Alexander’s law and the oculomotor neural integrator: three-dimensional eye velocity in patients with an acute vestibular asymmetry

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Abstract

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 to the fast phase direction. Adaptive changes in the velocity-to-position neural integrator are thought to cause AL. While 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. While velocity decreased in the slow phase direction, it was relatively unchanged more than 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, as vertical velocity increased in the vertical fast phase direction, but was unchanging 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 upon gaze direction.

Key words

oculomotor, neural integrator, vestibulo-ocular reflex, nystagmus, adaptation
Introduction

Alexander (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 towards the side of the slow component of nystagmus as compared to 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 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 counter-acting 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 20s or more (Cannon and Robinson 1987; Goltz HC 1997).

The NI explanation of Alexander’s Law is that the NI becomes leaky, which, when combined with the constant velocity vestibular nystagmus, reduces drift velocity in one direction, but 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 only produces horizontal nystagmus. Velocity is the same for all horizontal and vertical positions. In Figure 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 Figure 1A and the gaze evoke drift in Figure 1B is shown in Figure 1C, illustrating the pattern of Alexander’s Law 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 (Figure 1E) and both a leaky horizontal and vertical NI (Figure 1F) are also shown.

Recently, we showed that in most patients with nystagmus due to an acute vestibular asymmetry, Alexander’s law (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 (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 gaze. 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. (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 have also proposed that the NI can maintain different integrating time constants, depending upon gaze direction (Chan and Galiana 2005; 2007).

While Alexander’s Law is a frequent clinical observation, the few detailed studies of Alexander’s Law are limited to horizontal movements (Doslak et al. 1979; Doslak et al. 1982; Hegemann et al. 2007; Hess et al. 1984; Jeffcoat et al. 2008; Robinson et al. 1984). Alexander’s Law 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 Alexander’s Law 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 Alexander’s Law is also valid for the vertical and torsional components and whether we would find similar asymmetries like in horizontal gaze holding.
Methods

Patients and equipment
We investigated 11 patients, 5 women and 6 men, aged 21-67 years (mean 51) with an acute spontaneous nystagmus due to an 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 (Tab. 1) were also used in our previous study (Hegemann et al. 2007). Patients had an onset of vertigo seven or fewer days before measurements, a clinical diagnosis of a peripheral vestibular asymmetry and no other acute neurological deficits. Patients with Meniere’s disease, spontaneous nystagmus due to vestibular migraine, or any other cochleo-vestibular symptoms were excluded. The affected canals were identified with quantitative head impulse testing and caloric irrigation. The study adheres 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 Instruments, Delft, Netherlands) (Ferman et al. 1987; Remmel 1984; Robinson 1963). The calibration procedure was described by Bergamin et al. (Bergamin et al. 2001). Data were sampled at 1 kHz with 16 bit precision, and peak-to-peak noise in the system was less than 0.2°, in all directions. Visual targets were produced by a laser and directed by a 2-axis mirror galvanometer, which produced a 0.25° diameter target on a tangent screen, 1.25 m from the subject.

Procedure
We performed head impulse testing (Halmagyi et al. 1990) to determine the vestibulo-ocular reflex gain in all canal planes (horizontal, right-anterior left-posterior, left-anterior right-posterior plane) and for both directions of each plane (Hegemann et al. 2007; Schmid-Priscoveanu et al. 1999). Bithermal caloric vestibular testing with water at 44 and 30 deg C, respectively, was performed using a commercial caloric irrigator (Variotherm, Atmos
MedizinTechnik GmbH & Co. KG, Germany), and eye movements were recorded using a 50 Hz video-oculography system (VisualEyes, Micromedical™ Technologies Inc.). 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 side relative to the total response is defined as 100 X (W_L + C_L) –(W_R + C_R) / (W_L + C_L + W_R + C_R) 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 X (W_R + C_L) –(W_L + C_R) / (W_L + C_L + W_R + C_R). A canal paresis factor of 25% or more and a directional preponderance of 30% or more 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 five seconds in steps of 5° from 25° right to 25° left and back. The laser was pulsed (20 msec every 2 sec) 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® (MathWorks Inc, Natick, MA, USA). 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 at least 100 msec in duration. Short phases longer than 200 msec
were split into 2 or more shorter parts of at least 100 msec. 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, though 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 velocity. First we fit a simple plane to the data,

\[ \text{Vel}_{(hvr)} = \beta_0_{(hvr)} + \beta_1_{(hvr)} H + \beta_2_{(hvr)} V \]  

\[ \text{Vel} \] is velocity and the subscripts refer to horizontal (h), vertical (v), and torsional (t), \( H \) is horizontal position, and \( V \) is vertical position. The bias component, \( \beta_0 \) indicates the velocity at straight-ahead gaze \((V=H=0^\circ)\). \( \beta_1 \) 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 Alexander’s Law in one-dimension with a straight line. In a second analysis, we fit the following 2nd order equation to horizontal, vertical, and torsional velocity:

\[ \text{Vel}_{(hvr)} = \beta_0_{(hvr)} + \beta_1_{(hvr)} H + \beta_2_{(hvr)} V + \beta_3_{(hvr)} HV + \beta_4_{(hvr)} H^2 + \beta_5_{(hvr)} V^2 \]  

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

Both the plane and the 2nd 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-tests. 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, and performed the same fitting procedures described above 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 0.1 or less generally indicating a reliable model (Kleinbaum et al. 1988).

An integrator time constant can be inferred from the fitted equations by $-1/$slope. For the plane fits, the slope is given directly as the fitted parameters (see equation 1). For the 2nd order fits, the slope can be found with the partial derivatives of equation 2,

$$\frac{\partial V_{\text{vel}}(\text{hor})}{\partial H} = \beta_1(\text{hor}) + \beta_3(\text{hor})V + 2\beta_4(\text{hor})H$$

$$\frac{\partial V_{\text{vel}}(\text{hor})}{\partial V} = \beta_2(\text{hor}) + \beta_3(\text{hor})H + 2\beta_5(\text{hor})V$$

which describe how velocity varies with horizontal (equation 3) and vertical (equation 4) eye position. 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 on to 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 counter clockwise, 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 2nd order functions described above 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 (#1) or severe nausea (#2,3,8). Patient #7 showed a right beating nystagmus but had reduced right vestibular function both during head impulse and caloric testing, the latter being performed one 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 three days. We interpret this “paradox” nystagmus as a so-called recovery nystagmus. But since the nystagmus was right beating as in left sided UVD, 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) as they 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 to panel A magnifies the horizontal component when they looked left, straight
ahead, and to the right, which more clearly shows the greater nystagmus when the patient was looking to the right.

Figure 2 here

Figure 3 shows a summary of the results of another patient (#6). Panels A-C show median eye velocity of individual slow phases as a function of horizontal and vertical eye position, along with the best fit 2nd order equations (equation 2). Figure 3D combines the three-dimensional velocity components into a single figure. In this plot, we averaged the eye movement data in each 5 second period where the flashing fixation light was in the same position. Each circle indicates the average horizontal and vertical position. The thick line shows the horizontal and vertical velocity, 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 counter-clockwise velocity. Here the overall pattern of the change in nystagmus is more evident than in the plots in panels A-C, although these provide a more intuitive view of the fitted surface.

Figure 3 here
In Figure 3A and Figure 3D, a change in horizontal eye velocity with horizontal eye position is seen which is consistent with Alexander’s Law, with velocity increasing when the subject looked in the fast phase direction (to the right). The best fit planes to the data are

\[\begin{align*}
Vel_h &= -7.5 - 0.0955H - 0.058V \\
Vel_v &= -2.9 - 0.0015H - 0.077V \\
Vel_t &= -1.5 - 0.045H - 0.014V \\
\end{align*}\]

Thus, horizontal velocity varies more with horizontal position than with vertical position, vertical velocity varies more with vertical than with horizontal position, and torsional velocity varies more with horizontal than with vertical position.

The 2nd order fits provide a more detailed analysis of how velocity changes with position. The best fit 2nd order surface for horizontal velocity for this patient, shown in Figure 3A, is

\[\begin{align*}
Vel_h &= -7.2 - 0.087H - 0.058V + 0.00044HV + 0.00094H^2 - 0.0023V^2 \\
\end{align*}\]
All the fitted parameters were significantly different from 0 with all p-values (ps) < 0.01. Horizontal velocity was -7.2°/s at straight ahead. The change in velocity with horizontal position was determined mainly by the linear component, with a value of -0.087 °/s°. Nonetheless, the 2nd 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 (\( H=V=0° \)), the change of horizontal eye velocity is -0.087 °/s°, and with V= 0°, at 20° left and right the change is -0.12 and -0.049 °/s°, respectively. So, 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° and with vertical positions of 20°, 0°, and -20° was -0.15, -0.058, and 0.033 °/s°, respectively.

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

\[
\text{Vel}_v = -2.2 + 0.0016H - 0.080V + 0.0012HV - 0.00055H^2 - 0.0024V^2
\]

and all parameters except the \( H \) term were significantly different from 0 (all ps < 0.01). Note that the small change in vertical velocity in down gaze, compared to the much larger change in up gaze, is captured in the equation with combination of the \( V \) and \( V^2 \) terms. The rate change in vertical velocity with vertical and horizontal position are
So 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 and in down gaze was about zero, but increased to around -5°/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 ps < 0.01), except the \( H^2 \) term.

Torsional velocity varies slightly with both horizontal and vertical position, and this is reflected in the change in velocity with vertical and horizontal gaze position:

\[ \frac{\partial Vel_t}{\partial V} = -0.04 - 0.0024H - 0.0086V , \]

and

\[ \frac{\partial Vel_t}{\partial H} = -0.053 - 0.0024V - 0.0002H . \]

Figure 3E shows the fitted velocity values at the same eye positions, as in Figure 3D. In Figure 3F, we subtracted the velocity at gaze straight ahead (the biases in the best fit equations) from the fitted values in Figure 3E, which more clearly shows how eye velocity changes with gaze position. There is considerable gaze evoked nystagmus in left and up gaze, but less of a change down and to the right.

Figure 4 shows an example from a different patient (#4), where the horizontal velocity decreases both to the left and right of straight ahead, but increases in up and down gaze.

The best fit plane equations for this patient’s data are
and the best fit 2\textsuperscript{nd} order equations are

\[ Vel_h = -5.3 - 0.071H - 0.0041V \]
\[ Vel_v = -1.4 + 0.012H - 0.054V \]
\[ Vel_t = -2.6 - 0.035H + 0.25V \]

Quality of the fitted surfaces
The plane surface fits were highly significant for all patients (overall F-test, all ps << 0.001). A substantial amount of variation was nonetheless not accounted for by the regression. The mean R\textsuperscript{2} values were 0.43, 0.39, and 0.25 for horizontal, vertical, and torsional velocity, respectively. Shrinkage values were low, averaging 0.02, or about 6\% of the mean R\textsuperscript{2}, indicating reliable fits.

Likewise, the fitted 2\textsuperscript{nd} order surfaces were also highly significant in all cases (F-test, all ps << 0.001), though again much of the variation in the data was not accounted for by the regression. The 2\textsuperscript{nd} order fits accounted for about 28\% more of the variance than the plane fits. For horizontal velocity, R\textsuperscript{2} varied from 0.22 to 0.86, with a mean of 0.56. The mean R\textsuperscript{2} for the fits to vertical velocity was 0.48, and ranged from 0.15 to 0.77, and the mean torsional R\textsuperscript{2} 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 R\textsuperscript{2}.

Dependence of horizontal velocity on gaze position
All patients showed significant horizontal drift to the left at straight ahead gaze. The average plane and 2\textsuperscript{nd} order fits are shown in Table 2. The plane fits indicated an average velocity at straight ahead gaze of -10.04 °/s. All 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 11s. There was no consistent change of horizontal velocity with vertical eye position.

For the 2nd 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 Figure 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 $H^2$ term, with a mean value of 0.003. Positive $H^2$ indicates a concave up surface, which, when combined with negative $H$ term, reduces horizontal velocity in the fast phase direction compared to if the term is 0. The average $HV$, $V$ and $V^2$ 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, though the signs were not consistent.

Differentiating the average 2nd order function fitted to the horizontal eye velocity with respect to horizontal position gives

$$\frac{\partial Veh_h}{\partial H} = -0.054 + 0.00018V + 0.0059H .$$

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 °/s/°, and at 20° left (the slow phase direction), the slope is -0.17 °/s/°, and the slope = 0.064 °/s/° at 20° right (the fast phase direction). These slopes correspond to time constants of 6, 18, and -16s 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 more than 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, five patients had a significant negative slope, four had significant positive slopes, and two 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 Alexander’s Law, though the long time constant is in the normal range [>20s (Cannon and Robinson 1987; Goltz HC 1997)]. There was not a consistent change of vertical velocity with horizontal position.

For the 2nd 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 $V^2$ term. As shown in Figure 5B, this is concave down, meaning that, when combined with the negative $V$-term, vertical velocity increases in the fast phase direction compared to if the term is 0. Eight patients also showed a significant dependence of vertical velocity on $H^2$, 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

$$\frac{\partial Vel_v}{\partial V} = -0.046 - 0.00003H - 0.0040V$$

Thus, at gaze straight ahead, the rate of change of vertical velocity with vertical position is -0.046 °/s/° (time constant = 22s), at 20° in the slow phase direction the slope is 0.035 °/s/° (time constant = -29s) and at 20° in the fast phase direction the slope is -0.12 °/s/° (time constant=8s). The position where the partial derivative changes sign is -11° into the slow phase direction. So, on average, the NI is leaky in the fast phase direction, but is unstable in the slow phase direction. Note that this is opposite the pattern seen for horizontal velocity.

Separate plane fits to vertical velocity in down and up gaze also support for these findings of a change in the NI time constant. In up gaze, 10 of 11 patients showed a significant ($p<0.05$) negative slope of velocity versus position, and one had a significant positive slope. In
down gaze, six patients had a significant negative slope, and five had significant positive slopes.

**Dependence of torsional velocity on gaze position**
According to the average plane fits, all 11 patients had counter-clockwise torsion at gaze straight ahead, with a mean of -4.4°/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°/s, and all 11 patients showed a statistically significant torsional bias (Table 2, see also Figure 5). Torsional velocity was significantly dependent upon horizontal position, with 9 of the 11 patients showing a significant negative slope, with a grand mean of -0.03 °/s/°. Torsional velocity did not consistently depend upon any of the other parameters.

**Summary of changes in 3D nystagmus**
Figures 5A show the average 2nd order fits, and Figures 5D-F show the same fits as 5A plotted as 3D surfaces. Velocity was predominately to the left with smaller downward and counter-clockwise 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 if the change of eye velocity was related to the magnitude of the vestibular nystagmus. We used the bias of the 2nd order fit as an estimate of the vestibular contribution to the nystagmus, and computed the slope of the 2nd order fitted equation for each subject at straight ahead and +/- 20° in the fast and slow phase directions of the horizontal and vertical nystagmus. The horizontal slope of the function at -20° 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° right gaze (correlation = -0.74 p<0.01), and the
correlation at straight ahead was not significant (correlation = 0.11, p > 0.5) (Figure 6). The slope in the slow phase direction was less than the slope in fast phase direction in all but two patients, and in 7 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.

Figure 6 here

Nystagmus direction changed as a function of gaze direction, as indicated in the average fit in Figure 5B, as well as the examples in Figures 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 equations 1 and 2 to these angles for each patient, and the average fits are shown in Table 3. (For the 2nd order fit, the horizontal-vertical angle is shown directly in Figure 5B in the lines showing the horizontal and vertical velocity.) The bias indicates the slow phase direction at straight ahead gaze. The plane and 2nd 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.

Table 3 here

**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 2nd order functions. In all patients the fits were highly significant. All patients showed Alexander’s Law for horizontal velocity, with velocity being higher in the fast phase compared to the slow phase direction. In addition, the 2nd 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, but beyond 10° in the fast phase direction, the NI is on average unchanged. Some patients even showed an unstable NI in the fast phase direction. While 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 upon both vertical position and its square. Overall, vertical velocity varied in accord with AL, with velocity being higher in fast phase direction. Torsional velocity depended mostly on horizontal position.

The change of horizontal velocity with horizontal position was correlated with the horizontal bias (Figure 6A), which could be expected if Alexander’s Law is an adaptive mechanism sensitive to the magnitude of nystagmus. Similar correlations were not found for vertical and torsional velocity, 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 vertical eye position. If Alexander’s Law 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, rather, that the horizontal, vertical, and torsional NIs operate separately to modify the different 3D components.

A comparison of the plane and 2nd order fits shows that the 2nd 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 components 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, though cerebellar structures known to be important for NI performance (flocculus and paraflocculus, (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 Alexander’s Law 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 after-nystagmus (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, while 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 Figures 5D 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, namely, the NI becomes leaky in down gaze to reduce drift velocity (see Figure 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. While there have been a few studies of the viscoelastic properties of the orbit in the horizontal
(Robinson 1964; Sklavos et al. 2006; Sklavos et al. 2005) and torsional (Seidman et al. 1995) directions, little is known for vertical movements, and the actual location of 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, while 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 up 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 similar manner as 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).
2004; Bockisch and Haslwanter 2001)). It is possible, therefore, that the torsional modulation we see is actually due to a correlation with torsional position which varies with horizontal position.

**Neural integrator time constant depends on gaze direction**
The prominent 2nd order components for horizontal and vertical velocity show that velocity was not proportional to gaze position. Robinson’s classic explanation of Alexander’s Law 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. While 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 (Chan and Galiana 2005; 2007) in humans, and Mensh et al (Mensh et al. 2004) in goldfish. Cannon et al (Cannon et al. 1983) originally proposed a related idea, of functionally independent NIs that are sensitive to different gaze directions, and Crawford and Vilis (Crawford and Vilis 1993) proposed multiple vertical-torsional NIs based upon pharmacological inactivation studies. More recently, Aksay et al (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, though 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 (Glasauer et al. 2003) concluded that the NI null point 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 (Crawford 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, a 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, which, 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 deg into the fast phase direction for horizontal velocity, and about 11 degrees 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 dependent drift that affects horizontal, vertical, and torsional velocity components. Regression analysis found that horizontal velocity varied with horizontal, but not vertical position. The significant 2nd order term indicate 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 upon gaze direction.
Acknowledgements

We would like to thank Itsaso Olasagasti for insightful discussions, Thomas Haslwanter for programming assistance, Tanja Schmücke Meier, Elisabeth Schaffflützel and Elena Buffone for assistance with patient evaluation and data collection, and Albert Züger for technical help.

Grants

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Figure legends

Figure 1. Hypothetical combinations of vestibular and gaze evoked nystagmus. A. The drift pattern associated with a left vestibular lesion that evokes only horizontal nystagmus. Each circle indicates horizontal and vertical position, and the thick line shows the horizontal and vertical velocity, and so the orientation of the line indicates direction and the length represents the speed. Drift velocity is to the left, and does not vary with horizontal or vertical position. B. Drift pattern associated with a gaze evoked nystagmus caused by a leaky horizontal NI (time constant = 6.7s). For eccentric horizontal gaze positions, the eye moves back to the center with a velocity that increases with eccentricity. Velocity does not vary with vertical position. C. The combination of A and B. The nystagmus velocity changes linearly with horizontal but not vertical eye position. D. Vestibular nystagmus which has horizontal, vertical, and torsional components. Thin lines show torsional velocity, with an upward line indicating clockwise velocity, and a downward line indicating counter-clockwise velocity. E. The pattern of drift that occurs when combining the vestibular nystagmus of D with a leaky horizontal NI (B). F. The pattern of drift that occurs when combining the vestibular nystagmus of D with both a leaky horizontal NI, and a leaky vertical NI. All simulations ignore other possible gaze dependent changes in velocity, such as the half- or quarter angle rules (Crane et al. 2006; Misslisch et al. 1994; Palla et al. 1999; Tweed et al. 1990).

Figure 2. A) Example eye position traces from patient #4. Each panel shows horizontal (bold), vertical (medium), and torsional (light) eye position as the patient tracked a flashing laser spot (not shown) that moved from left to right in 5 deg 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 panel A shows horizontal eye position, magnified, when gaze was left, straight ahead, and to the right.

Figure 3. Example eye velocity in patient # 6. The median horizontal (A), vertical (B), and torsional (C) velocity of individual slow phases (•) is plotted against horizontal and vertical eye position. The best fit 2nd order surface is also shown. D) A summary of the 3D drift is shown for the same subject. Each circle indicates the average horizontal and vertical position
for the slow phase eye movements during each fixation period (5 seconds duration). The thick line shows the horizontal and vertical velocity, and so the orientation of the line indicates direction (for example, a line pointing down and to the left shows downward and leftward velocity) 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.

**Figure 4.** Example eye velocity in patient #4. The median horizontal (A), vertical (B), and torsional (C) velocity of individual slow phases (•) is plotted against horizontal and vertical eye position. The best fit 2nd order surface is also shown. D. A summary of the 3D drift is shown for the same subject. Each circle indicates the average horizontal and vertical position for the slow phase eye movements during each fixation period (5 seconds duration). The thick line shows the horizontal and vertical velocity, and so the orientation of the line indicates direction (for example, a line pointing down and to the left shows downward and leftward velocity) 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.

**Figure 5.** A) The average 2nd order surface fits, with the same format as Figure 3D. B) 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. C) Gaze dependent changes in drift velocity, which was found by subtracting the fitted drift at 25° up from all other gaze positions. See Discussion for details. D-F) The average 2nd order surface fits, shown as surfaces.

**Figure 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.

References


Chan WW, and Galiana HL. Integrator function in the oculomotor system is dependent on sensory context. *Journal of neurophysiology* 93: 3709-3717, 2005.


Table 1. Results of vestibular function tests.

<table>
<thead>
<tr>
<th>Patient No</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>0.41 / 0.56</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(^\text{+})</td>
<td>91(^\text{+})</td>
<td>IVP</td>
</tr>
<tr>
<td>8</td>
<td>0.60 / 0.55</td>
<td>0.7 / 0.87</td>
<td>0.94 / 0.61</td>
<td>NA</td>
<td>NA</td>
<td>IVP</td>
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<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>
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<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>
</tbody>
</table>

Normal \(\geq 0.71 / 0.70\) \(\geq 0.69 / 0.54\) \(\geq 0.67 / 0.68\) \(\leq +/\text{-} 25\) \(\leq +/-30\)

Gain values for the vestibulo-ocular reflex test as measured by head impulse testing in the SCC planes, horizontal right/left = horizontal plane, head movement towards right / left, respectively; RALP/LARP = plane of right anterior and left posterior SCC, down = head movement downwards in the respective plane testing mainly for anterior SCC function and up testing mainly for posterior SCC function. 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 bold, and reduced gain values of the supposed intact side are in grey. NA = not available. PLF = perilymphatic fistula and IVP = idiopathic vestibulopathy.
Table 3. The average best fit parameters to nystagmus direction.

<table>
<thead>
<tr>
<th></th>
<th>HV angle</th>
<th>HT angle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plane fits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bias</em></td>
<td>103° ** (+11/-0)</td>
<td>112° ** (+11/-0)</td>
</tr>
<tr>
<td><em>H</em></td>
<td>-0.063 (+4/-7)</td>
<td>0.041 (+8/-2)</td>
</tr>
<tr>
<td><em>V</em></td>
<td>0.21 ** (+9/-1)</td>
<td>-0.14 † (+3/-7)</td>
</tr>
<tr>
<td><em>R²</em></td>
<td>0.33</td>
<td>0.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2nd Order Fits</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bias</em></td>
<td>101° ** (+11/-0)</td>
<td>110° ** (+11/-0)</td>
</tr>
<tr>
<td><em>H</em></td>
<td>-0.069 (+4/-7)</td>
<td>0.056 (+8/-3)</td>
</tr>
<tr>
<td><em>V</em></td>
<td>0.25 ** (+10/-1)</td>
<td>-0.13 † (+3/-7)</td>
</tr>
<tr>
<td><em>H</em>×<em>V</em></td>
<td>-0.00048 (+5/-5)</td>
<td>0.0036 (+8/-2)</td>
</tr>
<tr>
<td><em>H</em>²</td>
<td>0.00015 (+6/-4)</td>
<td>0.00097 (+4/-3)</td>
</tr>
<tr>
<td><em>V</em>²</td>
<td>0.012 † (+8/-3)</td>
<td>0.012 (+5/-5)</td>
</tr>
<tr>
<td><em>R²</em></td>
<td>0.44</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Nystagmus direction is characterized by two angles. The 3D velocity vector was projected on the planes defined by the horizontal and vertical components, and the plane defined by the horizontal and torsional components, and the angles in the planes were calculated. For the horizontal-vertical angle, nystagmus direction 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, for the horizontal-torsional angle, 0° is clockwise torsion, 90° is leftward, 180° is counter clockwise, and 270° is rightward. The numbers in parenthesis indicate the number of patients for which that parameter was significantly different from 0 (p> 0.05) in the position and negative directions. ** p< 0.01; * p< 0.05, † p< 0.1
Table 2. Average best fit parameters across all subjects.

<table>
<thead>
<tr>
<th></th>
<th>Horizontal velocity</th>
<th>Vertical velocity</th>
<th>Torsional velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias</strong></td>
<td>-10.04** (+0/-11)</td>
<td>-2.06** (+2/-9)</td>
<td>-4.40* (+0/-11)</td>
</tr>
<tr>
<td><strong>H</strong></td>
<td>-0.088 ** (+1/-10)</td>
<td>-0.0074 (+3/-4)</td>
<td>-0.042** (+0/-11)</td>
</tr>
<tr>
<td><strong>V</strong></td>
<td>-0.027 (+4/-7)</td>
<td>-0.037* (+1/-9)</td>
<td>0.014† (+6/-2)</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.43</td>
<td>0.39</td>
<td>0.25</td>
</tr>
</tbody>
</table>

2nd Order Fits

<table>
<thead>
<tr>
<th></th>
<th>Horizontal velocity</th>
<th>Vertical velocity</th>
<th>Torsional velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bias</strong></td>
<td>-10.35** (+0/-11)</td>
<td>-1.82** (+2/-9)</td>
<td>-4.31* (+0/-11)</td>
</tr>
<tr>
<td><strong>H</strong></td>
<td>-0.054* (+1/-10)</td>
<td>-0.0020 (+4/-5)</td>
<td>-0.030** (+2/-9)</td>
</tr>
<tr>
<td><strong>V</strong></td>
<td>-0.026 (+3/-8)</td>
<td>-0.046 * (+1/-9)</td>
<td>0.016 (+7/-3)</td>
</tr>
<tr>
<td><strong>H*V</strong></td>
<td>0.00018 (+7/-4)</td>
<td>-0.00003 (+5/-5)</td>
<td>-0.00005 (+6/-5)</td>
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<tr>
<td><strong>H²</strong></td>
<td>0.0030* (+8/-0)</td>
<td>0.00051 † (+8/-3)</td>
<td>0.0015 (+7/-3)</td>
</tr>
<tr>
<td><strong>V²</strong></td>
<td>-0.00054 (+5/-6)</td>
<td>-0.0020 * (+1/-9)</td>
<td>-0.0021 (+3/-8)</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.56</td>
<td>0.48</td>
<td>0.42</td>
</tr>
</tbody>
</table>

The numbers in parenthesis 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 the plane fits, all 11 patients had a significant horizontal bias less than 0. ** p < 0.01, * p < 0.05, † p < 0.1