Alexander’s Law and the Oculomotor Neural Integrator: Three-Dimensional Eye Velocity in Patients With an Acute Vestibular Asymmetry

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1Department of Otorhinolaryngology, Head and Neck Surgery, 2Department of Neurology, and 3Department of Ophthalmology, Zürich University Hospital; and 4Zürich Center for Integrative Human Physiology, University of Zürich, Zurich, Switzerland

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Bockisch CJ, Hegemann S. Alexander’s law and the oculomotor neural integrator: three-dimensional eye velocity in patients with an acute vestibular asymmetry. J Neurophysiol 100: 3105–3116, 2008. First published September 17, 2008; doi:10.1152/jn.90381.2008. According to Alexander’s law (AL), the slow phase velocity of nystagmus of vestibular origin is dependent on horizontal position, with lower velocity when gaze is directed in the slow compared with the fast phase direction. Adaptive changes in the velocity-to-position relationship are thought to cause AL. Although these changes have been described for the horizontal neural integrator, nystagmus often includes vertical and torsional components, but the adaptive abilities of the vertical and torsional integrators have not been investigated. We measured 11 patients with a peripheral vestibular asymmetry and used second-order equations to describe how velocity varied with position. Horizontal velocity changed with horizontal position in accordance with AL and the second-order term for horizontal position was also significant. Whereas velocity decreased in the slow phase direction, it was relatively unchanged >10° into the fast phase direction. Vertical velocity was also highest in the vertical fast phase direction and the second-order term for vertical position was also significant, in that vertical velocity increased in the vertical fast phase direction, but was unchanged in the slow phase direction. Torsional velocity varied linearly with horizontal, but not vertical, position. These results show that the horizontal and vertical oculomotor neural integrators react to altered vestibular input by maintaining different integrating time constants depending on gaze direction.

INTRODUCTION

Alexander (1912) observed that in patients with spontaneous nystagmus due to an acute vestibular asymmetry, the slow phase velocity, or drift, of nystagmus is lower when the subject looks toward the side of the slow component of nystagmus compared with the fast phase direction. This observation is so frequently observed that it is referred to as “Alexander’s Law.” Hess (Hess et al. 1984) and Robinson (Robinson et al. 1984) proposed that Alexander’s Law (AL) results from changes in the neural mechanism that helps maintain steady eye position at eccentric positions. Without such a mechanism, elastic forces produced by the extraocular tissues would pull the eye back to a central position. Robinson (1968, 1975) proposed that the countering force is produced by integrating eye velocity commands, so this gaze-holding mechanism is referred to as a neural integrator (NI). If the NI produces a command that is too small to maintain fixation, the eye will drift back to an elastic equilibrium position and the NI is said to be “leaky,” whereas a command from the NI that is too large and causes the eye to drift eccentrically is termed “unstable.” Normally, the NI is slightly leaky, showing integrating time constants of ≥20 s (Cannon and Robinson 1987; Goltz et al. 1997). The NI explanation of AL is that the NI becomes leaky and, when combined with the constant velocity vestibular nystagmus, reduces drift velocity in one direction, increases velocity in the opposite direction. This mechanism is thought to be adaptive in the sense that it reduces drift velocity for some gaze positions, thus improving vision, albeit eye drift is higher in the opposite direction.

Figure 1A shows a simple, hypothetical drift pattern expected with a left vestibular lesion that produces only horizontal nystagmus. Velocity is the same for all horizontal and vertical positions. In Fig. 1B, the drift pattern that occurs with a leaky horizontal NI is shown, in which centrifugal drift increases with horizontal eccentricity, but does not vary with vertical position. The combination of the vestibular-evoked drift in Fig. 1A and the gaze evoked drift in Fig. 1B is shown in Fig. 1C, illustrating the pattern of AL where velocity is highest in the fast phase direction. Figure 1D shows a more realistic example of vestibular nystagmus, which has horizontal, vertical, and torsional components, and the patterns of drift that result from combining this with a leaky horizontal NI (Fig. 1E) and both a leaky horizontal and vertical NI (Fig. 1F) are also shown.

Recently, we showed that in most patients with nystagmus due to an acute vestibular asymmetry, AL does not change drift velocity linearly with horizontal gaze position (Hegemann et al. 2007), as would be predicted by the traditional leaky integrator model proposed by Robinson et al. (1984). Instead, drift velocity was reduced proportional to position in the slow phase direction but was not significantly increased in the fast phase direction, showing differential NI adaptation for right and left gazes. We suggested the differential adaptation was due to functionally separate NIs for left and right gaze, a hypothesis that originates in the modeling study of Cannon et al. (1983), and was suggested by physiologic work in monkey (Crawford and Vilis 1993) and goldfish (Aksay et al. 2007). Chan and Galiana (2005, 2007) also proposed that the NI can maintain different integrating time constants, depending on gaze direction.

Although AL is a frequent clinical observation, the few detailed studies of AL are limited to horizontal movements (Doslak et al. 1979, 1982; Hegemann et al. 2007; Hess et al. 1984; Jeffcoat et al. 2008; Robinson et al. 1984). AL has been
observed for vertical eye movements in patients with cerebellar disease (Glasauer et al. 2003; Straumann et al. 2000) and in healthy people with pursuit-afternystagmus (Marti et al. 2005). Here we investigate the characteristics of AL by having patients with a peripheral vestibular asymmetry look in different horizontal and vertical directions. Since vestibular nystagmus usually consists of horizontal, vertical, and torsional components, we asked whether AL is also valid for the vertical and torsional components and whether we would find asymmetries similar to those in horizontal gaze holding.

**METHODS**

**Patients and equipment**

We investigated 11 patients, 5 women and 6 men, ages 21–67 yr (mean 51 yr), with an acute spontaneous nystagmus due to a peripheral vestibular asymmetry (mean onset of vertigo 2.5 days before examination, range 0.25–6.5 days). Data from horizontal gaze changes without variation in vertical position from patients 1 through 6 (Table 1) were also used in our previous study (Hegemann et al. 2007). Patients had an onset of vertigo ≤7 days before measurements, a clinical diagnosis of a peripheral vestibular asymmetry, and no other acute neurological deficits. Patients with Ménière’s disease, spontaneous nystagmus due to vestibular migraine, or any other cochleovestibular symptoms were excluded. The affected canals were identified with quantitative head impulse testing and caloric irrigation. The study adhered to the principles of the Declaration of Helsinki and was approved by the local ethics committee. All patients gave their written informed consent after the experimental procedure had been explained.

Three-dimensional (3D) movements of the head and the right eye were recorded in a magnetic frame (Remmel-type system, modified by A. Lasker, Baltimore, MD) using dual scleral search coils (Skalar...
Gain values for the vestibuloocular reflex test as measured by head impulse testing in the SCC planes, horizontal right/left = horizontal plane, head movement toward right/left, respectively; RALP/LARP = plane of right anterior and left posterior SCC, down = head movement downward in the respective SCC planes. Results of caloric tests are provided as CP (canal paresis factor) and DP (directional preponderance) according to the Jongkees formulas. Negative values represent hypofunction on the left horizontal SCC relative to the right horizontal SCC and preponderance of right beating nystagmus, respectively. Pathologic values are in bold and reduced gain values of the supposed intact side are in italic. NA, not available; PLF, perilymphatic fistula; IVP, idiopathic vestibulopathy.

### Procedure

We performed head impulse testing (Halmagyi et al. 1990) to determine the vestibuloocular reflex gain in all canal planes (horizontal, right anterior-left posterior, left anterior-right posterior) and for both directions of each plane (Hegemann et al. 2007; Schmid-Prisovcanea et al. 1999). Bithermal caloric vestibular testing with water at 44 and 30°C, respectively, was performed using a commercial caloric irrigator (Varimetherm, ATIMOS MedizinTechnik, Lenzkirch, Germany) and eye movements were recorded with a 50-Hz video-oculography system (VisualEyes, Micromedical Technologies). Canal paresis factor and direction preponderance were calculated as relative differences in percentages in slow phase eye velocity using the Jongkees formulas (Jongkees et al. 1962). The canal paresis factor, the difference between left and right sides relative to the total response is defined as $100 \times \left[ \left( W_L + C_L \right) - \left( W_R + C_R \right) \right]/\left( W_L + C_L + W_R + C_R \right)$, where $W$ is warm, $C$ is cold, and the subscripts refer to the side of stimulation. The directional preponderance, the relative difference between rightward and leftward nystagmus, is $100 \times \left( W_L + C_L \right)/\left( W_L + C_L + W_R + C_R \right)$. A canal paresis factor of $\geq 25\%$ and a directional preponderance of $\geq 30\%$ were regarded as pathologic.

Gaze-dependent changes in nystagmus were measured by instructing patients to look in darkness at a pulsed target that moved every 5 s in steps of 5 from 25° right to 25° left and back. The laser was pulsed (20 ms every 2 s) so that we could direct the patient’s gaze direction without visually suppressing nystagmus. This was repeated at vertical elevations of 20° up and down.

### Data analysis

Data were analyzed using programs written in MATLAB (The MathWorks, Natick, MA). Eye movements are described by rotation vectors and component velocity (Hepp 1990; Tweed et al. 1990) and we report the results in degrees and degrees per second. Component velocity, the derivative of position, is not the same as angular velocity (Haslwanter 1995; Hepp 1990). Data are presented in a head-fixed coordinate system, with positive rotations being clockwise, right, and up. We mirrored the horizontal and torsional data of the patients with right-side lesions, so all patients appear to have a left-side lesion (slow phase drift to the left). Saccades were identified and removed with an interactive computer program that first automatically detected saccades based on velocity and noise criteria (Holden et al. 1992) and then allowed the user to adjust the automatically marked saccades and to remove blink artifacts. Individual nystagmus slow phases were included in later analysis if they were $\geq 100$ ms in duration. Short phases $>200$ ms were split into two or more shorter parts of $\geq 100$ ms. We calculated for each slow phase the median position and velocity for each component (horizontal, vertical, and torsional). For some graphs we then averaged the slow phase properties for each target direction, although all quantitative analysis was made without averaging.

To characterize how velocity varied with horizontal and vertical eye position, we fit two equations to horizontal, vertical, and torsional velocities. First we fit a simple plane to the data

$$Ve_{l(h,v)} = \beta_{0(h,v)} + \beta_{1(h,v)}H + \beta_{2(h,v)}V$$  

(1)

where $Ve$ is velocity and the subscripts refer to horizontal ($h$), vertical ($v$), and torsional ($t$) components; $H$ is horizontal position; and $V$ is vertical position. The bias component $\beta_0$ indicates the velocity at straight-ahead gaze ($V = H = 0$). $\beta_1$ and $\beta_2$ (with units of 1/s) indicate the proportional change of velocity with horizontal and vertical eye position and, together, represent a plane. This fit is the two-dimensional extension of the traditional method of analyzing AL in one dimension with a straight line. In a second analysis, we fit the following second-order equation to horizontal, vertical, and torsional velocities

$$Ve_{l(h,v)} = \beta_{0(h,v)} + \beta_{1(h,v)}H + \beta_{2(h,v)}V + \beta_{3(h,v)}HV + \beta_{4(h,v)}H^2 + \beta_{5(h,v)}V^2$$  

(2)

The equation can be visualized as representing a 3D, parabolic surface (see Figs. 3 and 4 for examples). The bias term $\beta_0$ indicates the velocity at straight-ahead gaze ($V = H = 0$) and the terms $\beta_1$ and $\beta_2$ (with units of 1/s) indicate the proportional change of velocity with horizontal and vertical eye positions. An interaction between horizontal and vertical positions is represented by the $\beta_3$ term (units of 1/s^2) and permits the plane to twist. The squared terms, $\beta_4$ and $\beta_5$ (1/s^2), permit the surface to have a parabolic shape as a function of horizontal and vertical eye positions.

### Table 1. Results of vestibular function tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Horizontal Right/Left</th>
<th>RALP/LARP Down</th>
<th>RALP/LARP Up</th>
<th>Caloric CP</th>
<th>Caloric DP</th>
<th>Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.40/0.54</td>
<td>0.35/0.64</td>
<td>0.64/0.54</td>
<td>NA</td>
<td>NA</td>
<td>Traumatic PLF</td>
</tr>
<tr>
<td>2</td>
<td>1.04/0.42</td>
<td>1.05/0.65</td>
<td>0.86/0.84</td>
<td>NA</td>
<td>NA</td>
<td>IVP</td>
</tr>
<tr>
<td>3</td>
<td>0.77/0.54</td>
<td>0.51/0.21</td>
<td>0.87/0.91</td>
<td>NA</td>
<td>NA</td>
<td>IVP</td>
</tr>
<tr>
<td>4</td>
<td>0.74/0.60</td>
<td>0.89/0.68</td>
<td>0.70/0.79</td>
<td>$-51$</td>
<td>$-55$</td>
<td>IVP</td>
</tr>
<tr>
<td>5</td>
<td>0.88/0.27</td>
<td>0.77/0.23</td>
<td>0.66/0.82</td>
<td>$-63$</td>
<td>$-59$</td>
<td>IVP</td>
</tr>
<tr>
<td>6</td>
<td>0.35/0.69</td>
<td>0.18/0.40</td>
<td>0.34/0.52</td>
<td>54</td>
<td>$-100$</td>
<td>IVP</td>
</tr>
<tr>
<td>7</td>
<td>0.31/0.63</td>
<td>0.68/0.79</td>
<td>0.60/0.81</td>
<td>24</td>
<td>91</td>
<td>IVP</td>
</tr>
<tr>
<td>8</td>
<td>0.60/0.55</td>
<td>0.70/0.87</td>
<td>0.94/0.61</td>
<td>NA</td>
<td>NA</td>
<td>IVP</td>
</tr>
<tr>
<td>9</td>
<td>0.56/0.41</td>
<td>0.72/0.40</td>
<td>0.75/0.18</td>
<td>76.5</td>
<td>57</td>
<td>IVP</td>
</tr>
<tr>
<td>10</td>
<td>0.62/0.27</td>
<td>0.60/0.31</td>
<td>0.88/0.52</td>
<td>$-67$</td>
<td>$-100$</td>
<td>IVP</td>
</tr>
<tr>
<td>11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>52</td>
<td>42</td>
<td>IVP</td>
</tr>
<tr>
<td>Normal</td>
<td>$\geq 0.71/0.70$</td>
<td>$\geq 0.69/0.54$</td>
<td>$\geq 0.67/0.68$</td>
<td>$\leq 25$</td>
<td>$\leq 30$</td>
<td></td>
</tr>
</tbody>
</table>
Both the plane and the second-order equations were fit to the velocity of each subject individually using standard multiple regression techniques, the 10\% of the individual data points with the largest residual error were classified as outliers and removed, and the fitting procedure was repeated. The overall fit was evaluated with an F-test and we then tested for significant differences from 0 of the average parameters, across subjects, with t-test. Correlations between parameters were performed with Pearson’s product-moment correlation coefficient.

To validate each fit, we performed a split-sample analysis. We randomly assigned each slow phase to one of two groups, performed the same fitting procedures described earlier to the first group, and computed the sample squared correlation ($R^2$). Next, we used the fitted equation to predict the values from the second group and computed the squared correlation between the predicted and the observed data. The difference between these $R^2$ values, called shrinkage, will be small for reliable fits, with a shrinkage value of $\approx 0.1$ generally indicating a reliable model (Kleinbaum et al. 1988).

An integrator time constant can be inferred from the fitted equations by $-1/\text{slope}$. For the plane fits, the slope is given directly as the fitted parameter (see Eq. 1). For the second-order fits, the slope can be found with the partial derivatives of Eq. 2

$$\frac{\partial \text{Vel}_{\text{hvt}}}{\partial H} = \beta_{3\text{hvt}} + \beta_{3\text{hvt}}V + 2\beta_{3\text{hvt}}H \quad (3)$$

$$\frac{\partial \text{Vel}_{\text{hvt}}}{\partial V} = \beta_{3\text{hvt}} + \beta_{3\text{hvt}}H + 2\beta_{3\text{hvt}}V \quad (4)$$

which describe how velocity varies with horizontal (Eq. 3) and vertical (Eq. 4) eye positions. A positive time constant indicates a leaky integrator and a negative time constant an unstable integrator.

To provide additional statistical support for these results, we split the data into halves (left and right for horizontal velocity and up and down for vertical velocity), fit separate planes to each half, and evaluated whether the slopes were different from zero for each subject with t-tests.

We analyzed the direction of nystagmus by decomposing the 3D eye velocity vector into two angles. We first projected the 3D velocity vector onto the plane defined by the horizontal and vertical components and calculated the angle of the projection in this plane. This angle varies from 0° (upward vertical velocity, with no horizontal component), to 90° (leftward, with no vertical component), to 180° (downward), and to 270° (rightward). Likewise, we projected the vector onto the plane defined by the horizontal and torsional components, which gives an angle related to the horizontal/torsional direction: 0° is clockwise torsion, 90° is leftward, 180° is counterclockwise, and 270° is rightward. When analyzed as a function of gaze position, this analysis shows how the direction of nystagmus, independent of the speed, varies with gaze position. We fit the same plane and second-order functions described earlier to characterize how the direction of nystagmus varied with eye position.

**RESULTS**

**Patient characteristics**

Table 1 shows the results of head impulse and caloric testing for each patient. In patient 11 the tape that fixed the coil to the forehead loosened due to severe sweating of the patient, which makes his head impulse results unreliable. In four patients, caloric vestibular testing could not be performed because of a perilymphatic fistula (patient 1) or severe nausea (patients 2, 3, and 8). Patient 7 showed a right beating nystagmus but had reduced right vestibular function during both head impulse and caloric testing, the latter being performed 1 day after the head impulse test. A central lesion was excluded by magnetic resonance imaging. The patient recovered completely from nystagmus as well as vertigo and unsteadiness within 3 days. We interpret this “paradox” nystagmus as a so-called recovery nystagmus. Since the nystagmus was right beating as in left-sided unilateral vestibular deafferentation (UVD), however, we analyzed it as a left UVD.

**Example nystagmus patterns**

Patients typically had nystagmus with slow phases directed to the left, down, and counterclockwise when looking straight ahead. As exceptions, two patients had upward drift. Figure 2 shows example eye position traces in one patient (4) who followed the flashing laser spot as it moved from left to right with gaze at zero elevation (A), 20° up (B), and 20° down (C). The inset in Fig. 2A magnifies the horizontal component when the patient looked left, straight ahead, and to the right, which more clearly shows the greater nystagmus when the patient was looking to the right.

**FIG. 2.** A: example eye-position traces from patient 4. Each panel shows horizontal (bold), vertical (medium), and torsional (light) eye positions as the patient tracked a flashing laser spot (not shown) that moved from left to right in 5° steps. In A, gaze elevation was about straight ahead, whereas in B gaze was about 20° down and in C about 20° up. The inset in A shows horizontal eye position, magnified, when gaze was left, straight ahead, and to the right.
Figure 3 shows a summary of the results of another patient (6). Figure 3, A–C shows median eye velocity of individual slow phases as a function of horizontal and vertical eye positions, along with the best-fit second-order equation (Eq. 2). Figure 3D combines the 3D velocity components into a single figure. In this plot, we averaged the eye movement data in each 5-s period where the flashing fixation light was in the same position. Each circle indicates the average horizontal and vertical positions. The thick line shows the horizontal and vertical velocities, and so the orientation of the line indicates direction and the length represents the speed. Thin lines show torsional velocity, with an upward line indicating clockwise velocity and a downward line indicating counterclockwise velocity. E: the fitted values of the best-fit 2nd-order surface. F: gaze-dependent changes in drift velocity, which was found by subtracting the fitted drift at straight ahead from fitted drift at all other gaze positions.

All the fitted parameters were significantly different from 0 with all P values <0.01. Horizontal velocity was $-7.2^\circ/s$ at straight ahead. The change in velocity with horizontal position was determined mainly by the linear component, with a value of $-0.087^\circ/s$ and $-0.015\text{deg}\cdot\text{s}^{-1}$. Nonetheless, the second-order term, $H^2$, was still significant. This indicates that the rate of change in velocity changes at different gaze positions, which is more obvious when considering the partial derivative of the fitted function with respect to horizontal position

$$\frac{\partial \text{Vel}_h}{\partial H} = -0.087 + 0.00044V + 0.0019H$$

With gaze straight ahead ($H = V = 0^\circ$), the change of horizontal eye velocity is $-0.087^\circ/s$ and $-0.0015\text{deg}\cdot\text{s}^{-1}$, and with $V = 0^\circ$, at $20^\circ$ left and right, the change is $-0.12$ and $-0.049\text{deg}\cdot\text{s}^{-1}$, respectively. Thus velocity changed the most in left gaze (the slow phase direction). Horizontal velocity also changed with vertical eye position in this patient. In particular, the $V^2$ term ($-0.0023$) shows that horizontal velocity increased when this patient looked up and down. The partial derivative with respect to vertical position is

$$\frac{\partial \text{Vel}_h}{\partial V} = -0.058 + 0.0004H - 0.0045V$$

so the rate of change of horizontal eye velocity with $H = 0^\circ$ and with vertical positions of 20, 0, and $-20^\circ$ was $-0.15$, $-0.058$, and $0.033\text{deg}\cdot\text{s}^{-1}$, respectively.

Figure 3B shows how vertical velocity varied with eye position in the same patient. Vertical eye velocity increased when the subject looked up, but velocity for down gaze was similar to that at gaze straight ahead. This is consistent with AL, with velocity being highest in the fast phase direction (up). The best-fit function was

$$\text{Vel}_v = -7.2 - 0.087H - 0.058V + 0.00044HV + 0.00094H^2 - 0.0023V^2$$

best-fit equation is

\[ Vel_t = -2.2 + 0.0016H - 0.080V + 0.0012HV - 0.00055H^2 - 0.0024V^2 \]

and all parameters except the \( H \) term were significantly different from zero (all \( P \) values <0.01). Note that the small change in vertical velocity in down gaze, compared with the much larger change in up gaze, is captured in the equation with a combination of the \( V \) and \( V^2 \) terms. The rate changes in vertical velocity with vertical and horizontal positions are

\[ \frac{\partial Vel_t}{\partial V} = -0.080 + 0.0012H - 0.0048V \]

and

\[ \frac{\partial Vel_t}{\partial H} = 0.0016 + 0.0012V - 0.0011H \]

Thus in this patient, vertical velocity varies more with vertical than with horizontal position. Figure 3C shows torsional velocity in this patient, which followed a similar pattern to the changes in vertical velocity in that velocity increased considerably in up gaze but was relatively unchanged in down gaze. Torsional velocity at straight ahead gaze and in down gaze was about zero, but increased to around \(-5^\circ/s\) in up gaze. The best-fit equation is

\[ Vel_t = -0.3 - 0.053H - 0.039V - 0.0024HV - 0.00012H^2 - 0.0043V^2 \]

and all parameters were significantly different from zero (all \( P \) values <0.01), except the \( H^2 \) term. Torsional velocity varies slightly with both horizontal and vertical positions and this is reflected in the changes in velocity with vertical and horizontal gaze positions.
Quality of the fitted surfaces

The plane surface fits were highly significant for all patients (overall F-test, all P values ≪ 0.001). A substantial amount of variation was nonetheless not accounted for by the regression. The mean R² values were 0.43, 0.39, and 0.25 for horizontal, vertical, and torsional velocities, respectively. Shrinkage values were low, averaging 0.02, or about 6% of the mean R², indicating reliable fits.

Likewise, the fitted second-order surfaces were also highly significant in all cases (F-test, all P values ≪ 0.001), although again much of the variation in the data was not accounted for by the regression. The second-order fits accounted for about 28% more of the variance than the plane fits. For horizontal velocity, R² varied from 0.22 to 0.86, with a mean of 0.56. The mean R² for the fits to vertical velocity was 0.48, ranging from 0.15 to 0.77, and the mean torsional R² was 0.42 and varied from 0.15 to 0.64. Shrinkage values were also low, indicating reliable fits, averaging 0.03, or about 5% of the mean R².

Dependence of horizontal velocity on gaze position

All patients showed significant horizontal drift to the left at straight ahead gaze. The average plane and second-order fits are shown in Table 2. The plane fits indicated an average velocity at straight ahead gaze of −10.04 °/s. Ten of 11 patients had a negative slope relating horizontal velocity to horizontal gaze position, which is in accord with AL, and indicates that velocity was higher in the fast phase direction. The average slope of −0.088 corresponds to an integrating time constant of 11 s. There was no consistent change of horizontal velocity with vertical eye position.

For the second-order fits, which provide a more detailed examination of the change of velocity with position, the average bias was −10.35 °/s (Table 2; see also Fig. 5). Ten of 11 patients had a negative slope relating horizontal velocity to horizontal gaze position. Eight of the 11 patients also showed a significant, positive H² term, with a mean value of 0.003. Positive H² indicates a concave up surface that, when combined with the negative H term, reduces horizontal velocity in the fast phase direction compared with that if the term is 0. The average HV, V, and V² terms were not significantly different from zero, indicating that, across patients, horizontal velocity did not depend on vertical eye position. Note, however, that for individual patients these parameters were usually significantly different from zero, although the signs were not consistent.

Differentiating the average second-order function fitted to the horizontal eye velocity with respect to horizontal position gives

$$\frac{\partial V_{el}}{\partial H} = -0.054 + 0.00018V - 0.0059H$$

Thus at gaze straight ahead (V = H = 0°), the change of horizontal velocity with horizontal position (or slope of the fitted function) is −0.054°/s²·deg⁻¹, at 20° left (the slow phase direction), the slope is −0.17°/s²·deg⁻¹ and at 20° right (the fast phase direction), the slope is 0.064°/s²·deg⁻¹. These slopes correspond to time constants of 6, 18, and −16 s for 20° in the slow phase direction, straight ahead, and 20° in the fast phase direction, respectively. The position at which the slope changes sign is 9.2° to the right. So, on average, the gaze-dependent drifts suggest the NI is leaky in the slow phase direction, but becomes unstable at >9° in the fast phase direction. Separate plane fits to horizontal velocity in left and right gaze provide statistical support for these changes in the time constant. In left gaze, all 11 patients showed a significant (P < 0.05) negative slope of velocity versus position. In right gaze, 5 patients had a significant negative slope, 4 had significant positive slopes, and 2 showed slopes that were not significantly different from zero.

Dependence of vertical velocity on gaze position

At straight ahead gaze, 9 of the 11 patients showed downward drift and 2 showed upward drift. From the best-fit plane (Table 2), 9 patients showed a negative change in vertical velocity with vertical eye position, with an average slope of −0.037 (time constant = 27 s). This indicates that velocity increased in the fast phase direction of nystagmus, in accord with AL, although the long time constant is in the normal range (>20 s; Cannon and Robinson 1987; Golz et al. 1997). There was not a consistent change of vertical velocity with horizontal position.

For the second-order fits, 9 of the 11 patients showed a significant negative relationship between vertical velocity and position. Nine of the patients also showed a significant negative V² term. As shown in Fig. 5B, this is concave down, meaning that, when combined with the negative V-term, vertical velocity increases in the fast phase direction compared with that if the term is 0. Eight patients also showed a significant dependence of vertical velocity on H², with an average value of 0.00051, which was not quite significantly different from zero (P < 0.1).

Differentiating the average function fit to the vertical eye velocity with respect to vertical position gives

$$\frac{\partial V_{el}}{\partial V} = -0.046 + 0.0003H - 0.0040V$$

Thus at gaze straight ahead, the rate of change of vertical velocity with vertical position is −0.046°/s · deg⁻¹ (time

### Table 2. Average best-fit parameters across all subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Horizontal Velocity</th>
<th>Vertical Velocity</th>
<th>Torsional Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Plane fits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>−10.04** (+0°−11)</td>
<td>−2.06*** (+2°−9)</td>
<td>−4.40* (+0°−11)</td>
</tr>
<tr>
<td>H</td>
<td>−0.088*** (+1°−10)</td>
<td>−0.0074*** (+3°−4)</td>
<td>−0.042** (+0°−11)</td>
</tr>
<tr>
<td>V</td>
<td>−0.027 (4°−7)</td>
<td>−0.037** (+1°−9)</td>
<td>0.014* (+6°−2)</td>
</tr>
<tr>
<td>R²</td>
<td>0.43</td>
<td>0.39</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>B. Second-order fits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bias</td>
<td>−10.35** (+0°−11)</td>
<td>−1.82** (+2°−9)</td>
<td>−4.31* (+0°−11)</td>
</tr>
<tr>
<td>H</td>
<td>−0.054* (+1°−10)</td>
<td>−0.0020 (4°−5)</td>
<td>−0.030* (+2°−9)</td>
</tr>
<tr>
<td>V</td>
<td>−0.026 (3°−8)</td>
<td>−0.046* (+1°−9)</td>
<td>0.016 (+7°−3)</td>
</tr>
<tr>
<td>HV</td>
<td>0.00018 (+7°−4)</td>
<td>−0.00003 (+5°−5)</td>
<td>−0.00005 (+6°−5)</td>
</tr>
<tr>
<td>H²</td>
<td>0.0030* (8°−0)</td>
<td>0.00051† (+8°−3)</td>
<td>0.0015 (+7°−3)</td>
</tr>
<tr>
<td>V²</td>
<td>−0.00054 (+5°−6)</td>
<td>−0.0020* (+1°−9)</td>
<td>−0.021 (+3°−8)</td>
</tr>
<tr>
<td>R²</td>
<td>0.56</td>
<td>0.48</td>
<td>0.42</td>
</tr>
</tbody>
</table>

The numbers in parentheses indicate the number of patients for which that parameter was significantly different from 0 (P > 0.05) in the position and negative directions. For example, for plane fits, all 11 patients had a significant horizontal bias <0. **P < 0.01, *P < 0.05, †P < 0.1.
Dependence of torsional velocity on gaze position

According to the average plane fits, all 11 patients had counterclockwise torsion at gaze straight ahead, with a mean of $-4.4^\circ/s$ (Table 2). Plane fits also revealed a highly significant dependence of torsional velocity on horizontal position, with an average slope of $-0.042$ (Table 2). A marginally significant dependence on vertical position was also found (slope $= 0.014$, $P < 0.1$).

Second-order fits found an average torsional velocity at gaze straight ahead of $-4.31^\circ/s$ and all 11 patients showed a statistically significant torsional bias (Table 2; see also Fig. 5). Torsional velocity was significantly dependent on horizontal position, with 9 of the 11 patients showing a significant negative slope, with a grand mean of $-0.035^\circ/s\cdot\text{deg}^{-1}$. Torsional velocity did not consistently depend on any of the other parameters.

Summary of changes in 3D nystagmus

Figure 5A shows the average second-order fits and Fig. 5, D–F shows the same fits as in Fig. 5A plotted as 3D surfaces. Velocity was predominately to the left with smaller downward and counterclockwise components. Figure 5B shows the gaze-dependent changes in velocity. Most of the gaze-dependent changes occur in left and up gaze, whereas in right gaze there is not much of a gaze-evoked component.

We tested whether the change of eye velocity was related to the magnitude of the vestibular nystagmus. We used the bias of the second-order fit as an estimate of the vestibular contribution to the nystagmus and computed the slope of the second-order fitted equation for each subject at straight ahead and $\pm 20^\circ$ in the fast and slow phase directions of the horizontal and vertical nystagmus. The horizontal slope of the function at $-20^\circ$ left (slow phase direction) was significantly correlated with the horizontal bias (correlation $= 0.82$, $P < 0.01$), whereas there was a significant negative correlation at $20^\circ$ right gaze (correlation $= -0.74$, $P < 0.01$); the correlation at
straight ahead was not significant (correlation = 0.11, \( P > 0.5 \)) (Fig. 6). The slope in the slow phase direction was less than the slope in the fast phase direction in all but two patients and in seven patients the slope became positive. We did not find significant correlations between the vertical bias and the vertical or torsional slopes, nor between the horizontal bias and the torsional slopes.

Nystagmus direction changed as a function of gaze direction, as indicated in the average fit in Fig. 5B, as well as the examples in Figs. 3D and 4D. We analyzed the direction change by decomposing the 3D eye velocity vector into two angles. We first projected the 3D velocity vector onto the planes defined by the horizontal and vertical components, and the planes defined by the horizontal and torsional components, and calculated the angles of the projections onto these planes (see METHODS). We then fit Eqs. 1 and 2 to these angles for each patient, the average fits of which are shown in Table 3. (For the second-order fit, the horizontal–vertical angle is shown directly in Fig. 5B in the lines showing the horizontal and vertical velocities.) The bias indicates the slow phase direction at straight ahead gaze. The plane and second-order fits give similar results, with both angles depending mainly on vertical position (only marginally significant in the case of the horizontal–torsional angle). For the horizontal–vertical angle, the \( V^2 \) term was also marginally different from zero.

**DISCUSSION**

We measured the effect of horizontal and vertical gaze shifts on the 3D velocity of nystagmus in patients with an acute vestibular asymmetry and we characterized the change of velocity with eye position with plane and second-order functions. In all patients the fits were highly significant. All patients showed AL for horizontal velocity, with velocity being higher in the fast phase compared with that in the slow phase direction. In addition, the second-order term for horizontal position was significant in most (8/11) patients, with the result that velocity did not increase in the fast phase direction as rapidly as expected from a linear relationship.

If we assume that the elastic equilibrium point of the eye in the orbit (null point of the eye) is near straight ahead, the gaze-dependent drifts suggest the horizontal NI is leaky in the slow phase direction; beyond 10° in the fast phase direction, however, the NI is on average unchanged. Some patients even showed an unstable NI in the fast phase direction. Although individual patients usually had a significant dependence of horizontal velocity on vertical position, the direction of the dependence was not consistent.

Vertical velocity also depended on both vertical position and its square. Overall, vertical velocity varied in accord with AL, with velocity being higher in the fast phase direction. Torsional velocity depended mostly on horizontal position.

The change of horizontal velocity with horizontal position was correlated with the horizontal bias (Fig. 6A), which could be expected if AL is an adaptive mechanism sensitive to the magnitude of nystagmus. Similar correlations were not found for vertical and torsional velocities, although the velocity of these components is small, making detection of any correlation difficult.

The direction of nystagmus, independent of the speed, changes as a function of eye position. If AL in 3D was due to a single mechanism operating on the magnitude of the nystagmus, we would expect proportional changes in velocity in all components and no change in nystagmus direction. The fact that nystagmus direction changes suggests that the changes in slow phase velocity are not due to a single mechanism, but rather, that the horizontal, vertical, and torsional NIs operate separately to modify the different 3D components.

A comparison of the plane and second-order fits shows that the second-order fits account for about 28% more of the variance in the data (since the plane fits are nested within the higher-order fits, the higher-order fits must account for at least as much of the variance). Clearly, though, the linear compo-

**TABLE 3. Average best-fit parameters to nystagmus direction**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HV Angle</th>
<th>HT Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
<td>103** (+11°/0)</td>
<td>112** (+11°/0)</td>
</tr>
<tr>
<td>( H )</td>
<td>-0.063 (+4°/7)</td>
<td>0.041 (+8°/2)</td>
</tr>
<tr>
<td>( V )</td>
<td>0.21** (+9°/1)</td>
<td>-0.141 (+3°/7)</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.33</td>
<td>0.27</td>
</tr>
</tbody>
</table>


**FIG. 6.** Correlations between horizontal nystagmus at straight ahead gaze and the change of horizontal eye velocity with eye position. The change of horizontal velocity with horizontal position was computed for left (−20°), right (20°), and straight ahead gaze. Each symbol indicates a single patient and the lines are the best linear fits for each direction.
ments are important contributors to the change of velocity, as expected from AL.

Our paradigm is not capable of determining the neural locus of the changes in the oculomotor system, although cerebellar structures known to be important for NI performance (flocculus and parafocculus; Zee et al. 1981) are likely candidates. It is also possible that other neural structures, particularly those that receive inputs for the NIs, might also be changing as a result of the altered vestibular input.

**Vertical Alexander’s law**

In our patients, vertical eye velocity varied with vertical position in a manner similar to the classically defined Alexander’s law for horizontal nystagmus, that is, velocity was highest in the fast phase direction. Vertical AL has been described for patients with downbeat nystagmus resulting from cerebellar lesions (Glasauer et al. 2003; Straumann et al. 2000), as well as in normal subjects with pursuit afternystagmus (Marti et al. 2005). In our patients, vertical velocity was lowest in down gaze, where reducing nystagmus may improve vision during walking and reading.

If we take drift velocity at straight ahead gaze as a reference, vertical eye velocity in the fast phase direction increased, whereas velocity in the slow phase direction was unchanged. This is different from what occurs for horizontal velocity, where velocity decreases in the slow phase direction and is relatively unchanged in the fast phase direction (compare Fig. 5, D and E). Assuming the NI is responsible for the gaze-dependent changes, and that the elastic equilibrium point is near straight ahead, this suggests the vertical NI changes are maladaptive. However, shifting the equilibrium point upward (∼25°) would result in a drift pattern more consistent with an adaptive mechanism—i.e., the NI becomes leaky in down gaze to reduce drift velocity (see Fig. 5C). Thus changing the reference position causes the gaze-dependent drift patterns for horizontal and vertical to become more similar, suggesting the horizontal and vertical NIs react similarly to altered vestibular input. Although there have been a few studies of the viscoelastic properties of the orbit in the horizontal (Robinson 1964; Sklavos et al. 2005, 2006) and torsional (Seidman et al. 1995) directions, little is known for vertical movements, and the actual location of the equilibrium point is unknown. Shifting the null point, however, does not account for why the shape of the fitted velocity function was concave down, whereas the surface for horizontal was concave up. One possibility is that the velocity when looking down (<2°/s) is low enough to be compensated by visually guided eye movements, and so there was no pressure for adaptive NI changes. Also, although the reactions of the horizontal and vertical NIs appear different, their velocity inputs due to the vestibular lesions in our patients also differ. A left-sided lesion will reduce the input for head turns to the left due to the reduced input from the left horizontal canal, but because both the posterior and anterior canal inputs could be affected, the velocity inputs for both upward and downward movements could also be influenced. Whether the vertical and horizontal NIs respond in a similar fashion in patients with nystagmus therefore remains an open question.

**Torsion**

Torsional velocity could be expected to vary in a manner similar to that of vertical velocity, since the vertical and torsional NIs share a common neurological location. However, we found that torsional velocity varied mostly with horizontal position, with the lowest velocity being in the horizontal slow phase direction. This implies an independence of the vertical and torsional NIs.

The reason torsion varied with horizontal position is not clear; conceivably, the torsional NI could be sensitive to horizontal position and thus the torsional velocity is modified with horizontal position. Static torsional position varies with horizontal position when the head is pitched backward and forward (Bockisch and Haslwanter 2001; Furman and Schor 2003; Haslwanter et al. 1992) and, if this torsional command passes through the torsional NI, then this NI must therefore be sensitive to horizontal position.

We did not compare torsional velocity with torsional position because of the technical difficulties in measuring small changes of torsional position (coil slippage; Bergamin et al. 2004; Bockisch and Haslwanter 2001). It is thus possible that the torsional modulation we see is actually due to a correlation with torsional position that varies with horizontal position.

**Neural integrator time constant depends on gaze direction**

The prominent second-order components for horizontal and vertical velocities show that velocity was not proportional to gaze position. Robinson’s classic explanation of AL in the horizontal direction was that the NI became “leaky,” thereby producing a centripetal nystagmus that superimposed with the vestibular-evoked nystagmus. This would reduce gaze velocity in one direction, but increase velocity in the opposite. Although some of our patients did show the increase in velocity, others showed a prominent decrease and, on average, there was little change in velocity in the horizontal nystagmus fast phase direction. These results suggest that the NI becomes leaky in the slow phase direction, but can be leaky, unchanged, or unstable in the fast phase direction. Becoming unstable in the fast phase direction is the most adaptive response in terms of reducing slow phase velocity.

Differential adaptation can be explained if the NI can maintain different integrating time constants depending on gaze direction, as suggested by Chan and Galiana (2005, 2007) in humans and Mensh et al. (2004) in goldfish. Cannon et al. (1983) originally proposed a related idea, of functionally independent NIs that are sensitive to different gaze directions, and Crawford and Vilis (1993) proposed multiple vertical–torsional NIs based on pharmacological inactivation studies. More recently, Aksay et al. (2007) provided evidence for separate horizontal NIs in goldfish when they pharmacologically lesioned the NI unilaterally and found impaired fixation over only half the oculomotor range.

**Null point of the NI**

We have interpreted the gaze-dependent changes in velocity in terms of the NI time constant, although changes in the NI null point (the NI’s representation of the eye position where the elastic forces of the plant pull the eye) could contribute to the results. Glasauer et al. (2003) concluded that the NI null point

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could shift, in addition to changes in the time constant, in patients with downbeat nystagmus. This was predicated on the assumption, based on Crawford et al. (1994), that the NI null point coincides with primary position. Our patients had torsional nystagmus and their eye movements violated Listing’s law, and so primary position could not be reliably determined.

Shifting the null point will result in a force command that is insufficient to maintain gaze position in the direction of the null point shift and will produce a command too large in the opposite direction. Thus the NI would appear leaky in the direction of the null point shift and unstable in the opposite direction. To explain our horizontal data, the NI null point shift would have to be to the left, into the slow phase direction. A shift in the null point would result in a change of the constant background activity of the NI that, in our patients with vestibular lesions, would shift the position where the rate of change of eye velocity changes sign. This eye position was about 9° into the fast phase direction for horizontal velocity and about 11° into the slow phase direction for vertical velocity.

Conclusion

We have shown that patients with 3D nystagmus caused by a peripheral vestibular lesion develop eye-position–dependence drift that affects horizontal, vertical, and torsional velocity components. Regression analysis found that horizontal velocity varied with horizontal, but not vertical, position. The significant second-order term indicates that the time constant of the horizontal NI can decrease in one gaze direction, while increasing or remaining unchanged in a different gaze direction. Vertical velocity also varied with vertical position and the results suggest the vertical NI also appears able to adapt differentially to gaze direction. Torsional velocity varied with horizontal position, an effect that we cannot explain. Our results also show that the oculomotor NIs cannot be characterized by a single time constant, but rather can maintain different integrating time constants depending on gaze direction.

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