latency of EMG onsets, with the exception of quadriceps, increased with increasing age. In addition, there was evidence that the rate of increase of EMG onset with age was larger for subjects older than about 55 y. This increased rate was most evident in the tibialis muscle. Studies of muscle strength in the elderly (16) have also shown proportionally larger losses in tibialis strength compared to other leg muscles. The loss of strength combined with the slowing of the tibialis muscle response to body perturbations would diminish an individual’s ability to control backward sway.

The distal before proximal muscle contraction synergy was observed in most subjects. However, during forward translations, \( Q_o \)
preceded $T_o$ in about 25% of the subjects. This may be related to initial knee position that was not carefully controlled. For example, if the knees of some subjects were slightly flexed prior to the translation, an early $Q$ contraction would hyperextend the knee and pull the lower part of the trunk slightly forward. A previous study (17) also noted that some subjects had reversed $Q_o - T_o$ timing. However, in that study the reversal was only found in their older subjects. Figure 2F shows that $Q_o - T_o$ reversal occurred across the entire age range, although there was a slightly larger incidence in older subjects.

Normalization of $CP_a$ and $CPV_a$ by the square of subject height ($h^2$) both removed a large age-related trend for subjects under 20 y, and reduced the variability relative to the mean of $CP_a$ for the entire population. The rationale for this normalization relates to the mechanics of movement. In order to correct for an external perturbation that causes AP sway, a subject exerts a torque, $T$, about the ankle joint. This torque produces a rotational acceleration, $\alpha$, according to $\alpha = T/I$ where $I$ is the moment of inertia of the subject. $I$ is related to the mass distribution of the subject relative to the rotation axis (ankle joint). Using the simplifying assumption that all of the subject’s mass, $m$, is located at the center of mass (about hip level), then $I = mr^2$ where $r$ is the distance from the ankle joint to the center of mass. The calculation of $CP$ gives a value proportional to $T/m$. Dividing
Age-Related Changes in Posture

Table 4. Linear Correlation Coefficients Comparing Motor Response Times

<table>
<thead>
<tr>
<th></th>
<th>( H_o )</th>
<th>( CP_o )</th>
<th>( CPV_t )</th>
<th>( CPV_t^* )</th>
<th>( \theta_t^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backward translation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( G_o )</td>
<td>0.38</td>
<td>0.37</td>
<td>0.37</td>
<td>0.33</td>
<td>0.22</td>
</tr>
<tr>
<td>( H_o )</td>
<td>0.34</td>
<td>0.41</td>
<td>0.61</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
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<td>0.34</td>
<td>0.41</td>
<td>0.61</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
<td>( CPV_t )</td>
<td>0.34</td>
<td>0.41</td>
<td>0.61</td>
<td>0.40</td>
<td>0.31</td>
</tr>
<tr>
<td>( CPV_t^* )</td>
<td>0.34</td>
<td>0.41</td>
<td>0.61</td>
<td>0.40</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>( Q_o )</th>
<th>( CP_o )</th>
<th>( CPV_t )</th>
<th>( CPV_t^* )</th>
<th>( \theta_t^* )</th>
</tr>
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<tbody>
<tr>
<td>Forward translation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>( T_o )</td>
<td>0.34</td>
<td>0.54</td>
<td>0.48</td>
<td>0.12</td>
<td>0.23</td>
</tr>
<tr>
<td>( Q_o )</td>
<td>0.39</td>
<td>0.54</td>
<td>0.48</td>
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<td>( CPV_t^* )</td>
<td>0.39</td>
<td>0.54</td>
<td>0.48</td>
<td>0.12</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Only includes values with right and left \( CP_t < 300 \) ms.

†Only includes \( \theta_t < 300 \) ms.

\( CP \) by \( h^2 \) gives a value proportional to \( T/I \) and to \( \alpha \) since \( r^2 \) is proportional to \( h^2 \). \( CP_o/\hbar^2 \) data versus age is fairly constant, indicating that the peak angular acceleration in response to a sudden translation changes little with age.

Clinical Significance

Postural motor coordination tests similar to those described here are being used increasingly for clinical evaluation. For patients with balance disorders, these motor tests serve a function similar to optokinetic and pursuit tests for the evaluation of the ascending visual and visual-vestibular system control of eye movements. That is, they provide information on the integrity of spinal and central nervous system function important for the interpretation of sensory organization tests of posture control (13).

The clinical use of postural motor coordination tests requires an appropriate selection of response parameters and a definition of the range of these parameters in a normal population. Ideally these parameters should have narrow distributions for normal subjects and should be sensitive to abnormalities. This paper does not address abnormal response patterns, but the results do suggest that some of the potential motor response parameters may be difficult to use clinically. In general, the variability of the parameters was large even though age-related trends contributed very little to the variability. Among timing measures, \( G_o \) and \( CP_o \) for backward translations and \( T_o \) for forward translations showed the least variability, followed by \( Q_o \) and \( CP_o \) for forward, \( H_o \) for backward, and \( CPV_t \) for both forward and backward translations. Despite their narrow distributions, EMG onset times are problematic in routine clinical tests since they are often difficult to measure.

The bimodal distributions of \( CP_t \) and \( \theta_t \) make them less attractive candidates for clinical functional measures. Although there were differences between some motor response measures related to the bimodal distributions of \( CP_t \), there was no clear indication of the source(s) of these bimodal responses. Perhaps the support surface perturbations evoked different movement patterns in different subjects, with some subjects moving like inverted pendulums, while others used more complex motions to maintain their upright posture.
Among response amplitude measures, there appeared to be little range for abnormally low $CP_a$ and $CPV_a$ responses since many subjects in our putatively normal population showed responses only slightly above the passive-platform artifact level. Different force platform designs with smaller mechanical artifacts might improve the separation of abnormal subjects from normal subjects with low amplitude responses. $CP_a$ and $CPV_a$ values normalized by $h^2$ were better parameters for comparisons across populations than $CP_a$ and $CPV_a$ alone.

Different mechanical platform systems, instrumentation, data analysis, and particularly stimulus parameters, could influence the conclusions drawn in this paper. As other motor coordination tests with different stimulus conditions are developed, it will be important to consider the possible presence of bimodal parameter distributions, to determine the neural or biomechanical factors that cause these bimodal responses, and to test a large enough population to clearly define the range of normal function.

Acknowledgment—We wish to thank Monika Schoenhoff, Christopher Newell, Patrick Shea, and Martha Benolken for their assistance, and Drs. Charlotte Shupert, Fay Horak, and Alar Mirka for insightful comments. This research was supported by NASA grants NCC9-8 and NAG 9-117, and NIH grant NS-19222.

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REDUCTION OF GAIN AND TIME CONSTANT OF VESTIBULO-OCULAR REFLEX IN MAN INDUCED BY DIAZEPAM AND THIOPENTAL

Serge Padoan, * Kari Korttila, † Måns Magnusson, * Ilmari Pyykkö, † and Lucyna Schalén *

*Department of Otorhinolaryngology, University Hospital of Lund, Lund, Sweden, Departments of †Anesthesiology and †Otolaryngology, University Hospital of Helsinki, Helsinki, Finland

Reprint address: Dr. Serge Padoan, Department of Otorhinolaryngology, University Hospital of Lund, S-221 85 Lund, Sweden

Abstract — The effect of intravenous administration of two sedatives, diazepam (0.3 mg/kg) and thiopental (6.0 mg/kg), on the vestibulo-ocular reflex (VOR) in man was investigated on 9 volunteers. The VOR was evoked with a velocity step rotation test and gain and time constant of perrotatory and postrotatory nystagmus were measured. Both drugs reduced VOR gain. Diazepam-induced reduction lasted 8 h and thiopental-induced reduction 1 h. A reduction of the VOR time constant was found lasting about 1 h for both drugs, but with a tendency for the thiopental effect to last longer. These findings, not previously described in man, differ from what has been found in macaques and rabbits injected with diazepam. The reduction of gain and time constant were not correlated with the blood concentration of either drug.

The present results suggest that in man the VOR gain and time constant are both reduced by different types of sedatives although with different time courses. On the basis of previously shown effect of alertness on the VOR, it is hypothesized that diazepam and thiopental, besides having a specific effect on central nervous system structures important to the VOR, also induce reduction of the VOR through a general sedation of the CNS.

Keywords — VOR; diazepam; thiopental; time constant.

Introduction

Benzodiazepines and barbiturates are known to affect voluntary and reflexive eye movements in humans (1–4), and benzodiazepines are known to affect reflexive eye movements in animals (5–7). The neurophysiological correlate for this effect is presumed to be a depressant action on neurons important to eye movements (1,2,5–8). Nevertheless an unspecific effect of the drugs is also plausible, the possible mechanism being general depression of the central nervous system (CNS), causing reduction of alertness.

An effect of alertness on vestibulo-ocular reflex (VOR) gain has been described previously (9). Recently an effect of arousal on the velocity storage mechanism has been described, causing a prolongation of the time constant of the VOR in rabbit (10) and increasing optokinetic afternystagmus (OKAN) in man (11). Thus reduction of alertness due to CNS depression accomplished by benzodiazepines or barbiturates could be expected to reduce the time constant of the VOR.

To our knowledge no studies on the effect of benzodiazepines or barbiturates on the human VOR refer to the time constant. As animal studies (5,7) indicate an increasing effect of diazepam on the time constant and a reducing effect on gain with different time courses, it seemed important to test the validity of these findings in humans. Furthermore most studies on man have been performed with oral administration of drugs, while in animal studies drugs have been given intravenously. Besides species differences, time
courses may thus differ enough to make it difficult to compare results. In this experiment, doses were chosen corresponding approximately to those used in clinical practice for intravenous induction of anesthesia.

We also considered it clinically important to elucidate the effect of these drugs on reflexive eye movements and alertness, given the wide use of intravenous (i.v.) administration of benzodiazepines for short-term anesthesia of outpatients, who only a few hours after an operation may have to deal with complicated traffic situations.

The aim of the present study was to investigate the effect of i.v. diazepam and thiopental on VOR gain and time constant in man, and to probe the correlation of the effects with blood concentrations of the drugs.

Materials

Nine paid volunteers, 5 females and 4 males, age 22 to 38 (mean age 30.3), took part in the study. They were all healthy and had no history of vertigo or of any neurological or metabolic disorder. All had normal hearing, vision, and weight and were nonsmokers.

Methods

Each subject was tested 3 times at 2-week intervals, which enabled these drugs to be virtually eliminated between trials. On each test occasion, the subjects were assigned to diazepam, thiopental, or no drug according to a latin square design. No placebo was used, as the effects of the drugs were so obvious to the subjects. Both drugs were given intravenously in quantities equivalent to 0.3 mg/kg body weight for diazepam, and 6.0 mg/kg body weight for thiopental, corresponding to doses used for induction of anesthesia with thiopental and half that amount with diazepam (12). The drugs were given at 8 AM and the tests were performed at 9 AM, at noon, and at 4 PM.

Food intake was standardized for the participants and consisted of two cheese sandwiches and a cup of tea after concluding the tests at noon. Alcoholic beverages or any kind of drugs were forbidden during the 48 h prior to each trial.

Before each recording, blood samples were taken with a disposable cannula from a cubital vein in the arm contralateral to the arm in which the drugs were given. The samples were frozen and subsequently analyzed by gas chromatography for concentration of the respective drug. Because of incomplete blood collection, thiopental blood concentrations were analyzed in only 7 subjects at 9 AM and in only 8 subjects at noon and 4 PM.

The subjects were seated in a rotation chair, provided with an occipital support fixating the head in the center of the vertical rotation axis and with the ear–eye axis horizontal. Clockwise and counterclockwise (CW and CCW) rotation-induced vestibular nystagmus was achieved by 60°/s² acceleration and deceleration in darkness for 2 s each giving a velocity step of 120°/s. Rotation lasted 90 s. Eye movements were recorded with DC electro-oculography (13).

Analysis

Starting from the first beat after reaching the plateau of each velocity step, the peak velocity of the slow phase of the nystagmus beat occurring every 5 s was calculated manually from the recordings. The mean of the slow phase velocity of the corresponding nystagmus beats from the 4 stimuli, ie, the velocity steps of acceleration/deceleration of CW and CCW rotation, was calculated. To these mean nystagmus velocities an exponential decay was fitted and the time constant was calculated by a computer (DEC Professional 380 with RS/1 software, Bolt Beranek & Newman, Cambridge, MA). Gain was calculated as the initial peak slow phase velocity divided by the velocity step.

Individual values of gain and time constant for each drug test occasion were normalized, ie, divided by their respective control value, to yield a relative value. This was done to avoid bias from possible variations in alert-
Both drugs reduced the gain and time constant to about the same extent for the 2 parameters at 1 h post injection. Due to the pharmacokinetics of thiopental and diazepam, mean concentrations of each drug were approximately equal at 4 and 8 h post injection. When comparing results from these two later measurements a difference between the effect of thiopental and diazepam on VOR gain and time constant was found. Since no prediction about any possible difference could be made, contrary to the expected general reduction of the VOR of both drugs, two-tailed tests were applied.

The effect of thiopental on the relative time constant did not differ significantly from its effect on relative gain ($0.10 < P < 0.20$). The effect of diazepam on the relative time constant was significantly smaller than its effect on relative gain ($P < 0.025$). The effect of thiopental on the relative time constant was significantly greater than that of diazepam ($P < 0.05$). The effect of thiopental on relative gain was significantly smaller than that of diazepam ($P < 0.025$) (Figure 2).

There were considerable individual variations in blood concentration. Means and standard deviations at 9 AM, noon and 4 PM for thiopental were 5.84 and 1.38, 2.00 and 0.76, 1.35 and 0.96 µg/mL, respectively, and for diazepam 783 and 521, 279 and 89, 300 and 95 ng/mL.

In general, diminishing blood concentration coincided in time with recovery of VOR gain and time constant. But when testing for correlation between individual blood concentrations and VOR parameters at each trial, no significant correlation was found. Logarithmic transformation only gave a marginal im-

### Table 1. Means and Standard Deviations of Gain and Time Constant in 9 Test Subjects at 9 AM, noon, and 4 PM. (Control values and values after intravenous injection of thiopental and diazepam at 8 AM are given.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Thiopental</th>
<th>Diazepam</th>
<th>Control</th>
<th>Thiopental</th>
<th>Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 AM</td>
<td>69.7 ± 15.4</td>
<td>54.8 ± 18.9</td>
<td>47.4 ± 28.4</td>
<td>15.1 ± 4.15</td>
<td>9.60 ± 3.31</td>
<td>10.9 ± 5.57</td>
</tr>
<tr>
<td>12 noon</td>
<td>70.7 ± 15.6</td>
<td>68.2 ± 18.6</td>
<td>55.6 ± 16.7</td>
<td>13.3 ± 2.84</td>
<td>12.0 ± 4.08</td>
<td>13.8 ± 3.99</td>
</tr>
<tr>
<td>4 PM</td>
<td>69.3 ± 16.8</td>
<td>79.7 ± 16.4</td>
<td>58.2 ± 19.6</td>
<td>13.5 ± 3.28</td>
<td>11.6 ± 2.81</td>
<td>12.9 ± 4.09</td>
</tr>
</tbody>
</table>
Figure 1. The relationship between drug concentration (thiopental or diazepam) and VOR parameter (relative gain or relative time constant). Individual values are indicated. Results for 9 AM, noon, and 4 PM are denoted by squares, circles, and triangles, respectively. The $f(x) = 1.0$ line represents the arithmetic control value. Means and standard errors of the mean from the three test occasions are indicated by the corresponding filled symbols connected by a line. (Figure continued on facing page.)

Improvement in correlation (Pearson’s coefficient for a log-log fit at the 3 trials, ie, 9 AM, noon, and 4 PM, was 0.097, 0.039, and 0.113 between thiopental concentration and the time constant; 0.580, 0.488, and 0.456 between thiopental concentration and gain; 0.020, 0.640, and 0.136 between diazepam concentration and the time constant; 0.116, 0.482, and 0.241 between diazepam concentration and gain).
Discussion

In the present study two sedatives, thiopental and diazepam reduced human VOR gain and time constant. Apparently diazepam had a longer effect on the gain than on the time constant, while thiopental tended to show an opposite effect profile. In regression analysis, however, individual values of either VOR parameter were not correlated with blood concentrations of either drug.

A reduction of VOR gain by diazepam and thiopental is in accordance with most previous studies in man and in animals. The impairment of the VOR caused by both drugs is presumed to be a result of their effect on infratentorial neuronal populations of the central nervous system, in the case of diazepam,
in the vestibular nuclei (1–8,15,16). The VOR time constant in rabbits is prolonged by increased alertness (10) as is OKAN in man (11). Diazepam and thiopental may thus be expected to diminish gain and, by sedation, to shorten the VOR time constant.

**Differences between Humans and Animals**

There are few previous reports on the effect of sedating agents on the VOR time constant. In the macaque, diazepam reduces gain but increases the VOR time constant (5). In the rabbit the same drug does not seem to affect the time constant although it reduces gain (6,7).

The difference between the findings in our results in man, with a clear reduction in VOR gain and time constant, may be due to the differences between the species studied, the amount of drug given, and to the intervals chosen for measuring the VOR.

Very little sedation was reported in the macaque, though 0.7 mg/kg diazepam was used (5). This can be compared to the present 0.3 mg/kg, which clearly causes sedation in humans. Furthermore, gaze nystagmus was noticed immediately after injection of diazepam on macaques. We observed no pronounced gaze nystagmus after diazepam and a transient gaze nystagmus after thiopental, which is consistent with previous reports (17). In the rabbit experiment (7), 0.6 mg/kg diazepam was used and one group of rabbits showed excitatory response in VOR.

Furthermore, the first test of the VOR function in the present human experiment could not be done until 1 h after injection because the subjects were simply unable to cooperate earlier. In the above mentioned experiment on macaques, VOR tests were com-

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**Figure 2.** The difference between the effect of two drugs on the two VOR parameters at the two later measurements, thiopental affecting the time constant more than diazepam and diazepam affecting gain more than thiopental. Error bars indicate standard error of the mean.
Reduction of Gain and Time Constant of VOR

menced only 5 min after injection and the effect on the VOR time constant lasted less than 1 h (significantly only 16 min), while the effect on gain lasted several hours. In the rabbit experiment, tests also started shortly after injection and gain was significantly reduced for 1 h.

Moreover, one should bear in mind that the pharmacological profile of benzodiazepines varies between species to the extent that in some cases alertness instead of CNS depression is achieved (18). In a study of benzodiazepine binding in human brains (19), a good correlation has been shown between in vitro inhibition of (3H)flunitrazepam binding to human cerebral cortex homogenate and in vivo tests of pharmacological potency of several benzodiazepines in humans, while correlation with in vivo potency tests on monkeys was low.

A common finding in our study and in the animal experiments mentioned above is that benzodiazepines affect VOR gain and time constant with different time courses. The interpretation of Blair and Gavin (5); that this could be due to diazepam having multiple sites of action, is plausible. In our experiment thiopental also tended to have different time courses in its effect on the 2 parameters of the VOR, but in a fashion opposite to that of diazepam.

Possible Contributing Effect of Sedation

To some extent benzodiazepines and barbiturates share sites and mechanisms of action in the CNS (18). Benzodiazepine binding is low in the human brainstem and intermediate in the cerebellum (19), which has extensive projections to and from the vestibular nuclei (20). Nevertheless, the reticular formation and the vestibular nuclei are both located in the brainstem and seem to be major sites of the CNS depressant action of benzodiazepines (21,22). However, the VOR has also been shown to be influenced by mental activity (9,23). Thus diazepam or thiopental could also affect the VOR either by reducing alertness and/or by acting on higher centers of the CNS disrupting the ability to choose a frame of reference, the latter known to be of importance when willingly modulating the VOR (23).

Lack of Correlation between Drug Concentration and Effect

There seems to be some controversy regarding the correlation between serum levels of benzodiazepines and peak velocity of voluntary saccades (24,25). The apparent lack of correlation between the effect of the diazepam and thiopental on the VOR and their concentration in blood, as observed in the present study, might be explained by individual variations in pharmacokinetics and pharmacodynamics of diazepam and thiopental (26–28). Furthermore, large interindividual variations in the VOR, as found in the present experiment, make it necessary to investigate larger groups of subjects to demonstrate any possible significant correlation.

Conclusions

The effects of two sedatives, diazepam and thiopental, on the human vestibulo-ocular reflex were investigated in the present study. VOR evoked by a velocity step was reduced by both drugs. But while diazepam-induced reduction of gain lasted up to 8 h, thiopental was only effective for 1 h. The time constant was only reduced for 1 h by both drugs, although thiopental-induced reduction tended to last longer.

Different sedating agents are thus demonstrated to have different profiles in their reduction of the human VOR. Both specific and unspecific action in the brainstem due to sedation may be responsible for the impairing effect of diazepam and thiopental on the human VOR.

Acknowledgments—The present work was supported by the Swedish Medical Research Council, grant no:17X-05693, and the Söderbergs foundations.
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