Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation

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Summary
To investigate age dependent changes we analysed torsional eye movement responses to binaural and monaural galvanic vestibular stimulation (GVS) in 57 healthy subjects (20–69 years old). GVS (1–3 mA) induced torsional eye movements consisting of static torsion toward the anode (amplitude 1–6°) and superimposed torsional nystagmus (slow phase velocity 0.5–3°/s, quick phase amplitude 0.5–2°, nystagmus frequency 0.75–1.5 s⁻¹). Static ocular torsion and torsional nystagmus increased from the third to the sixth decade and decreased in older subjects, e.g. slow phase velocity increased from 1.5°/s (20–29 years) to 2.9°/s (50–59 years) and decreased to 2.5°/s for the seventh decade (60–69 years). Thus, an inverse U-shaped curve was found for the dependence of torsional eye movement responses on age. All structures relevant for vestibular function degenerate with age, but at varying times. Since hair cell loss precedes those seen in the vestibular nerve and Scarpa’s ganglion, the decrease in hair cell counts could be compensated for by increased sensitivity of afferent nerve fibres or central mechanisms. Increased sensitivity could thus maintain normal function despite reduced peripheral input. As GVS acts at the vestibular nerve (thereby bypassing the hair cells), electrical stimulation should be more efficient in subjects with the beginning of hair cell degeneration, as seen in our data up to the sixth decade. The degeneration of nerve fibres, ganglion cells and central neurons becomes evident at older ages. Thus, the compensatory increase in sensitivity breaks down and GVS-induced eye movements decline—a finding that is reflected by the inverse U-shaped curve for age dependency presented in this study.

Keywords: galvanic vestibular stimulation; vestibular system; aging

Abbreviations: GVS = galvanic vestibular stimulation; OTP = ocular torsion position; SCC = semicircular canal; SPV = slow phase velocity; VOG = video-oculography; VOR = vestibulo-ocular reflex

Introduction
Post-mortem histopathological studies in humans have demonstrated that vestibular hair cells begin to degenerate at birth and vestibular pathways in middle age (Bergström, 1973; Rosenhall, 1973; Richter, 1980; Alvarez et al., 2000; Merchant et al., 2000; Velazquez-Villasenor et al., 2000). An age-dependent decline in vestibular function has also been shown for different vestibular tests (Peterka et al., 1990a; Baloh, 1993; Enrietto et al., 1999; Welgampola and Colebatch, 2001). However, age-related changes in vestibulo-ocular responses seem to vary in their time course and do not quantitatively reflect the progressive degenerative loss of vestibular hair cells and nerve fibres (Brandt, 1999). This dissociation of morphology and function as well as the question of how the age-dependent deterioration of vestibular input is compensated for are not yet clear. Central compensation and sensory substitution, e.g. by muscle spindle input, are among the proposed mechanisms (Strupp et al., 1999; Schweigart et al., 2002; Welgampola and Colebatch, 2002).

The aim of this study was to investigate age-dependent changes in vestibular function using galvanic vestibular stimulation (GVS). Under physiological conditions, vestibular stimulation by head accelerations always involves multisensory activation of the vestibular, somatosensory and visual systems. While GVS provides non-physiological stimulation,
it is more selective than natural head accelerations and is thus an attractive tool for experimental testing of vestibular function (Day, 1999). Eye movement responses elicited by GVS mainly consist of torsional and horizontal components. They were first described by Hitzig in 1871 (Hitzig, 1871; Buys, 1909; Mackenzie, 1909). Animal experiments have shown that GVS increases the vestibular afferent spike frequency at the cathodal side and decreases it at the anodal site of stimulation (Goldberg et al., 1982). In the present study, 3D eye movement responses to GVS were recorded by video-oculography (VOG) in healthy subjects, aged 20 to 69 years, using monaural and binaural transmastoidal GVS. The question addressed was whether the eye movement response is age-dependent as a consequence of the known differences in the time courses of hair cell and vestibular pathway degeneration.

Methods
Subjects
Fifty-seven healthy subjects (age 20–69 years, 33 females) gave their informed consent to participate in the study after being briefed about the experiments. The experiments were performed in accordance with the Declaration of Helsinki and were approved by the ethics committee of the Ludwigs-Maximilians University of Munich (approval numbers 87/96 and 212/96). None of the subjects had any history of motor disability, visual or vestibular disorders, and none took medication that would interfere with vestibulo-ocular motor function.

VOG
Eye movements were measured by means of binocular VOG. The eye position angles (including ocular torsion) were determined from a pair of artificial markers applied to the sclera just outside the left and the right edges of the iris (Clarke et al., 1999). The markers consisted of a black cosmetic pigment (Chronos Vision, Berlin, Germany), which was applied to the sclera by means of a sterile surgical pen. The eyes were illuminated by infrared light-emitting diodes, while two infrared sensitive cameras were used together with a frame grabber (Meteor II Multichannel, Matrox Graphics, Dorrel, Quebec, Canada) to capture and transfer digitized images of the eyes to the working memory of a PC. Since the image sensors of the cameras were only partially scanned, a sampling rate of 100 Hz was achieved. A custom-made image processing software performed on-line analysis of the captured images (Schneider et al., 2002). In short, the implemented image-processing algorithm first estimated roughly the pupil position from a centre-of-intensity calculation of the dark pupil pixels and then, starting from this position, two regions of interest in the vicinity of the expected marker positions were defined outside the left and the right edges of the iris. The dark marker pixels, which were detected in these regions, entered a centre-of-intensity calculation, from which the desired marker positions were obtained. Due to the large number of marker pixels contributing to the calculation, the obtained resolution (0.05°) remained in a sub-pixel range (Schneider et al., 2002). The marker coordinates relative to image space were recorded to a file and were later analysed off-line by custom-made MATLAB scripts (Mathworks Inc., Natick, MA, USA). VOG data were converted into angles by a calibration procedure: subjects sequentially fixated dots aligned at horizontal and vertical viewing angles of ±10°.

Galvanic stimulation
Grass-gold electrodes (5 mm in diameter) were coated with electrode paste and placed over both mastoid processes for binaural stimulation. For monaural stimulation, one electrode was placed over the mastoid and the second, indifferent electrode at the posterior neck over the C7 spinous process. Rectangular, unipolar electric direct current pulses of 10 s duration with an amplitude of either 1 mA or 3 mA were delivered by a battery-powered current generator. Pulses were started via the VOG software and synchronized to the eye-movement recording. Polarity was switched during each trial (see below). Subjects held a push-button, which on release immediately interrupted the current flow. Most subjects reported a mild burning sensation at the stimulation site.

Experimental procedure
A series of ten sequential recordings (runs 1–10, see below) was performed in each subject. Runs 1–3 were for calibration and to detect spontaneous eye movements. Each of the stimulation runs (4–10) had the following sequence: 10 s eyes open rest; 10 s stimulation polarity A (e.g. cathode left); 10 s rest; 10 s stimulation polarity B (e.g. anode left); and 10 s rest.

(i) Calibration: horizontal and vertical viewing angles of ±10° (20 s).
(ii) Looking straight with fixation of a dot 1.2 m ahead (30 s).
(iii) Looking straight ahead in complete darkness (30 s).
(iv) Binaural GVS 1 mA during fixation (40 s).
(v) Binaural GVS 3 mA during fixation (40 s).
(vi) Binaural GVS 3 mA in complete darkness (40 s)
(vii) Left monaural GVS 3 mA during fixation (40 s).
(viii) Left monaural GVS 3 mA in complete darkness (40 s).
(ix) Right monaural GVS 3 mA during fixation (40 s).
(x) Right monaural GVS 3 mA in complete darkness (40 s).

Data analysis
The ocular torsion positions (OTPs) were calculated off-line from the recorded scleral marker coordinates. After detecting torsional quick phases with an interactive software package, we determined mean values from the 10 s periods of stimulation for the following variables to characterize torsional nystagmus: slow phase velocity (SPV); nystagmus frequency; quick phase amplitude; and the tonic OTP that
would have been present without nystagmus. The latter variable was determined by a nystagmus compensation algorithm (Schneider et al., 2000, 2002). In this algorithm, compensatory inverse nystagmus is generated in a model-based approach by processing the detected quick phases with a leaky integrator, which resembles the dynamics of the neural integrator of the torsional vestibulo-ocular reflex (VOR) (Robinson 1974; Seidman et al., 1995). This artificially inverted nystagmus is added to the original OTP to eliminate the effect of nystagmus on torsional eye movements. The sensitivity and the time constant of integration of the galvanically activated VOR pathways were estimated by minimizing in a least squares sense the error between the compensated OTP and a low-pass filtered version of the galvanic stimulus. This analysis method is preferred to the slow cumulative eye position method, which is usually used for horizontal and vertical eye movements, because the time constant of integration for torsional eye movements (2 s) is an order of magnitude smaller than the time constants for horizontal and vertical eye movements (20–30 s). There is an additional problem of the marked interindividual variability of ocular torsion responses to GVS: some subjects exhibit rather tonic responses, some show a pronounced nystagmic reaction, while others respond with an intermediate pattern of a tonic component on which nystagmus is superimposed. In some cases, the two extremes can be observed in the same subject or patient (Fig. 1). With such variable nystagmus patterns, it can be difficult to estimate variables, such as sensitivities and time constants, that reliably characterize the VOR dynamics. If SPV and the beating field alone were used in the analysis of the original data from Fig. 1, different results would have been obtained for the two stimulation polarities. Although the SPV for the first stimulation period is not significantly different from zero, a considerable offset of the beating field or tonic response can be observed. In contrast, the SPV is increased and the beating field offset is decreased during the second stimulation period. However, after nystagmus is eliminated, the thus compensated OTP becomes similar to original ocular torsion traces in which no nystagmus beats are apparent (compare the first and second stimulation period in Fig. 1A and D). Hence, the ‘compensated OTP’ is the ocular torsion expected in the absence of nystagmus.

**Statistical analysis**

A repeated measures ANOVA (analysis of variance) was performed on the data for each parameter (static ocular torsion, SPV, quick phase amplitude, nystagmus frequency) with one categorical predictor (age, grouped by decades) and two within subject variables [stimulation, seven levels: (i) binaural 3 mA fixation; (ii) binaural 3 mA darkness; (iii) binaural 1 mA fixation; (iv) left monaural 3 mA fixation; (v) right monaural 3 mA fixation; (vi) left monaural 3 mA darkness; and (vii) right monaural 3 mA darkness] and side (two levels: cathode left versus cathode right for binaural

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**Fig. 1** Scleral markers and example for the processing of eye movement recordings using a nystagmus compensation algorithm. The upper panel shows a photograph of one subject’s eye and the scleral markers used for analysis of torsional eye movements. The lower panel shows ocular torsion data and how they are processed. (A) Original recording from one subject during binaural GVS steps of ±3 mA (bars). (B) The amplitudes of nystagmus quick phases were detected and plotted as bursts with inverted directions. (C) After the bursts were processed by a leaky integrator with a gain (g) and a time constant (τ; constant value of 1.8 s), inverse nystagmus was obtained. (D) When the inverse nystagmus of C was added to the original ocular torsion of A, a compensated ocular torsion position was obtained (continuous line). For direct comparison, the original trace from A is repeated in D (dashed line). The necessary calculations (a summation and a leaky integration) are outlined schematically at the right side of the figure.
stimulation; and cathode versus anode over mastoid for monaural stimulation). Post hoc analysis was performed using the Bonferroni method to control for multiple testing (Statistica 6, StatSoft, Tulsa, OK, USA). Means, SDs and 95% confidence intervals were determined for all data. A side-to-side ratio was calculated by dividing the larger by the smaller value for the respective parameter for each subject.

Results

General findings

Without GVS, none of the subjects showed nystagmus (SPV >0.5°/s) or ocular oscillations, neither in darkness nor during fixation. During GVS in darkness, eye movement responses consisted mainly of torsional and horizontal deviations (Fig. 2). An ocular torsion to the side of the anode was superimposed by torsional nystagmus with quick phases beating toward the cathode (see below for quantitative data). Horizontal nystagmus, also directed to the side of cathodal stimulation, had a mean SPV of 0.7 ± 0.2°/s (binaural stimulation 3 mA in darkness, n = 46). As shown in Fig. 2, eye movement responses in darkness were overlapped by involuntary spontaneous eye movements, which reduced the quality of the data. During fixation, the spontaneous eye movements as well as the GVS-induced vertical and horizontal nystagmus could be largely suppressed, thus ensuring a high quality of torsional eye-movement data (Fig. 3). The means, 95% confidence intervals and SDs of the parameters analysed are given for all subjects in Table 1.

Responses for all parameters tested were larger for female subjects (P = 0.02). For binaural 3 mA stimulation with fixation, OTP was 2.55 ± 1.2° for male (n = 24) and 3.30±1.5° for female subjects (n = 33). Mean SPV (male 1.29 ± 0.6°/s; female 1.73 ± 0.8°/s), quick phase amplitude (male 0.76 ± 0.4°; female 1.04 ± 0.5°) and torsional nystagmus frequency (male 1.20 ± 0.5 s⁻¹; female 1.34 ± 0.5 s⁻¹) also showed gender-dependent differences.

Ocular torsion position during GVS

The amplitude of tonic OTP was determined after nystagmus compensation as described in Methods. Subjects showed large interindividual differences in the amount of superimposed nystagmus. OTP ranged from ~1° (stimulation binaural 1 mA during fixation) to ~6° (binaural 3 mA in darkness). Mean values for all subjects are given in Fig. 4A and Table 1. A comparison of the test conditions showed that OTP amplitude for binaural 1 mA stimulation was about one-third of binaural 3 mA fixation stimulation. When the same current (3 mA) was used, monaural amplitudes were about half the binaural amplitudes. In darkness, OTP amplitude was about one-third larger than during fixation (Fig. 4A). Responses were approximately symmetric for left and right stimulation. Side-to-side ratios as a measure of asymmetry are given in Fig. 5. The largest values found for side-to-side ratio of OTP amplitude were around 2.4 in single subjects (Fig. 5A).

Torsional nystagmus during GVS

Three parameters (mean SPV, quick phase amplitude and nystagmus frequency of torsional nystagmus during GVS) were determined in each subject and for each test condition. Mean SPV values ranged from ~0.5°/s (binaural 1 mA fixation) to ~3°/s (binaural 3 mA darkness). Quick phase amplitudes were between 0.5 and 2°, and torsional nystagmus frequencies ranged from 0.75 to 1.5 s⁻¹. Fig. 4B–D shows the mean values and 95% confidence intervals for five different stimulation conditions.

Whereas SPV and quick phase amplitude strongly depended on stimulus strength (Fig. 4B and C), the...
nystagmus frequency was much less influenced by current amplitude (Fig. 4D). Depending on subject’s age, the SPV for binaural 3 mA stimulation was between 2- and 4-fold larger than SPV for binaural 1 mA and monaural 3 mA stimulation. Responses in darkness were larger than during fixation. Responses for all parameters were symmetric, but again large inter-individual differences were apparent (error bars in Fig. 4). As illustrated in Fig. 5, nystagmus parameters in healthy subjects showed a greater tendency to be asymmetric than OTP amplitude (side-to-side ratios >4.5 in single cases).

**Age dependency of torsional eye movement responses to GVS**

The major question in the present study was whether GVS-induced eye movements depend on age. Subjects were therefore grouped in five decades. OTP, torsional nystagmus (SPV, amplitude, frequency) and side-to-side ratio were analysed for age-related changes (Figs 4 and 5). Binaural 3 mA stimulation caused an increase in responses with increasing age from the third (20–29 years) to the sixth (50–59 years) decade, but a decrease for more advanced ages (60–69 years). Tonic OTP amplitude in darkness (3 mA) increased from ~3.5° (20–29 years) to ~5.5° (50–59 years) and decreased to ~4.7° for the seventh decade. This effect was less pronounced for lower intensity stimulation (binaural 1 mA and monaural 3 mA).

With respect to torsional nystagmus, the age-dependent increase of the responses was most pronounced for SPV: mean values for binaural stimulation in darkness (3 mA) increased from 1.5°/s at age 20–29 years to 2.9°/s at age 50–59 years, and decreased to ~4.7° for the seventh decade. This caused increasing differences among the stimulation conditions with increasing age. In the sixth decade, mean SPV for binaural 3 mA fixation stimulation was ~4-fold but, in younger ages, it was only 2-fold the value of binaural 1 mA fixation stimulation. The quantitative data for age dependency of eye movement responses to 3 mA binaural stimulation during fixation are given in Table 2. Horizontal nystagmus showed similar age-dependent changes, but was not included here to avoid redundant information.

Statistical analysis was performed for all seven stimulation conditions tested. The repeated measures ANOVA showed a significant effect of the factor age for mean SPV \[F(4,12) = 8.59, P = 0.0016\] and quick phase amplitude \[F(4,12) = 3.99, P = 0.027\]. There were also significant differences between stimulation conditions for all parameters {e.g. \[F(6,66) = 57.14, P < 0.000001\] for tonic ocular torsion}. In addition, there was a significant interaction between the categorical predictor age and the stimulation paradigms for OTP amplitude \[F(24,66) = 2.38, P = 0.0029\] and mean SPV \[F(24,72)=6.14, P < 0.000001\]. This means that the eye movement parameters behave differently with age, depending on the stimulation paradigm used. No significant difference was found between left and right side stimulation. Side-to-side ratio for the detection of asymmetry increased only slightly and insignificantly with age (SPV and quick phase amplitude; Fig. 5).

**Discussion**

Although increasing gait unsteadiness in the elderly is well known (Bergin et al., 1995; Dominguez and Bronstein, 2000), commonly used tests of vestibular function show variable age-related changes. Caloric irrigation and other VOR tests showed very little change with age (Mulch and Petermann, 1979; Peterka et al., 1990b; Welgampola and Colebatch, 2002). A decrease was seen for VOR to large amplitude sinusoidal stimulation and to high acceleration rotational stimuli as well as for vestibulo-colic responses (Balogh, 1993;
Interestingly, medium latency EMG responses in the soleus muscle to GVS increased with age up to the sixth decade—a finding that is similar to the observations made in our study (Welgampola and Colebatch, 2002). There was also a differential age dependency for vestibulo-collic reflex, whether induced by GVS or clicks. Using GVS, the response remained stable up to the sixth decade and decreased thereafter. With click stimulation (known to involve hair cell input), the vestibulo-collic reflex decline started earlier (Welgampola and Colebatch, 2001).

GVS-induced torsional eye movements: general findings and clinical application

Our study showed that normal values for torsional eye movement responses to GVS are dependent on age. The two stimulation current amplitudes (1 mA and 3 mA) resulted in qualitatively similar eye movement responses—although a better signal to noise ratio was obtained for 3 mA, which is well tolerated and preferable for clinical uses. Monaural stimulation might be helpful for diagnosing unilateral pathologies. We recommend that measurements be made during the fixation of a stationary target because this provides higher quality for quantitative analysis of torsional eye movements. Further studies are required to prove whether GVS is a suitable tool for differentiating between hair cell and vestibular nerve pathology.

Eye movement responses to GVS are known to show large inter-individual variability but good intra-individual reliability (Zink et al., 1997, 1998; Watson et al., 1998; MacDougall et al., 2002; Schneider et al., 2002). Proposed explanations for increased inter-individual variability have been based on the assumption of different thresholds for subpopulations of afferents (Zink et al., 1998), varying contribution of otolith input (Kleine et al., 1999) and inter-individually different nystagmus frequencies and amplitudes (Schneider et al., 2000, 2002).

We found a gender difference with GVS, which has also been described in other studies (Welgampola and Colebatch, 2001, 2002). It has been attributed to more efficient delivery of the galvanic stimulus due to differences in skull anatomy (Krogman, 1962). A gender difference was not found when vestibulo-collic reflexes were evoked by a click or a tap instead of GVS (Welgampola and Colebatch, 2001). In our study, the relation between males and females was very similar within the decade groups.

Age dependency of torsional eye movement responses to GVS

Torsional eye movements during vestibular nerve stimulation by GVS show an inverse U-shaped curve indicating age dependency; the most pronounced increase of responses occurs between the fourth and sixth decade of life. Responses also show a slight increase for the third and a decrease for the fourth decade.

Table 1 Quantitative data for torsional eye movements responses to GVS in healthy subjects

| Stimulation      | Cathode left |               |               |               |  |               |               |  |               |               |  |               |               |
|------------------|--------------|---------------|---------------|---------------|  |               |               |  |               |               |  |               |               |
|                  | Ocular torsion position (°) | 1.24 | 1.11 | 1.36 | 30 | 0.34 | 1.24 | 1.08 | 1.40 | 30 | 0.42 |               |               |
|                  | Nystagmus SPV (°/s) | 0.66 | 0.55 | 0.78 | 37 | 0.33 | 0.63 | 0.54 | 0.73 | 37 | 0.28 |               |               |
|                  | Nystagmus amplitude (°) | 0.45 | 0.37 | 0.53 | 37 | 0.25 | 0.48 | 0.38 | 0.57 | 37 | 0.28 |               |               |
|                  | Nystagmus frequency (s⁻¹) | 0.94 | 0.79 | 1.10 | 36 | 0.46 | 0.92 | 0.80 | 1.04 | 36 | 0.36 |               |               |
| Binaural 3 mA    | Ocular torsion position (°) | 2.90 | 2.53 | 3.28 | 57 | 1.43 | 3.07 | 2.62 | 3.51 | 57 | 1.67 |               |               |
|                  | Nystagmus SPV (°/s) | 1.46 | 1.26 | 1.65 | 57 | 0.75 | 1.63 | 1.39 | 1.87 | 57 | 0.91 |               |               |
|                  | Nystagmus amplitude (°) | 0.90 | 0.77 | 1.02 | 57 | 0.46 | 0.95 | 0.81 | 1.09 | 57 | 0.53 |               |               |
|                  | Nystagmus frequency (s⁻¹) | 1.22 | 1.07 | 1.37 | 57 | 0.57 | 1.34 | 1.20 | 1.47 | 57 | 0.51 |               |               |
| Monaural left 3 mA | Ocular torsion position (°) | 1.89 | 1.66 | 2.11 | 48 | 0.79 | 1.88 | 1.66 | 2.11 | 48 | 0.77 |               |               |
|                  | Nystagmus SPV (°/s) | 0.78 | 0.66 | 0.91 | 56 | 0.46 | 0.77 | 0.66 | 0.88 | 56 | 0.42 |               |               |
|                  | Nystagmus amplitude (°) | 0.54 | 0.44 | 0.63 | 56 | 0.36 | 0.53 | 0.44 | 0.62 | 56 | 0.32 |               |               |
|                  | Nystagmus frequency (s⁻¹) | 0.92 | 0.79 | 1.04 | 56 | 0.47 | 0.91 | 0.78 | 1.05 | 56 | 0.51 |               |               |
| Monaural right 3 mA | Ocular torsion position (°) | 1.97 | 1.73 | 2.20 | 46 | 0.78 | 1.99 | 1.76 | 2.22 | 46 | 0.77 |               |               |
|                  | Nystagmus SPV (°/s) | 0.80 | 0.69 | 0.91 | 56 | 0.42 | 0.75 | 0.64 | 0.86 | 56 | 0.41 |               |               |
|                  | Nystagmus amplitude (°) | 0.51 | 0.44 | 0.58 | 56 | 0.26 | 0.49 | 0.39 | 0.58 | 56 | 0.35 |               |               |
|                  | Nystagmus frequency (s⁻¹) | 0.99 | 0.87 | 1.12 | 56 | 0.47 | 1.00 | 0.88 | 1.11 | 56 | 0.43 |               |               |

Summarized means, 95% confidence intervals, standard deviations and number of subjects for monaural and binaural GVS during fixation for ocular torsion position, torsional nystagmus slow phase velocity, quick phase amplitude and frequency.
Fig. 4 Torsional eye movement responses to GVS as dependent on age. Age-dependent means and 95% confidence intervals for static ocular torsion position amplitude (A), mean slow phase velocity (B), quick phase amplitude (C) and nystagmus frequency (D). An increase in ocular torsion position amplitude can be observed for 3 mA binaural stimulation up to the sixth decade; it is most pronounced for SPV. Age-dependent changes over all stimulation paradigms are significant for SPV and amplitude. Note the dependency of SPV and amplitude on current amplitude, which is less prominent for nystagmus frequency. Squares: binaural 3 mA stimulation (dotted line: darkness; solid line: fixation). Circles: binaural 1 mA stimulation (fixation). Diamonds: left monaural stimulation (fixation). Triangles: right monaural stimulation (fixation). Black symbols for clockwise eye movements (cathode left for binaural and left monaural stimulation; anode right for right monaural stimulation) and grey symbols for counterclockwise eye movements.

Fig. 5 Asymmetry of eye-movement responses to GVS expressed as side-to-side ratio (larger number divided by smaller number). A ratio of 1.0 would indicate perfect symmetry. All values were closest to one for static torsion (A). For the nystagmus parameters slow phase velocity (B), quick phase amplitude (C) and torsional nystagmus frequency (D), single values went up to five, indicating asymmetric responses. These extreme values slightly increased with age. The lines in the graphs are regression lines for all data showing the slight increase for SPV and amplitude. Squares: binaural 3 mA stimulation (black: darkness, open: fixation). Circles: binaural 3 mA stimulation (fixation). Diamonds: left monaural stimulation (fixation). Triangles: right monaural stimulation (fixation).
seventh decade. To interpret this at first seemingly paradoxical finding, one has to consider the site of action of GVS and age-related degenerative processes in the vestibular structures.

It is generally accepted that GVS stimulates the vestibular nerve rather than the hair cells. It acts at the spike trigger site of primary vestibular afferents, which extends 10–50 μm from the synapse to the first level of myelinization and is thought to involve afferents from all vestibular endorgans (semicircular canals [SCCs] and otolith) to a similar extent (Goldberg et al., 1984; Kleine and Grüsser, 1996). Since otolith afferent stimulation induces tonic ocular torsion (Suzuki et al., 1969), many studies attributed these responses to the activation of otolith afferents (Inglis et al., 1995; Day et al., 1997; Zink et al., 1997, 1998; Watson et al., 1998). However, by modelling the expected responses (Wardman and Fitzpatrick, 2002) or mimicking GVS-induced eye movements by pure SCC stimulation (Schneider et al., 2002), it could be shown that the evoked eye movements can be attributed mainly to SCC activation.

All structures relevant for vestibular function have been shown to degenerate with age, but the onset and time vary. Sensory vestibular hair cell counts decrease from birth to old age by ~6% per decade (Rosenhall, 1973; Richter, 1980; Baloh et al., 1989). Type I hair cells in the SCC seem to degenerate earlier than type I hair cells in the maculae (Merchant et al., 2000; Rauch et al., 2001). In addition to cell loss, morphological and functional changes have been demonstrated in the remaining cells (Anniko, 1983; Gleeson and Felix, 1987; Sloane et al., 1989).

Primary vestibular afferents, mainly large myelinated fibres, degenerate from middle age on. About 35% of the afferents remain in 70–85 year olds (Bergström, 1973; Baloh et al., 1989). Irregular afferents have large diameters and fast conduction velocities (Goldberg, 2000) and degenerate more than regular afferents. Several post mortem studies showed that the decline in cell number for Scarpa’s ganglion begins at age 30 years (Park et al., 2001), with a steep decrease from age 60 years onward (Richter, 1980; Velazquez-Villasenor et al., 2000; Park et al., 2001). Neurons in vestibular nuclei decrease by ~3% per decade from 40–90 years of age (Lopez et al., 1997; Alvarez et al., 2000). Cells involved in the inhibition of vestibular input also decrease, for example, the cerebellar volume and Purkinje cell density in the vermis (Torvik et al., 1986; Luft et al., 1999; Raz et al., 2001).

An increase of eye movement responses to GVS with aging was found only at the higher stimulus intensity (3 mA). This might be due to differential degeneration of regular and irregular afferents. Both regular and irregular afferents contribute to the horizontal VOR, but they are thought to be involved in different pathways (Minor and Goldberg, 1991; Angelaki and Perachio, 1993). Functional ablation of irregular afferents leads to a decrease in gain of VOR if angular velocity steps are applied, but does not change VOR

### Table 2: Age dependency of ocular torsion position and nystagmus parameters for binaural 3 mA GVS during fixation

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Cathode left</th>
<th>Cathode right</th>
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<tbody>
<tr>
<td></td>
<td>Mean ±95% +95% n SD</td>
<td>Mean ±95% +95% n SD</td>
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<tr>
<td><strong>Ocular torsion position (°)</strong></td>
<td></td>
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<tr>
<td>20–29</td>
<td>2.34 ± 1.56 3.13 ± 1.47 16</td>
<td>2.41 ± 1.87 2.95 ± 1.95 16</td>
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<tr>
<td>30–39</td>
<td>2.98 ± 2.19 3.78 ± 1.25 12</td>
<td>2.68 ± 1.99 3.37 ± 1.37 12</td>
</tr>
<tr>
<td>40–49</td>
<td>2.69 ± 1.51 3.87 ± 1.65 10</td>
<td>2.96 ± 1.45 4.47 ± 2.11 10</td>
</tr>
<tr>
<td>50–59</td>
<td>3.64 ± 2.70 4.59 ± 1.22 9</td>
<td>4.61 ± 3.00 6.22 ± 2.09 9</td>
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<tr>
<td>60–69</td>
<td>3.25 ± 2.29 4.21 ± 1.34 10</td>
<td>3.29 ± 2.18 4.40 ± 1.56 10</td>
</tr>
<tr>
<td><strong>Nystagmus SPV (°/s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>1.12 ± 0.81 1.44 ± 0.59 16</td>
<td>1.11 ± 0.79 1.42 ± 0.59 16</td>
</tr>
<tr>
<td>30–39</td>
<td>1.23 ± 0.86 1.61 ± 0.59 12</td>
<td>1.20 ± 0.82 1.59 ± 0.61 12</td>
</tr>
<tr>
<td>40–49</td>
<td>1.50 ± 1.02 1.99 ± 0.68 10</td>
<td>1.84 ± 1.21 2.48 ± 0.89 10</td>
</tr>
<tr>
<td>50–59</td>
<td>2.14 ± 1.41 2.87 ± 0.95 9</td>
<td>2.59 ± 1.86 3.32 ± 0.95 9</td>
</tr>
<tr>
<td>60–69</td>
<td>1.59 ± 1.10 2.09 ± 0.69 10</td>
<td>1.91 ± 1.31 2.52 ± 0.84 10</td>
</tr>
<tr>
<td><strong>Nystagmus amplitude (°)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>0.74 ± 0.47 1.01 ± 0.51 16</td>
<td>0.70 ± 0.51 0.88 ± 0.63 16</td>
</tr>
<tr>
<td>30–39</td>
<td>1.01 ± 0.69 1.33 ± 0.50 12</td>
<td>0.88 ± 0.48 1.29 ± 0.64 12</td>
</tr>
<tr>
<td>40–49</td>
<td>0.96 ± 0.71 1.22 ± 0.36 10</td>
<td>1.15 ± 0.77 1.52 ± 0.53 10</td>
</tr>
<tr>
<td>50–59</td>
<td>1.11 ± 0.73 1.49 ± 0.50 10</td>
<td>1.32 ± 0.89 1.75 ± 0.56 10</td>
</tr>
<tr>
<td>60–69</td>
<td>0.75 ± 0.51 0.99 ± 0.34 10</td>
<td>0.89 ± 0.59 1.19 ± 0.42 10</td>
</tr>
<tr>
<td><strong>Nystagmus frequency (s⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>1.04 ± 0.81 1.28 ± 0.44 16</td>
<td>1.17 ± 0.93 1.41 ± 0.45 16</td>
</tr>
<tr>
<td>30–39</td>
<td>1.06 ± 0.77 1.34 ± 0.45 12</td>
<td>1.18 ± 0.93 1.44 ± 0.40 12</td>
</tr>
<tr>
<td>40–49</td>
<td>1.17 ± 0.85 1.49 ± 0.44 10</td>
<td>1.27 ± 0.89 1.65 ± 0.53 10</td>
</tr>
<tr>
<td>50–59</td>
<td>1.60 ± 0.96 2.24 ± 0.83 9</td>
<td>1.72 ± 1.32 2.12 ± 0.52 9</td>
</tr>
<tr>
<td>60–69</td>
<td>1.43 ± 1.02 1.84 ± 0.57 10</td>
<td>1.52 ± 1.12 1.92 ± 0.56 10</td>
</tr>
</tbody>
</table>

Means, 95% confidence intervals and standard deviations are given.
parameters during sinusoidal stimulation (Angelaki and Perachio, 1993). In the vestibular nerve, irregular afferents have a 6-fold greater sensitivity to GVS than regular afferents due to their smaller post-spike recovery time constant (Goldberg et al., 1984). These irregular fibres with low stimulation thresholds degenerate primarily with age. Regularly discharging fibres, however, have a higher threshold to stimulation and degenerate less (Goldberg, 2000). This means that with increasing age, vestibular function relies increasingly on regular fibre input. Due to their higher threshold to stimulation, higher current amplitudes are required, thus explaining the differential effects of GVS at 1 and 3 mA.

Proposed mechanism explaining the inverse U-shaped curve for age dependency of eye movement responses to GVS

All in all, hair cell decline starts early and continues at a constant rate throughout life, whereas vestibular nerve and central neuron decline begins at midlife, increasing in rate at an older age. This has potential functional implications as to compensatory mechanisms. A schematic view of the proposed mechanism is illustrated in Fig. 6.

Since hair cell loss precedes those seen in the vestibular nerve and Scarpa’s ganglion, the decrease in hair cell counts could be compensated by increased sensitivity of afferent nerve fibres or central mechanisms. Increased sensitivity could maintain normal function despite reduced peripheral input. If this were true, the direct stimulation of vestibular nerve should cause larger responses than hair cell stimulation. As GVS acts at the vestibular nerve, thereby bypassing the hair cells, electrical stimulation should be more efficient in subjects with beginning hair cell degeneration but increased vestibular afferent sensitivity, as seen in our data for age dependency. This holds only as long as the vestibular nerve and central structures remain unaffected. In more advanced ages, the degeneration of nerve fibres, ganglion cells and central neurons become evident. Thus, the compensatory increase in sensitivity breaks down and GVS-induced eye movements decline. This is reflected in the inverse U-shaped curve for age dependency found in our study.

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References


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