

Prolonged Asymmetric Smooth-Pursuit Stimulation Leads to Downbeat Nystagmus in Healthy Human Subjects

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PURPOSE. Downbeat nystagmus (DBN) is a typical ocular motor sign in patients with lesions of the vestibulocerebellum. A vertical vestibular tone asymmetry, an upward shift of the eyes' null position for vertical gaze holding, or an imbalance of vertical smooth-pursuit signals have been proposed as mechanisms of DBN. The purpose of this study was to elaborate a possible link between an imbalance in the vertical smooth-pursuit system and DBN by relying on a healthy human model.

METHODS. Healthy subjects ($n = 6$) were exposed to continuous asymmetric smooth-pursuit stimulation over 20 minutes.

RESULTS. Prolonged asymmetric smooth-pursuit stimulation induced a drift lasting >5 minutes in the direction of the prior pursuit. Upward drift was faster than downward drift and showed eye-position dependence in accordance with Alexander's law, but no increase of drift velocity with lateral gaze. Upward drift violated Listing's law in three of four subjects tested.

CONCLUSIONS. An experimentally induced vertical smooth-pursuit imbalance leads to DBN in healthy human subjects. Accordingly, because in patients with cerebellar disease upward smooth-pursuit eye movements are typically better preserved than downward, the resultant sustained imbalance of vertical smooth-pursuit input may play a major role in the generation of DBN. (*Invest Ophthalmol Vis Sci.* 2005;46:143-149) DOI: 10.1167/iovs.04-0235

Patients with cerebellar atrophy, especially if the flocculus and paraflocculus are involved, often exhibit downbeat nystagmus (DBN), a jerk nystagmus consisting of a slow upward-directed drift and of quick phases beating downward.¹ Typically, cerebellar DBN increases with lateral gaze² and obeys Alexander's law.^{3,4} The upward drift is composed of two components: a bias drift that is already present in gaze straight ahead and a gaze-evoked drift.⁵ The gaze-evoked drift is thought to be caused by leakiness of the vertical neural integrator for gaze-holding⁵; however, the mechanism of the bias drift remains unclear.

While the gravity-dependent component of the bias drift may represent an overactive otolith-ocular reflex,⁶ various hypotheses have been proposed to explain the origin of the

gravity-independent component. Most investigators favor the theory of a vestibular tone imbalance due to a central⁷⁻¹¹ or peripheral¹² pathway asymmetry—specifically, a relative predominance of anterior over posterior semicircular canal pathways. Another hypothesis suggests an upward shift of the eyes' null position for vertical gaze holding, which, in combination with leakiness of the vertical velocity-to-position integrator, leads to upward drift in gaze straight ahead.¹³ Finally, Zee et al.¹⁴ proposed a model based on asymmetric vertical smooth-pursuit signals, in which the overbalance of upward visual velocity commands results in spontaneous upward drift. The assumption of an asymmetry of vertical smooth-pursuit signals was based on the observation of the tracking behavior of patients with cerebellar disease who show relatively smooth upward, but saccadic downward tracking during smooth-pursuit stimulation.²

The role of a vertical smooth-pursuit imbalance in the generation of cerebellar DBN has not been investigated further so far. The purpose of our study was to find a human model for DBN based on an acquired vertical smooth-pursuit asymmetry. We therefore exposed healthy human subjects to asymmetric vertical smooth-pursuit stimulation and measured eye velocity in the dark before and after stimulation. To minimize any contribution of the optokinetic system, for which stimulation of the peripheral retina is essential,^{2,15} and to guarantee an optimal pursuit response, we applied a small laser stimulus that was moved in otherwise complete darkness.

In human subjects, asymmetric smooth-pursuit stimulation of 1 to 2 minutes can induce a pursuit afternystagmus in the direction of the prior pursuit that lasts a few seconds.^{15,16} Our goal, however, was to reproduce in healthy subjects the sustained upward drift seen in patients with cerebellar disease. Therefore, we prolonged the asymmetric smooth-pursuit stimulation to 20 minutes to explore whether this could induce a long-lasting ocular drift.

METHODS

Subjects

Six healthy subjects (four women, two men; 25–41 years of age) gave their informed consent to participate in this study after the experimental procedure had been explained. The experimental protocol was approved by a local ethics committee at Zurich University Hospital, and adhered to the Declaration of Helsinki for research involving human subjects. All subjects were free of symptoms, and none of them was taking any medication at the time of the experiments.

Experimental Setup

Subjects were seated upright with the head restrained by an individually molded thermoplastic mask (Sinmed BV, Reeuwijk, The Netherlands). By way of two computer-controlled mirror-galvanometers, a laser dot (diameter: 0.1°) was projected onto a sphere with a radius of 1.4 m from the center of the head.

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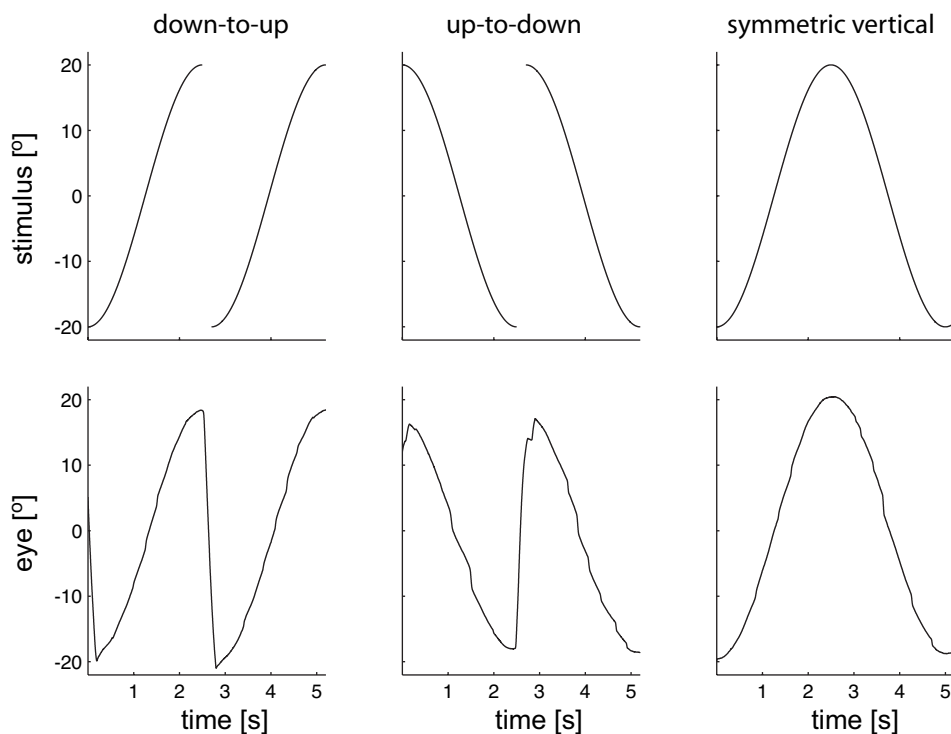


FIGURE 1. Vertical asymmetric (first and second columns) and symmetric (third column) paradigms of continuous smooth-pursuit stimulation. Representative sections of 5 seconds are depicted. The entire trial lasted 20 minutes. *Top row:* laser positions. *Bottom row:* vertical eye positions of a typical subject (SM).

Eye Movement Recordings

Eye movements were recorded monocularly using dual search coils (Skalar Instruments, Delft, The Netherlands). The coil frame (side length: 0.5 m) generated three orthogonal digitally synchronized magnetic wave field signals of 80, 96, and 120 Hz. 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 <7% over a range of $\pm 30^\circ$ and with a noise level of $<0.05^\circ$ (root mean square deviation). Search coil annuli were calibrated¹⁷ and then placed around the cornea of the right eye after local anesthesia with oxybuprocaine 0.4%. Eye-position signals were digitized at 1000 Hz per channel with 16-bit resolution.

Experimental Paradigms

Figure 1 depicts position traces of the target (top row) and of the right eye (bottom row) during continuous vertical smooth-pursuit stimulation in a typical example (subject SM). For stimulation, the laser dot was sinusoidally moved in the vertical or horizontal direction with a positional amplitude of 20° (40° peak-to-peak) and a peak velocity of 25.1 deg/s at a frequency of 0.2 Hz. Asymmetric vertical smooth-pursuit stimulation (first and second column) consisted of consecutive half sines, between which the target jumped from one eccentric quasistationary position to the opposite side. This jump elicited a 40° saccade. The laser was always extinguished for 200 ms before reappearing on the opposite side, allowing time for refixation. Symmetric vertical stimulation consisted of uninterrupted sinusoidal stimulation (third column). The same stimulus pattern was also applied in the horizontal direction, by using a left-to-right and a symmetric paradigm (not shown).

All subjects performed each of the five paradigms (down-to-up, up-to-down, symmetric vertical, left-to-right, and symmetric horizontal) twice: once for 2 minutes (short trials) and once for 20 minutes (long trials). Before each trial and every 5 minutes during the long trials, ocular drift velocity was measured during attempted consecutive fixations in gaze 20° up, straight ahead, and 20° down for the vertical paradigms and in gaze 20° left, straight ahead, and 20° right for the

horizontal paradigms. To prevent suppression of ocular drift by these fixations, the laser dot appeared for only 20 ms every 2 seconds in otherwise complete darkness. Instantaneously (with time 0 seconds) after both long and short trials, ocular drift was recorded at the three gaze positions over several minutes until eye velocity was close to zero. In another set of experiments, in four of the six subjects, ocular drift before and after long trials was measured during fixation on the flashing laser dot that was presented straight ahead and on a $\pm 20^\circ$ square.

Data Analysis

Calibrated eye position from the right eye was processed with interactive programs (written in MatLab; The Math Works, Natick, MA). The slow-phase velocity of nystagmus was determined by computing the median velocity for consecutive sections of 400 ms. Such a procedure implicitly desaccades eye-movement signals, because of the short duration of saccades.¹⁸ Analyzed sections were interactively discarded, if the slow phase velocity was inconstant (i.e., changed by more than approximately 20% over the whole 400-ms period). To characterize ocular drift in the dark during attempted fixations on the flashing laser dot, eye velocity was plotted versus eye position for the three gaze directions (target at -20° , 0° , and 20°) along the vertical or horizontal meridians. Slope and bias drift (i.e., offset) were computed by fitting first-order regression lines through these scatterplots. Slope was set to zero, if $R^2 < 0.5$. Note that bias drift is equivalent to the intercept of the linear regression.

Direction-specific smooth-pursuit gain during tracking of the sinusoidally moving laser dot was computed by dividing eye velocity by target velocity at the moments of maximum target velocity in one direction. Data recorded over a period of 2 minutes were averaged.

To analyze whether ocular drift obeys Listing's law, we fitted three-dimensional eye positions and their temporal derivatives (component eye velocities, which are not the same as angular velocities¹⁹) of nystagmus slow phases, to the equation^{13,20}

$$\dot{\mathbf{r}} = \mathbf{T} \cdot \mathbf{r} + \dot{\mathbf{r}}_0$$

with the free parameters $\dot{\mathbf{r}}_0$ and \mathbf{T} . \mathbf{T} is a 3×3 matrix describing the dependence of the ocular drift on eye position. A significant ($P < 0.05$)

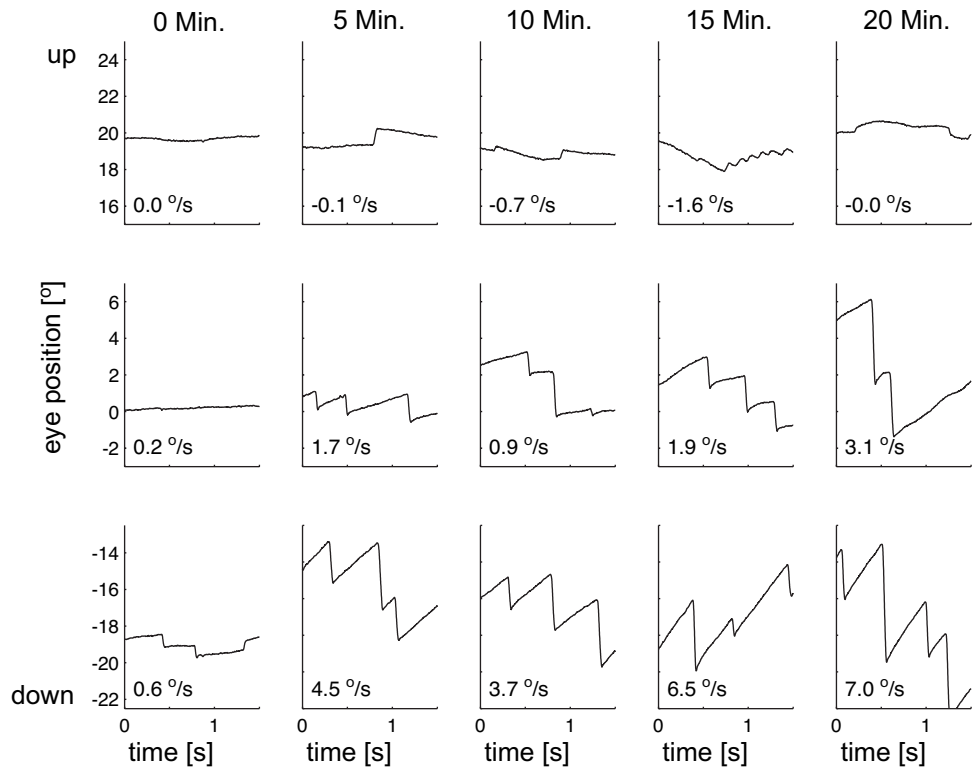


FIGURE 2. Example (subject SM) of eye position traces elicited by continuous asymmetric smooth-pursuit stimulation in the upward direction over 20 minutes (long down-to-up paradigm). Representative sections of 1.5 seconds are depicted in gaze up (top row), straight ahead (middle row), and down (bottom row). In each subpanel, the median upward drift velocity of the whole section is indicated. Eye velocity was measured in the dark before the stimulation started (0 Min.), immediately after the stimulation stopped (20 Min.), and every 5 minutes during the stimulation (5, 10, and 15 Min.). Note that the pursuit stimulus was turned off during the recording of ocular drift, and the subject had to fix on the flashing (20 ms every 2 seconds) laser dot at three positions (-20° , 0° , and 20°) along the vertical meridian in otherwise complete darkness.

torsional drift velocity as a function of eye position or a significant torsional offset velocity represented violations of Listing's law.

Statistical Analysis

Parameters measured from all subjects in different experimental paradigms were statistically compared by paired *t*-tests. The significance of linear regressions was computed by F statistics.

RESULTS

Figure 2 shows typical eye-position traces (subject SM) evoked by continuous upward smooth-pursuit stimulation over 20 minutes (long down-to-up trial). Before the stimulation started (0 min), there was minimal ocular drift in gaze straight ahead (middle row) and down (bottom row). In gaze up (top row),

there was no drift. After only 5 minutes of continuous upward smooth-pursuit stimulation, downbeat nystagmus (DBN) appeared in gaze down and straight ahead, whereas, in gaze up, the vertical drift velocity stayed close to zero. This dependence of drift velocity on eye position is known as Alexander's law.^{3,4} Further stimulation led to a small additional increase of vertical drift velocity in both down and straight ahead gaze positions, but drift velocity in gaze up became negative (at 10 and 15 minutes) or was close to zero (at 20 minutes).

After 20 minutes of continuous upward smooth-pursuit stimulation, subjects ($n = 4$) fixed on a flashing laser dot in nine cardinal gaze positions (see the Methods section). Figure 3 depicts average gaze positions (open circles) and associated drift velocities (arrows) in two typical subjects (Fig. 3A, same subject as in Figs. 1 and 2; Fig. 3B, subject with the

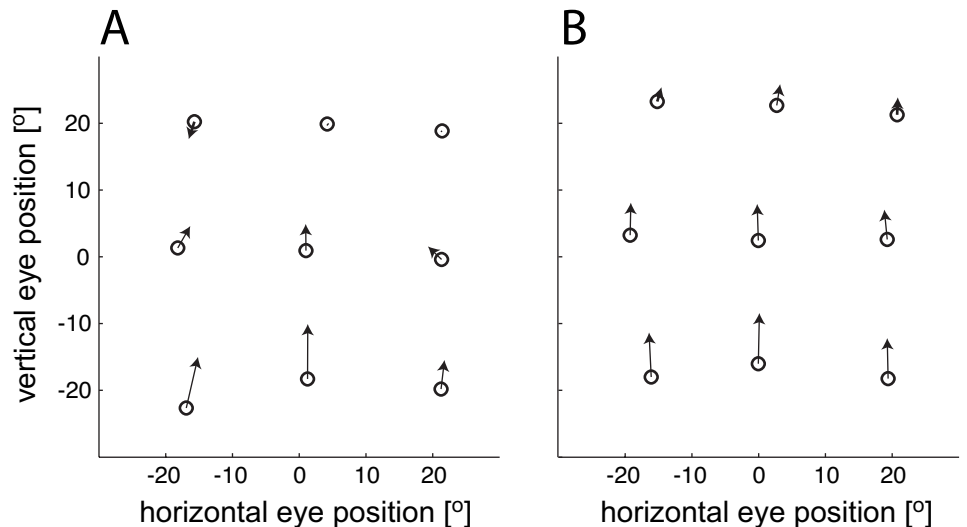


FIGURE 3. Median eye positions (○) and corresponding drift velocities (arrows; length corresponds to the scaling of the coordinate system, but in deg/s) in nine cardinal gaze directions (target: flashing laser dot) in two subjects. (A) Subject SM, (B) subject TS.

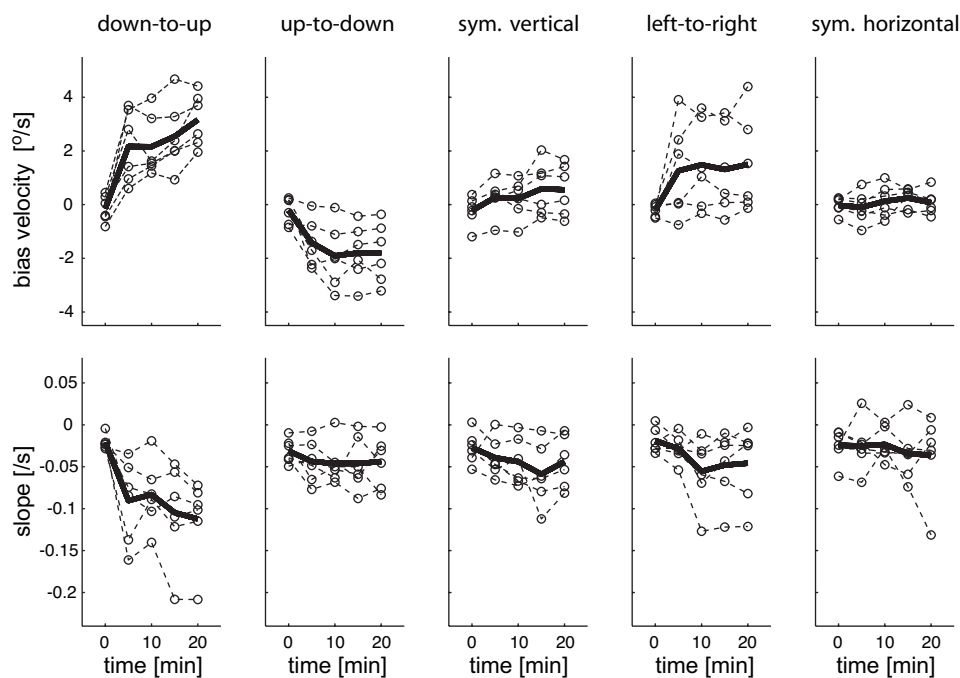


FIGURE 4. Bias ocular drift velocity (*top row*) and slope (*bottom row*) of first-order linear regression fits during the five different paradigms of continuous asymmetric and symmetric smooth-pursuit stimulation over 20 minutes (long paradigms). For regressions with $R^2 < 0.5$, the slope was set to zero. Ocular drift was recorded before (0 minutes) and after (20 minutes) pursuit adaptation, as well as during short interrupts (5, 10, and 15 minutes), for which the ongoing pursuit stimulus was transiently turned off. During recordings, subjects had to fix on the flashing laser dot that was presented as in Figure 2. (○): median values in each subject; *solid bold lines*: corresponding averages ($n = 6$).

largest drift induced by continuous upward smooth-pursuit stimulation). In all gaze positions, the drift was directed upward. Alexander's law was valid, both along the vertical meridian, in which the smooth-pursuit stimulation occurred, and along eccentric altitudes. There was no consistent modulation of vertical drift velocity as a function of horizontal gaze position.

Figure 4 summarizes the effect of continuous vertical and horizontal smooth-pursuit stimulation in all six subjects. A linear regression line was fitted to drift velocity as a function of gaze position (see the Methods section). For measurements every 5 minutes, the top row depicts the velocity bias, the bottom row the slope of the fits. The bias represents drift velocity during gaze straight ahead, while the slope is a measure of the drift's dependence on eye position (negative values: Alexander's law; positive values: inverse Alexander's law). Asymmetric vertical smooth-pursuit stimulation had a strong effect. Down-to-up stimulation elicited upward drift (first column, top row; average velocity bias after 20 minutes: 3.2 deg/s), and up-to-down stimulation elicited downward drift (second column, top row; 1.8 deg/s). Down-to-up stimulation was significantly more effective than up-to-down stimulation (paired t -test: $P < 0.05$). Symmetric vertical smooth-pursuit stimulation led to a small, but significant upward-directed change of the vertical velocity bias after 20 minutes (third column, top row; average: -0.6 deg/s, paired t -test: $P = 0.002$). For all three vertical paradigms, the major change of the velocity bias occurred within the first 5 minutes, whereas a further increase of the velocity bias over the next 15 minutes was only significant for the down-to-up paradigm. In three of the six subjects, a notable horizontal velocity bias to the right developed (fourth column, top row). In these subjects, asymmetric horizontal (left-to-right) smooth-pursuit stimulation was similar to vertical in effectiveness. Finally, a significant change of the slope occurred only during long down-to-up stimulation (first column, bottom row).

Figure 5 compares the effects of short (2 minutes; left column) and long (20 minutes; right column) asymmetric smooth-pursuit stimulation. Short asymmetric vertical smooth-pursuit stimulation (left column, top and middle row) led to a small increase of vertical drift velocity in the direction of the

stimulus. This drift decayed rapidly toward zero. For short left-to-right stimulation, no consistent drift was evoked among the six subjects (left column, bottom row).

Long stimulation differed from short stimulation in two ways: The initial drift velocity in the direction of the stimulus was higher, and the time constant of the drift decay was longer. On average, long asymmetric vertical stimulation evoked an initial upward drift of 3.2 deg/s (right column, top row) and a downward drift of 1.8 deg/s (right column, middle row). The time constants of averaged velocity decays were 258 seconds for upward drift and 614 seconds for downward drift. Long horizontal left-to-right stimulation (right column, bottom row) was only effective in three subjects. In those, however, the initial velocity (average: 2.8 deg/s) and the time constant (average: 186 seconds) were comparable to the upward drift after down-to-up pursuit stimulation.

We asked whether the gain of smooth pursuit in the down-to-up direction was higher than in the up-to-down direction, which could explain why down-to-up stimulation was more effective, i.e., elicited a faster drift. Average gains ($n = 6$) in the vertical directions were not significantly different (upward: 0.94; downward: 0.90; paired t -test: $P > 0.05$). Similarly, horizontal smooth pursuit to both sides had equal gains (leftward: 0.91; rightward: 0.90; paired t -test: $P > 0.05$).

In another set of experiments (see the Methods section), we also asked whether the upward drift after 20 minutes of down-to-up stimulation is in accordance with Listing's law.²¹⁻²⁴ The drift obeyed Listing's law in one subject (no significant torsional drift velocity as a function of eye position and no significant torsional offset velocity; $P > 0.05$). In the other three subjects, the ocular rotation axis tended to move in the direction of gaze, similar to the pattern observed during vestibular nystagmus.²⁵

DISCUSSION

Smooth-Pursuit Hypothesis of Downbeat Nystagmus

The purpose of the study was to investigate whether asymmetric vertical smooth-pursuit signals can lead to DBN, a hypoth-

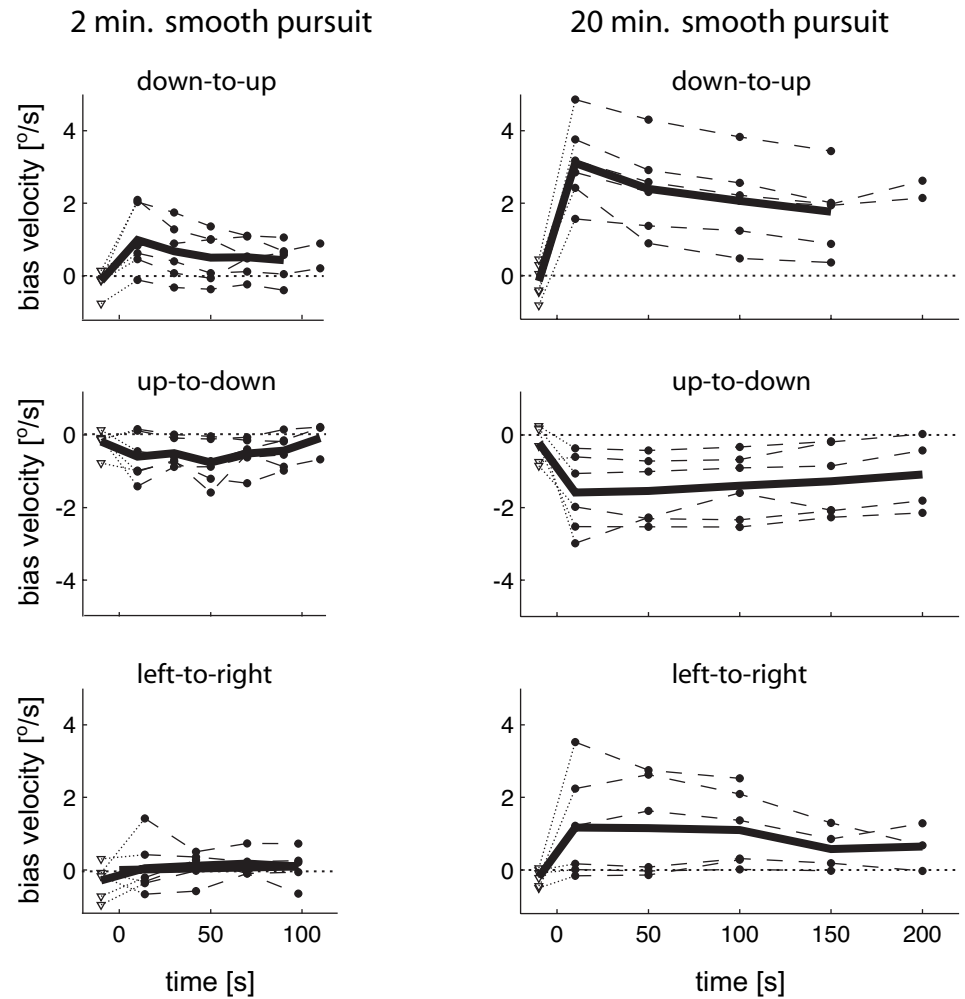


FIGURE 5. Time course of ocular drift velocities elicited after 2 (short trials) and 20 (long trials) minutes of continuous asymmetric vertical (*top* and *middle row*) and horizontal (*bottom row*) smooth-pursuit stimulation. Immediately after stimulation stopped, subjects had to fix on the flashing laser dot at three positions (-20° , 0° , and 20°) along the vertical or horizontal meridians in otherwise complete darkness. The sequence of the three target locations was repeated continuously. (∇) Median drift velocities before pursuit adaptation; (\bullet) median drift velocities after pursuits adaptation; *solid bold lines*: connected corresponding averages ($n = 6$). Abscissa: elapsed time after the stop of pursuit adaptation.

esis first proposed by Zee et al.,¹⁴ especially for DBN of cerebellar origin. As shown by clinical observations^{2,14} and quantitative measurements (Glasauer S, personal communication, 2004), in patients with cerebellar disease, upward smooth-pursuit eye movements are typically better preserved than downward. The model by Zee et al.¹⁴ was based on the assumption that a defect within the vertical smooth-pursuit system leads to an overbalance of upward visual velocity commands and therefore results in spontaneous upward drift. To test this hypothesis, we exposed healthy human subjects to continuous asymmetric vertical smooth-pursuit stimulation. Although 2 minutes of stimulation only induced short-pursuit afternystagmus, 20 minutes of asymmetric smooth-pursuit stimulation elicited a strong and enduring ocular drift that outlasted the visual stimulation for several minutes in the dark. The evoked drift was stronger in the upward than in the downward direction, a finding that cannot be explained by a higher gain of smooth-pursuit stimulation in the down-to-up direction than in the up-to-down direction, because the gains of upward and downward smooth pursuit at maximum target velocity were similar. An increase of ocular drift velocity when gaze moved in the direction of the nystagmus quick phases (i.e., an eye-position dependence according to Alexander's law^{3,4}) was found only for drift evoked in the upward direction.

We conjecture that an imbalance in the vertical smooth-pursuit system is the basis of upward drift in both healthy subjects and patients with cerebellar disease. In healthy subjects, a sustained overbalance of vertical smooth-pursuit signals in one direction was induced experimentally and led to a bias

drift in the dominant direction, probably by activating an adaptive mechanism, which we shall call the pursuit-adaptation mechanism. In patients with cerebellar disease, vertical smooth pursuit is asymmetrically impaired, predominantly in the downward direction. The resultant imbalance of vertical smooth pursuit may be at least partly responsible for the spontaneous upward drift in cerebellar DBN.

The direction and speed of elicited smooth-pursuit eye movements are based on combined cell activity such as vector averaging.^{26,27} A directionally selective or asymmetric smooth-pursuit input, as induced by our paradigms, leads to an imbalance of firing rates and shifts the pooled response away from zero in the direction of the asymmetric input signal. If the increase of combined cell activity in one direction is transitory, the evoked drift declines rapidly toward zero, with a time constant similar to that in vestibular velocity storage.^{28,29} However, with an ongoing asymmetric smooth-pursuit input, drift velocity is increasingly stored in an adaptive mechanism with a longer time constant, apart from velocity storage. This pursuit-adaptation mechanism, then, could induce a bias drift velocity in the direction of asymmetric smooth-pursuit stimulation. Probably through efference copy or sensors in the eye muscles, the ocular motor system may be provided with an eye drift signal that is used to shorten the time constant of the velocity-to-position integrator, such that the drift velocity decreases when the eyes look in the direction of the drift in accordance with Alexander's law. We found this law to be valid for upward drift after down-to-up stimulation.

Stimulation of the pursuit system occurs constantly in daily life either by moving targets or visual suppression of the vestibulo-ocular reflex. Assuming that the pursuit adaptation mechanism may still operate in patients with cerebellar disease, as it does for podokinetic stimulation,³⁰ the overbalance of upward visual velocity commands, resulting from the relatively better preserved upward smooth pursuit, may be at least partly responsible for this adaptive mechanism and may finally lead to spontaneous upward drift. In the light, healthy subjects quickly suppress the upward drift by the intact smooth-pursuit system. Patients with cerebellar disease, on the other hand, are unable to suppress their ongoing upward drift in the light, since smooth pursuit in the downward direction is deficient and hence not able to counteract the upward retinal slip.

Our results do not rule out another possible mechanism that causes the bias drift (drift in gaze straight ahead) in patients with cerebellar disease, which was recently proposed by Glasauer et al.¹³ They assumed that a lesion of pathways from the cerebellum to the neural integrator in the brain stem affects both the intrinsic coordinate system of the integrator and its time constant. In other words, the bias drift could also be the result of an upward shift of the null position for vertical gaze holding, in combination with leaky velocity-to-position integration. We cannot exclude the possibility that continuous asymmetric smooth-pursuit stimulation may directly affect the null position of the neural integrator.

Smooth-Pursuit Adaptation Versus Pursuit or Optokinetic Afternystagmus

Earlier studies on short asymmetric horizontal¹⁵ and vertical¹⁶ pursuit stimulation demonstrated a so-called pursuit afternystagmus in the direction of prior pursuit. In these studies, asymmetric pursuit stimulation was applied for 1 to 2 minutes (stimulus velocities: 7.5–50 deg/s). The elicited drift decayed toward zero velocity within 15 seconds. Asymmetric pursuit stimulation was more effective upward than downward.¹⁶ Because of similar decay time constants, pursuit afternystagmus was thought to be induced by a common velocity storage mechanism shared with the vestibular and optokinetic systems.^{28,29} Our results suggest otherwise. The long time constants (3–10 minutes) after 20 minutes of asymmetric smooth-pursuit stimulation cannot be explained on the basis of the velocity storage mechanism alone. In fact, earlier studies on horizontal and vertical optokinetic afternystagmus reported time constants not exceeding 50 seconds in humans.^{2,31,32} In addition, the visual target in our experiments (diameter of laser spot: 0.1°), although a strong stimulus for the smooth-pursuit system, is a poor stimulus for optokinetic nystagmus (OKN) and therefore afternystagmus (OKAN), because OKN essentially depends on stimulation of the peripheral retina.^{14,15} Similar to findings in monkeys,³³ there is no downward OKAN after full-field downward optokinetic stimulation in healthy human subjects, which suggests a lack of velocity storage in the downward direction.^{32,34} These results provide further evidence that our findings cannot be explained by a velocity storage mechanism alone, since continuous asymmetric smooth-pursuit stimulation elicits strong ocular drifts in both upward and downward directions. With a center-only OKN stimulus (width: 6°; height: 10°), downward OKAN can be observed in some subjects.³² We think that such stimulus rather activates the pursuit and not the OKN system, and therefore the ocular drift that occurs after stimulation does not represent true OKAN.

Pursuit-Induced Upward Drift in Violation of Listing's Law

Listing's law states that rotation vectors describing eye positions lie in a plane—the so-called Listing's plane.^{21,22,35–37} Downbeat nystagmus in patients with cerebellar disease violates Listing's law, while pursuit eye movements remain in Listing's plane. Three of the four subjects, in whom we were able to measure the induced ocular drift at horizontal and vertical gaze eccentricities, showed significant violations of Listing's law. The fact that the drift after continuous upward smooth-pursuit stimulation was not in Listing's plane, although smooth-pursuit eye movements elicited during visual stimulation obeyed Listing's law,³⁸ is noteworthy. The signal from the adaptation mechanism that stores unidirectional smooth-pursuit velocity does not seem to be kinematically processed with eye-position signals to conform with Listing's law.

CONCLUSION

We have demonstrated in healthy human subjects that continuous asymmetric smooth-pursuit stimulation evokes a long-lasting ocular drift. Our healthy human model offers an explanation of how asymmetrically impaired vertical smooth pursuit (upward pursuit better preserved than downward pursuit), as it exists in cerebellar ocular motor syndrome, can lead to DBN. Of course, additional ocular motor signs typically associated with cerebellar DBN, such as the increase of drift with lateral gaze and the additional horizontal and torsional eye-position dependent drift,^{5,13} as well as gravity-dependence,⁶ involve other mechanisms and are not explained by the pursuit hypothesis alone. Finally, our experiments show that pursuit adaptation represents a useful technique by which strong and enduring vertical nystagmus can be generated in healthy human subjects.

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