Three-Dimensional Eye Position and Slow Phase Velocity in Humans With Downbeat Nystagmus

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Glasauer, S., M. Hoshi, U. Kempermann, T. Eggert, and U. Büttner. Three-dimensional eye position and slow phase velocity in humans with downbeat nystagmus. J Neurophysiol 89: 338–354, 2003; 10.1152/jn.00297.2002. Downbeat nystagmus (DN), a fixation nystagmus with the fast phases directed downward, is usually caused by cerebellar lesions, but the precise etiology is not known. A disorder of the smooth-pursuit system or of central vestibular pathways has been proposed. However, both hypotheses fail to explain why DN is usually accompanied by gaze-holding nystagmus, which implies a leaky neural velocity-to-position integrator. Because three-dimensional (3-D) analysis of nystagmus slow phases provides an excellent means for testing both hypotheses, we examined 19 patients with DN during a fixation task and compared them with healthy subjects. We show that the presentation of DN patients is not uniform; they can be grouped according to their deficits: DN with vertical integrator leakage, DN with vertical and horizontal integrator leakage, and DN without integrator leakage. The 3-D analysis of the slow phases of DN patients revealed that DN is most likely neither caused by damage to central vestibular pathways carrying semicircular canal information nor by a smooth pursuit imbalance. We propose that the observed effects can be explained by partial damage of a brain stem-cerebellar loop that augments the time constant of the neural velocity to position integrators in the brain stem and neurally adjusts the orientation of Listing’s plane.

INTRODUCTION

Downbeat nystagmus (DN) is defined as fixation nystagmus in which the fast phase is directed downward during gaze straight ahead. The drifts of the eyes show a linear increasing or decreasing velocity (Leigh and Zee 1999). Pathoanatomically, lesions of the cerebellum, mainly the vestibulo-cerebellum and seldom of the brain stem, have been shown (Baloh and Yee 1989; Büttner et al. 1995). Several explanations for the pathogenesis of DN have been considered. One hypothesis, probably the most favored one, assumes DN to be a central vestibular syndrome (Baloh and Spooner 1981; Böhmer and Straumann 1998; Brandt and Dieterich 1995; Büchele et al. 1983; Marti et al. 2001). Another hypothesis is that an imbalance of the vertical smooth pursuit tone implies a constant vertical velocity offset (Zee et al. 1974). To explain the dependence of DN on vertical eye position (vertical integrator failure), these authors additionally assumed a neural integrator deficit that results in an inability to hold the eyes in eccentric positions.

Recently Straumann et al. (2000) investigated a homogenous group of subjects with hereditary cerebellar atrophy, most of whom had DN. With three-dimensional search-coil recordings they demonstrated that all subjects had a uniform eye movement pattern consisting of the DN component as well as a horizontal centripetal drift and a torsional drift that increased with horizontal eye eccentricity. The torsional drift component was accompanied by an increase of vertical drift velocity during lateral gaze. Straumann et al. (2000) proposed that the torsional drifts observed in DN constitute a mismatch between torsional postsaccadic position of the eye defined by the saccadic burst and the torsional resting position defined by the mechanical properties of the eye plant.

In healthy subjects, small postsaccadic torsional drifts called blips can be observed (Straumann et al. 1995). Pathologically large amplitude blips were found in a patient with a dorsolateral medulla and cerebellar lesion (Helmchen et al. 1997). Torsional drifts violate Listing’s law, a fundamental property of ocular fixations. It states that the eye position has a zero torsional component when expressed as single rotations from a certain starting position, the so-called primary position. Fixations and to a lesser degree smooth pursuit and saccades in normal human subjects obey Listing’s law with SDs of maximum 1° (Straumann et al. 1996; Tweed and Vilis 1990; Tweed et al. 1992). It has been shown experimentally that Listing’s law represents an intrinsic property of brain stem regions such as the burst generator or the velocity-to-position integrator (Crawford 1994). In addition, peripheral structures, the pulleys of the eye plant, are possibly an important factor in implementing Listing’s law (Quaia and Optican 1998; Schnabolk and Raphan 1994). Other eye movements such as the vestibulocular reflex (VOR) or optokinetic nystagmus do not obey Listing’s law. Therefore disorders of the smooth pursuit system or a leaky neural integrator are supposed to obey Listing’s law, whereas nystagmus due to vestibular imbalance violates it.

The compliance of a vertical drift, as found with DN, with Listing’s law in a head-fixed coordinate system can best be evaluated during different horizontal eye positions. If the axis of rotation of the eye is head-fixed, the rotation leads at all horizontal eye positions to a purely vertical angular velocity...
drift. In contrast, if the rotation axis is eye-fixed, a torsional component proportional to the change in horizontal eye position is introduced. For drifts related to smooth pursuit eye movements, the rotation axis of the eye is actually between eye- and head-fixed (half-angle rule) (Tweed and Vilis 1987, 1990). Thus the half-angle rule reflects Listing’s law. It has been shown that during low-velocity VOR (such as oscillations used for clinical testing) the ocular rotation axis changes its orientation by one-fourth of the horizontal eye position (quarter-angle rule) (Misslisch and Tweed 2001; Misslisch et al. 1994; Palla et al. 1999). This implies a smaller torsional component of the angular velocity than in the half angle rule.

To analyze the dependence of downbeat nystagmus slow phase velocity on eye position, we recorded three-dimensional (3-D) eye movements with the search-coil technique and used multiple regression to answer the following questions: does DN have different etiologies and present with different features? Which different subtypes of DN can be distinguished? Do all types of DN violate Listing’s law? Are the observed slow phases compatible with the hypothesized vestibular or smooth pursuit origins of the nystagmus? The answer to these questions might help us better understand the transformation of premotor oculomotor signals into ocular motor neuron activity.

In the following, we show that 3-D analysis of the slow phases of DN patients reveals that DN is probably neither caused by damage to central vestibular pathways carrying semicircular canal information nor by a smooth pursuit imbalance. We propose that the observed effects can be explained by partial damage of a brain stem-cerebellar loop that augments the time constant of the neural velocity to position integrators in the brain stem and neurally adjusts the orientation of Listing’s plane. A preliminary account of the present data were given elsewhere (Hoshi et al. 2001).

**METHODS**

**Subjects**

Nineteen patients (ages: 29–84 yr, mean: 61.5 yr) with DN were examined with standard clinical methods and by MRI scans of the brain stem and cerebellum. Two patients had a cerebellar atrophy, three had an Arnold-Chiari malformation, two had a paraneoplastic syndrome, and three patients had lesions affecting cerebellar structures; the disorder of the remaining nine patients had no specific etiology. This distribution is generally seen in patients with DN (Leigh and Zee 1999). Eighteen healthy subjects served as controls (ages: 23–91 yr, mean: 46.9 yr). All patients and subjects gave their informed consent after explanation of the experimental procedure that was in accordance with the Declaration of Helsinki.

**Experimental paradigm**

A laser dot (size: 0.1°, screen distance: 140 cm) jumped to eight positions arranged on a square around the gaze straight ahead position (Fig. 1C). Positions were placed ±18° from the center on the horizontal and vertical meridians and ±25.46° on the two oblique meridians. Subjects were seated in the center of the coil frame in an otherwise dark environment and were asked to fixate the visible target, which jumped every 2.5 s between gaze straight ahead and one of the peripheral targets. The head of the subject was immobilized in an upright position by an adjustable chin rest. An additional search coil fixed to the patient’s forehead monitored immobility. The conjunctiva of the left eye, in which the dual search coil was placed, was anesthetized with oxybuprocain HCl.

**Search-coil recordings**

The field coil system consisted of a cubic (side length: 140 cm) aluminum frame that produced three orthogonal magnetic fields (Remmel Systems). Ocular rotation of the left eye around the horizontal (z axis), vertical (y axis), and the torsional (x axis) was recorded with a dual search coil (Skalar, Delft, Netherlands). Coil and target position data were sampled at a rate of 1 kHz.

**FIG. 1.** Original recordings from a control subject. Eye positions are expressed as rotation vector components following the right-hand rule and converted to degrees for convenience. Thus positive vertical eye position indicates downward gaze, positive horizontal eye position leftward gaze as seen from the subject, and positive torsion clockwise eye rotation, again seen from the subject’s perspective. Slow phases and fixation phases are shown as big dots, saccadic eye movements are shown as small dots. A–C: data in head-fixed coil coordinates. A: eye positions viewed from above. B: eye positions viewed from the side. - - -, the fitted displacement plane (Listing’s plane). The tilt of the plane of eye positions corresponds to an angle of 16.8° upward tilt of primary position. The plane has a SD of 0.44°. C: frontal view of eye positions. The 9 target positions are clearly visible as horizontal-vertical eye positions. D–F: data after rotation to Listing’s plane. Note the different axis range; the 0 position is not aligned with gaze straight ahead. D and E: torsional eye position components align with the torsional axis.
Calibration

Immediately before each eye movement recording, the coil was moved manually within the coil frame to determine the magnitude and relative orientation of the three magnetic fields and the gain of the directional coil (see Appendix for detailed description). Then the offsets and the gain of the torsional coil as well as the relative orientation of the coil on the eye were determined on the basis of data recorded while the subject was wearing the eye coil and was looking at different target positions. The calibration did not depend on accurate fixation of these targets. The resulting eye positions were expressed as rotation vectors (Haustein 1989).

Data analysis

Data were analyzed off-line in MATLAB. The calibrated data were low-pass filtered with a digital Gaussian filter having a band width of 30 Hz. Saccade and fast phase were automatically detected and removed from the data using a combined velocity-acceleration criterion in interactive software so that detection errors could be corrected manually. Slow phases shorter than 25 ms were discarded. For each remaining slow phase, the median slow phase component velocity and eye position were used for analysis. Slow phases longer than 200 ms were divided into two or more parts of equal length to avoid collecting fewer data points for periods without frequent fast phases. Most of the analysis was performed after fitting Listing’s plane to the data and transforming the whole data set into Listing’s coordinates.

Slow phase component velocity, the temporal derivative of eye position, is not equal to angular velocity (Haslwanter 1995; Hepp 1994). In the figures, component velocity was expressed in /s and multiplied by 2 for easy comparison with the more familiar angular velocity.

The dependence of slow phase component velocity \( r \) on eye position \( r \) was analyzed by a linear least-squares fit procedure to the equation

\[
\dot{r} = T \cdot r + r_0
\]  

with the free parameters \( T \) and \( r_0 \). \( T \) is a 3x3 matrix describing this dependence on eye position (see Crawford 1994), and \( r_0 \) is a component velocity vector describing an eye-position independent velocity offset. A single velocity component is, therefore, described as a linear combination of all three eye position components and a velocity offset. As an example, the equation for the vertical eye component velocity \( v \) is

\[
v = t_v \cdot \dot{r}_v + r_v + t_{v0} \cdot r_{v0}\) (2)

with \( r_v, \dot{r}_v, r_{v0} \) being the torsional, vertical, and horizontal eye position components, \( r_0 \) the fitted vertical velocity offset; and \( t_v, \dot{t}_v, t_{v0} \) the fitted factors (elements of the matrix \( T \)), describing the influence of the respective eye position component on vertical eye velocity. In the following, \( t_v \) is called a “principal” dependence because it describes the relationship between vertical eye velocity and vertical eye position; \( t_h \) and \( t_{h0} \) are called “nonprincipal” dependencies. Therefore to describe each eye velocity component, four free parameters are computed. To describe 3-D eye velocity, 12 free parameters are fitted. During this general fit, which is equivalent to a multiple linear regression analysis, those 10% of the data points having the largest residual error were classified as outliers and removed from the data. The multiple regression results are used in the following to derive parameters such as the null position of the nystagmus.

To test for different types of eye-position dependence, three types of analysis were performed.

In the first analysis, the nonprincipal (or off-diagonal) elements of \( T \) are set to zero. In this case, the slow phase eye velocity obeys Listing’s law, if the torsional offset is zero. It can thus be interpreted as a leaky integrator with vertical and/or horizontal offsets. This procedure is equivalent to a simple linear regression of each eye velocity component over the respective eye position component. Thus each eye velocity component is described by

\[
\dot{r}_i = t_i \cdot \dot{r}_i + r_i + \tau_i \cdot \dot{r}_0 \]  

with \( i = t, v, h \) for torsional, vertical, horizontal. Here \( t_i \) is the slope between velocity and position and \( \tau_i \) is the slow phase velocity at zero eye position (primary position). In this case, each velocity component is described by only two free parameters, which gives six parameters for 3-D eye velocity. Note that \( \tau_i = -1/t_i \) can be interpreted as the respective integrator time constant.

In the second analysis, best subset multiple regression was performed to validate the results from the complete regression analysis. For best subset regression, each possible combination of the parameters \( t_i \) of the matrix \( T \) was fitted to the data, and the best combination was determined according to the minimal Mallows’ \( \text{Cp} \) statistics. The minimally possible number of fitted parameters is three: the three velocity offsets.

In the third analysis, a quadratic multiple regression (21 parameters) was performed to validate clinical and experimental reports about increasing vertical drift velocity during lateral gaze (e.g., Straumann et al. 2000).

Statistical analysis

As mentioned in the preceding text, fitting Eq. 1 is equivalent to a multiple linear regression, and fitting Eq. 3 is equivalent to a simple linear regression analysis using the eye position components as independent variables and the derivatives of the eye position components as dependent variables. Thus the statistical analysis is based on tests for multiple regression analysis. A fit was considered significant if \( P < 0.01 \) as computed by the \( F \) test. As a further indicator of the goodness of fit and to compare the different types of analysis described in the preceding text, the \( R^2 \) value was used. It gives the percentage of variance of the data described by the respective model. For one-dimensional regression, the \( R^2 \) value is equivalent to the squared correlation coefficient. If the \( R^2 \) value was below 50%, the fit was considered to insufficiently describe the data. For further analysis of single parameter values, the SDs of each fitted parameter and the respective probability that the parameter is different from zero was computed. A parameter with a \( P \) value of \( P < 1-(1-0.025)^{1/10} \) with \( n \) being the number of parameters is considered significantly different from zero (Bonferroni correction). Comparison of simple regression (Eq. 3), multiple regression (Eq. 1), and quadratic regression was done using \( F \) statistics, which evaluates whether adding the parameters yields a significant increase (\( P < 0.01 \)) in explained variance.

Coil slippage

As has been noticed previously during recordings, torsional slippage of the search coil is frequently observed (Straumann et al. 2000; Van Rijn et al. 1994). To minimize these effects, the whole duration of the experiment lasted only 45 s. In addition, the torsional eye position at gaze straight ahead, to which the eye returned after each eccentric position, served as a control. Coil slips happened exclusively from the previous fixation period. In such a case, all subsequent eye position data were rotated by an eye-fixed torsional angle so that the median torsion during both fixation periods remained the same. However, the results depended only negligibly on whether slip was removed or not. For example, the SDs of Listing’s plane decreased by only 0.1° for both patients and healthy subjects. Therefore the results of the original data set are reported.
Definitions

Three-dimensional eye positions were determined according to the right-hand rule with right rotation around the x axis referring to exocyclorotation of the right and incyclerotation of the left eye, around the y axis to downward, and around the z axis to leftward movements. Eye positions are expressed as components of rotation vectors (Haustein 1989) and, for convenience, converted to Listing’s angles given in degrees using $\varphi = \arctan(z) \times 360/\pi$.

Gaze straight ahead, i.e., the midposition of the eye in the orbit, was maintained during fixation of the center position of the target. It is the reference position for analysis performed in head coordinates.

Primary position is the reference position in a 3-D coordinate system, from which ocular positions during fixation can be obtained by single rotations with all rotation axes lying in a plane (Listing’s plane) and with gaze direction in primary position being orthogonal to Listing’s plane.

Null position is defined as the eye position at which an eye position-dependent nystagmus reverses its direction. Gaze straight ahead, primary position, and null position do not have to coincide. The direction of nystagmus always refers to the fast phase if not stated otherwise.

“Eye velocity” refers to the temporal derivative of eye position (component velocity) rather than to angular eye velocity, if not stated otherwise.

To distinguish between different position-velocity dependencies, we define a dependence as “principal” if it relates velocity to position of the same dimension, e.g., dependence of vertical velocity on vertical position. In contrast, other dependencies such as dependence of vertical velocity on horizontal position are called “nonprincipal.”

RESULTS

Listing’s plane

Listing’s plane was determined from eye positions of slow phases for subjects with DN and fixation periods for healthy subjects.

For healthy subjects, the SD for the width of Listing’s plane ranged from 0.39 to 1.33 (average: 0.79°) and the primary positions ranged from 10.0° down to 21.0° up (average: 7.0 ± 9.7° up, see Fig. 1 for an example) in the vertical and from 11.5° left to 16.3° right (average: 0.8 ± 8.0° right) in the horizontal plane. These data correspond well to previous findings (Haslwanter et al. 1994). We also computed the mean angle between gaze straight ahead and primary position. This angle quantifies the distance the eye has to be rotated from the gaze straight ahead position to primary position. For healthy subjects, it was $13.0 \pm 5.3°$.

Results for the patients with DN were similar (see Fig. 2 for an example). For all patients SD of Listing’s plane ranged from 0.59 to 1.47° (average: 0.92°), which is on average slightly larger but not significantly different from that of healthy subjects ($t$-test, $P = 0.12$). Primary position was on average 9.5 ± 8.4° (range: 5.4° down to 23.9° up) above gaze straight ahead in the vertical plane and ranged from 25.4° left to 18.8° right (average: 2.4 ± 11.9° left) in the horizontal plane. The mean angle between straight ahead and primary position (14.5 ± 9.4°) was not different from that of healthy subjects ($t$-test; $P = 0.58$). Thus as in healthy subjects, primary position is on average above gaze straight ahead with very little horizontal deviation.

General characteristics

To analyze DN during gaze straight ahead, a multiple linear regression (Eq. 1) was fitted to the data before rotation to Listing’s plane. According to the regression, all patients had a significant upward vertical drift during fixation of the center target (DN at gaze straight ahead) with vertical slow phase velocity ranging from $-0.63$ to $-9.40/\text{s}$. Some healthy subjects also exhibited small but significant vertical offsets, which were, however, mostly downward and smaller than 0.57/\text{s} (range: $-0.08$ to 0.38/\text{s}) except for the 91-year-old control subject (minor upbeat nystagmus, 0.60/\text{s}). Vertical drift in patients showed no inversion of Alexander’s law (Robinson et
al. 1984), i.e., the vertical drift velocity increased with downward gaze for all patients (range of difference between upward and downward gaze 0.23–8.9°/s). Six patients (31%) showed upbeat nystagmus during upward gaze (up to 2.7°/s), i.e., slow phase velocity reversed sign. In these cases, DN during downward gaze was always larger than upbeat during upward gaze.

**Slow phases**

For further analysis, only slow phases or fixation periods were considered. Slow phase component velocity was separated into the vertical, horizontal and torsional drift components. First, the regression results (12 parameters for multiple regression or 6 parameters for simple regression, see METHODS) will be considered, then the results will be compared with best subset regression. To evaluate possible reasons of velocity offsets, the fitted parameters will then be compared with predictions for different offsets, such as head- or eye-fixed angular velocity offsets. The results of the quadratic regression will be considered separately.

Multiple regression yielded significant fits for all subjects. The \( R^2 \) values of complete multiple regression after rotation to Listing’s plane for patients ranged from 0.50 to 0.93, for healthy subjects from 0.06 to 0.34. Thus the statistical model explained more than 50% of the variance of the median slow phase data for all patients, while only up to 34% was explained for healthy subjects. The low \( R^2 \) values for healthy subjects indicate that, contrary to those for patients, drift velocities were close to noise level or resulted from noise. The root-mean-squared error (RMSE) ranged from 0.51 to 1.65°/s for patients and from 0.17 to 0.76°/s for healthy subjects. The RMSE reflects scatter in the data (see center position in Fig. 3 for an example) and measurement noise.

Figure 3 gives an example for the differences between simple, multiple linear, and multiple quadratic regression. In Fig. 4, an example of original median slow phases and pre-
cate horizontal and vertical integrator failure (diagonal elements), violation of Listing’s law by significant influence of horizontal eye position on torsional drift velocity (upper right element of the matrix), and a vertical velocity offset. In the following, it is shown that considering only mean results may give the incorrect impression of a homogeneous patient population.

Primary position and vertical drift velocity

An increasing vertical velocity on downward gaze implies an integrator failure. Ocular drifts due to an integrator failure reverse direction at the null position. Recent studies suggest that this null-position might coincide with the primary position (Crawford 1994). If a vertical drift is present at the primary position, an additional vertical velocity offset has to be assumed. Therefore a multiple linear regression (Eq. 1) was performed after rotation to Listing’s plane. For two patients (11%), the null-position coincided with primary position. For one patient, the sign reverted, i.e., this patient had upbeat nystagmus in primary position. For 11 patients (58%), the vertical offset decreased with respect to the fit in head coordinates, i.e., with respect to gaze straight ahead. Thus their null position was closer to primary position than to straight ahead. The null positions computed from Eq. 1 showed considerable variation because some patients exhibited only moderate integrator leakage but strong offsets (see following text). For them, the theoretical null position was out of the vertical oculomotor range (±40°); this was the case for seven patients. For all patients, the median vertical null position was 14.9° above primary position.

FIG. 4. Median values of slow phase angular velocity (torsional, vertical, horizontal) for patient V (○, same data as in Fig. 3) compared with the predicted values obtained from the multiple linear regression (+, \( R^2 = 0.90 \)). Each data point reflects a time period of 50–200 ms (depending on nystagmus frequency, see METHODS) of slow phase velocity. Bottom: target position (solid: horizontal, dashed: vertical). All vertical slow phases had values below 0, implying large vertical offsets. † (in the torsional velocity plot), a high postcaccadic torsional velocity accompanied by a torsional-horizontal drift toward the small torsional offset. ↑ (in the vertical velocity plot), the time that eye position is close to the vertical null position, i.e., when the subject looks to the upper-right target.

dicted slow phases is given for the same patient as in Fig. 3 to show how well the predictions from the multiple linear regression coincide with the data. Figure 5 further shows that prediction of positional drift directions from the fitted median slow phase velocity agrees well with the recorded data.

For the patient depicted in Figs. 2–5, the multiple linear regression fit assumes the following form

\[
\mathbf{L} = \begin{bmatrix}
-0.8975^* & -0.0042 & 0.0868^* \\
0.0769 & -0.2079^* & -0.0672^* \\
0.8863^* & -0.0149 & -0.2234^*
\end{bmatrix} \begin{bmatrix}
\mathbf{r} \\
\mathbf{z}
\end{bmatrix}
\]

with the asterisks indicating parameters (units 1/s for matrix and 0.5 × rad/s for offset) significantly different from zero. For example, the lower right value in the matrix (−0.2234) indicates that horizontal eye position induces horizontal drift; for 10° of lateral gaze with respect to primary position, a horizontal drift of about 2.2°/s is induced. The middle right value (−0.0672) indicates that horizontal position also influences vertical drift; the lateral gaze of 10° thus not only causes the eye to move horizontally, but also vertical drift of about 0.7°/s is induced. The vertical offset (−0.0520) indicates a vertical upward drift of 0.05° × 360/π = 5.7°/s in primary position (compare with Fig. 3).

The mean results (± SD) for all 19 patients are summarized in the following equation

\[
\mathbf{L} = \begin{bmatrix}
-0.13 ± 0.29 & 0.01 ± 0.02 & 0.04 ± 0.04^* \\
-0.12 ± 0.26 & -0.11 ± 0.07^* & -0.01 ± 0.04 \\
0.03 ± 0.26 & -0.01 ± 0.02 & -0.08 ± 0.10^*
\end{bmatrix} \begin{bmatrix}
\mathbf{r} \\
\mathbf{z} \\
\mathbf{t}
\end{bmatrix}
\]

with the asterisks denoting elements significantly different from zero (t-test, Bonferroni corrected). These elements indicate horizontal and vertical integrator failure (diagonal elements), violation of Listing’s law by significant influence of horizontal eye position on torsional drift velocity (upper right element of the matrix), and a vertical velocity offset. In the following, it is shown that considering only mean results may give the incorrect impression of a homogeneous patient population.

FIG. 5. Eye position during slow phases (thick lines, same data as in Figs. 2–4) and prediction of slow phase drift from multiple regression (thin lines; arrows indicate drift direction; positive vertical positions correspond to gaze down). Data are shown for torsional 0 position in Listing’s coordinates. Even though the fit was performed only for slow phase median values (see Fig. 4), the predicted drift directions coincide well with the real data. According to the fit, the vertical and horizontal components of eye velocity become 0 for an eye position within Listing’s plane of 25.3° up and 9.1° right from primary position. In this position, the patient would still show torsional nystagmus. The true null position at which the eye stops drifting is 2.0° clockwise (and thus out of Listing’s plane), 27.0° up, and 1.4° right from primary position.
Velocity dependence on nonprincipal eye position components

To determine if there are significant dependencies on nonprincipal eye position components, e.g., vertical velocity dependence on horizontal eye position, the simple regression (6 parameters, Eq. 3) and the complete regression (12 parameters, Eq. 1) were compared for each subject using an F test. For 15 patients (79%) but only 5 healthy subjects (28%), the fit was significantly better when including nonprincipal eye position dependence, i.e., when fitting all 12 rather than only 6 parameters. The data of the remaining four patients could sufficiently be described by a simple regression.

To evaluate the number of necessary parameters for each patient, a best-subset multiple regression analysis was performed. This type of analysis finds the minimal number of parameters, taking into account that more parameters always result in better fits. For patients, 8–12 parameters yielded best results (healthy subjects: 5–11 parameters; Mallow’s Cp statistics). Table 1 shows the number of statistically significant parameters for this analysis. It closely resembles that of the complete multiple linear regression analysis (not shown).

Velocity dependence on principal position components and velocity offsets

As can be seen from Table 1 (white areas), 18 patients (95%) exhibited a significant dependence of vertical velocity on vertical eye position; this can be interpreted as vertical integrator failure. Thirteen patients (68%) showed a significant horizontal dependence (see Fig. 6). The negative principal dependencies can be interpreted as inverse integrator time constants. Positive principal dependencies would reflect an inversion of Alexander’s law that was not found in our patients. Hence, vertical integrator failure did not imply horizontal integrator failure. Figure 6 also shows that six patients (above the diagonal line) had more horizontal than vertical integrator failure, i.e., in these patients the gaze-dependent changes of drift velocity were more prominent for the horizontal than for the vertical direction. Only seven patients (37%) had a torsional dependence significantly different from zero. For patients, the mean time constants were 4.5 s torsional, 8.8 s vertical, and 11.8 s horizontal. Only two patients had vertical time constants larger than 50 s. Healthy subjects showed 8.8 s torsional, 119 s vertical, and 374 s horizontal. Vertical time constants in the control group were larger than 50 s, except for the 91-year-old control subject, who had 15.7 s. The low time constant for the torsional integrator in both patients and healthy subjects confirms other results demonstrating that the torsional velocity-to-position integrator is also leaky in healthy subjects (Seidman et al. 1994).

Significant offsets (reflecting nystagmus at primary position) were found in 17 patients (89%) for vertical, 11 patients (58%) for horizontal, and 14 patients (74%) for torsional velocity. Mean offsets for all patients were 0.36 ± 0.63°/s torsional (range: −0.63–1.73°/s), −2.9 ± 2.7°/s vertical (range: −9.54–1.56°/s), and −0.06 ± 1.4°/s horizontal (range: −3.26–3.62°/s). Thus some patients not only had vertical but also considerable horizontal nystagmus at primary position. For healthy subjects, mean offsets were 0.05 ± 0.28°/s torsional (range: −0.72–0.54°/s), 0.13 ± 0.17°/s vertical (range: −0.11–0.46°/s), and −0.07 ± 0.09°/s horizontal (range: −0.25–0.15°/s).

Different groups of patients

The patients could be grouped according to the kind of integrator failure and offset (see Fig. 7). Basically, three groups were distinguished with respect to integrator failure (see also Fig. 6): patients with vertical and horizontal integrator failure (13, see numbers at connecting lines in Fig. 7, 13 = 1 + 3 + 9), patients with only vertical integrator failure (5 = 1 + 3 + 1), and one patient with normal horizontal and vertical integrator function.

VERTICAL NYSTAGMUS. All patients except one showed a significant dependence of vertical velocity on vertical position.

![Graph](http://jn.physiology.org/)

**TABLE 1.** Significant dependencies of eye velocity on eye position for all 19 patients following best-subset multiple regression of slow phase data after rotation to Listing’s plane

<table>
<thead>
<tr>
<th>Position Component</th>
<th>Torsional Position</th>
<th>Vertical Position</th>
<th>Horizontal Position</th>
<th>Velocity Offset</th>
</tr>
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<tr>
<td>Torsional velocity</td>
<td>7</td>
<td>8</td>
<td>15</td>
<td>14</td>
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<tr>
<td>Horizontal velocity</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

Each number represents the number of patients for whom the respective element was significantly different from 0. Shaded areas denote nonprincipal dependencies of eye velocity on eye position. The last column shows the offsets. For example, in 11 patients a significant horizontal velocity offset was found (rightmost lowest number). Dependencies on torsional position are less reliable due to the small range of torsional eye positions which were caused by torsional nystagmus, transient post-saccadic deviations from Listing’s plane, or gaze-dependent torsional drifts (mostly induced by lateral gaze).
corresponding to vertical integrator failure (all patients: mean time constant, 8.9 s; range, 4.0–119 s). Two patients did not show a significant vertical velocity offset, i.e., they had no vertical nystagmus in primary position.

HORIZONTAL NYSTAGMUS. Thirteen patients (68%) showed horizontal velocity dependence on horizontal eye position (see Table 1 and Fig. 7) corresponding to horizontal integrator failure (these patients: mean time constant, 22.8 s; range, 3.9–77.0 s). With respect to downbeat velocity in straight ahead position, these patients were not significantly different from the remaining patients (t-test, \( P = 0.25 \)). A horizontal offset was found in 11 patients (58%). Nine patients had both a significant horizontal offset and a significant horizontal integrator failure.

Furthermore (not considered in Fig. 7), a dependence of vertical velocity on horizontal eye position (or the reverse) was found in 13 patients (68%). These dependencies do not violate Listing’s law but suggest that vertical and horizontal integrators are nonorthogonal or not aligned with Listing’s plane (see following text).

Figure 8 shows the slow phase velocity derived from multiple linear regression for four different patients. The sample patient shown in Figs. 2–5 is shown in Fig. 8A, a similar patient with no torsional component velocity is shown in Fig. 8B, a patient showing no horizontal velocity components in Fig. 8C, and the patient without integrator failure in Fig. 8D. The figure gives an idea of the large variety of eye movement patterns seen in patients with DN.

Violations of Listing’s law

As mentioned in the preceding text, the simple regression was sufficient to describe the data for four patients. One of them showed a significant torsional offset which constitutes a violation of Listing’s law in the strict sense. In the remaining three patients, slow phase velocity did not violate Listing’s law.

However, not only patients but also healthy subjects exhibited violations of Listing’s law as documented by significant nonprincipal components of the multiple regression or by statistically significant torsional offsets. We used these small violations of healthy subjects to decide whether a patient fell into the normal range of minor violations even though his slow phase velocity violated Listing’s law in the strict sense. The following three parameters, derived by multiple regression after rotation to Listing’s plane, indicated a violation of Listing’s law: a torsional velocity offset (healthy: \( 0.06 \pm 0.28°/s \)),...
a dependence of torsional velocity on vertical position (healthy: $-0.002 \pm 0.010$ 1/s), and a dependence of torsional velocity on horizontal position (healthy: $0.003 \pm 0.007$ 1/s).

This means that, for example, a horizontal gaze position of $18^\circ$ with respect to primary position induced in healthy subjects, on average, a torsional drift velocity of $0.05^\circ$/s ($18^\circ \times 0.003$ 1/s $= 0.05^\circ$/s).

Thus for the 15 patients requiring multiple regression fits, we determined whether one or more of the three values indicating violation of Listing’s law was outside of the normal range (as determined by a 99% confidence interval). This was the case for 13 patients. For 12 of them, the dependence of torsional velocity on horizontal position violated Listing’s law significantly more than in healthy subjects, 6 patients had a significant torsional offset, and for 4 patients, torsional velocity depended significantly more on vertical position than in healthy subjects. This result shows that the main reason for violations of Listing’s law was a dependence of torsional slow phase velocity on horizontal eye position.

When the results of comparing simple regression to multiple regression (3 patients) and specific violations of Listing’s law in control subjects and patients (2 patients) were combined, five patients (26%) had slow phases that did not violate Listing’s law. Note that these patients were not significantly different from the remaining 14 patients with respect to their vertical drift velocity on gaze straight ahead ($t$-test, $P = 0.95$; range: $-6.03$ to $-1.25^\circ$/s). All five patients in whom slow phase velocity obeyed Listing’s law had both vertical and horizontal integrator failure.

Possible reasons for velocity offsets

Several factors can cause vertical drift of the eyes. Nearly all patients show signs of a vertical integrator failure. However, most patients also show velocity offsets which are not expected from integrator deficits. Theoretically, velocity offsets could be present at the integrator level (head-fixed component offset) with horizontal and vertical components resulting, e.g., from smooth-pursuit imbalance, could be attributed to constant angular velocity of the eye resulting from vestibular imbalance (angular velocity offsets remaining essentially head-fixed) or could be explained by constant eye-fixed velocity, i.e., a constant angular or component velocity rotating with the eye. Intermediate values are, of course, possible. Hence, while varying with eye position in one coordinate system (when expressed as head-fixed component velocity), the slow phase drifts would remain constant in another (e.g., when expressed as angular velocity in an eye-fixed coordinate system). For constant vestibular or head-fixed angular velocity, the fitted off-vertical elements of the matrix $T$ in Eq. 1 should assume a very specific dependence on the fitted offsets.

This dependence should become clearest for the change in large torsional-vertical slow phase drifts with horizontal eye position. This change can be computed from the offset in primary position and the nonprincipal elements in the matrix $T$. For example, a constant eye-fixed component velocity should rotate with the eye. Its angle thus co-varies with the change in horizontal gaze. In contrast, its length stays constant over different eye positions. A constant head-fixed angular velocity translates to a component velocity that rotates halfway against the eye but does not change length. Thus by examining the change in angular position of the torsional-vertical slow phase drift with horizontal gaze, one can determine whether the drift shows an eye-fixed, head-fixed, or other rotation. Its change in length shows whether the found rotation is a true rotation in the sense that rotating a vector does not change its length. Figure 9A shows the torsional-vertical drift of patient $P$. In this patient, it rotated with the eye but changed length. As a theoretical example, Fig. 9B shows a purely eye-fixed constant torsional-vertical component velocity. Figure 9C shows the data of all patients by comparing changes in angle and changes in relative length for horizontal gaze positions at $\pm 20^\circ$ laterally from gaze straight ahead position. It can be seen that the torsional-vertical drift changed considerably with horizontal eye position in length and angle in most patients. Note that a torsional-vertical drift that does not change angle with horizontal position may still violate Listing’s law due to a constant torsional component. Most importantly, except for one patient, none of the shifts showed the behavior expected from that caused by vestibular imbalance. Therefore we concluded that the assumption of nonprincipal dependencies caused by angular velocity offsets of vestibular, head-fixed, or eye-fixed origin has to be rejected.

3-D dependence of slow phase velocity on eye position

Rather than looking at either the principal dependencies or the nonprincipal dependencies alone, one can analyze the general form of the fitted matrix $T$ (Eq. 1), which results from the multiple regression analysis. Theoretically, if three orthogonal leaky integrators operating in the coordinate system determined by Listing’s plane caused the observed slow phases, the matrix $T$ should be diagonal, i.e., contain only principal dependencies. As reported in the preceding text, this was the case for only four patients. Such a diagonal matrix has column vectors (each column of the matrix can be understood as a 3-D vector), which are perpendicular to each other, thus each vector points along the respective axis of the coordinate system.

The question for the remaining patients, for whom nonprincipal dependencies have been found, is whether the matrix is still composed of vectors perpendicular to each other. If this was the case, it would mean that the three integrators are independent of each other but that their coordinate system is rotated with respect to Listing’s plane. If it is not the case, then the three integrators do not operate independently of each other; in other words, the integrator coordinate system would be distorted and not perpendicular. We therefore plotted the vertical and horizontal column vectors of the fitted matrices, i.e., the vectors describing the effect of a vertical or horizontal eye position on drift velocity (Fig. 10). The torsional vector showed too much scatter to be useful because the effect of torsional position on slow phase velocity could be determined less reliably due to the small range of adopted torsional eye positions. For the sample patient (shown in Figs. 3–5 and 10, top row), it can be seen (data in Eq. 5) that vertical position significantly contributed only to vertical velocity (significant value in the 2nd column of the matrix). This corresponds to the alignment of the vector with the vertical $y$ axis. In contrast, torsional, vertical, and horizontal velocity significantly depend on horizontal position (3rd column); i.e., the corresponding
vector is not aligned with the horizontal z-axis but is tilted in the vertical-torsional direction.

As can be seen from Fig. 10, most vectors for the vertical component (y axis, black arrows) aligned well with the vertical y axis. Thus vertical eye position had only a minor effect on torsional or horizontal drifts. The vectors for the horizontal axis show much larger tilts away from the horizontal z axis, both in the vertical and torsional directions. The tilts in the torsional directions indicate violation of Listing’s law. In conclusion, different vertical eye position mainly caused changes in vertical slow phase drift (corresponding to the alignment of the vertical vector with the y axis), while different horizontal eye positions caused changes of drift in all three components of slow phase velocity. One possible explanation for this is that, apart from the horizontal integrator failure, projections from the horizontal integrator to the torsional-vertical velocity-to-position integrator are damaged or incorrectly weighted and thus produce eye-position dependent drifts. Conversely, projections from the vertical-torsional integrator to the horizontal integrator seem to be less affected because vertical eye position has almost no effect on horizontal eye velocity.

Increase of vertical drift with eccentric gaze

An increase of vertical drift velocity with lateral gaze is often reported clinically (Leigh and Zee 1999; Straumann et al. 2000). The multiple linear regression analysis can, so far, not explain this due to its linear model. We therefore applied a quadratic regression to the data. For nine patients, but none of the healthy subjects, the quadratic regression yielded significantly better results. All nine patients showed a significant negative quadratic dependence of vertical drift velocity on horizontal position (for an example see Fig. 3). In eight of these patients, vertical drift velocity with both right- and leftward lateral gaze was larger than with gaze straight ahead. We assume that these side-dependent changes in vertical drift velocity are caused by asymmetric damage to the torsional-vertical integrator (see DISCUSSION).

Pre- and postsaccadic eye positions

Inspection of the slow phase eye velocity data revealed that torsional eye velocity often had increased values at the begin-
neering of an attempted fixation period and decreased to zero or to a constant velocity offset over time (see Fig. 4 for an example). This suggests that torsional eye position shortly after a saccade to a new target position is different from that at the same gaze position before the next saccade started. Such transient torsional deviations, called blips, have been found in healthy subjects (Straumann et al. 1995), but also with much larger amplitude in a patient (Helmchen et al. 1997). Therefore the orientation of Listing’s plane was examined before and after large saccades. Depending on the amount of nystagmus, 10–26 saccades larger than 10° were found. For each saccade, eye positions 100 ms immediately before and after the saccade were selected. In patients, the angle between primary positions corresponding to the planes fitted to the eye positions before and after saccades was 6.2 ± 3.7° (see Fig. 11 for an example), in healthy subjects, 3.5 ± 1.6°. The difference was statistically significant (t-test, P = 0.007). In patients, the angle between pre- and postsaccadic data correlated with the amount of DN during gaze straight ahead (r = 0.50, P = 0.03), i.e., patients with larger slow phase velocities showed a larger angle between pre- and postsaccadic Listing’s planes.

If the same analysis was performed for all saccades, taking also small saccades and nystagmus beats into account, the angle was no longer significantly different between patients and healthy subjects. This is possibly due to the fact that saccadic corrections for torsional deviations from Listing’s plane depend on the amplitude of the saccade (Lee et al. 2000): while large saccades bring the eye close to the torsional position defined by the burst generator, small nystagmus beats cannot achieve the necessary torsional correction and, therefore the torsional position of the eye remains close to the torsional null position defined by the neural integrator.

**DISCUSSION**

Multiple linear regression sufficiently described 3-D slow phase component velocity of eye position data in patients with DN. This method considerably simplified the quantitative analysis and statistical evaluation of the data and allowed a physiologically meaningful interpretation of the fitted parameters.

The analysis of slow phases in patients with DN revealed two important results. First, while a vertical integrator failure could be found for all except one patient, only about half of the patients also showed a horizontal integrator failure. This result, which agreed with previous findings (Leigh and Zee 1999), suggests different etiologies of DN. Second, about one-fourth of the patients showed slow phases that essentially obeyed Listing’s law, i.e., in the range of observed eye positions, the slow phase component velocity of nystagmus did not show significantly more torsion than in healthy subjects. These patients did not show torsional offsets, and the (nonprincipal) dependence of torsional velocity on horizontal or vertical eye position was negligibly small. This result casts doubt on one of the major hypotheses of DN, i.e., that DN is caused by a disruption of central vestibular pathways. In such a case,
resulting vestibular imbalance would cause a nystagmus offset that would violate Listing’s law, as does any vestibular nystagmus. Furthermore, a closer inspection of the torsional-vertical offsets in the remaining patients further corroborated our finding that these offsets do not agree with the hypothesis of a vestibular or head-fixed angular velocity offset.

**Previous studies**

While the literature provides a wealth of studies on patients with DN (e.g., Baloh and Spooner 1981; Baloh and Yee 1989; Gresty et al. 1986; Yee 1989; Zee et al. 1974), only one study employed a detailed analysis of 3-D eye movement recordings in patients with DN. This recent investigation of patients with cerebellar atrophy (Straumann et al. 2000) reported that these patients show upward drift (DN), horizontal centripetal drift during lateral gaze (gaze-evoked nystagmus), and torsional drift depending on horizontal position which violated Listing’s law. The vertical nystagmus component was composed of a gaze-evoked component and a velocity bias. Vertical nystagmus increased with lateral gaze. Although our study confirmed these results for about 50% of our 19 patients (see significant parameters in Eq. 5), we found that two of our DN patients did not show a bias component (offset) if slow phase velocity was analyzed with respect to Listing’s plane (corresponding to a vertical integrator failure without offset), six patients did not show gaze-evoked horizontal slow phase components (no horizontal integrator failure), slow phases in five patients did not violate Listing’s law, and only nine of our patients showed significantly increased vertical nystagmus with right and left lateral gaze.

**Different etiologies**

Most hypotheses on DN assume that there is one type of DN. Our results show, however, that three distinct groups of patients can be distinguished: DN patients with vertical-horizontal integrator failure, with vertical integrator failure only, and without integrator failure (1 patient). A plausible explanation for the first two groups is that, physiologically, the horizontal and vertical-torsional integrators are at separate locations in the brain stem. The first is located in the nucleus prepositus hypoglossi and the medial vestibular nucleus (Cannon and Robinson 1987), while the other is located in the interstitial nucleus of Cajal (Crawford 1994). Even though these structures may not be damaged themselves, it is reasonable to assume that cerebellar projections to the two integrators, which are assumed to improve the integrator time constants (Zee et al. 1980, 1981), are affected differently by cerebellar lesions. The third distinct type, DN without integrator failure, appeared to be the exception.

**Main hypotheses about DN**

Two hypotheses about DN focus on the vertical bias component of slow phase velocity, i.e., the vertical slow phase velocity that cannot be explained by the vertical integrator failure found in all except one of our patients.

The first hypothesis, vestibular imbalance due to central damage of semicircular canal pathways (Baloh and Spooner 1981; Böhmer and Straumann 1998) can be excluded in our patients because the nystagmus slow phase velocity did not agree with vestibular origin (Fig. 9). Furthermore, this hypothesis requires that two distinct functions of the brain stem oculomotor circuitry are affected: the vertical integrator that causes the gaze-dependent vertical nystagmus and the cerebellar structures that project to the vestibular nuclei to suppress the vertical offset (Böhmer and Straumann 1998).

The alternative hypothesis of smooth pursuit imbalance (Zee et al. 1974) poses a similar problem: it requires that both pursuit pathways and the vertical integrator are damaged. This is still more appealing because lesions of floccular regions are known to cause both gaze-evoked nystagmus and smooth-pursuit deficits (Waespe 1992; Zee et al. 1981). Another study showing that horizontal pursuit deficits and horizontal gaze-evoked nystagmus usually occur in combination further supports this hypothesis (Büttner and Grundei 1995). However, the pursuit theory only explains why DN patients usually have pursuit deficits and why they cannot suppress their nystagmus in light. It does not explain the various findings associated with DN slow phase velocity described in the preceding text, specifically it does not explain why slow phases do not obey Listing’s law in the majority of our patients.

The most recent hypothesis by Straumann et al. (2000) specifically addresses the violations of Listing’s law, suggesting that the impaired cerebellum can no longer hold torsional eye positions, which then drift back to a mechanically determined resting position. Thus Straumann et al. propose a mismatch between two different Listing’s planes, a neural plane and a mechanical plane. This proposal does not explain why torsional drifts, if present at all, show time constants larger (mean 4.5 s) than that of the eye plant (about 200 ms) (Seidman et al. 1994). It also requires separate explanations for the gaze-dependent drifts (leaky integration) and for the vertical velocity bias.

**Integrator function**

Because the most common finding in our patients, except for DN in gaze straight ahead, was gaze-evoked vertical nystagmus, we first consider velocity-to-position integrator function. As Cannon and Robinson (1987) showed, loss of the neural integrator in the brain stem leads to gaze-evoked nystagmus. However, this nystagmus does not necessarily drift toward the zero position of the integrator but may have its null position at different points if combined with an offset. Such an offset, caused, for example, by a difference in push-pull firing rate, may be the result of a vestibular imbalance, but it may also have its origin in any other imbalance, for example, a smooth-pursuit imbalance. Pharmacological lesions of the horizontal oculomotor integrator in monkeys induced different types of nystagmus (Arnold et al. 1999): slow phases showed exponential eye position dependent drifts with null positions not coinciding with gaze straight ahead, but also linear eye position-independent drifts. These results suggest that integrator lesions, and not only lesions of integrator input structures, may cause shifts of the null position of nystagmus: in other words, the zero position of the integrator may be altered intrinsically. To summarize, in the simple one-dimensional case integrator function can be described by a gain (not important for the current analysis), a time constant, and an offset that shifts the null position of the nystagmus.
Whereas a one-dimensional analysis of only vertical eye position and velocity cannot determine the origin of the offset, a 3-D analysis as employed here can differentiate between several possibilities. However, the situation becomes more difficult when considering 3-D eye movements because the integrator has now not only a time constant and an offset, but it can also be rotated with respect to the observer’s coordinate system, and the axes of the integrators need not be perpendicular to each other. These modifications correspond to the nonprincipal dependencies between eye position and eye velocity found in our patients. Physiologically, the rotation of the integrator coordinate system is indeed relevant: Listing’s plane shifts and rotates depending on vergence (Van Rijn and Van den Berg 1993) and head position with respect to gravity (Bockisch and Haslwanter 2001). Thus the intrinsic coordinate system is modified neurally.

In a model-based study, Glasauer and co-workers (2001) have proposed a mechanism for such a neural adjustment of the orientation of Listing’s plane by central pathways carrying otolith information. The authors suggested that disruption of these pathways may cause central positional nystagmus, a head-position dependent pathological nystagmus usually involving lesions of the cerebellum (Bertholon et al. 2002). Glasauer and colleagues showed that neutral modification of the orientation of Listing’s plane, defined by the neural integrator, theoretically requires not only an offset (e.g., to shift Listing’s plane during ocular counterroll) but also nonprincipal components in the integrator feedback matrix as found in our patients. In healthy subjects, both the coordinate systems of the burst generator and the integrator would be modified by head tilt (or vergence), and thus stay aligned, producing the required change in orientation of Listing’s plane. If, however, the pathways to the neural integrator adjusting the orientation of Listing’s plane are decalibrated with respect to that of the burst generator, nystagmus would occur. Depending on the lesion, nystagmus may be confined to off-vertical head positions (as in central positional nystagmus) or may occur in head-upright positions, too, especially if the pathways or structures augmenting the integrator time constants are also affected.

**Interpretation of the slow phase velocity results**

The equation used for multiple regression (Eq. 1) can be interpreted as a differential equation describing the 3-D velocity-to-position integration in the brain stem, with the integrator being fed by a component velocity offset. As shown in the preceding text, the data of about 20% of our patients could be described by an orthogonal leaky integrator (Eq. 3) aligned with Listing’s plane (see Fig. 8B for an example). In these patients, torsional, vertical, and horizontal drift velocity depended only on the respective eye position component. Thus these data confirm lesion data from monkey experiments showing that the neural velocity-to-position integrators operate in Listing’s plane (Crawford 1994).

The found time constants, being in the order of several seconds, strongly suggest that the gaze-dependent drifts are neither caused by complete integrator failure nor by the missing ability to correct for torsional resting positions of the eye plant (Straumann et al. 2000) because, in both cases, the resultant time constants would be close to the much shorter mechanical time constant of the eye plant. The same holds for drifts caused by a low gain of the neural integrator. Hence, we assume that a partial failure of the neural integrators, as found, e.g., following lesions of the cerebellar flocculus (Zee et al. 1981), causes the observed gaze evoked nystagmus components.

For the majority of patients, nonprincipal dependencies of velocity on position (corresponding to off-diagonal matrix elements in the feedback matrix of the integrator, see Table 1) were necessary for a sufficient fit. These nonprincipal dependencies can be interpreted depending on their size and relationship to each other. For example, a purely head-fixed velocity offset such as a VOR imbalance that did not affect the neural integrator would be reflected by off-diagonal elements, leaving the principal dependencies (diagonal elements) at zero value. This interpretation was, however, not the case for our patients as shown in RESULTS.

As we were able to show by our 3-D analysis, the nonprincipal dependencies we found rather reflect mainly a distortion (nonorthogonality) of the coordinate system of the neural integrator with respect to Listing’s plane. While the effect of vertical eye position is, in most cases, confined to vertical eye velocity (see Fig. 10), horizontal eye position influences both vertical and torsional eye velocity components in most patients. Crawford (1994), who analyzed post-saccadic drifts in monkeys after unilateral INC lesions by multiple linear regression, also found larger nonprincipal dependencies of horizontal position on torsional and vertical drift velocity than of vertical position on torsional and horizontal drift velocity.

This indicates incorrect weighting of horizontal eye position information for the generation of torsional-vertical eye position. This may be due to lesioned (in the unilateral INC lesion study) or incorrectly weighted pathways from the horizontal integrator to the torsional-vertical integrator. It is likely that the cerebellum, which is involved in neural velocity-to-position integration (Zee et al. 1980, 1981) (see following text), also affects the way in which Listing’s plane is adjusted neurally within the integrators.

**Listing’s law**

Violations of Listing’s law by slow phase drifts were indeed found in the majority of our patients but could not be explained by the current hypotheses about DN (see preceding text). We further showed that pre- and post-saccadic eye positions in patients violated Listing’s law significantly more than in our control subjects. Planes fitted to pre- and post-saccadic eye positions should be identical if Listing’s law is obeyed during saccades (Helmchen et al. 1997; Straumann et al. 1996); this was the case for healthy subjects but not for patients. The finding that these planes differed only if large saccades (>10°) were analyzed can be explained by the fact that, in healthy subjects, only large saccades correct significantly for torsional deviations (Lee et al. 2000). Because presaccadic eye positions are mainly determined by the gaze-holding function of the integrator, and immediate post-saccadic eye positions are almost exclusively determined by the direct premotor pathway from the saccadic burst generator, we conclude that the neural integrator and the saccadic burst generator in patients implement two separate displacement planes (Listing’s planes). In other words, the intrinsic coordinate systems of the burst generator and the neural integrator do not align. Thus a saccade...
brings the eye to a position defined by the burst generator, then the eye drifts due to the integrator failure until the next nystagmus quick phase brings the eye again closer to the eye position defined by the burst generator. This result has, by itself, different possible interpretations: either the plane of the burst generator or the plane of the integrator may be misaligned due to pathway failures or lesions because both unilateral lesions of the vertical-torsional burst generator (Crawford and Vilis 1992) and of the neural integrator (Crawford 1994) cause changes in the orientation of Listing’s plane or the integrator failure found in our patients may have disclosed a mismatch of burst generator and integrator coordinate systems that was present before the lesion. In healthy subjects, such a mismatch would not necessarily cause drifts because gaze holding, i.e., vertical and horizontal integrator function, is almost perfect. Thus apart from torsional drifts, gaze would remain in the postsaccadic position determined by the burst generator. While the eye position data alone do not allow us to decide whether the dissociation of pre- and postsaccadic Listing’s planes is due to incorrect saccadic bursts, to a failure to correct for a misaligned mechanical Listing’s plane (Straumann et al. 2000), or to an incorrect integrator coordinate system, the analysis of nystagmus slow phases showed that an incorrectly operating integrator is a likely reason for the present results.

**New hypothesis on DN**

Hence we propose that a possible reason for DN is that pathways from the cerebellum to the neural integrator are damaged. These pathways not only affect the integrator time constant but also define the intrinsic coordinate system of the neural integrator. Such putative damage would cause gaze-dependent nystagmus, different Listing’s planes for pre- and postsaccadic eye positions due to misalignment of the burst and integrator coordinates, and offsets due to different primary positions for burst generation and gaze holding.

Our findings in the current study match well with the conclusions of the modeling study (Glasauer et al. 2001). In patients, the saccadic burst generator and the neural integrator no longer share a common coordinate system as shown by the fact that planes fitted before and after large saccades differ considerably in most DN patients. Moreover, the analysis of slow phases showed that the integrator coordinate system is no longer orthogonal. We therefore hypothesize that the dissociation of pre- and postsaccadic primary positions, the integrator leakage, the nonprincipal dependencies of slow phase eye velocity on eye position, and the velocity offset itself share a common cause: a lesion of the pathways that augment the brain stem integrator function and define its primary position, thereby determining both the integrator time constants and the neural orientation of Listing’s plane during fixation.

As an example of the different possible reasons for offsets, a simulation of DN slow phases starting from different eye positions is shown in Fig. 12. The four rows show different possible reasons for DN offset, all for the data of our sample patient (see Fig. 2 for original data, but note different scale for torsional eye position). All simulations assume a leaky integrator that matches the patient data but different reasons for DN offset. The rows show an offset applied in the integrator coordinate system (simple regression results), a vestibular offset, a modified orientation of Listing’s plane defined by the neural integrator, and the multiple regression results. While the rightmost column, showing vertical and horizontal components of eye position during the drifts, does not depend much on the hypothesis, the left and middle columns depicting the predictions for torsional drifts, differ considerably. Note that rotation and shift of the coordinate system in addition to integrator leakage in the third row are quite similar to the actual multiple regression result (bottom).

Our hypothesis of DN does not apply to all patients in the same way. For patients without horizontal integrator leakage, apparently only the pathways to the torsional-vertical integrator are affected which augment the time constants and mediate horizontal eye position information. The present hypothesis can even account for one patient who showed severe DN but no integrator leak at all. This patient may only have a lesion of pathways adjusting Listing’s plane but not affecting the time constant of the neural integrator.

Another often reported finding in patients with DN, variation of nystagmus intensity with head position (Baloh and Spooner 1981; Gresty et al. 1986; Marti et al. 2001), vergence (Yee 1989), or both (Chambers et al. 1983), can easily be explained by our hypothesis. The damaged pathways affect the neural implementation of Listing’s plane which, as mentioned in the preceding text, is modified by head position and vergence. Thus a neural change in orientation of Listing’s plane will necessarily affect DN.

Our hypothesis can, however, not explain why the assumed mechanism causes DN and not, for example, upbeat nystagmus. Nevertheless, experimental results in the monkey (Helmchen et al. 1998) of unilateral or bilateral lesions of the torsional-vertical integrator, the interstitial nucleus of Cajal (INC), further corroborate our hypothesis that damage to torsional-vertical velocity-to-position integration may cause DN. After the lesions, monkeys always showed DN with gaze straight ahead. Also, a patient with a unilateral midbrain lesion not only had torsional nystagmus, but also a significant downbeat component (Helmchen et al. 1996). In this patient, a lesion of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which constitutes the torsional-vertical burst generator was found together with involvement of the rostral part of the INC.

A possible neural substrate for the augmentation of the time constant of the brain stem integrator has been suggested by Nakamagoe and colleagues (2000), who lesioned burst-tonic cells in the paramedian tract (PMT) of the cat and found severe downbeat nystagmus. This nystagmus was dependent on gaze position (severe integrator leak), had a marked offset (null-position above straight ahead), and was associated with horizontal gaze evoked nystagmus. Because PMT cells heavily project to the cerebellar flocculus and receive input from brain stem areas containing preoculomotor neurons (Büttner-Ennever and Horn 1996), the authors suggested that this brain stem-cerebellar loop may be responsible for augmentation of the brain stem integrator time constant. Therefore, we now hypothesize that DN involves lesions of this feedback loop, which possibly also adjusts the position and orientation of Listing’s plane. Involvement of the flocculus, which is known to participate in both the gaze-holding function and smooth pursuit (Zee et al. 1981), would explain why DN patients cannot suppress their nystagmus and why most of them, if not all, show associated failure of downward smooth pursuit.
Conclusion

Using a 3-D multiple regression analysis, we assessed the relation between eye position and slow phase component velocity in DN patients. We were able to show that patients can be divided into three main groups, DN with vertical integrator leakage, DN with vertical and horizontal integrator leakage, and DN without integrator leakage. Furthermore, we showed that the integrator coordinate system did not coincide with Listing’s coordinates in about 75% percent of our patients. The analysis of pre- and postsaccadic displacement planes further corroborates this finding: the angle between these planes in patients is significantly larger than in healthy subjects. These findings led to the conclusion that the coordinate systems of burst generator and neural integrator in patients no longer match. As a result, the eye drifts away from the position defined by the saccadic burst, with the following quick phase attempting to restore this eye position. On the basis of the multiple regression results, we had to reject both the hypotheses of lesions of central vestibular pathways carrying canal information and of DN caused by a smooth pursuit imbalance. Instead, we propose a new hypothesis on the generation of DN: DN is a result of a partial lesion of cerebellar structures and pathways to the neural integrators, which augment the neural integrator time constants and, at the same time, adjust the orientation of Listing’s plane for static eye positions.

APPENDIX

Calibration

The linear relation between the normal vectors $c_d/c_t$ of the effective plane of the directional/torsional coils and the induced voltages $u_d/u_t$ was expressed as

$$u_d = g_d \cdot H^T \cdot c_d + \varphi_d$$

$$u_t = g_t \cdot H^T \cdot c_t + \varphi_t$$
where the vectors $\mathbf{o}_t / \mathbf{o}_r$ denote the offsets due to induction in the nonmoving parts of the lead wire of the coil (e.g., connectors). The columns of the matrix $H$ represent the three magnetic fields and the scalar factors $g_t / g_r$ represent the total gain combining the inductance of the coil and the amplifier gain.

In a first step, the coil was moved manually covering all possible directions between $-\pi$ and $+\pi$ of horizontal eccentricity and between $-\pi/2$ and $+\pi/2$ of vertical elevation. The measured voltages $u_{r,t}$ were used to determine the field matrix $H$ and the gain factor $g_d$ by minimizing the distance between the endpoints of the coil-vectors $c_d / c_t$, and the surface of a sphere with radius 1 under the additional constraint that the angle between the directional and the torsional coil vector stayed constant. In a second step of the calibration, the subject was wearing the coil and fixing target positions within $\pm 20^\circ$ horizontal eccentricity and $\pm 15^\circ$ of vertical elevation. These data were used to determine the offsets $\mathbf{o}_t / \mathbf{o}_r$ and the gain factor $g_d$ by the same minimization procedure, again assuming that the angle between the directional and the torsional coil stayed constant and did not depend on accurate fixation of the target. In a third step, the subject repeatedly fixated a target at straight ahead. From these data, the relative rotation of the coil on the eye was computed.

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