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Transmastoid galvanic stimulation does not affect the vergence-mediated gain increase of the human angular vestibulo-ocular reflex

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Abstract

Vergence is one of several viewing contexts that require an increase in the angular vestibulo-ocular reflex (aVOR) response. A previous monkey study found that the vergence-mediated gain (eye/head velocity) increase of the aVOR was attenuated by 64% when anodic currents, which preferentially lower the activity of irregularly firing vestibular afferents, were delivered to both labyrinths. We sought to determine if there was similar evidence implicating a role for irregular afferents in the vergence-mediated gain increase of the human aVOR. Our study is based upon analysis of the aVOR evoked by head rotations, delivered passively while subjects viewed a near (15cm) or far (124cm) target and applying galvanic vestibular stimulation (GVS) via surface electrodes. We tested 12 subjects during 2–3 sessions each. Vestibular stimuli consisted of passive whole-body rotations (sinusoids from 0.05 – 3Hz and 12 – 25°/s, and transients with peak ~15°, 50°/s, 500°/s²) and head-on-body impulses (peak ~30°, 150°/s, 3000°/s²). GVS was on for 10s every 20s. All polarity combinations were tested, with emphasis on uni- and bi-lateral anodic inhibition. The average stimulus current was 5.9 ± 1.6 mA (range: 3 – 9.5 mA), vergence angle (during near-viewing) was $22.6 \pm 2.8^\circ$ and slow phase eye velocity caused by left anodic current stimulation with head stationary was $-3.4 \pm 1.1^\circ/\text{s}$, $-0.2 \pm 0.6^\circ/\text{s}$ and $2.5 \pm 1.4^\circ/\text{s}$ (torsion, vertical, horizontal). No statistically significant GVS effects were observed, suggesting that surface electrode GVS has no effect on the vergence-mediated gain increase of the aVOR at the current levels (~6 mA) tolerated by most humans. We conclude that clinically practical transmastoid GVS does not effectively silence irregular afferents and hypothesize that currents > 10mA are needed to reproduce the monkey results.

Keywords

Vestibulo-ocular reflex; vergence; transmastoid galvanic stimulation; irregular vestibular afferents

Introduction

The vestibulo-ocular reflex (VOR) stabilizes images on the retina by rotating the eyes at the same speed, but in the opposite direction of head motion. When viewing a far target, the gain of the horizontal angular VOR (aVOR), defined as the instantaneous angular eye velocity divided by inverted head velocity, is ~1, whereas when viewing a near target (<50

cm) the aVOR gain is >1 (Viirre et al., 1986; Snyder and King, 1992; Paige and Tomko, 1991). This vergence-mediated aVOR gain increase compensates for the translation of the eyes with respect to the target during the head rotation and changes with target distance (for example, at 15cm the aVOR gain is ~ 1.3). Vergence is one of several viewing contexts requiring aVOR gain increase or adaptation. Models of the aVOR in the alert monkey suggest the existence of a highly modifiable, phasic component of the reflex. This phasic component is probably mediated by irregularly discharging vestibular afferents (because regularly discharging afferents have relatively tonic response dynamics between 2–20Hz) (Hullar and Minor, 1999). This phasic component appears to be highly adaptable and has a short latency. It appears to be responsible for most of the increase in gain that occurs for contexts such as lens magnification (Minor et al., 1999; Clendaniel et al., 2001) and, thus, could be responsible for the vergence-mediated aVOR gain increase. A model of the aVOR, which included both tonic/linear and phasic/non-linear components, predicted that vergence-mediated increases of the aVOR gain would most likely be eliminated by removal of the phasic component (Lasker et al., 2002).

Galvanic vestibular stimulation (GVS) delivered via an electrode in perilymph with respect to a reference in the middle ear acts on the post-synaptic spike trigger zone of the primary vestibular neurons (Goldberg et al., 1984). Cathodic currents increase and anodic currents decrease neuronal activity (Goldberg et al., 1984). Irregularly firing neurons are more sensitive to galvanic inhibition than are regularly firing neurons, which are only slightly modulated even by large stimulus currents (Ezure et al., 1983; Goldberg, 1984; Goldberg et al., 2000). While direct measurement of vestibular nerve activity in human subjects during transmastoid application of galvanic currents is not feasible, ample evidence demonstrates that transmastoid galvanic currents can stimulate the vestibular system in humans, including patients treated with intratympanic gentamicin (de Waele et al., 2002; Aw et al., 2006). Such galvanic stimulation can induce nystagmus, tonic ocular torsion, tilt of subjective visual vertical and postural shifts (Breson et al., 1971; Quarck et al., 1998; Kleine et al., 1999; Watson et al., 1998; Zink et al., 1998; Magnusson et al., 1990; Day et al., 1997; MacDougall et al., 2002, 2003). Depending on the electrode polarities, transmastoid galvanic stimulation can also produce an asymmetry in the aVOR gain during low frequency (<0.5 Hz) head rotations (Karlberg et al., 2000).

In the vestibular nuclei, sensitivities of position-vestibular-pause and eye-head-velocity neurons to head movement increase during near viewing (McConville et al., 1996). It has been suggested that irregular vestibular nerve afferents modify the gain and phase of the vestibular response of these secondary vestibular neurons (Chen-Huang et al., 1997). In support of this hypothesis, the vergence-mediated gain increase of the aVOR is reduced by $\sim 64\%$ during galvanic inhibition of irregular vestibular afferent activity in the monkey (Chen-Huang and McCrea, 1998). Chen-Huang et al. (1997) showed that irregular afferent inputs to secondary vestibular neurons are primarily ipsilateral. Thus, the effect of a reduction in irregular afferent inputs on one side would be most pronounced for rotations towards that side and during near-viewing.

We sought to determine if there is similar evidence implicating a role for irregular afferents in the vergence-mediated gain increase in the human aVOR. Our study is based upon analysis of the aVOR evoked by horizontal head rotations, delivered passively while subjects viewed a near or far target during GVS via surface electrodes. Head rotational stimuli consisted of sinusoids (0.05 – 3 Hz, 12–25°/s) and transients (peak 15–30°, 50–150°/s and 500–3000°/s²).

Methods

Subjects

We studied 12 normal subjects (mean age 32 years, range 23–53 years) during 2 – 3 sessions each. None of these subjects had a history or clinical signs of vestibular disease.

Participation in this study was voluntary, and informed consent was obtained as approved by the Johns Hopkins School of Medicine Institutional Review Board.

Recording System

The movements of both eyes were recorded in three dimensions using dual axis scleral search coils embedded in a silicon annulus. The system, setup and technique have been described in detail elsewhere (Straumann et al., 1995; Migliaccio et al., 2004). A search coil embedded in a bite block was used to measure head rotation. Chair, eye and head angular position signals were filtered with a single-pole, low-pass analog filter that had a 3-dB bandwidth of 100 Hz. They were then sampled at 500Hz at 16-bit resolution and digitally filtered with a 50-tap zero-phase low pass finite impulse response filter with a bandwidth of 50 Hz.

Each subject was tested while seated upright with the head centered within a uniform magnetic field with the interpupillary line and each Frankfort line (from the top of the external acoustic meatus to the infraorbital foramen) in the Earth-horizontal plane. The magnetic frame was a 102 cm cube. There was a 10 cm³ region of linearity at the center of this cube within which there was no effect of translation of the search coil on its orientation within the magnetic field. The chair and magnetic field system were coupled and could rotate together about an Earth-vertical axis.

Experimental Protocol

Using electrode paste (Redux Crème, Hewlett-Packard) and adhesive tape 600–900mm² surface electrodes were placed over each mastoid and on the dorsal neck over C7 vertebra. Galvanic stimuli were delivered using an optically isolated, current-limited current source with electrical ground fault isolation (A-M Systems 2100).

All head rotations were in the Earth horizontal plane only (see conditions A–E below).

- A. HEAD IMPULSE (TRANSIENT):** Passive, manual, low-amplitude, high-velocity ($\sim 150^\circ/\text{s}$), high-acceleration ($\sim 3000^\circ/\text{s}^2$), head-on-trunk rotations.
- B. WHOLE-BODY IMPULSE (TRANSIENT):** Passive, manual, low-amplitude, low-velocity ($\sim 50^\circ/\text{s}$), low-acceleration ($\sim 500^\circ/\text{s}^2$), whole-body rotations.
- C. MID-FREQUENCY, LOW-VELOCITY (SINUSOIDS):** Whole-body chair rotations at 1.5Hz ($9.4^\circ/\text{s}$ and $18.8^\circ/\text{s}$), 2.2Hz ($9.4^\circ/\text{s}$) and 3Hz ($9.4^\circ/\text{s}$).
- D. LOW-FREQUENCY, LOW-VELOCITY (SINUSOIDS):** Whole-body chair rotations at 0.05Hz ($11.9^\circ/\text{s}$), 0.08Hz ($19.1^\circ/\text{s}$), 0.1Hz ($23.9^\circ/\text{s}$), 0.2Hz ($23.9^\circ/\text{s}$), 0.5Hz ($25.1^\circ/\text{s}$) and 1Hz ($25.1^\circ/\text{s}$).
- E. STATIONARY:** The subject's head was held fixed during galvanic pulse DC trains.

During whole-body rotations the subject's head was held fixed in position using a custom molded bite block attached to a bar rigidly fixed to the chair and coils system. During each trial the subject was instructed to visually fixate either a far (124cm) or near (15cm) Earth-

fixed LED (Light Emitting Diode) target positioned straight-ahead. Apart from the LED, subjects were tested in complete darkness.

For conditions A–C the LED target was always on. For conditions D–E, we sought to reduce the contribution of smooth pursuit while maintaining constant vergence, so the subject was instructed to fixate a periodically flashing LED target (1s on, 5s off).

For conditions A–C the galvanic DC stimulus was on/off every 10s, for condition D it was on/off every T sec (where T is the period of the sinusoidal stimulus waveform) and for condition E it was on for 100ms and off for 900ms at 1 Hz for 100 seconds.

For condition A the electrode polarities were: AL (anode left and cathode C7), AR (anode right and cathode C7), CL (cathode left and anode C7), CR (cathode right and anode C7), CLAR (cathode left and anode right), CRAL (cathode right and anode left), AB (anode bilateral and cathode C7) and CB (cathode bilateral and anode C7). For conditions B–D, only the AB electrode polarity was applied, as per Chen-Huang and McCrea (1998). For condition E, the CLAR and CRAL polarities were applied, as per Aw et al. (2006).

Data Analysis

Eye and head angular positions were represented by rotation vectors with roll (positive – right ear downward), pitch (positive – nose downward), and yaw (positive – nose towards left) coordinates (Haslwanter, 1995; Migliaccio and Todd, 1999). The orientation of each eye relative to the head was also represented using rotation vectors. The velocity vectors of head-in-space, eye-in-space, and eye-in-head were calculated from the corresponding rotation vectors (Hepp, 1990). Head velocity was calculated with reference to a head-fixed coordinate frame using the methods of Aw et al. (1996), so that eye and head velocities were expressed with reference to exactly the same coordinate frame.

Transient stimuli analysis—The onset of each head impulse was calculated by fitting a polynomial curve to the head-in-space velocity vector's magnitude versus time (Migliaccio et al., 2004). The point where the magnitude of the fitted curve was greater than 2% of the curve's peak magnitude (typically this threshold was 4°/s) was defined as the time of onset. As the time between impulse onset and maximum impulse velocity was <150 ms, the analysis of the impulse data was restricted to a period of 150 ms from the onset. This meant that the effects of non-vestibular systems such as smooth pursuit, optokinetic and predictive oculomotor systems were minimized because these generally have longer latencies than the aVOR (Halmagyi et al., 1990; Carl and Gellman, 1987; Tychsen and Lisberger, 1986). The horizontal aVOR gain was calculated by dividing inverted eye velocity by head velocity during the 30 ms period prior to peak head velocity (Migliaccio et al., 2004). The aVOR latency was calculated by fitting (with a least squares algorithm) a line to the eye velocity traces and a line to the head velocity traces (during the acceleration phase of the eye movement, typically ~50–100 ms after the stimulus onset). The latency was defined as the difference in time where these lines intersected with the zero velocity baseline (Migliaccio et al., 2004).

Sinusoidal stimuli analysis—Quick phases were removed from each trace and cycles were overlaid and averaged (10–20 cycles for stimuli >0.05 Hz, 3–5 cycles for lower frequencies) on a point-by-point basis. Quick phases occurring at stimulus frequencies >2Hz were infrequent but distorted most of a cycle, so affected cycles were excluded from the analysis. Gain was defined as the amplitude of the least-squares best-fit sinusoidal eye velocity response divided by the similarly fitted head velocity stimulus. Gain and phase were expressed with the convention that unity gain and zero phase imply a perfectly compensatory aVOR, and positive phase implies that eye movements lead head movements.

The vestibular evoked eye movement response to pulsed galvanic stimulation while the head was kept stationary was measured by removing traces with artifacts, e.g., blinks and saccades, and overlaying the responses, as per Aw et al. (2006), i.e., using the output triggers from the galvanic stimulator. The peak values of the three components of eye velocity during pulsed DC galvanic stimulation but immediately prior to the first quick-phase were manually extracted.

In order to ensure that subjects were verging on the near target, vergence angles were determined at the start of each experiment. The average vergence angles as determined from the scleral coil data during near- and far-viewing were $22.6 \pm 2.8^\circ$ and $2.9 \pm 0.2^\circ$, respectively. The average fixation distance as determined from the vergence angles and inter-pupillary distances measured for each subject during near- and far-viewing were 16.0 ± 2.2 cm and 124.7 ± 7.9 cm, respectively, which agreed well with the directly measured target distances of 15 and 124 cm.

Statistical analysis

We used four separate ANOVAs (multi-way analysis of variance) with two-factor interactions to analyse the: head impulse (condition A), whole-body impulse (B), sinusoidal (C–D) and pulse train (E) data (Diggle et al., 1994). Each dependent factor was analysed using a separate ANOVA. For the head impulse data ANOVA the independent variables included: *eye* ('left', 'right'), head rotation *direction* ('left', 'right'), target *distance* ('far', 'near'), *galvanic* stimulation ('off', 'on') and electrode *polarity* (AL, AR, CL, CR, AB, CB, CRAL, CLAR). For the ANOVA on whole-body impulse data the electrode *polarity* variable was removed. The dependent variables were gain and latency. For the ANOVA on sinusoidal data, two variables were added, stimulus *frequency* (0.05, 0.08, 0.1, 0.2, 0.5, 1, 1.5, 2.2 and 3 Hz) and *velocity* (9.4, 9.5, 11.9, 18.8, 19.1, 23.9 and 25.1°/s), and one variable was removed, electrode *polarity*. The dependent variables were sinusoidal gain and phase. For the ANOVA on pulse train data three variables were added, galvanic eye velocity components (horizontal, vertical and torsional), and two variables were removed, head rotation *direction* and electrode *polarity*. The dependent variable was slow-phase eye velocity. All variables were included in the ANOVA initially, and those found insignificant were subsequently removed. All the interaction effects found to be significant are included in the results. Pooled data are described as mean $\pm$ 1 SD, whereas pooled means are described as mean $\pm$ 1 SE.

A power analysis reveals that a difference of 7% in near-viewing horizontal aVOR gain (galvanic stimulation off versus on) should be detectable with probability >80% (one-tail, $\alpha=0.05$; parameters: mean aVOR gain=1.19, SD=0.12, $n=12$). Similarly, a difference of 5% in far-viewing horizontal aVOR gain should be detectable with probability >80% (one-tail, $\alpha=0.05$; parameters: mean aVOR gain=0.91, SD=0.07, $n=12$). A difference of 17% in aVOR latency should be detectable with probability >80% (one-tail, $\alpha=0.05$; parameters: mean aVOR latency=7.8ms, SD=1.8ms, $n=12$).

Results

The DC galvanic stimulus ranged from 3 – 9.5mA and depended on individual tolerance levels. The average current stimulus was 5.9 ± 1.6 mA. As a stimulation control for each subject, we measured slow phase eye velocity during AL (anode left and cathode C7) current stimulation with the head-fixed and the subject in complete darkness. The mean slow phase velocity was: $-3.4 \pm 1.1^\circ/\text{s}$, $-0.2 \pm 0.6^\circ/\text{s}$ and $2.5 \pm 1.4^\circ/\text{s}$ (torsion, vertical and horizontal).

A - High-acceleration transient head impulses (head-on-trunk)

The data show that the aVOR gain increased upon near viewing and that this increase was unaffected by galvanic stimulation. There was no anode-cathode configuration that had a significant effect on the horizontal aVOR gains (Figure 1).

A multi-way ANOVA analysis showed that target distance was the only parameter to affect the horizontal aVOR gain ($P < 0.001$). Across all conditions, the mean aVOR gain was 0.91 ± 0.07 during far viewing and 1.19 ± 0.12 during near viewing, an increase of ~31%. The mean latency, which was unaffected by all factors, was 7.8 ± 1.8 ms. There was a significant interaction between head rotation 'direction' and 'eye', during far-viewing ($P < 0.005$) and near-viewing ($P < 0.001$). The eye rotating nasally (adducting) during the head rotation had a 5–15% larger aVOR gain than the eye rotating temporally (abducting). In one subject (verging 41° , galvanic stimulation 9.5mA) there was a significant decrease in the near-viewing aVOR gain (galvanic stimulation off versus on) for head rotations towards the side with anodic stimulation (ANOVA, target = 'near', interaction between 'direction' and 'polarity', $P < 0.05$). In three other subjects, there was a similar trend, but it was not statistically significant ($P = 0.08$, $P = 0.10$, $P = 0.09$). It is interesting to note that these subjects were the only other ones tested with galvanic stimulation > 7.5 mA.

B - Low-acceleration transient head impulses (whole-body)

For this test condition the electrode configuration was AB (anode bilateral and cathode C7) only. The mean horizontal slow phase eye velocity during AB current stimulation with the head-fixed and the subject in complete darkness was $< 0.1^\circ/\text{s}$. This minimal nystagmus was probably due to nearly, but not exactly, symmetric cancelation of the inhibitory signals coming from both horizontal canals.

Figure 2A shows the typical aVOR response during whole-body impulses during far and near viewing, with and without galvanic stimulation. There was an increase in aVOR gain during near viewing; however, the magnitude of this increase was not affected by galvanic stimulation.

A multi-way ANOVA analysis showed that target distance was the only factor that significantly affected the aVOR gain ($P < 0.001$). The mean aVOR gain was 1.10 ± 0.01 during far viewing and 1.32 ± 0.04 during near viewing, an increase of ~20% (see Figure 2B). The mean latency, which was unaffected by all factors, was 6.8 ± 3.3 ms.

C - Mid-frequency, low-velocity sinusoids (whole-body)

During these whole-body sinusoidal rotations only AB stimulation was used. Figure 3 shows the gains and phases of the aVOR during these mid-frequency sinusoidal rotations during far (left column) and near (right column) viewing, with and without galvanic stimulation. There was an increase in aVOR gain during near viewing; however, the magnitude of this increase was not affected by galvanic stimulation. Similarly, the aVOR phase lead increased during near viewing, but was not affected by galvanic stimulation.

A multi-way ANOVA analysis showed that the aVOR gain was only affected by target distance ($P < 0.001$). The mean aVOR gain was 0.86 ± 0.03 during far viewing and 0.99 ± 0.04 during near viewing, an increase of ~15% (see Figure 3, top row). The aVOR phase was affected by both the target distance ($P < 0.01$) and sinusoidal stimulus frequency ($P < 0.05$). In addition, there was a significant interaction between these two factors (ANOVA: 'distance'*'frequency', $P < 0.05$) because the phase lead increased at higher frequencies, especially during near viewing (see Figure 3, bottom row).

D - Low-frequency, low-velocity sinusoids (whole-body)

During these whole-body sinusoidal rotations only AB stimulation was used. Figure 4A shows the typical aVOR response in one subject during 0.05 Hz whole-body rotations while viewing a near target. Although the near target LED is off for 83% of the time (5/6s), the sinusoidal eye velocity response (gray trace) does not vary in amplitude during the rotational stimulus.

Figure 4B shows the gains and phases of the aVOR during low-frequency sinusoidal rotations during far (left column) and near (right column) viewing, with and without galvanic stimulation. There was an increase in aVOR gain during near viewing; however, the magnitude of this increase was not affected by galvanic stimulation. Similarly, the aVOR phase lead increased during near viewing, but was not affected by galvanic stimulation. A multi-way ANOVA analysis showed that the aVOR gain was affected by both the target distance ($P < 0.001$) and sinusoidal stimulus frequency ($P < 0.01$). In addition, there was a significant interaction between these two factors (ANOVA: 'distance'*'frequency', $P < 0.05$) because the gain decreased at higher frequencies, especially during near viewing (see Figure 4B, bottom row). The mean aVOR gain was 0.90 ± 0.06 during far viewing and 1.13 ± 0.06 during near viewing, an increase of ~25% (see Figure 4B, top row). The aVOR phase lead increased during near viewing ($P < 0.001$), but decreased with increasing sinusoidal stimulus frequency ($P < 0.001$) (see Figure 4B, bottom row).

E – Pulse train galvanic stimulation (head stationary in space)

During these head stationary, pulsed DC, galvanic stimuli only CRAL (Cathode Right and Anode Left Mastoid) or CLAR (Cathode Left and Anode Right Mastoid) electrode configurations were used. Figure 5 shows the three components of eye velocity (torsional, vertical and horizontal) during the four test conditions ([CLAR, CRAL] $\times$ [FAR, NEAR]).

A multi-way ANOVA analysis showed that the electrode configuration affected torsional (ANOVA: 'polarity' variable, $P < 0.001$) and horizontal ($P < 0.001$) eye velocity. During CLAR, torsional eye velocity was positive (clockwise from subject's perspective) and horizontal eye velocity was negative (rightward), whereas during CRAL, the torsional and horizontal eye velocities were negative and positive, respectively. For torsional eye velocity there was a close to significant interaction between electrode polarity and target distance (ANOVA: 'polarity'*'distance', $P = 0.08$) because during near viewing the torsional eye velocity magnitude tended to be smaller (see Figure 5).

Discussion

GVS elicits vestibular-evoked eye movements and activity (either excitatory or inhibitory) in muscles involved with balance, e.g., GVS reliably induces short and medium latency vestibulospinal reflexes in the soleus electromyogram (EMG) of standing subjects (e.g., Watson and Colebatch 1997 e.g., Watson and Colebatch 1998; Fitzpatrick et al., 1994). These EMG responses are seen only when the muscle is engaged in a balance task, i.e., presumably there is a task-dependent gating of descending vestibulospinal influences (Fitzpatrick, 2004). The response is distributed in proportion to the load borne by each muscle and relatively small changes can heavily influence the result (Day et al., 1997). A previous human study showed that anodic inhibition using externally applied GVS did not suppress the vestibulospinal reflex response of the soleus muscle (Bacsi and Colebatch, 2003). The authors concluded that externally applied anodic inhibition did not sufficiently silence the firing of irregular vestibular afferents. Our results confirm their finding; however our method was different. First, we examined the effect of GVS on the aVOR because: a) there is evidence suggesting that irregular afferents, those most sensitive to GVS, play a

particularly important role in the human vergence-mediated gain increase of the aVOR (Migliaccio et al., 2004, 2008), and b) we wanted to reproduce in humans the Chen-Huang and McCrea (1998) study, which stimulated the vestibular organs using two different types of stimuli simultaneously, i.e., GVS for the tonic component and head rotation for the phasic component. This is in contrast to Bacsí and Colebatch (2003) who used GVS for both the tonic (0, 2, 4, 6, 8mA) and phasic (4mA) components. The limitation of this latter approach is that it restricts the vestibular stimulus to a small range and magnitude, e.g., at 4mA the slow-phase eye velocity is only 1–2 deg/s. The effects observed by Chen-Huang and McCrea (1998) were during (rotational) vestibular stimuli that were 1–2 orders of magnitude larger. Using the aVOR allowed us to examine the effect of galvanic inhibition over the complete physiologically relevant dynamic range of the vestibular system. The second key difference is that Bacsí and Colebatch (2003) provided tonic GVS (which increased between trials) that was continually delivered for 10–15 min, which could have resulted in adaptation in some of their subjects (the authors controlled for adaptation in 2/9 subjects). In our study, GVS was on for at most 20 sec (i.e., during the 0.05 Hz chair rotations), but typically 10 sec.

We investigated the effect of transmastoid GVS (3–9.5mA) on the vergence-mediated gain increase of the human aVOR across a large range of head rotation frequencies (DC, 0.05 – 5Hz; high acceleration head impulse has a dominant frequency component at ~5Hz) and velocities (12 – 150°/s). Based on the results of Chen-Huang and McCrea (1998), we expected a reduction in the vergence-mediated gain increase of the human aVOR using transmastoid GVS, especially for high-frequency head rotations, which should activate the most galvanically-sensitive irregular vestibular afferents. We found that during head-on-trunk head impulses there was a small change in the near-viewing aVOR gain due to GVS in subjects who could tolerate currents > 7.5mA. Also, during galvanic pulse train stimulation with a near target, there was a trend towards a reduction in the torsional eye velocity magnitude due to GVS. Apart from these instances in which results approached but did not reach statistical significance, no other galvanic effects were observed. This suggests that surface electrode GVS at levels (~6 mA) limited by human subject comfort has no measurable effect on the vergence-mediated gain increase of the aVOR. There are two possible explanations for this result.

First, irregular afferents may not play a significant role in modulating the vergence-mediated aVOR gain increase. However, this conclusion would run contrary to previous findings in animal and human studies and would not be consistent with data from this study. For example, we found that during sinusoidal stimulation aVOR phase lead increases for near-viewing (see Figure 3, lower row). In addition, especially during near viewing, this phase lead increases with frequency, i.e., head acceleration (see Figure 3, bottom right panel). Such increasing phase leads with increasing frequency correspond better to the physiology of mammalian irregular afferents than that of regular afferents, and irregular units have transfer functions suggesting sensitivity and phase shifts better aligned with head acceleration than velocity (Hullar et al., 2005). Thus, our present human data are consistent with previous findings showing that: a) irregular afferents are most sensitive to head acceleration, and b) irregular afferents modify the gain and phase of the vestibular response of secondary vestibular neurons as appropriate during viewing conditions such as vergence.

A second more likely explanation is that tolerable levels of human transmastoid GVS cause insufficient current to reach the vestibular nerve to elicit effects that have been achieved in animal studies using electrodes implanted directly in perilymphatic spaces. The largest slow-phase horizontal nystagmus we measured was ~9°/s at 9.5mA (using our surface electrodes). In the monkey, ~30μA delivered via a stimulating electrode in the perilymphatic space of the vestibule results in similar nystagmus and reduces the baseline firing rate of irregular

afferents by ~70 spikes/s, which is sufficient to silence most irregular afferents (Chen-Huang et al., 1997). A similar calculation using human data was performed by Schneider et al. (2002), who estimated that 1 mA external GVS would reduce the firing rate of regular vestibular afferents by only 1 spike/s. Assuming that the sensitivity of irregular vestibular afferents is 6 times greater than that of regular afferents (Goldberg et al., 1984), then 1 mA would reduce their firing rate by 6 spikes/s (Bacsi and Colebatch, 2003). Assuming a linear relationship, 9.5 mA would correspond to a decrease of ~57 spikes/s. Most of our subjects, however, were not comfortable at current levels > 6mA, resulting in typical horizontal slow-phase eye velocities of only 2–3°/s. It's likely that in these subjects the baseline irregular afferent firing rate was only reduced by 20–35 spikes/s (i.e., $[2.5 \text{ mA}/9 \text{ mA}] * 70 \text{ spikes/s} - 5.9 \text{ mA} * 6 \text{ spike/s}$). This reduction is probably insufficient to silence irregular afferents in humans enough to elicit the effects we sought to observe. Bacsi and Colebatch (2003) reached the same conclusion in their study examining anodic inhibition on galvanic-evoked vestibulospinal reflexes. Transmastoid current delivery limits the effective current that can be delivered to the inner ear. For example, Kim and Curthoys (2004) reported a 10 fold decrease in current efficacy comparing surface versus implanted galvanic stimulation in the guinea pig. It is likely that there is a significantly larger decrease in the effective current reaching the labyrinth from transmastoid GVS in humans given the much greater intervening tissue volumes involved, i.e., the current should scale geometrically. It appears that 6–10 mA is the upper limit of current deliverable by surface electrodes in humans because above these levels the stimuli become painful, and there is a real danger, even with very large surface area electrodes (limited to the post auricular area for each ear), of skin burn.

Galvanic stimulation had minimal to no effect on the vergence-mediated gain increase across *all* the frequencies tested. We employed a large number of electrode configurations to test various predictions. For example, if galvanic stimulation was affecting the resting firing rate of irregular afferents, then we might have expected the aVOR gain to decrease during rotations towards the anode and increase for rotations towards the cathode. Perhaps during transient head rotations the vestibular signal carried by the irregular afferents was so large that any change in the afferent firing rate due to galvanic stimulation had a comparatively negligible impact on the aVOR. However, this contrasts a study by Chen-Huang and McCrea (1998) in which they elicited a robust reduction in the vergence-mediated gain increase due to bilateral anodic galvanic inhibition during rotational stimuli with accelerations similar to ours (acceleration steps 200–400°/s²). In our study, even during low-frequency, low-velocity (i.e., low-acceleration) sinusoidal head rotations, where one might expect modulation of the irregular afferent signal to be small, there was no noticeable reduction in aVOR gain, while near-viewing, due to bilateral anodic galvanic inhibition.

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References

- Aw ST, Haslwanter T, Halmagyi GM, Curthoys IS, Yavor RA, Todd MJ. Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations. I. Responses in normal subjects. *J Neurophysiol.* 1996; 76:4009–20. [PubMed: 8985896]
- Aw ST, Todd MJ, Halmagyi GM. Latency and initiation of the human vestibuloocular reflex to pulsed galvanic stimulation. *J Neurophysiol.* 2006; 96:925–30. [PubMed: 16641374]
- Bacsi AM, Colebatch JG. Anodal vestibular stimulation does not suppress vestibular reflexes in human subjects. *Exp Brain Res.* 2003; 150:525–8. [PubMed: 12739094]

- Breson K, Elberling C, Fangel J. Galvanic nystagmography. *Acta Otolaryngol.* 1971; 71:449–55. [PubMed: 5314904]
- Carl JR, Gellman RS. Human smooth pursuit: Stimulus-dependent responses. *J Neurophysiol.* 1987; 57:1446–1463. [PubMed: 3585475]
- Chen-Huang C, McCrea RA, Goldberg JM. Contributions of regularly and irregularly discharging vestibular-nerve inputs to the discharge of central vestibular neurons in the alert squirrel monkey. *Exp Brain Res.* 1997; 114:405–22. [PubMed: 9187277]
- Chen-Huang C, McCrea RA. Contribution of vestibular nerve irregular afferents to viewing distance-related changes in the vestibulo-ocular reflex. *Exp Brain Res.* 1998; 119:116–30. [PubMed: 9521542]
- Clendaniel RA, Lasker DM, Minor LB. Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. IV. Responses after spectacle-induced adaptation. *J Neurophysiol.* 2001; 86:1594–611. [PubMed: 11600623]
- Day BL, Séverac Cauquil A, Bartolomei L, Pastor MA, Lyon IN. Human body-segment tilts induced by galvanic stimulation: a vestibularly driven balance protection mechanism. *J Physiol.* 1997; 500:661–72. [PubMed: 9161984]
- De Waele C, Meguenni R, Freyss G, Zamith F, Bellalimat N, Vidal PP, Tran Ba Huy P. Intratympanic gentamicin injections for Meniere disease: vestibular hair cell impairment and regeneration. *Neurology.* 2002; 59:1442–4. [PubMed: 12427902]
- Diggle, PJ.; Liang, KY.; Zeger, SL. *Analysis of Longitudinal Data.* New York: Oxford University Press; 1994.
- Ezure K, Cohen MS, Wilson VJ. Response of cat semicircular canal afferents to sinusoidal polarizing currents: implications for input-output properties of second-order neurons. *J Neurophysiol.* 1983; 49:639–648. [PubMed: 6834091]
- Fitzpatrick R, Burke D, Gandevia SC. Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *J Physiol.* 1994; 478:363–72. [PubMed: 7965852]
- Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. *J Appl Physiol.* 2004; 96:2301–16. [PubMed: 15133017]
- Goldberg JM, Smith CE, Fernandez C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J Neurophysiol.* 1984; 51:1236–56. [PubMed: 6737029]
- Goldberg JM. Afferent diversity and the organization of central vestibular pathways. *Exp Brain Res.* 2000; 130:277–297. [PubMed: 10706428]
- Halmagyi GM, Curthoys IS, Cremer PD, Henderson CJ, Todd MJ, Staples MJ, D'Cruz DM. The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation before and after unilateral vestibular neurectomy. *Exp Brain Res.* 1990; 81:479–490. [PubMed: 2226683]
- Haslwanter T. Mathematics of three-dimensional eye rotations. *Vis Res.* 1995; 35:1727–1739. [PubMed: 7660581]
- Hepp K. On Listing's law. *Commun Math Phys.* 1990; 132:285–295.
- Hullar TE, Minor LB. High-frequency dynamics of regularly discharging canal afferents provide a linear signal for angular vestibuloocular reflexes. *J Neurophysiol.* 1999; 82:2000–5. [PubMed: 10515990]
- Hullar TE, Della Santina CC, Hirvonen T, Lasker DM, Carey JP, Minor LB. Responses of irregularly discharging chinchilla semicircular canal vestibular-nerve afferents during high-frequency head rotations. *J Neurophysiol.* 2005; 93:2777–86. [PubMed: 15601735]
- Goldberg JM, Smith CE, Fernandez C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J Neurophysiol.* 1984; 51:1236–1256. [PubMed: 6737029]
- Karlberg M, McGarvie L, Magnusson M, Aw ST, Halmagyi GM. The effects of galvanic stimulation on the human vestibulo-ocular reflex. *Neuroreport.* 2000; 11:3897–901. [PubMed: 11117511]
- Kim J, Curthoys IS. Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetised guinea pig. *Brain Res Bull.* 2004; 64:265–71. [PubMed: 15464864]

- Kleine JF, Guldin WO, Clarke AH. Variable otolith contribution to the galvanically induced vestibulo-ocular reflex. *Neuroreport*. 1999; 10:1143–8. [PubMed: 10321499]
- Lasker DM, Ramat S, Carey JP, Minor LB. Vergence-mediated modulation of the human horizontal angular VOR provides evidence of pathway-specific changes in VOR dynamics. *Ann N Y Acad Sci*. 2002; 956:324–37. [PubMed: 11960816]
- MacDougall HG, Brizuela AE, Curthoys IS. Linearity, symmetry and additivity of the human eye-movement response to maintained unilateral and bilateral surface galvanic (DC) vestibular stimulation. *Exp Brain Res*. 2003; 148:166–75. [PubMed: 12520404]
- MacDougall HG, Brizuela AE, Burgess AM, Curthoys IS. Between-subject variability and within-subject reliability of the human eye-movement response to bilateral galvanic (DC) vestibular stimulation. *Exp Brain Res*. 2002; 144:69–78. [PubMed: 11976760]
- Magnusson M, Johansson R, Wiklund J. Galvanically induced body sway in the anterior-posterior plane. *Acta Otolaryngol*. 1990; 110:11–7. [PubMed: 2386025]
- McConville KM, Tomlinson RD, NAEQ. Behavior of eye-movement-related cells in the vestibular nuclei during combined rotational and translational stimuli. *J Neurophysiol*. 1996; 76:3136–48. [PubMed: 8930261]
- Migliaccio AA, Todd MJ. Real-time rotation vectors. *Australas Phys Eng Sci Med*. 1999; 22:73–80. [PubMed: 10474978]
- Migliaccio AA, Minor LB, Carey JP. Vergence-mediated modulation of the human horizontal vestibulo-ocular reflex is eliminated by a partial peripheral gentamicin lesion. *Exp Brain Res*. 2004; 159:92–8. [PubMed: 15221168]
- Migliaccio AA, Minor LB, Carey JP. Vergence-mediated modulation of the human angular vestibulo-ocular reflex is unaffected by canal plugging. *Exp Brain Res*. 2008; 186:581–7. [PubMed: 18188548]
- Minor LB. Intratympanic gentamicin for control of vertigo in Meniere's disease: vestibular signs that specify completion of therapy. *Am J Otol*. 1999; 20:209–19. [PubMed: 10100525]
- Paige GD, Tomko DL. Eye movement responses to linear head motion in the squirrel monkey. I. Basic characteristics. *J Neurophysiol*. 1991; 65:1170–82. [PubMed: 1869911]
- Schneider E, Glasauer S, Dieterich M. Comparison of human ocular torsion patterns during natural and galvanic vestibular stimulation. *J Neurophysiol*. 2002; 87:2064–2073. [PubMed: 11929924]
- Snyder LH, King WM. Effect of viewing distance and location of the axis of head rotation on the monkey's vestibuloocular reflex. I. Eye movement responses. *J Neurophysiol*. 1992; 67:861–74. [PubMed: 1588387]
- Straumann D, Zee DS, Solomon D, Lasker AG, Roberts DC. Transient torsion during and after saccades. *Vision Res*. 1995; 35:3321–34. [PubMed: 8560803]
- Tychsen L, Lisberger SG. Visual motion processing for the initiation of smooth-pursuit eye movements in humans. *J Neurophysiol*. 1986; 56:953–968. [PubMed: 3783238]
- Viirre E, Tweed D, Milner K, Vilis T. A reexamination of the gain of the vestibuloocular reflex. *J Neurophysiol*. 1986; 56:439–50. [PubMed: 3489820]
- Quarck G, Etard O, Normand H, Pottier M, Denise P. Low intensity galvanic vestibulo-ocular reflex in normal subjects. *Neurophysiol Clin*. 1998; 28:413–22. [PubMed: 9850951]
- Watson SRD, Colebatch JG. EMG responses in the soleus muscles evoked by unipolar galvanic vestibular activation. *Electroencephalogr Clin Neurophysiol*. 1997; 105:476–483. [PubMed: 9448650]
- Watson SRD, Colebatch JG. Vestibular-evoked EMG responses in soleus: a comparison between click and galvanic stimulation. *Exp Brain Res*. 1998; 119:504–510. [PubMed: 9588785]
- Watson SR, Brizuela AE, Curthoys IS, Colebatch JG, MacDougall HG, Halmagyi GM. Maintained ocular torsion produced by bilateral and unilateral galvanic (DC) vestibular stimulation in humans. *Exp Brain Res*. 1998; 122:453–8. [PubMed: 9827864]
- Zink R, Bucher SF, Weiss A, Brandt T, Dieterich M. Effects of galvanic vestibular stimulation on otolithic and semicircular canal eye movements and perceived vertical. *Electroencephalogr Clin Neurophysiol*. 1998; 107:200–5. [PubMed: 9803950]

Figure 1.

Shows the mean $\pm$ SD aVOR gain during FAR (124cm) and NEAR (15cm) viewing for all the electrode configurations (C7 denotes the cervical 7 vertebra) employed across all subjects ($n=12$). The vestibular stimulus consisted of horizontal (leftward or rightward) head impulses (transient head rotations with peak $\sim 30^\circ$, $150^\circ/\text{s}$, $3000^\circ/\text{s}^2$). The aVOR gain was calculated using the left (LE) and right (RE) eyes. The light gray and dark gray bars denote the aVOR gain when the galvanic stimulus is OFF and ON, respectively. Galvanic stimulation had no effect on the vergence-mediated gain increase of the aVOR for all the electrode configurations tested.

Figure 2.

(A) Shows the typical (raw data) responses from one subject during whole-body chair rotations (head fixed with respect to chair) during FAR (124cm) and NEAR (15cm) viewing, without (top row) and with (bottom row) 7 mA bilateral anodic galvanic inhibition (C7 denotes the cervical 7 vertebra). The vestibular stimulus consisted of horizontal (leftward or rightward) whole-body rotations with peak $\sim 15^\circ$, $50^\circ/\text{s}$, $500^\circ/\text{s}^2$. The black traces denote inverted head velocity and the gray solid and dashed traces denote the left and right eye velocities, respectively. The head velocity stimuli are similar for all 4 conditions. The aVOR gain (eye velocity response) increases upon near viewing, but does not appear to be affected by galvanic stimulation. (B) Shows the mean $\pm$ SD aVOR gain during FAR and NEAR viewing, during bilateral anodic galvanic inhibition, across all subjects. The aVOR gain was calculated using the left (LE) and right (RE) eyes. The light gray and dark gray bars denote the aVOR gain when the galvanic stimulus is OFF and ON, respectively. Galvanic stimulation had no effect on the vergence-mediated modulation of the aVOR.

Figure 3.

Shows the mean $\pm$ SD aVOR gain (top row) and phase (bottom row) during FAR (124cm) and NEAR (15cm) viewing, during bilateral anodic galvanic inhibition, across all subjects. The aVOR gain and phase was calculated using the left (LE) and right (RE) eyes. The light gray and dark gray bars denote the aVOR gain and phase when the galvanic stimulus is OFF and ON, respectively. The vestibular stimulus consisted of whole-body chair rotations (head fixed with respect to chair) at 1.5Hz (9.4°/s and 18.8°/s), 2.2Hz (9.4°/s) and 3Hz (9.4°/s). Galvanic stimulation had no effect on the aVOR gain and phase for all test conditions.

Figure 4.

(A) Shows the typical (raw data) responses from one subject during whole-body chair sinusoidal rotations (head fixed with respect to chair) at 0.05 Hz (25.1°/s) during NEAR (15cm) viewing, without and with 7 mA bilateral anodic galvanic inhibition. The black trace denotes inverted head velocity and the gray solid and dashed traces denote the left and right eye velocities, respectively. Although the near target LED is OFF for 83% of the time the sinusoidal eye velocity response does not vary in amplitude during the rotational stimulus.

(B) Shows the mean $\pm$ SD aVOR gain (top row) and phase (bottom row) during FAR (124cm) and NEAR (15cm) viewing, during bilateral anodic galvanic inhibition, across all subjects. The aVOR gain and phase was calculated using the left (LE) and right (RE) eyes. The light gray and dark gray bars denote the aVOR gain and phase when the galvanic stimulus is OFF and ON, respectively. The vestibular stimulus consisted of whole-body chair rotations at 0.05Hz (11.9°/s), 0.08Hz (19.1°/s), 0.1Hz (23.9°/s), 0.2Hz (23.9°/s), 0.5Hz

(25.1°/s) and 1Hz (25.1°/s). Galvanic stimulation had no effect on the aVOR gain and phase for all test conditions.

Figure 5.

Shows the peak values of the three components of eye velocity (torsional, vertical and horizontal) during pulsed galvanic stimulation (galvanic stimulus ON for 100ms and OFF for 900ms at 1 Hz for 100 seconds), but immediately prior to the first quick-phase. During this test the subject's head was held fixed. There were two electrode configurations, CLAR (Cathode left and Anode right mastoid; light gray bars) and CRAL (Cathode right and Anode left mastoid; dark gray bars), and two viewing conditions, FAR (124cm; solid bars) and NEAR (15cm; cross-hatched bars). The magnitude of torsional eye velocity was slightly reduced during near-viewing, however, this trend was not statistically significant. Pulsed galvanic stimulation had no effect on the aVOR for all test conditions.