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## Linearity, symmetry and additivity of the human eye-movement response to maintained unilateral and bilateral surface galvanic (DC) vestibular stimulation

Received: 20 June 2002 / Accepted: 17 September 2002 / Published online: 22 November 2002  
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**Abstract** Recent studies have shown that, although responses to long-duration, constant-current surface galvanic vestibular stimulation (GVS) show substantial interindividual variability, individual subjects show a reliable, repeatable, idiosyncratic oculomotor response pattern to GVS. It follows that GVS may be a more reliable stimulus than may have been anticipated from the literature. The aim of the present study was to examine the metrics of 3D eye-movement responses to maintained (120 s), unilateral and bilateral surface GVS. Eye movements were measured using computerised video-oculography. Two experiments were conducted: Experiment 1 examined whether the normal response is linear over increasing levels of current; and Experiment 2 examined (1) whether the normal response to surface GVS is symmetrical when comparing stimulated sides, (2) whether the normal response to surface GVS is symmetrical when the polarity of the stimulating current was reversed, and (3) whether there is additivity in the normal response to combinations of unilateral/bilateral surface GVS. Five subjects participated in Experiment 1 and eight subjects participated in Experiment 2. In both experiments, the onset of stimulation produced characteristic eye-movement responses: changes in torsional position with the upper pole of both eyes rolling towards the anode and away from the cathode; together with horizontal and torsional nystagmus with slow phases towards the anode and away from the cathode; and negligible vertical nystagmus. These responses reversed direction at stimulus offset. In the fixation condition of Experiment 1, the magnitude of ocular torsional position (OTP) and torsional nystagmus responses showed a linear relationship over conditions of increasing current strength, as did OTP, torsional and horizontal nystagmus responses in darkness. The results of Experiment 2 showed that

responses to unilateral stimulation are symmetrical between stimulated sides, symmetrical between stimulating polarities, and additive (with respect to responses to bilateral stimulation). The principles derived from these findings, as well as those of recent studies, provide a foundation for future work investigating eye-movement responses to surface GVS in patients with known types of vestibular dysfunction.

**Keywords** Galvanic vestibular stimulation (GVS) · Labyrinth · Eye movement · Linearity · Symmetry

### Introduction

Applying galvanic current by large-surface electrodes placed on the skin over the mastoids produces sensations of dizziness by activating the vestibular system. Goldberg et al. (1984) showed that, in animals, cathodal galvanic stimulation results in activation of vestibular afferents and anodal stimulation results in their inhibition, through an action at the spike trigger zone of primary afferents. Unlike many other vestibular stimuli, such as tilts and translations, galvanic vestibular stimulation (GVS), like caloric or click stimulation, can be applied unilaterally, and may, therefore, ultimately be used to compare vestibular function between healthy and affected sides in patients. Many studies have sought to determine the usefulness of GVS in a clinical diagnostic setting (e.g. Pfaltz 1969; Coats 1972; Watanabe et al. 1985). Some have measured horizontal eye movements using nystagmography (Straub and Thoden 1992) or torsional eye movements using video-oculography (Kleine et al. 1999; Schneider et al. 2000); others, postural responses such as body sway (Coats 1973; Magnusson et al. 1991), EMG (e.g. Britton et al. 1993; Watson et al. 1998b) or regional cerebral blood flow in vestibular cortex (Lobel et al. 1998, 1999; Bense et al. 2001). Responses to GVS have, however, been highly variable in both normals and patients. The overall high variability of the results of GVS initially led some researchers to discount the utility

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of GVS as a test of peripheral vestibular function at all (Blonder and Davis 1936; Pfaltz and Richter 1965).

Recent research has shown that, although the 3D eye-movement response to long-duration, large-amplitude GVS does vary substantially between normal subjects, these responses are highly reliable within subjects, showing idiosyncratic patterns in the relative proportions of eye-movement response components over repeated sessions (MacDougall et al. 2002). GVS is thus more reliable than might have been anticipated from earlier findings, and may yet provide the basis for clinical tests of vestibular function. Before testing patients, however, it is vital to understand as much as possible about characteristics of the response to this stimulus in normals.

The aim of the present study was to examine the metrics of 3D eye-movement responses to maintained, unilateral and bilateral surface GVS. In particular, this study sought to answer four questions.

First, we sought to examine the nature of the relationship between stimulating current level (mA) and the magnitude of 3D eye-movement responses in normals, both with and without fixation. This relationship is controversial because Zink et al. (1997, 1998) found a non-linear relationship between GVS current and slow phase velocity (SPV) responses, which they observed only above 3 mA. These non-linearities may result from the fact that very short stimuli of only 5 s duration were used and that SPV responses to smaller currents did not have time to build up to levels that the researchers could detect. Kleine et al. (1999), however, used sinusoidal bilateral GVS and found a linear relationship between GVS and both ocular torsional position (OTP) and torsional slow-phase velocity (TSPV; with visual suppression of other components by fixation).

Second, the present study sought to examine whether the normal 3D eye-movement response to surface GVS is symmetrical when comparing stimulated sides (i.e. left vs. right). Zink et al. (1997) presented 3D velocity responses (to short-duration GVS) from which some measure of lateral symmetry can be inferred. The issue of lateral symmetry is more explicitly addressed by Clarke and Engelhorn (1998), who found a symmetrical response in ocular counterroll (OCR) from unilateral stimulation of each otolith; however, this finding was obtained with linear acceleration rather than with GVS. Third, the present study sought to examine whether the normal 3D eye-movement response to surface GVS is symmetrical when comparing polarities of stimulating current (i.e. anode vs. cathode). Data presented in Schneider et al. (2000) suggest some measure of symmetry in the response to anodal and cathodal phases of sinusoidal current; however, this can only be gleaned from the ocular torsion responses (as vertical and horizontal eye movements were suppressed using visual fixation).

Fourth, the present study sought to examine whether there is an additive relationship in OCR and the other eye-movement response components to combinations of matched unilateral/bilateral long-duration surface GVS in normals. Clarke and Engelhorn (1998) studied the

unilateral testing of utricular function by rotating subjects at constant velocity around an axis that passes through one (unstimulated) utricle, to deliver a centripetal linear acceleration to the other utricle. They attempted to show the additive relationship of unilateral and bilateral stimulation by comparing the response to this unilateral linear acceleration with the response to a bilateral linear acceleration generated by roll-tilt. Although these two classes of stimuli are similar in terms of magnitude of interaural linear acceleration, they differ in a number of important ways, including the canal stimulation resulting from the dynamic phases of these stimuli, differences in the magnitude of naso-occipital linear acceleration (from Coriolis effects on the centrifuge) and, most importantly, the differences in dorsoventral linear acceleration which are recognised by many authors (de Graaf et al. 1996; Merfeld 1996; MacDougall et al. 1999; Moore et al. 2001) to contribute to the OCR response. Two experiments were conducted: the first experiment addresses the first of the above questions, and the second experiment addresses the remaining three.

As in our previous study (MacDougall et al. 2002), Experiment 1 of the present study investigated the response to GVS both in the presence of fixation and in complete darkness. Results obtained in darkness permit an analysis of the complex, 3D eye-movement response to GVS, whereas the results obtained with a fixation light allow the isolation of torsional components by suppressing vertical and horizontal nystagmus. The presence of a fixation light is known to significantly affect the eye movements of normal subjects. The presence of a fixation light largely suppresses horizontal and vertical nystagmus, and has been shown to reduce slightly the instability of torsional position (Enright 1990). In addition, Smith et al. (1995) have shown that, during on-centre rotation without fixation, the unsuppressed horizontal nystagmus tends to reduce or 'dump out' the OTP response, which is thought to be produced by the angular accelerations stimulating canals during these on-centre rotations (Smith et al. 1995). We chose to carry out all testing in Experiment 2 in darkness because, now that we have developed an understanding of the OTP response by comparison of the results with and without fixation, responses to GVS obtained in darkness are sufficient to allow interpretation of all the components of the eye-movement response (and the function of their likely sources). Ultimately, results from this experiment will provide the normal control data for testing patients.

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## Materials and methods

### Subjects

Five subjects (three females and two males; mean age = 27 years, SD = 5.6 years) volunteered to participate in Experiment 1: 'Linearity'. Eight subjects (five females and three males; mean age = 45.9 years, SD = 17.6 years) volunteered to participate in Experiment 2: 'Symmetry and Additivity'. No subject reported any history of vestibular dysfunction. All procedures were approved by

the University of Sydney Human Ethics Committee and all subjects gave informed written consent.

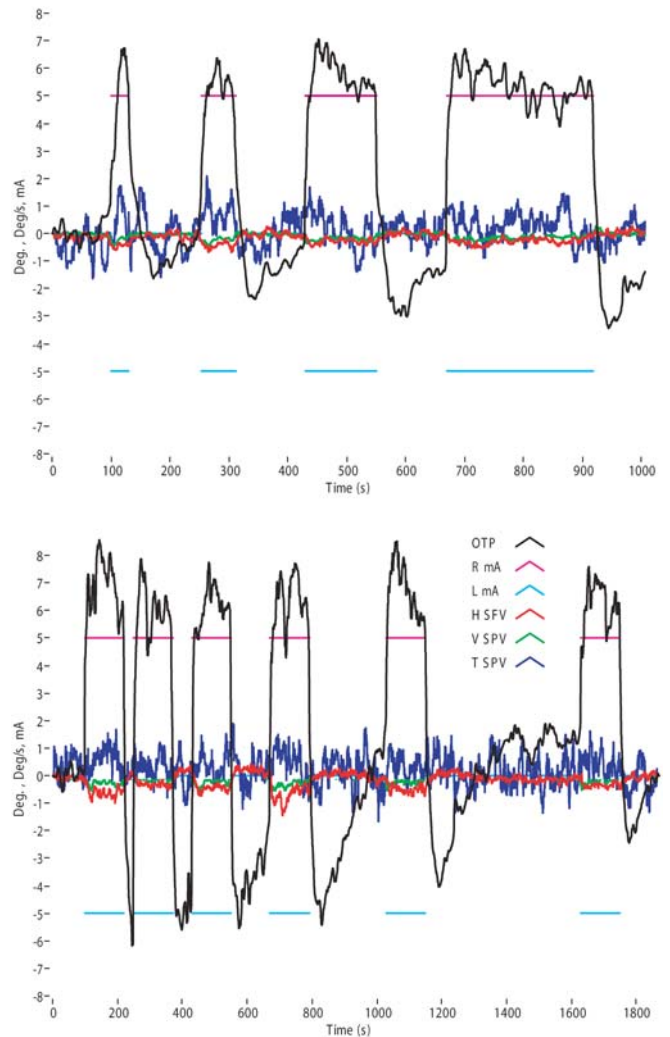
### Galvanic stimulation

Galvanic stimulation was delivered via surface electrodes of approx. 1,000 mm<sup>2</sup>, individually cut from electrosurgical plating (split-plate patient return plating, model no. 7180: 3M Health Care, USA) generously coated with electrode gel (Spectra 360: Parker Laboratories, USA) and placed over each mastoid process (see, e.g. Watson et al. 1998a). A custom-designed battery-powered isolated current stimulator was used to deliver the desired current over a prolonged period.

Electrode placement was always bilateral in Experiment 1: 'Linearity' (cathodal current delivered to the electrode over the left mastoid, anodal to the right mastoid's electrode – CLAR). In Experiment 2: 'Symmetry and Additivity', electrodes were again placed over the left and right mastoids, and an additional large-surface-area electrode was placed over the *vertebra prominens* (C7) to act as a neutral (reference) electrode during unilateral stimulation conditions. For this reason, unilateral stimulation conditions are hereafter referred to only by their active electrode (e.g. 'AR' refers to 'anode right cathode C7'). In this experiment, stimulation was unilateral in four conditions and bilateral in the remaining two conditions (see 'Procedure').

In our previous study (MacDougall et al. 2002) we used galvanic stimulation lasting 300 s and recorded offset responses for another 300 s, in order to investigate adaptation. This study showed systematic and significant decays of the eye-movement responses to maintained GVS with time constants of hundreds of seconds and a large overshoot or reversal of responses at stimulus offset. Since the present study aims to compare a number (11–13) of stimulus and offset conditions of different amplitudes or of different polarities and sides of stimulation, it was necessary to reduce the duration of the stimuli, and of the recovery period after stimuli, in order to keep the durations of whole test sessions within the limits of subject stamina. It is important to deliver all the stimuli to be compared in one test session, to avoid contamination by within-subject variables such as the subject's level of arousal and fatigue. Since responses to GVS adapt, overshoot, and recover with such long time constants, it was important for us to investigate the effect of an adapted baseline, or 'carryover' from a previous stimulus, through a relatively short recovery period, to the next stimulus response. To address the issue of 'carryover' effects we conducted a number of preliminary tests that systematically varied the adapted baseline preceding a number of GVS conditions. This was done by: first, varying the duration (30 s, 60 s, 120 s, 240 s) of identical 5-mA galvanic stimuli while holding the interstimulus interval constant at 120 s (see upper half of Fig. 1), and then varying the interstimulus interval (30 s, 60 s, 120 s, 240 s, 480 s) between identical 5-mA (120 s) stimuli (see lower half of Fig. 1), and by varying the order of a sequence of unilateral and bilateral, anodal and cathodal stimuli. All these manipulations systematically altered the direction and magnitude of the adapted baseline preceding each GVS condition (by as much as 5 deg), but to our surprise none of them had any effect on the absolute magnitudes of eye-movement responses to subsequent stimuli. This observation suggests that the adapted overshoots or reversals of eye movements at stimulus offset are immediately 'dumped', overpowered, or ignored by central processes and that there is no 'carryover' from previous conditions over a range of interstimulus intervals as short as 30 s.

In this study we chose to gather, and average over, at least 100 s of data at each baseline and stimulus condition because eye movements, especially in torsion, are unstable (for instance there is a spontaneous oscillation of OTP of  $\pm 1$  deg over a period of as much as 60 s), so measuring OTP over short periods (<60 s) can result in a relatively large variation in the estimate of position (of as much as 2 deg, or more than enough to swamp the effects from GVS). An interstimulus interval of 2 min was also used to permit an accurate assessment of offset responses, while allowing us to



**Fig. 1** Two time series of the raw 3D eye-movement traces for one subject (with fixation), in response to GVS. The strength and side of delivery of the stimulus are indicated on the plot by the cyan (left mastoid) or magenta (right mastoid) horizontal bars. The upper trace shows the systematic manipulation of baseline conditions by varying the duration of identical 5-mA stimuli. The first galvanic stimulus lasts 30 s and produces a small overshoot in OCR of about 1 deg. The second 60-s stimulus produces more adaptation and a larger overshoot of about 2 deg. The third 120-s stimulus produces again more adaptation and a larger overshoot of nearly 3 deg, etc. The second raw data trace shows the systematic manipulation of baseline conditions by varying the duration of the interstimulus interval (ISI) between identical 5-mA bilateral stimuli. The longer this ISI (30 s, 60 s, 120 s, 240 s and 480 s) the greater the recovery of the overshoot back towards 0 deg (the initial baseline) and the smaller the amplitude of OCR baseline preceding each of the 120-s galvanic stimuli. A comparison of the absolute magnitude of responses to galvanic stimuli shows that there is no carryover effect from the adapted baselines

deliver all the stimuli to be compared within one session, and without exceeding the limits of subject stamina.

### Procedure

Drops of pilocarpine (used to constrict the pupil for video-oculography) were administered to subjects' left and right eyes,

then subjects were allowed to rest for 20 min, to allow the pilocarpine to take effect. Following the rest period, subjects donned the video headset required for continuous eye-movement recording (see below). Subjects were seated such that Reid's line (the line joining the inferior margin of the orbit and the upper margin of the external auditory meatus) was held approximately earth horizontal. This is a standard position that is both comfortable and allows for comparable orientation of the otoliths across subjects. Head and shoulders were held firmly by padded supports.

For Experiment 1, testing was carried out both in darkness (FIX OFF) and with fixation (FIX ON). In the FIX ON session, subjects fixated a small light-emitting diode that was positioned 80 cm straight ahead (i.e. at eye level and centred horizontally). The FIX ON session was always conducted first, followed by FIX OFF, which was tested in a separate session, no less than 1 h and no more than 1 month later. Within a session, there were five conditions, each consisting of 2 min of eye-movement recording prior to the onset of GVS, followed by 2 min of recording during GVS delivery. At the end of 2 min of 'baseline' recording, the stimulator was simply switched on, delivering a stimulus of the desired amplitude with square-wave onset, left at this level and monitored for 2 min and then switched off (square-wave offset). An interstimulus interval of 2 min was used to permit an accurate assessment of the magnitude of offset responses (particularly in OTP). The order of conditions was a pseudo-random sequence: 5 mA, 3 mA, 1 mA, 4 mA, and 2 mA. Bilateral stimulation electrode placement was chosen for this experiment because bilateral delivery generates larger eye-movement responses (Watson et al. 1998a) to allow more effective analysis. Bilateral delivery, in effect, supplies twice as strong a stimulus as unilateral delivery in that this configuration is equivalent to delivering two unilateral stimuli simultaneously. The benefit of delivering a bilateral stimulus is that the proportion of the eye movements resulting from the GVS (signal) is larger in comparison with the eye movements resulting from other sources (noise due to the biological instability of eye movements, including spontaneous oscillations in OTP, voluntary fixation changes in darkness, etc.). Further, in this experiment, there is no reason to expect asymmetry of response from each side (see Experiment 2: 'Symmetry and Additivity').

For Experiment 2, all testing was conducted in darkness in a single session. There were six conditions, four conditions of unilateral stimulation followed by two conditions of bilateral stimulation. The order of conditions was: Anode Right Cathode C7 (AR), Anode Left Cathode C7 (AL), Cathode Right Anode C7 (CR), Cathode Left Anode C7 (CL), Cathode Left Anode Right (CLAR), Anode Left Cathode Right (ALCR). For each condition, eye movements were recorded for 2 min of baseline data prior to the onset of GVS. At the end of these 2 min, the stimulator was switched on at zero, and the current strength was manually increased to 5 mA (in all conditions). The current was left at this level for 2 min, before being manually returned to zero, and then the stimulator was switched off. This was repeated until all conditions were completed. Manual adjustment of the current was gradual, taking an average of 5 s for a 5-mA change (increase or decrease). Ramp onset and offset of stimulation was chosen, rather than stimulation with square-wave onset and offset, because ramped delivery of current is more comfortable for more sensitive subjects. Since we will eventually be comparing the results of normals with those of patients, and patient testing will require unilateral stimulation with ramp onset (similarly to this experiment), we chose a procedure in this experiment with normals that we are confident that patients will also be able to tolerate well.

Synchronisation with our video eye-movement recording system was achieved using the audio channel on the videocassette. Each time the galvanic stimulator was energised, it emitted a click, which was recorded on the audio channel of the videocassette and converted into a synchronised "stimulus" trace during the eye-movement analysis. An electronic timer was used to signal the start and end of the stimulation period to the operator and this signal was also recorded on the audio channel of the videocassette.

## Eye movement measurement and analysis

Eye movements were recorded using video recording techniques based on those described previously (Moore et al. 1991, 1996). This method has a resolution of 0.1 deg of ocular torsion and the sampling rate was 30 Hz (NTSC frame rate). The pupils of both eyes were constricted by 2% pilocarpine hydrochloride (Chauvin Pharmaceuticals, UK); the eyes were illuminated with infrared light sources. Half-silvered ("hot") mirrors (Coolbeam, OCLI, Santa Rosa) reflected a close-up image of the iral pattern onto a lipstick-sized CCD camera (Panasonic WV-CD1E) while permitting the subject unobstructed vision. The cameras, mirrors and infrared light sources were mounted on thermoplastic masks (Polyflex II, Smith & Nephew) individually moulded to the subject's face and held in place by Velcro straps. This tight-fitting but comfortable "wrap-around" mask minimised camera slippage relative to the eye, and comparisons of eye position at the start and end of the test show that there was no detectable camera slippage.

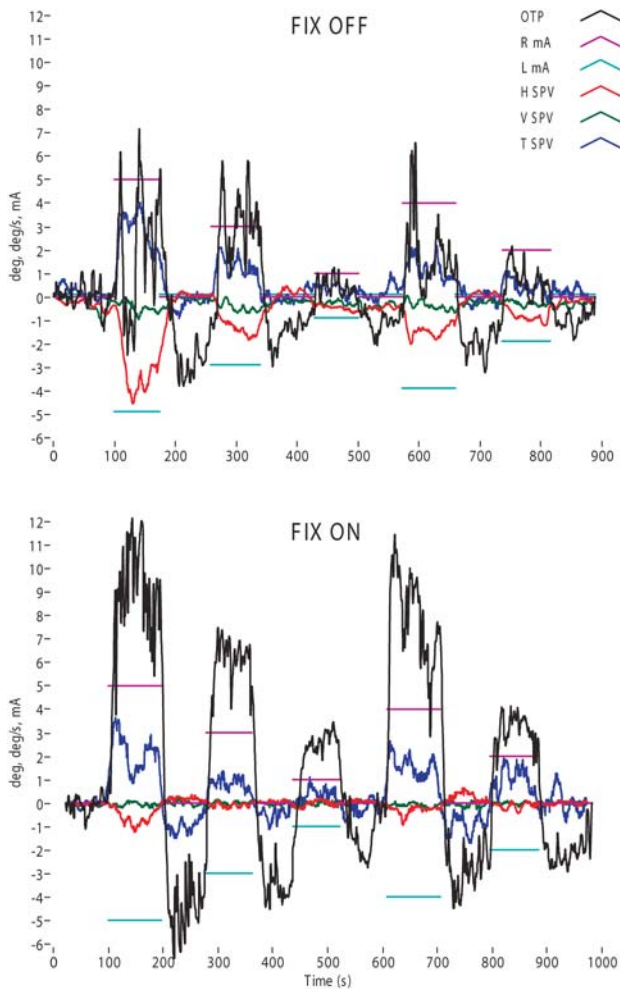
All data were recorded onto S-VHS videotape using two VCRs and analysed after the test session. Eye position and velocity were processed for all three dimensions, giving a total of six possible measures (horizontal, vertical and torsional eye position and horizontal, vertical and torsional slow-phase velocity); however, results for horizontal and vertical eye position were not included in any analysis, as these responses are under the voluntary control of subjects. Due to the high degree of conjugacy of eye-movement responses to GVS (e.g. MacDougall et al. 2002), we chose to analyse data for each subject from the eye that had the best image (i.e. highest polar auto-correlation). The right-hand rule was used; that is, clockwise ocular torsional position and slow-phase velocity (clockwise from the subject's perspective) are positive; leftward horizontal position and slow-phase velocity are positive; and downward vertical position and slow-phase velocity are positive (Hixson et al. 1966). At the start of each condition, reference images of both eyes were recorded while the subject gazed at the fixation point. The average value of the response measured during this period was taken as the baseline measure for each dimension for a particular subject and arbitrarily given the value of 0 deg (position measures) or 0 deg/s (velocity measures).

## Results

### Experiment 1: 'linearity'

#### *General findings*

Surface GVS produced systematic eye-movement responses in all subjects. In response to the onset of GVS, the OTP of all subjects rolled in the positive direction (i.e. upper pole of the eye rotated toward the anode and away from the cathode). GVS also produced horizontal and torsional nystagmus, with slow phases directed toward the anode and away from the cathode. This change in eye position and velocity generally reached a maximum magnitude soon after (30–130 s) stimulus onset, and then started to decay. At the offset of GVS, the OTP and nystagmus of all subjects reversed direction (i.e. the upper pole of the eye rotated away from the anode and toward the cathode, nystagmus with slow phases directed toward the cathode and away from the anode), reaching a peak offset response before returning towards the baseline levels (Fig. 2). Two measures were thus calculated in this experiment: onset responses (the average change in position and/or velocity over the 2 min of stimulation in each trial) and offset responses (the average change in



**Fig. 2** Time series of the raw 3D eye-movement traces for a single subject for the duration of Experiment 1. The *upper half* shows responses obtained in darkness and the *lower half* shows responses obtained with fixation. The strength and side of delivery of the stimulus are indicated on the plot by the *cyan* (left mastoid) or *magenta* (right mastoid) horizontal bars. The figure shows that with fixation there is clearly a larger change in OTP, and the horizontal velocity components are markedly reduced

position and/or velocity over the 2 min immediately following the offset of stimulation in each trial).

In the FIX ON session (lower half, Fig. 3), the fixation light suppressed horizontal and vertical eye movements to negligible levels, thus making it possible to isolate the torsional position and velocity components of the eye-movement response. An analysis of variance (with repeated measures contrasts; Winer et al. 1991) showed that the magnitude of the OTP response tended to be larger with fixation than in darkness; however, this difference was not statistically significant ( $F_{(1,4)}=0.17$ ,  $P=0.70$ ), due to the high degree of variability between subjects (grey trace, lower half of Fig. 3). Similarly, although the magnitude of TSPV tended to be smaller with fixation than in darkness, the difference was not statistically significant ( $F_{(1,4)}=5.79$ ,  $P=0.07$ ). As expected, the magnitude of HSPV was significantly smaller with

fixation than in darkness ( $F_{(1,4)}=70.88$ ,  $P=0.001$ ). There was, however, no effect of fixation on the magnitude of VSPV ( $F_{(1,4)}=0.20$ ,  $P=0.68$ ), due to the very small vertical SPV response in all conditions.

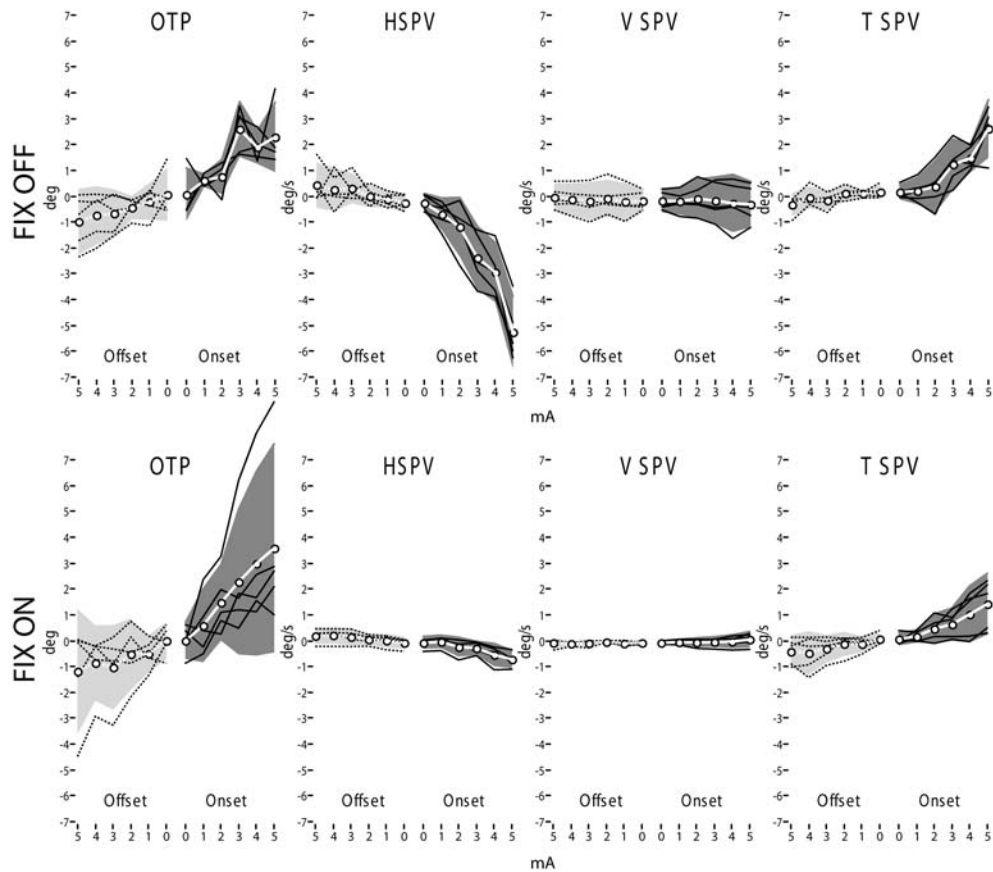
The magnitudes of OTP ( $F_{(1,4)}=9.91$ ,  $P=0.03$ ), TSPV ( $F_{(1,4)}=10.38$ ,  $P=0.03$ ) and HSPV ( $F_{(1,4)}=34.00$ ,  $P=0.004$ ) responses were all significantly larger to galvanic onset than to offset. Again, the negligible VSPV response in all conditions meant that there was no difference in the magnitude of vertical SPV between galvanic onset and offset ( $F_{(1,4)}=0.02$ ,  $P=0.90$ ), as can be seen in Fig. 3.

### Linearity

There was a significant linear trend in the magnitude of OTP responses to GVS onset over conditions of increasing current strength ( $F_{(1,4)}=17.00$ ,  $P=0.01$ ). Although the response to galvanic offset tended to show a similar linear trend, this contrast did not reach significance ( $F_{(1,4)}=3.14$ ,  $P=0.15$ ), which may be due to the small overall magnitude of OTP responses to galvanic offset. Although there was a significant quadratic trend in the magnitude of both TSPV ( $F_{(1,4)}=20.01$ ,  $P=0.01$ ) and HSPV ( $F_{(1,4)}=10.23$ ,  $P=0.03$ ), responses to galvanic onset over conditions of increasing current strength, the linear trend contrast demonstrated a much stronger result in these conditions for both TSPV ( $F_{(1,4)}=37.47$ ,  $P=0.004$ ) and HSPV ( $F_{(1,4)}=83.89$ ,  $P=0.001$ ). Also, the only interaction contrast to reach significance was between the linear trend contrast in galvanic onset responses and the conditions of fixation for both TSPV ( $F_{(1,4)}=11.78$ ,  $P=0.03$ ) and HSPV ( $F_{(1,4)}=47.46$ ,  $P=0.002$ ). These responses can therefore best be described as strongly linear (with a minor quadratic component). Although HSPV and TSPV responses to galvanic offset tended to show a slight linear trend, linear trend contrasts did not achieve significance for these responses (HSPV:  $F_{(1,4)}=7.00$ ,  $P=0.06$ ; TSPV:  $F_{(1,4)}=5.2$ ,  $P=0.08$ ), which is again a reflection of the reduced magnitude of responses to GVS offset. There was no quadratic component to HSPV ( $F_{(1,4)}=0.44$ ,  $P=0.54$ ) or TSPV ( $F_{(1,4)}=0.01$ ,  $P=0.92$ ) responses to galvanic offset.

There were no significant results for either linear (onset:  $F_{(1,4)}=0.02$ ,  $P=0.90$  offset:  $F_{(1,4)}=4.21$ ,  $P=0.11$ ) or quadratic (onset:  $F_{(1,4)}=0.63$ ,  $P=0.47$ ; offset:  $F_{(1,4)}=0.07$ ,  $P=0.80$ ) trends in VSPV responses to GVS of increasing current, again probably due to the negligible VSPV responses in these conditions.

Least squares best fitting lines were calculated using the mean of five subjects' onset responses for those measures with significant linear relationships. The sensitivity of OTP responses to onset of GVS of increasing current strength was 0.74 deg/mA with fixation, and 0.48 deg/mA in darkness. The sensitivity of horizontal nystagmus to GVS onset in darkness was  $-0.94$  deg/s/mA, and that of torsional nystagmus (also in darkness) was 0.48 deg/s/mA.



**Fig. 3** Means (centre white symbols), 95% confidence intervals (shaded regions) and individual traces of the OTP, HSPV, VSPV and TSPV responses to GVS for five subjects in Experiment 1. The magnitude of the onset responses (deg for OTP, deg/s for H, V and T SPV) is plotted as a function of the strength of current delivered (mA), and the offset responses are plotted against the strength of the immediately preceding stimulus. The *upper half of the figure* shows responses obtained in the FIX OFF session, and the *lower half* shows the results obtained in the FIX ON session. In each plot, the responses to GVS onset are indicated by an *unbroken line*

(mean) and by the *heavier-shaded region* (confidence intervals), whereas the offset responses are indicated by *dotted lines* (mean) and by the *lighter-shaded region* (confidence intervals). The linearity of response magnitude with increasing current strength can clearly be seen, especially in the onset responses to GVS for OTP and TSPV in the presence of fixation, and for OTP, HSPV and TSPV in darkness. Note that the confidence intervals for OTP responses in the FIX ON condition are inflated by the results of one subject, who shows a particularly strong OTP response to GVS

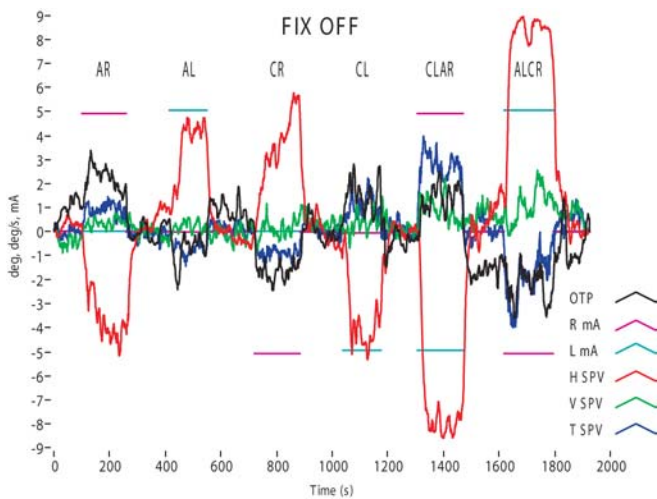
## Experiment 2: symmetry and additivity

Surface GVS onset produced characteristic eye-movement responses in all subjects, as described above (i.e. OTP change towards anode/away from the cathode; torsional and horizontal nystagmus, both with slow phases directed toward anode/away from cathode, and negligible VSPV responses). In general, the magnitudes of responses to unilateral stimulation were smaller than those for bilateral stimulation. A time series of raw eye-movement of a single subject's responses for the entire experiment is shown in Fig. 4; means and 95% confidence intervals for all subjects are shown in Fig. 5.

Ninety-five percent confidence intervals were calculated to determine whether responses in all conditions were significantly different to zero (see Fig. 5). Only VSPV responses were found to be not significantly different to zero (in all conditions); therefore, VSPV was not analysed further.

For OTP, HSPV and TSPV, responses to unilateral left anodal stimulation were not statistically significantly different to those for unilateral right cathodal stimulation (Fig. 5). Similarly, OTP, HSPV and TSPV responses to unilateral left cathodal stimulation were not statistically significantly different to those for unilateral right anodal stimulation (Fig. 5). OTP, HSPV and TSPV responses for the pairs (CL and AR; vs. AL and CR) were, however, significantly different (in direction, but not magnitude) to one another (Fig. 5).

Responses to bilateral stimulation were generally in the same direction but of different magnitude when compared to the responses recorded in separate conditions of unilateral stimulation of the same components of that bilateral stimulus. That is, CLAR responses were in the same direction but not of the same magnitude as either CL or AR (for HSPV and TSPV, but not OTP; Fig. 5). ALCR responses were in the same direction but not of the same magnitude as either CR or AL for all three measures (for

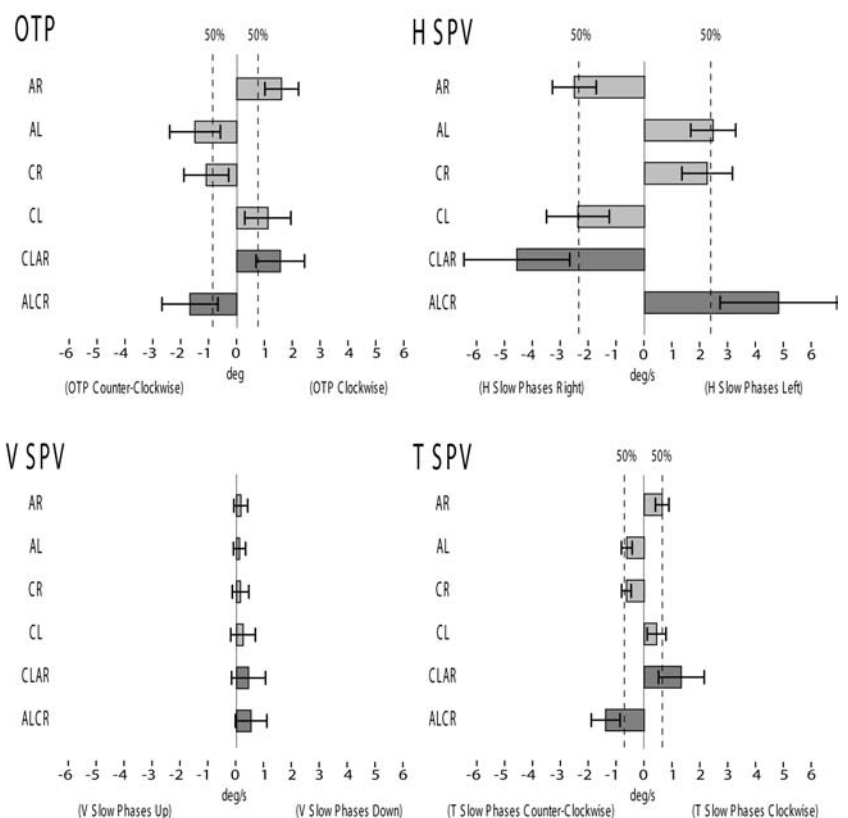


**Fig. 4** Time series of the raw 3D eye-movement traces for a single subject for the duration of Experiment 2. The strength and side of delivery of the stimulus are indicated on the plot by the *cyan* (left mastoid) or *magenta* (right mastoid) horizontal bars

HSPV and TSPV but not OTP, dumping; Fig. 5). The two bilateral stimulation conditions produced OTP, HSPV and TSPV responses that were different (in direction but not magnitude) to each other (Fig. 5).

In order to be able to conduct a repeated measures analysis of variance (ANOVA) to assess questions of additivity and symmetry, responses in half the conditions (AL, CR and ALCR for OTP and TSPV; CL AR, and

**Fig. 5** Means (*horizontal bars*) and 95% confidence intervals (*error bars*) of the OTP, HSPV, VSPV and TSPV responses to GVS for eight subjects in Experiment 2. Results (deg, deg/s) are plotted on the *abscissa*, as a function of condition (on the *ordinate*). Significant responses were observed in all conditions for OTP, HSPV and TSPV (but not VSPV) responses were not different to zero in any condition. Symmetry in the magnitude of OTP, HSPV and TSPV (but not VSPV) responses can be observed between the two mastoids receiving the stimulus, and between the two polarities of the stimulating current. It can also be seen that, generally, responses in the unilateral conditions are about half the magnitude (*dashed lines*) of responses in the bilateral conditions



CLAR for HSPV) were inverted, in order to compare the magnitudes of these responses, irrespective of their direction.

An ANOVA with repeated-measures contrasts was conducted with factors of laterality of stimulation, polarity of stimulation, and additivity of unilateral compared to bilateral stimulation. There was no difference in the magnitude of eye-movement response depending on the laterality (side) of stimulation for either OTP ( $F_{(1,7)}=0.07$ ,  $P=0.80$ ), HSPV ( $F_{(1,7)}=0.22$ ,  $P=0.65$ ) or TSPV ( $F_{(1,7)}=2.15$ ,  $P=0.19$ ). Similarly, there was no difference in the magnitude of eye-movement response depending on the polarity of stimulating current for either OTP ( $F_{(1,7)}=4.0$ ,  $P=0.09$ ), HSPV ( $F_{(1,7)}=1.42$ ,  $P=0.27$ ) or TSPV ( $F_{(1,7)}=1.04$ ,  $P=0.34$ ). Finally, the magnitudes of responses to bilateral stimulation were not significantly different to the sum of responses recorded in separate conditions of unilateral stimulation of the components of the bilateral stimulus for either OTP ( $F_{(1,7)}=0.22$ ,  $P=0.65$ ), HSPV ( $F_{(1,7)}=2.09$ ,  $P=0.19$ ) or TSPV ( $F_{(1,7)}=0.07$ ,  $P=0.80$ ).

## Discussion

The results of the present study show that unilateral surface GVS elicits systematic eye-movement responses that are similar in magnitude, whether stimulation is delivered to the left or right mastoid; and similar in magnitude, whether induced by anodal or cathodal

stimulation. Further, the magnitude of response to bilateral stimulation is similar to the sum of the magnitudes of responses from separate delivery of unilateral stimulation of the components of the bilateral stimulus. That is, responses to unilateral stimulation are symmetrical between stimulated sides (or mastoids), symmetrical between stimulating polarities, and additive (with respect to responses to bilateral stimulation).

In each subject, unilateral 5-mA cathodal stimulation of the left labyrinth produced horizontal slow-phase eye velocity to the right. Unilateral 5-mA anodal stimulation of the right labyrinth also produced slow-phase eye velocity to the right of comparable value. When these two separate unilateral stimuli were combined: bilateral 5-mA stimulation (cathode left, anode right), the bilateral stimulus produced horizontal slow-phase eye velocity to the right, the value of which was almost exactly the sum of the eye velocity produced by the two separate unilateral stimuli (see Fig. 5). We conclude that bilateral galvanic stimulation elicits responses, which are the sum of the effects of the two separate unilateral stimuli. That result has an interesting implication for the neural processing of bilateral, symmetrically opposite stimulation of the two labyrinths.

Commissural interaction in the horizontal canal system between the two vestibular nuclei has been well documented since its discovery by Shimazu and Precht (1966). In brief, the axons of some excitatory type I horizontal canal neurons cross the midline and project to and excite type II neurons in the contralateral vestibular nuclei. Type II neurons are inhibitory, projecting to and inhibiting some ipsilateral type I neurons (cf. also Nakao et al. 1982). The consequence is that horizontal canal stimulation on one side not only facilitates horizontal canal neurons in the ipsilateral vestibular nucleus, but also acts indirectly, to inhibit type I neurons on the contralateral side. It has been assumed that the effect of such functionally inhibitory commissural interaction is to enhance the sensitivity (gain) of second order horizontal canal neurons to natural stimulation (e.g. Galiana et al. 1984; see Curthoys and Halmagyi 1995 for a review). Some modellers (Orsmy 1974; Cannon and Robinson 1985) have assumed that there is simple additivity of input from the two sides and that the function of the commissures is simple addition. However, others (Galiana et al. 1984) have assumed that the commissures are not just additive, but are highly modifiable and function as multiplying elements so gains greater than 2 are possible.

The results here are in agreement with an assumption of enhancement but point strongly to that functional "enhancement" being simple addition. If there had been a gain enhancement greater than simple addition, then one would have expected that bilateral stimulation should have produced a slow-phase eye velocity significantly greater than the simple sum of the eye-velocity responses to each separate unilateral stimulus. That was not the result obtained. Our additive result points to the function of commissural inhibition being simple summation, as is

in fact assumed in Minor et al.'s (1999) recent model of bilateral interaction in the horizontal canal system. This observation justifies the use of a linear addition of input from the two sides for use in biologically based neural network models. This observation is also consistent with some of our own data (Markham et al. 1977), which showed additivity of input in the horizontal canal system at the physiological level but which could not give any indication of additivity or otherwise at the behavioural level.

The results of the present study also show that the onset of bilateral surface GVS produces reflexive eye-movement responses that show a linear relationship over conditions of increasing current strength, at least over the range up to 5 mA. The increase of OTP responses in conditions of fixation is about 0.75 deg/mA. In darkness, the increase of both OTP and torsional nystagmus is about 0.5 deg/s per mA, whereas the gain of horizontal nystagmus is almost 1 deg/s per mA. Responses to unilateral GVS would be expected to show linear relationships similar to those seen with bilateral stimulation but with half the gain, since responses to bilateral GVS are effectively the sum of responses to unilateral GVS. Our findings of linearity do not contradict those of other authors, who found non-linear relationships of responses to stimuli of much larger effective magnitudes. For instance, non-linearities in response to the angular accelerations in thousands of deg/s delivered during a head-impulse test (Halmagyi and Curthoys 1988) are so large that an asymmetry in the ability to increase and decrease spontaneous firing rates is caused by the limit at zero spikes/s (Ewald 1892). These asymmetries do not appear over the much smaller GVS stimuli used in the present study, equivalent to just a few deg/s of angular acceleration, which would not be expected to modulate firing rates beyond a linear range. The use of galvanic vestibular stimuli of much larger amplitude which can be delivered in animal studies may also lead to asymmetries in responses by selectively silencing irregular afferents (Minor and Goldberg 1991).

In the present study, responses to GVS offset were not found to show a statistically significant linear relationship. This is in contrast to the findings of a statistically significant offset response in our recent study (MacDougall et al. 2002); however, the present results are most likely attributable to smaller amplitudes of offset responses with smaller stimuli (lower current amplitudes and unilateral delivery) and to comparatively short adaptation times. In our previous study (MacDougall et al. 2002) we showed that the decay of responses to GVS had time constants of up to 6 min. In the present study, we restricted each stimulation trial (in both experiments) to no longer than 2 min (both to ensure stability of pupil constriction over extended periods, and because of the demanding nature of the experimental design on subjects). Had each stimulation trial in the present study been of the order of 5–6 min, responses would have had time to adapt substantially, and we would expect that GVS offset responses in both present experiments would have shown

the substantial overshoot typically seen with longer durations of stimulation and higher current intensities.

In a previous study (MacDougall et al. 2002) we showed that temporal responses to surface GVS were systematic (i.e. responses tended to reach a peak soon after GVS onset and decayed to a maintained value; with the offset of GVS, responses reversed direction, reaching a peak offset response before returning to baseline levels by the end of the trial; OTP deviated towards anode/away from the cathode; both torsional and horizontal nystagmus appeared with slow phases directed toward anode/away from cathode, accompanied by negligible VSPV responses), and that, although there was considerable variability between subjects in the relative proportions of eye-movement response components, each subject consistently displayed the same idiosyncratic pattern of eye movement. We have previously suggested that individual differences in the morphology of the vestibular system are likely to entail individual differences in impedance through the vestibular labyrinth (affecting how the current delivered at the surface influences each endorgan), as well as differences in central compensation for peripheral geometry, resulting in various patterns of eye-movement response (MacDougall et al. 2002). The present study adds a number of principles (linearity, symmetry, additivity) to our knowledge of the metrics of eye-movement responses to GVS. Taken together, the principles derived from these two studies provide a solid foundation for modelling the normal response to surface GVS; and such a model should, consequently, be able to accurately predict the responses to surface GVS in patients with known types of vestibular dysfunction. This type of model of the action of GVS will be vital for interpreting what we expect to be even more complex 3D eye-movement responses in a pathologically diverse vestibular patient population.

**Acknowledgements** We gratefully acknowledge the support of NHMRC of Australia. Mr. H. MacDougall was supported by a Medical Research Scholarship provided by the Garnett Passe and Rodney Williams Memorial Foundation during the period of this study.

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