Gravity Dependence of Ocular Drift in Patients with Cerebellar Downbeat Nystagmus

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Downbeat nystagmus is a frequent ocular motor sign in patients with lesions of the vestibulocerebellum. The upward drift in downbeat nystagmus is a combination of a gaze-evoked drift, due to an impaired vertical neural integrator, and a velocity bias. Using a three-dimensional turntable, we analyzed the influence of gravity on these two mechanisms. Patients with cerebellar downbeat nystagmus (n = 6) and healthy subjects (n = 12) were placed in various whole-body positions along the roll, pitch, and oblique vertical planes of the head. Ocular drift was monitored with scleral search coils. Although there was no gravity dependence of the vertical gaze-evoked drift, the vertical velocity bias consisted of two components: a gravity-dependent component that sinusoidally modulated as a function of body position along the pitch plane, and a gravity-independent component that was directed upward. The combination of the two components led to an overall drift that was minimal in supine and maximal in prone position. In healthy subjects, only the gravity-dependent component was present, but in a scaled-down manner. Our results suggest that the intact vestibulocerebellum minimizes an overacting otolith-ocular reflex elicited by pitch tilt and cancels an inherent upward ocular drift that is independent of gravity-modulated otolith signals.

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Downbeat nystagmus (DBN) is a common ocular motor sign in patients with posterior cerebellar lesions close to the midline, especially if the flocculus and paraflocculus are involved.[1] There are also other disorders causing DBN, the most frequent among them lesions near the craniocervical junction and drug intoxication.[2,3] Typically, additional ocular motor signs are associated with DBN: horizontal gaze-evoked nystagmus, deficient vertical smooth pursuit and vertical optokinetic nystagmus, as well as reduced visual suppression of the vestibuloocular reflex.[3,4]

DBN increases with downward gaze, according to Alexander's law,[5,6] but in some patients this relation can be reversed.[7,8] Regularly, there is also an increase of DBN with lateral gaze and with convergence.[2,3,9] The waveform of the slow phase is often linear, but waveforms with exponentially increasing or decreasing velocity have been described as well.[1,7,10]

How impaired cerebellar function leads to DBN is unknown. Asymmetrical alterations of the vertical smooth pursuit system,[11] the vertical velocity-to-position integrator (gaze-holding network),[7] or the vertical vestibuloocular reflex pathways[2,12,13] have been suggested.

DBN may be influenced by gravity. Both rapid positional change and static head-hanging position increases the slow-phase velocity of DBN.[2,14,15] Head roll (ear to shoulder) also can lead to an increase of DBN.[16] The most obvious explanation for the influence of gravity on DBN is that the patients with DBN may suffer from lesions involving otolith-ocular pathways.[9] Another hypothesis suggests that DBN is caused by an asymmetry of vertical vestibuloocular reflexes, which may (tilt-sensitive DBN with a minimum in supine position) or may not (tilt-insensitive DBN with no minimum) be modulated by otolith signals.[16,17] Spontaneous vertical drift also is found in healthy human subjects, if measured in darkness. On average, the drift is directed downward in nose-up and upward in nose-down head positions.[18,19]

Vertical ocular drift in patients with DBN due to cerebellar lesions consists of two major components: (1) an upward directed velocity bias, which corresponds to the upward drift present at gaze straight

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ahead and is independent of eye-in-orbit position, and (2) gaze-evoked vertical centripetal drift that increases with vertical gaze eccentricity.[1,8] To clarify how gravity influences these two components of DBN, we analyzed the vertical drift velocity as a function of the three-dimensional orientation of the gravity vector relative to the head.

Patients and Methods

Patients

Six patients with DBN due to cerebellar disease (three men, three women; 40–75 years old) participated in this study. The ocular motor findings were typical for the syndrome of floccular/parafloccular lesions (see introduction). In all patients, DBN was present during gaze straight ahead and increased with down gaze (according to Alexander's law) and lateral gaze with the head in upright position. Magnetic resonance imaging demonstrated global cerebellar atrophy in four patients (patients 1, 2, 3, 4) and atrophy of predominantly paramedian cerebellar structures in one patient (patient 5). Another patient (patient 6) developed a cerebellar syndrome after a subarachnoidal bleeding. The median duration of cerebellar symptoms was 12 years (range, 2–20 years). None of the patients was taking medication known to influence ocular motility at the time of the measurements. The comparison group consisted of 12 healthy human subjects (six men, six women; 25–59 years old).

All subjects gave consent to participate in this study after being informed of the experimental procedures. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Experimental Setup

Subjects were seated upright on a turntable with three servo-controlled motor driven axes (prototype built by Acutronic, Jona, Switzerland). The head was restrained with an individually molded thermoplastic mask (Sinmed BV, Reeuwijk, The Netherlands). The subject was positioned so that the center of the interaural line was at the intersection of the three axes of the turntable. Movements of the body were minimized by evacuation pillows and safety belts.

Eye Movement Recording

Three-dimensional eye movements were recorded binocularly with dual search coils (Skalar Instruments, Delft, The Netherlands). The coil frame (side length, 0.5m) generated three orthogonal digitally synchronized magnetic wave field signals of 80, 96, and 120Hz. A digital signal processor computed a fast Fourier transform in real time on the digitized search coil signal to determine the voltage induced on the coil by each magnetic field (system by Primelec, Regensdorf, Switzerland). Coil orientation could be determined with an error of less than 7% over a range of ± 30 degrees, and with a noise level of less than 0.05 degrees (root mean squared deviation).

Search coil annuli were calibrated[20] and then placed around the cornea of both eyes after local anesthesia with oxybrucaine 0.4%. Eye and chair position signals digitized at 1,000Hz per channel with 16-bit resolution and stored on a computer hard disk for offline processing.

Experimental Protocol

A chair-fixed laser dot was projected onto a chair-fixed tangent screen at a distance of 0.59m in front of the subject. The left eye was covered with a patch. Every 2 seconds, the laser dot was turned on for a duration of 20 milliseconds. Subjects were instructed to look at the laser dot and to keep their eyes at this position during the off periods. The short duration of on periods ensured that the pursuit system was not activated by the fixation dot. In three healthy subjects and one patient, we compared ocular drift velocities during this paradigm with drift velocities in total darkness and found no differences.

The chair was rotated in 45-degree steps from the prone to the supine position (prone, 45 degrees nose-down, upright, 45 degrees nose-up, supine). Each position was held for 15 seconds. The sequence of five positions was repeated in the roll plane, and the two planes in between pitch and roll, that is, the right ear anterior, left ear posterior (RALP) plane and the left ear anterior, right ear posterior (LARP) plane. The rotations in the four planes were repeated four times with the laser dot projected to different locations on the tangent screen: straight ahead, 15 degrees up, 15 degrees down, and 15 degrees left. In two patients and three healthy subjects, the rotation in the pitch plane was repeated to include positions along the entire 360-degree circle with gaze pointing straight ahead.

Data Analysis

Search coil signals from the right eye were processed with interactive programs written in MATLAB Version 6 (MathWorks, Inc., Natick, MA). Three-dimensional eye positions were expressed as rotation vectors,[21] and three-dimensional eye velocities as angular velocity vectors.[22] For convenience, the lengths of rotation vectors and angular velocity vectors are given in degrees and degrees per second, respectively. We present the data in coordinates used by clinicians, that is, eye rotations to the right, up, and clockwise from the subject's point of view are positive.

At each position of the turntable, eye movements during only the last 5 seconds were analyzed to avoid contamination of the vestibuloocular reflex elicited by the previous 45-degree turntable rotation. Each section of 5 seconds then was partitioned into intervals of 200 milliseconds. For every interval, the median position and the median angular drift velocity were computed. This procedure implicitly desaccaded the eye movement traces.[23] Sections that did not contain eye positions necessary to fix the target were discarded.

Effect of Convergence

In the patients with reliable binocular recordings (five of six), we checked whether the orientation of the chair along the pitch plane influenced the convergence angle (recall that the left eye was covered). We were not able to detect systematic changes of vergence as a function of body position.

Applied Statistical Methods

To compute the regression between eye position and eye velocity at a particular chair position, the following robust fit-

ting procedure was used.[8] First-order linear regressions were iterated. After each regression, the data point farthest away from the best-fit line was discarded. The procedure was repeated until 30% of the data points were excluded from the fit. The offset, slope and correlation coefficient (R^2) of the last regression were used for analysis.

To compute amplitude and offset of the sinusoidal modulation of eye velocity as a function of head position, we fitted a first-harmonic sine to the data using the nonlinear least squares algorithm implemented in the MATLAB function lsqnonlin.m (Levenberg-Marquardt method).

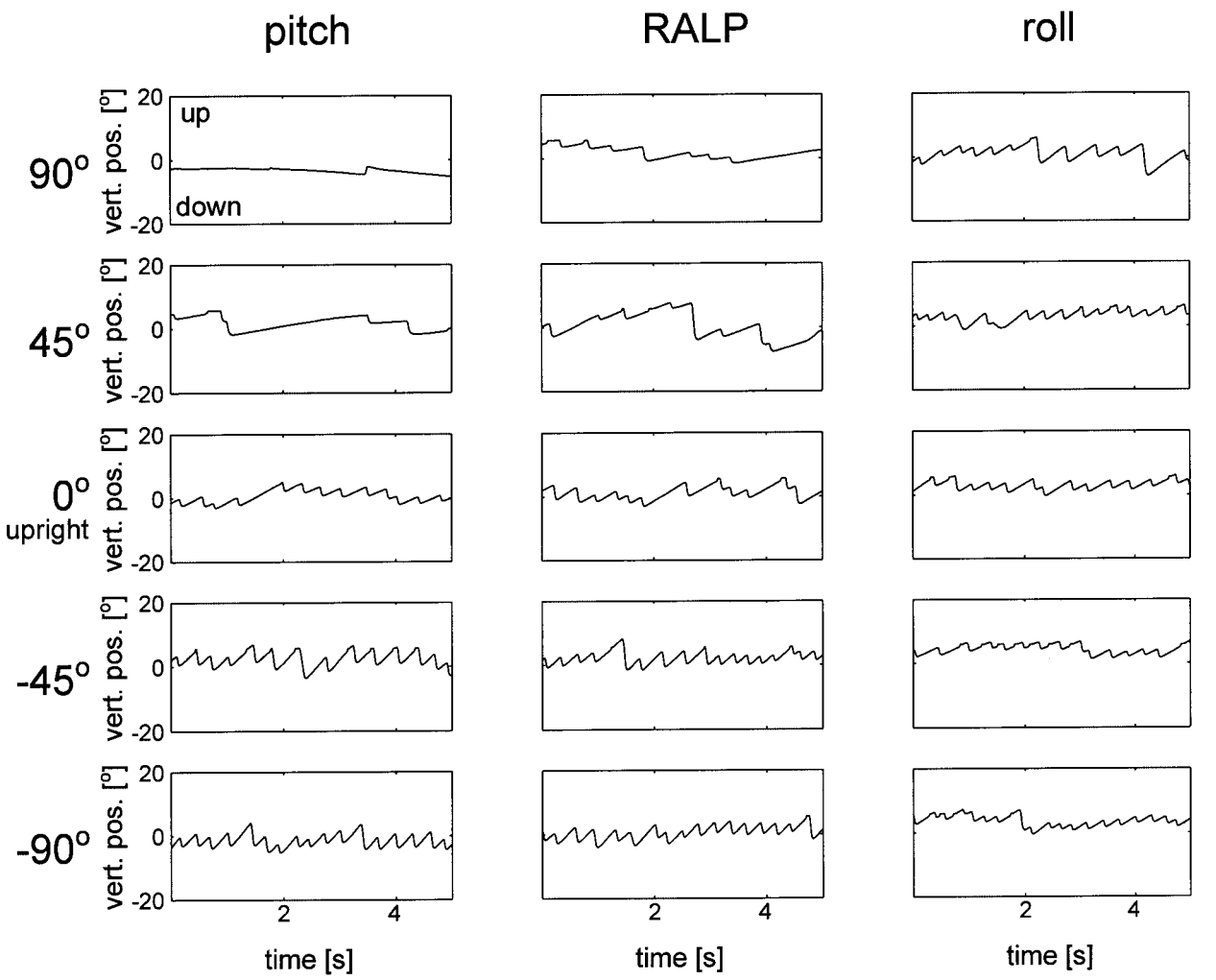
Results

We first analyzed vertical ocular drift at straight ahead gaze. Figure 1 illustrates typical vertical eye position traces measured at different whole-body orientations in a cerebellar patient (Patient 2, right eye). In the pitch plane, there was a clear gradient of decreasing upward drift velocity from prone to supine. In fact, the vertical drift slightly reversed its direction in the supine position. The frequency of DBN became less as drift velocity decreased. A similar pattern was seen in the RALP and LARP (not shown) planes. In the roll plane, however, there was no modulation of vertical drift velocity as a function of chair position.

Figure 2 summarizes the vertical drift velocities as a function of chair position in the different planes (pitch, roll, RALP, LARP) for the same patient (Patient 2, right eye). The following sine function was fitted to the data:

$$\omega_y = A_y \cdot \sin(\vartheta + \phi_y) + offset_y$$

Fig 1. Vertical eye position traces of a patient with cerebellar atrophy (Patient 2, right eye) in the pitch, right ear anterior, left ear posterior (RALP), and roll planes. Target (switched on during 20 milliseconds every 2 seconds) was straight ahead. Panels correspond to various chair orientations in 45-degree steps. Pitch plane (from top to bottom): 90 degrees nose-up (= supine); 45 degrees nose-up; 0 degrees (= upright); 45 degrees nose-down; 90 degrees nose-down (= prone). RALP plane: same sequence as in the pitch plane. Roll plane: 90 degrees right ear down; 45 degrees right ear down; 0 degrees (= upright); 45 degrees left ear down; 90 degrees left ear down.



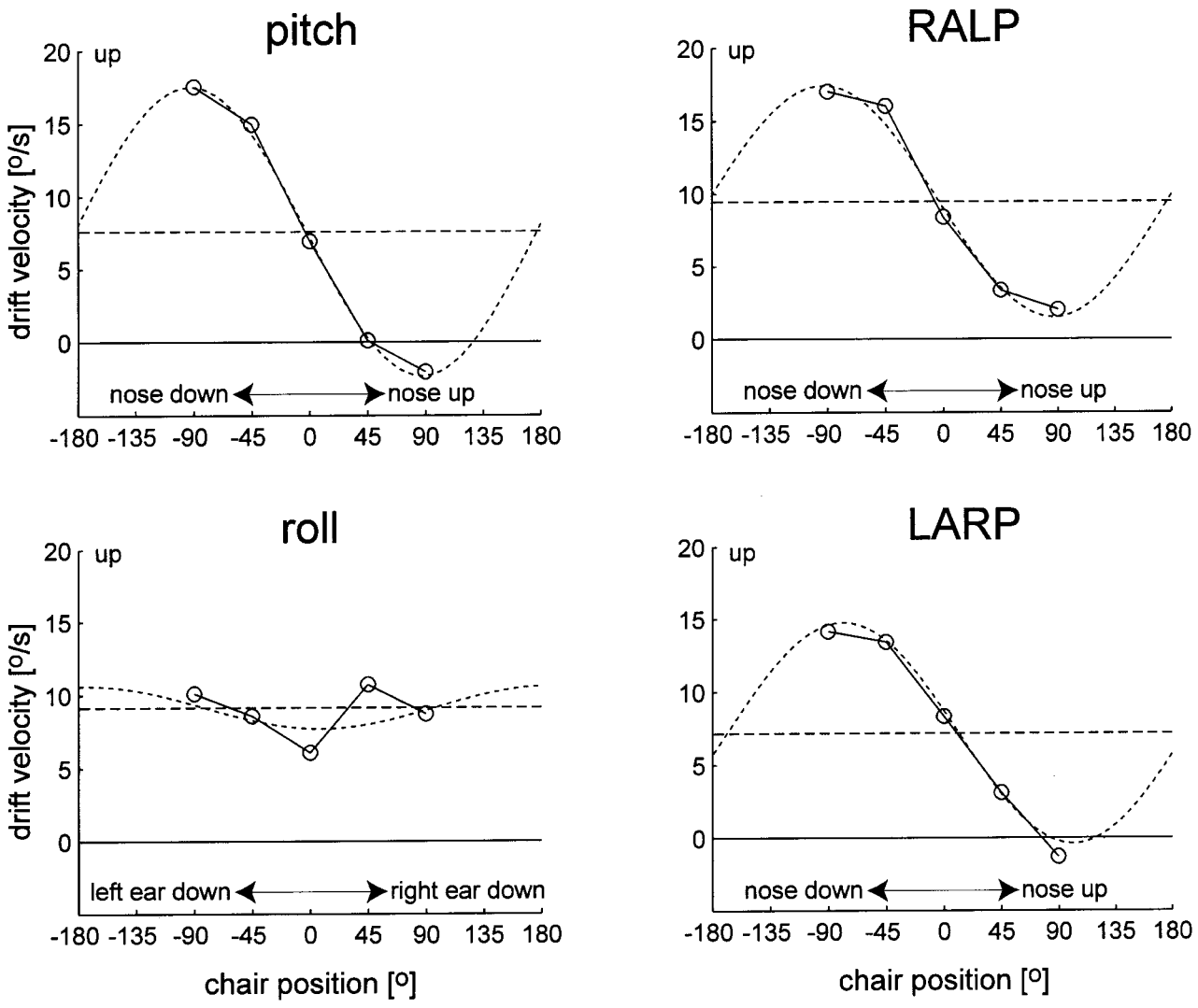


Fig 2. Vertical ocular drift velocity as a function of chair position in a patient with cerebellar atrophy (same patient as in Fig 1, right eye). Panels show data in the pitch, roll, right ear anterior, left ear posterior (RALP), and left ear anterior, right ear posterior (LARP) planes. Target was straight ahead. (open circles connected with solid lines) *Median velocities of slow phases.* (curved dashed lines) *First-harmonic sine fits.* (horizontal dashed lines) *Offsets of the sine fits. In all panels, 0 degrees corresponds to the upright position.*

where ω_y is the vertical component of angular eye velocity, and ϑ the chair position in the respective plane. A_y (amplitude), ϕ_y (phase), and $offset_y$ were iteratively optimized. In the pitch, RALP, and LARP planes, data points modulated in a sinusoidal manner and were close to the best-fit sine. The amplitude of the sine is a measure of the modulation of the gravity-dependent (GD) component; the offset corresponds to the gravity-independent (GI) component of the vertical velocity bias. The GI component was directed upward and of similar magnitude in all planes of chair orientation (pitch, RALP, LARP, and roll), whereas the GD component was only seen in the pitch, RALP, and LARP planes. The minimal drift occurred in supine and the maximal drift in prone position. In upright position, vertical drift almost exclusively consisted of the GI component.

In two of the patients, we measured eye movements over the entire 360 degrees of chair positions along the pitch plane, as shown in figure 3. Again, the data closely followed a first-harmonic best-fit sine in both patients.

The Table gives the parameters of the sine fits in all six patients for drift velocities measured in the pitch, RALP, LARP, and roll planes. Note that the fits only applied to chair positions in the range of 180 degrees, that is, from supine to prone and from 90 degrees right ear to 90 degrees left ear down. In individual patients, A_y and ϕ_y in the pitch, RALP, and LARP planes were

Table. Vertical Ocular Drift Velocity as a Function of Chair Position in Various Planes of Body Orientation

	A_y (°/s)				ϕ_y [°]				$offset_y$ [°/s]			
Patient	*Pitch*	*RALP*	*LARP*	*Roll*	*Pitch*	*RALP*	*LARP*	*Roll*	*Pitch*	*RALP*	*LARP*	*Roll*
S.K.	5.9	6.3	5.8	4.3	29.8	39.0	28.7	92.2	5.7	5.7	7.9	6.4
U.S	5.4	5.4	7.2	3.1	51.0	57.9	51.6	100.1	0.6	1.7	−0.4	1.6
H.H.	1.5	0.9	0.9	0.6	−28.0	−59.0	−37.8	−74.4	2.6	3.3	2.4	2.5
H.N.	4.7	3.8	3.7	1.5	24.7	48.8	57.4	135.6	4.1	4.4	3.7	4.2
R.W.	9.9	7.6	7.6	1.4	−2.8	−3.4	11.5	−97.7	7.6	9.5	7.2	9.2
G.B.	2.5	1.8	1.1	0.4	−10.8	98.8	52.8	24.5	2.9	2.2	1.7	2.2

Amplitude (A_y), phase (ϕ_y), and offset ($offset_y$) of the sine fits in the six patients. A phase of $\phi_y = 0$ means that, in upright body position, the upward velocity bias only consists of the gravity-independent component and that the maximal upward drift velocity is found in the prone body position.

RALP = right ear anterior, left ear posterior; LARP = left ear anterior, right ear posterior.

similar. In the roll plane, A_y was minimal and ϕ_y varied widely in the roll plane. In all four planes, however, $offset_y$ was relatively constant.

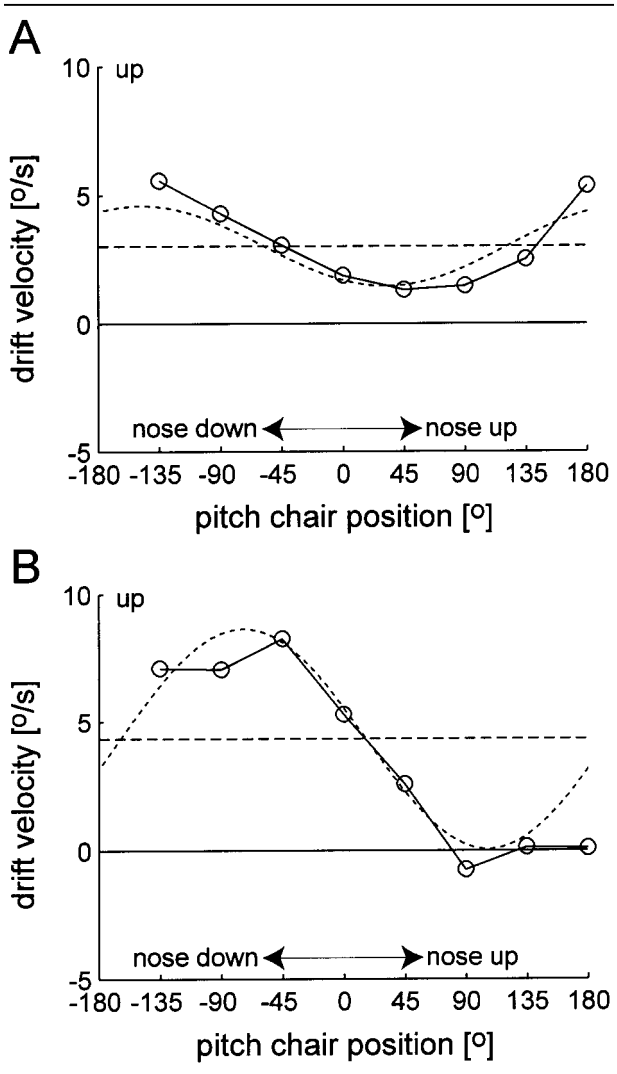
As illustrated in Figure 4, we pooled median ocular drift velocities of patients and healthy subjects for chair positions along single planes and fitted a sine function to these global data. The best-fit sine in cerebellar patients showed similar patterns in the pitch (see Fig 4A), RALP (not shown), and LARP (not shown) planes with a maximal upward drift velocity around prone. The body position associated with the maximal negative slope (= crossing of the offset level) was around the upright position in the pitch plane and slightly shifted toward supine in the RALP (not shown) and LARP (not shown) planes. There was no sinusoidal modulation of data in the roll plane (see Fig 4B). In all planes, the offset of the best-fit sine, that is, the GI-component of the vertical velocity bias, was directed upward and of similar magnitude.

Most healthy subjects showed small vertical drift at gaze straight ahead, but the direction was not consistent (see Fig 4C). The pattern of the best-fit sine through the pooled data was similar as in cerebellar patients, with consistent modulations in the pitch (see Fig 4C), RALP (not shown), and LARP (not shown) planes. The amplitudes, however, were considerably smaller than in the patients. Again, the body position associated with the maximal negative slope was around the upright position for the pitch, RALP, and LARP planes. No sinusoidal modulation occurred in the roll plane (see Fig 4D).

Amplitudes of sine fits differed widely among patients (see Table) and, at the same time, were considerably larger than in healthy subjects. For better comparison between patients and healthy subjects, we computed normalized amplitude

$$^{norm}A_i = A_i \Big/ \sum_{i=1:4} A_i$$

Fig 3. Vertical ocular drift velocity as a function of chair position in the pitch plane over the whole range of 360 degrees. Target was straight ahead. (A) Patient 3, right eye. (B) Patient 5, right eye. Symbols and lines as in Figure 2.



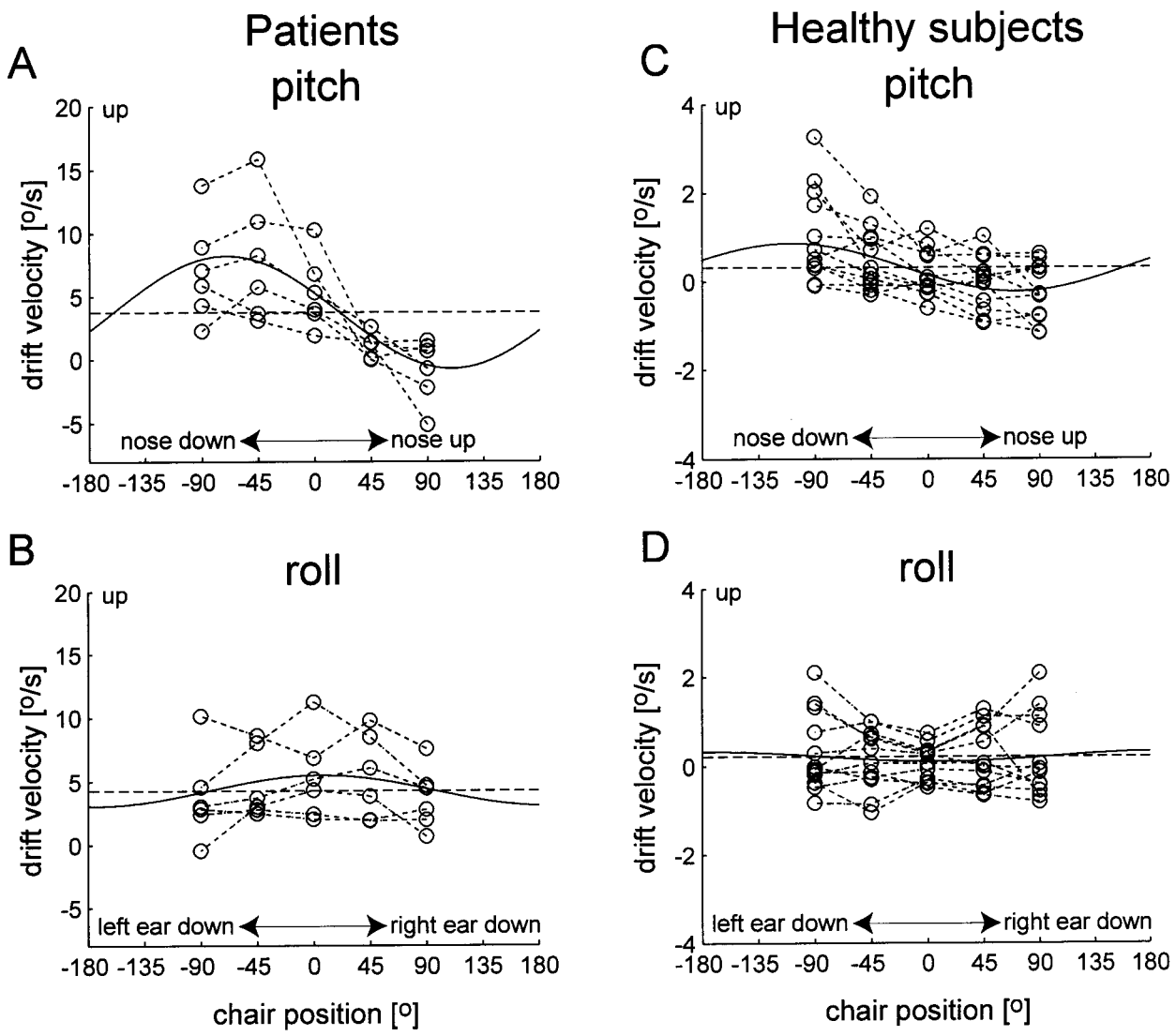


Fig 4. Vertical ocular drift velocity as a function of chair position in the pitch (A, C) and roll (B, D) planes in cerebellar patients and healthy subjects. Target was straight ahead. (open circles) *Median drift velocities.* (dashed lines) *Connect values measured in individual subjects.* (solid lines) *First-harmonic sine fits.* (horizontal dashed lines) *Offsets of sine fits. Note that the abscissa in panels A and B is five times wider than in panels C and D.*

whereby *i* denotes the four planes (pitch, RALP, LARP, roll). Figure 5 summarizes the normalized amplitudes and the absolute offset values of individual best-fit sines as a function of body orientation in the respective planes. The patients showed a maximal amplitude of the GD component in the pitch plane with a symmetrical decay toward the RALP and LARP planes, and a minimum amplitude in the roll plane (see Fig 5A). Absolute offset values (GI component), however, remained constant, independent of planes tested (see Fig 5B). The wide standard deviations reflect the large interindividual differences among patients.

The healthy subjects showed a similar relation between normalized amplitudes and body orientation planes, but the distribution of amplitudes of the GD component was flatter, that is, values between pitch, RALP, and LARP overlapped widely (see Fig 5C). Offset values varied around zero, independent of the planes tested (see Fig 5D). Standard deviations were much smaller than in the group of patients.

Thus far, the analysis of vertical drift was limited to the bias component of vertical velocity, that is, the vertical drift at gaze straight ahead. DBN also consists of a component that is gaze evoked and typically obeys Alexander's law (see introduction). Figure 6 demonstrates a typical scatterplots of vertical ocular drift velocity as a function of vertical eye position in the pitch,

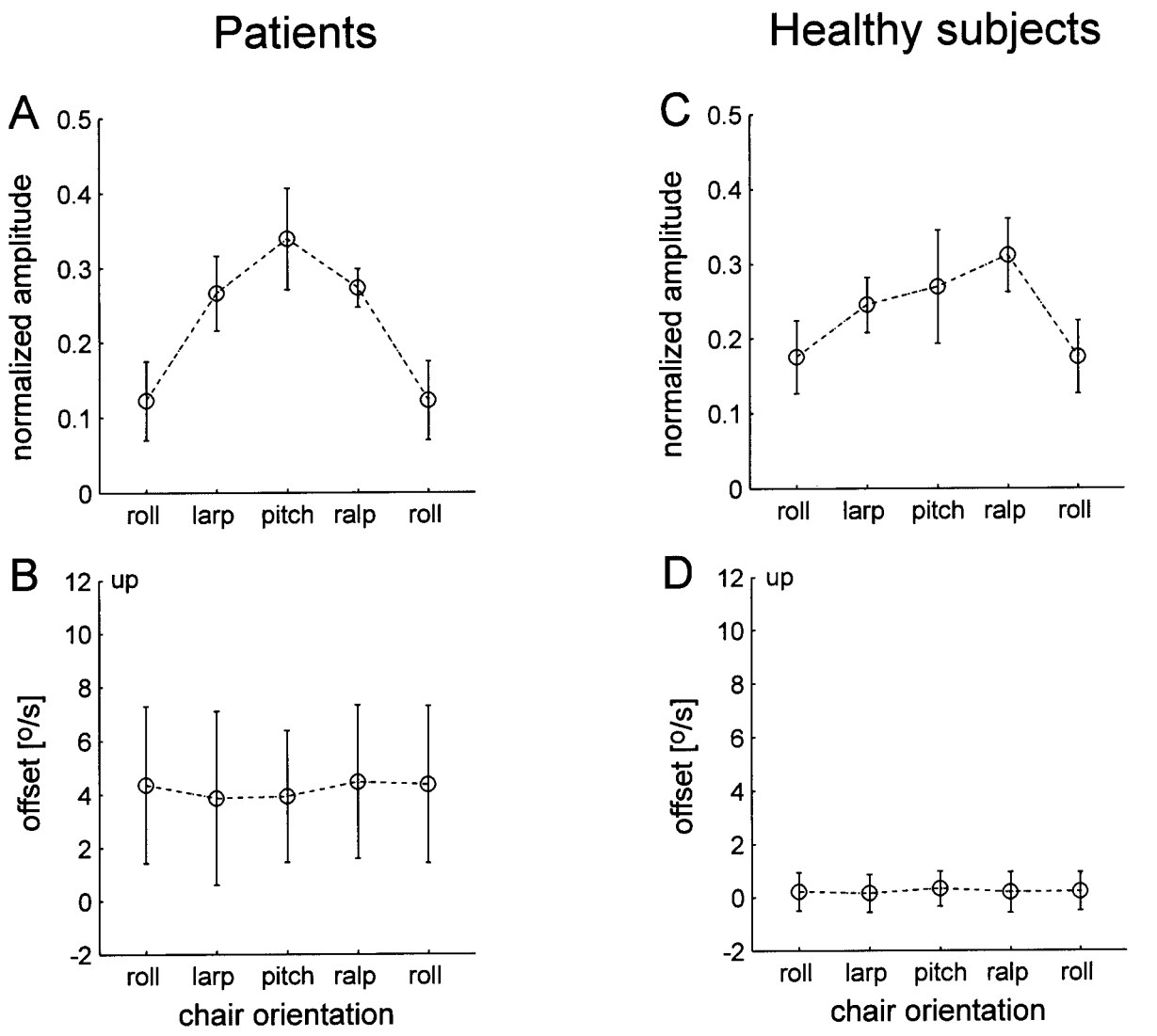


Fig 5. Summary plot describing the sine fits of vertical drift velocity as a function of chair orientation along the pitch, roll, right ear anterior, left ear posterior, and left ear anterior, right ear posterior planes in cerebellar patients and healthy subjects. (A, C) Normalized amplitudes of individual sine fits as a function of orientation planes. (B, D) Absolute offset values (average) of individual sine fits as a function of orientation planes. (open circles connected with dashed lines) *Averages. Error bars = ±1 standard deviation. Note that, in all panels, values for the roll plane are given twice.*

RALP, and roll planes (patient R.W., right eye). By a first-order linear robust fit (see Patients and Methods), the slope of this relation and the correlation coefficient R^2 was determined.

Scatterplots in which the correlation coefficient R^2 was above 0.5 after discarding 30% of the data always had a negative slope of the linear regression, in accordance with Alexander's law. In all six patients, we found no evidence for a dependence of slopes from body orientation in any of the planes tested (not shown).

We also examined whether horizontal and torsional drift velocities at gaze straight ahead are influenced by the orientation of the gravity vector relative to the head. In the patients, the sinusoidal modulation of torsional drift was small in all four planes (amplitudes in pitch: 0.56 degrees/sec; RALP: 0.52; LARP: 0.4; roll: 0.49). Offset values were below 0.4 degrees per second in all planes. The horizontal drift modulation was somewhat larger (amplitudes in pitch: 0.5 degrees/sec; RALP: 0.7; LARP: 0.85; roll: 0.95). Offset values of horizontal drift velocity also were relatively small (offsets in pitch: 0.29 degrees/sec; RALP: 0.39; LARP: 0.64; roll: 0.59). In healthy subjects, no horizontal or torsional velocity bias at gaze straight ahead was found.

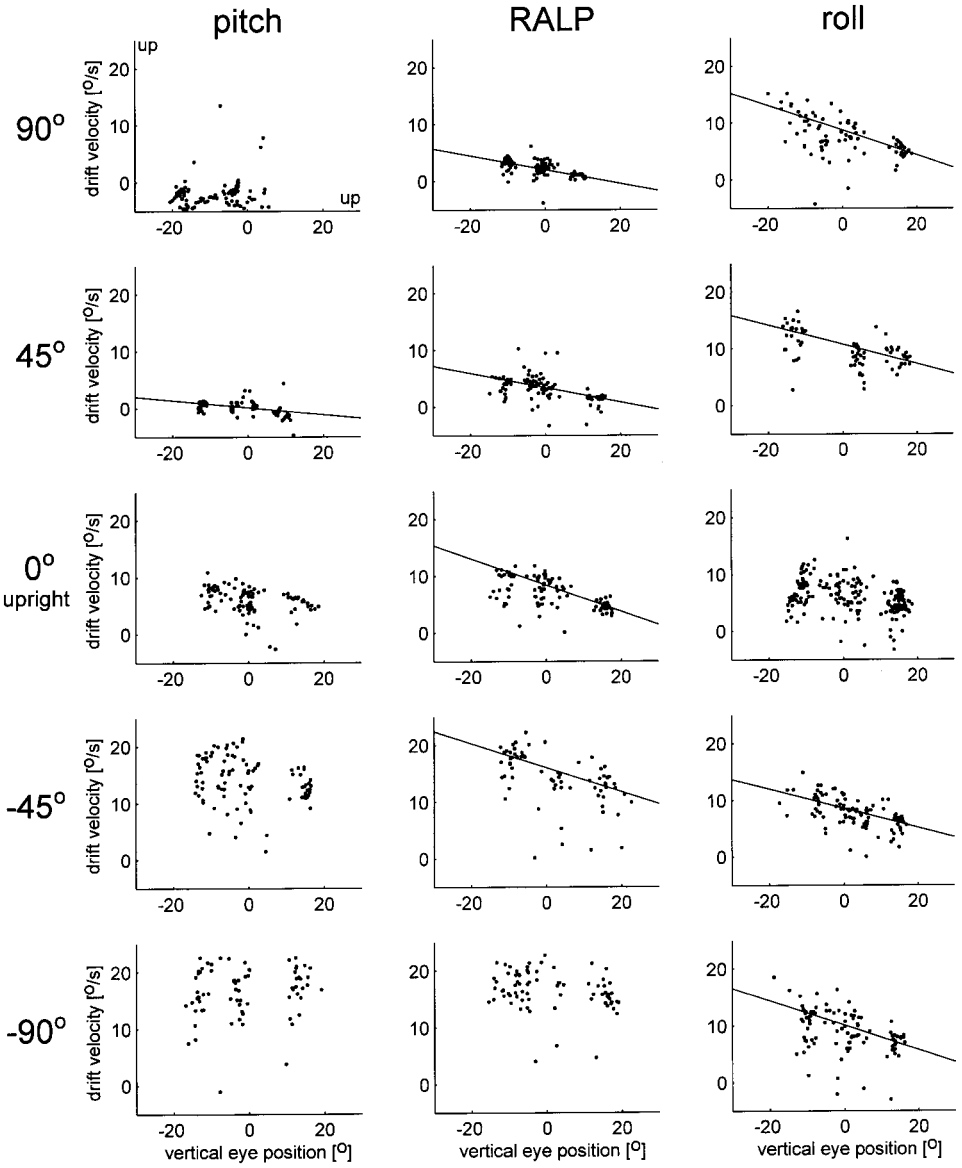


Fig 6. Scatterplots of vertical ocular drift velocity as a function of vertical eye position in a patient with cerebellar atrophy (same patient as in Fig 1, right eye) during chair orientations along the pitch, right ear anterior, left ear posterior (RALP), and roll planes. Target was straight ahead, 15 degrees down, and 15 degrees up. Coding of chair position is analogous to Figure 1. Regression lines were determined by a robust first-order linear fit (see Patients and Methods) and plotted if R^2 *was above 0.5 after discarding 30% of the data (in 9 of 15 panels). Negative slopes correspond to Alexander's law.*

Discussion

This study analyzed ocular drift as a function of the three-dimensional orientation of the gravity vector relative to the head in cerebellar disease. Patients with ocular motor signs typical for floccular/paraflocculer lesions, including DBN, showed two components of the vertical velocity bias (= vertical ocular drift at gaze straight ahead): an upward drift component (GI component) that was independent of gravity, and a component (GD component) that sinusoidally modulated with the gravity vector in the pitch plane, but not in the roll plane. The least vertical drift velocity occurred around the supine position, in which the GD component showed its maximal downward drift, counteracting the upward drift of the GI component. Conversely, the maximal vertical drift velocity was observed around the prone position, in which both drift components were directed upward. In upright position, the GD component was close to zero, and thus vertical ocular drift in this position consisted mainly of the GI component. As in earlier studies,[18,19] the same modulation of the GD component was found in healthy subjects. The amplitude of the GD component in cerebellar patients, however, was approximately 10 times larger than in healthy subjects.

The sinusoidal modulation of the GD component of vertical drift velocity in the pitch plane is most likely otolith driven and may represent an overacting otolith-ocular reflex. The normal function of the otolith-ocular reflex at low frequencies driven by pitch tilt is to keep the vertical gaze direction stable in space.[24] Thus, when the head is pitched downward, the eyes move upward and vice versa. The direction of the GD component is consistent with this pattern. The finding that healthy subjects showed the very same pattern of the GD component, but in a scaled-down version, supports the notion that the intact cerebellum minimizes the overacting otolith-ocular reflex driven by pitch tilt. In fact, previous clinical studies have demonstrated a substantial role of the cerebellum in controlling translational vestibuloocular reflex.[25–27] In electrophysiological studies, both the flocculus[28] and the nodulus[29] modulated otolith-ocular reflexes.

The upward directed GI component represents the "true velocity bias" and was found only in cerebellar patients, but not in healthy subjects. This component could represent a tone imbalance of the otolith or semicircular canal pathways[2,12,13,30] or be of nonvestibular origin.[1,11] Impaired function of the cerebellum may create or unmask an asymmetry of vertical ocular motor signals.

Vertical gaze-evoked drift in patients with DBN reflects an impairment of neural structures implementing vertical gaze holding. In cerebellar patients, we did not find a consistent relation between the gaze-evoked drift and the orientation of the gravity vector. The small individual variations of the vertical centripetal drift with changing head position could reflect short-term gain changes of the neural integrator because of its leakiness and instability after the cerebellar lesion.[10]

A recent model of central positional nystagmus predicted both torsional and horizontal nystagmus in ear-down positions by combining impaired neural integration with otolith-dependent modifications of eye movement kinematics.[31] In cerebellar patients, there were indeed small modulations of the horizontal and torsional velocity bias with changing gravity, but, in contrast with the model, they occurred not only in the roll, but also in the pitch plane. Moreover, amplitudes and offsets of drift velocity in the horizontal and torsional planes were approximately 10 times smaller compared with the vertical drift velocity. Thus, impaired integration probably does not play a major role in the generation of DBN.

Our study concentrated on the static influence of gravity on DBN. When a patient's head position is changed quickly into the head hanging position, DBN may transiently increase because of the rapid reorientation of the gravity vector, which probably reflects an addition sensitivity of DBN to dynamic otolith stimulation.[2,3,9] To assess steady state DBN in the clinical routine, it therefore is important to keep the patient in a given position long enough. Furthermore, the clinician should keep in mind that the GD and GI components of the velocity bias might cancel each other in the supine position, and that DBN is best detected with the patient in prone position. An increase of the static slow-phase velocity of DBN in the head-hanging position (ref 2) is compatible with our results, since in this position the magnitude of the downward-directed GD component is already smaller than in the supine position. Fierce increases of the static slow phase velocity, however, may represent an exacerbation of DBN as a result of compressive effects on neural structures by neck hyperextension during head hanging, e.g. in Chiari malformation (ref 3). In our experiments, such effects were excluded by using whole-body rotations. Moreover, none of our patients with typical ocular motor findings of floccular/parafloccular lesions showed craniocervical junction abnormalities.

In conclusion, impaired vestibulo-cerebellar structures play crucial roles in at least two different pathological mechanisms associated with the upward velocity bias of cerebellar DBN: one mechanism is gravity-dependent, the other gravity-dependent. Manipulating the gravity-dependent component by changing the body position can be used to reduce the overall intensity of DBN. Patients with cerebellar DBN should be told that the optimal body position for reading is around the supine position.

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