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ORIGINAL ARTICLE

Impaired fixation suppression of horizontal vestibular nystagmus during smooth pursuit: pathophysiology and clinical implications

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Abstract

Background and purpose: A peripheral spontaneous nystagmus (SN) is typically enhanced or revealed by removing fixation. Conversely, failure of fixation suppression of SN is usually a sign of a central disorder. Based on Luebke and Robinson (*Vision Res* 1988, vol. 28 (8), pp. 941–946), who suggested that the normal fixation mechanism is disengaged during pursuit, it is hypothesized that vertical tracking in the light would bring out or enhance a horizontal SN.

Methods: Eighteen patients with acute vestibular neuritis were studied. Eye movements were recorded using video-oculography at straight-ahead gaze with and without visual fixation, and during smooth pursuit. The slow-phase velocity and the fixation suppression indices of nystagmus (relative to SN in darkness) were compared in each condition.

Results: During vertical tracking, the slow-phase velocity of horizontal SN with eyes near straight-ahead gaze was significantly higher (median 2.7°/s) than under static visual fixation (median 1.2°/s). Likewise, the fixation index was significantly higher (worse suppression) during pursuit (median 48%) than during fixation (median 26%). A release of SN was also suggested during horizontal pursuit, if one assumes superposition of SN on a normal and symmetrical pursuit capability.

KEYWORDS
fixation suppression, nystagmus, pursuit, vestibular

INTRODUCTION

Fixation suppression of a spontaneous nystagmus (SN) is a hallmark sign of a peripheral vestibular disorder. Nystagmus is enhanced or brought out by removing fixation, for example with Frenzel lenses or recording in darkness. SN is an important sign in dizzy patients [1,2] but it may be subtle or absent when fixation is allowed. Even with Frenzel lenses, the ability to detect a SN is low (~30%) compared to infrared video-Frenzel goggles (85%) [3] Nowadays, specialists predominantly use video-oculography (VOG) to detect and quantify SN [4]; however, such VOG devices are not available in most clinics or emergency departments. Because identifying a SN is an important clinical clue any new way to elicit a SN or evaluate the effect of fixation on SN at the bedside without new tools advances the bedside examination.

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There are many clinical tests of the different types of eye movements such as smooth pursuit and saccades [5,6] During clinical tests of pursuit the patient follows the physician's finger or any small object moving at a relatively low velocity (usually <30°/s). The clinician then decides if the eye movements are smooth, implying a normal pursuit response, or if there are saccadic corrections implying that pursuit is abnormal. However, what happens to pursuit when there is a strong SN but no underlying pursuit disorder as in vestibular neuritis? If pursuit is tested in the same plane as a SN, how much can the SN be suppressed so that the test of pursuit can be interpreted correctly? It was also hypothesized that suppression by visual fixation could be lessened, and nystagmus enhanced, during vertical pursuit since prior work [7] suggests that the normal fixation mechanism might be disengaged during pursuit. If so, vertical or horizontal tracking in the light could be a convenient way to look for a fixation suppression effect without having to put the patient in darkness or use Frenzel lenses. In this prospective cross-sectional study, the ability of patients with an archetypal peripheral vestibular disorder—acute vestibular neuritis—to suppress SN whilst fixating a stationary target and whilst tracking a pursuit target were compared.

MATERIALS AND METHODS

Twenty-one patients (mean age 55 years, SD ± 14, range 32–77, 10 females, 11 males) were recruited as part of a prospective cross-sectional study of patients seen for vertigo in the emergency department (Dizziness Evaluation Tool for Emergent Clinical Triage, DETECT) between July 2015 and April 2020. Patients with a diagnosis of vestibular neuritis or labyrinthitis were included. The diagnosis was based on the clinical history, vestibular function tests (caloric test and video head impulse test) and negative diffusion-weighted magnetic resonance imaging 72 h after the onset of symptoms to exclude a central disorder. Inclusion criteria were continuous dizziness, with nausea or vomiting, head-motion intolerance, new gait or balance disturbance and SN. Patients younger than 18 years were excluded, as were those whose symptoms lasted <24 h or if the index emergency department visit was >72 h after the onset of symptoms.

From our 21 patients, two overlapping groups were created with the exclusion criterion from one or the other group being a horizontal (one group) or vertical (the other group) nystagmus less than 1°/s slow-phase velocity (SPV) in darkness. Each group had 18 patients. Fifteen patients were in common, that is, they had both a horizontal and a vertical component of nystagmus greater than 1°/s. Horizontal nystagmus ranged from 1.3°/s to 27.3°/s, the upbeat nystagmus component ranged from 1.1°/s to 10.9°/s (n = 17) and the downbeat nystagmus component ranged from 1.4°/s to 3.2°/s (n = 4).

The mean time interval between symptom onset and eye movement recordings was 36 h (SD ± 21, range 6–69 h). Some of the patients received metoclopramide (9/21), ondansetron (6/21), methylprednisolone (2/21) or domperidon (1/21) before the recordings. Left-sided deficits were mirrored to right-sided and results are reported from ipsilesional and contralesional deficits throughout the paper.

Nystagmus in light (visual fixation) and in darkness (no fixation) were recorded using a VOG device (EyeSeeCam, Munich) with an infrared video camera and a frame rate of 250 Hz. The VOG device was calibrated by projecting dots on a TV screen or a tablet (tablet—distance eyes to target 260 mm, target size 4 mm, luminosity 6.17 lx, angular size 0.89°; TV screen—distance eyes to target 55 cm, target size 5 mm, luminosity 11.8 lx, angular size 0.23°). Visual fixation was removed by testing in darkness and covering the patient's head with a black veil. The patients looked at a straight-ahead white dot (visual fixation) or a flashing dot (no visual fixation, with the target visible for 750 ms and invisible for 2.5 s) displayed in the center of a TV screen or tablet. Pursuit was tested by tracking the same dot moving vertically or horizontally at 0.1 Hz with a peak velocity of 9.4°/s for horizontal pursuit and 6.3°/s for vertical pursuit. Peak target amplitude was 15° for horizontal and 10° for vertical pursuit [8]

Horizontal and vertical SPV (°/s) of SN for straight-ahead gaze (defined as within a ±5° window, horizontally and vertically) was measured by differentiating positional signals and removing fast phases using a MATLAB (MATLAB R2019b, Mathworks, Natick, MA, USA) script.

Assessment of horizontal nystagmus

The horizontal component of SN was assessed in darkness (no fixation), in light (visual fixation) and during both horizontal and vertical pursuit. Pursuit of a target moving orthogonal to the horizontal SN was chosen since any change in the horizontal component of SN would be easier to see during vertical tracking. The effect of a pursuit stimulus in the same direction as the SN (horizontal nystagmus during horizontal pursuit) was also assessed, but with a correction based on the pursuit target speed, either subtracting or adding an inferred bias depending on the relative directions of the SN and the pursuit stimulus. The SPV for rightward (ipsilesional directed) and leftward (contralesional directed) pursuit was compared.

Assessment of vertical nystagmus

The effect of horizontal pursuit on the vertical component of the SN was tested in a similar way (stimulus orthogonal to the nystagmus direction), but not needing any correction for the horizontal pursuit response.

The degree of fixation suppression of SN was found by calculating the difference of SPV with and without visual fixation, during vertical and horizontal pursuit. A fixation index (FI) was also calculated during visual fixation

$$FI_{fix}(\%) = \frac{\text{SPV with fixation}}{\text{SPV without fixation}} \times 100$$

and during pursuit

$$FI_{sp}(\%) = \frac{\text{SPV during smooth pursuit}}{\text{SPV without fixation}} \times 100$$

The higher the FI score is, the less is the visual suppression.

Statistics

Horizontal SN pairwise between different conditions (ipsilesional vs. contralesional directed pursuit and upward vs. downward pursuit) was compared using a non-parametric test (Wilcoxon signed-rank test). A one-sided Wilcoxon test was used to compare visual fixation versus pursuit since impaired fixation suppression was expected with pursuit [7] Vertical SN (visual fixation vs. horizontal pursuit) was compared in a similar way. An uncorrected versus corrected (using an inferred bias based on pursuit target speed) effect on horizontal SPV during horizontal pursuit was also compared and the FI scores were analyzed. A Bonferroni correction with a significance level of $p = 0.05$ was used to correct for multiple tests. The Pearson correlation was applied to assess the relationship between SPV during pursuit and SPV with fixation. All analyses including descriptive statistics were performed in SPSS (IBM Corp., released 2017, IBM SPSS Statistics for Windows, Version 25.0).

Ethics

The institutional review board approved this study. All patients gave written informed consent.

RESULTS

Figure 1 shows an example of a VOG recording from a patient with vestibular neuritis. The SPV of horizontal SN was higher without visual fixation (8.4°/s, Figure 1a) than with fixation (1.3°/s, Figure 1b). During vertical pursuit, the SPV of horizontal SN was also higher (3.9°/s, Figure 1c) but less so than without fixation. The SPV of vertical SN was also higher without visual fixation (Figures 1d, 4°/s) but there was no difference between visual fixation (0°/s, Figure 1e) and horizontal pursuit (0.9°/s, Figure 1f).

A video example from a patient with acute unilateral vestibulopathy and a right-beating SN after removal of visual fixation illustrates the increase in the right-beating horizontal nystagmus during both up and down vertical pursuit compared to fixation (see Appendix S1, Video S1). The horizontal nystagmus is seen on both the video recording and the VOG traces.

Horizontal SN during vertical pursuit

For the group, median baseline horizontal SPV in darkness (no visual fixation) at center gaze position was 7.0°/s ± SE 1.5. The horizontal SPV of SN was significantly reduced (median reduction of 5.8°/s SPV, $p < 0.001$) during visual fixation of the stationary target (Figure 2a) and during vertical pursuit (median reduction of 4.3°/s SPV, $p < 0.001$).

Median horizontal SPV during vertical pursuit at center gaze was 2.7°/s ± SE 1.1 and under static visual fixation 1.2°/s ± SE 1.1 with a statistically significant difference of 1.5°/s SPV ($p = 0.043$) (Figure 2a). Horizontal SPV was higher during vertical pursuit than under static visual fixation in 14 of 18 patients (Figure 3a). A significant difference was also found between the FI with stationary fixation (FI_{fix}) (median 26% ± SE 6%) and during vertical pursuit (FI_{vsp}) (median 48% ± SE 5%) (Figure 4a, $p = 0.016$). In 14 of 18 patients, FI_{fix} was smaller than FI_{vsp}. The effect on the horizontal SN was the same for upward and downward tracking with a median SPV of 2.8°/s ± SE 1.0 for downward movements and 2.7°/s ± SE 1.0 for upward movements. The SPVs of horizontal SN under visual fixation of a stationary target and during vertical pursuit were positively correlated (Figure 3a, correlation coefficient 0.954, $p < 0.001$).

Horizontal SN during horizontal pursuit

During horizontal pursuit a bias was introduced by the SN. The median (absolute) values of the SPV were significantly lower (5.7°/s ± SE 0.4) for ipsilesional pursuit than contralesional pursuit (10.0°/s ± SE 1.4, $p < 0.001$). These values were therefore corrected by either adding or subtracting the pursuit target velocity for ipsilesional and contralesional pursuit. The corrected value was smaller, but still showed a significant ispilesional/contralesional asymmetry (median 4.2°/s SPV ± SE 1.3 vs. median 1.8°/s SPV ± SE 0.8, $p = 0.008$).

The median SPV of the corrected value for horizontal SN during horizontal pursuit at center gaze was 3.1°/s ± SE 0.9 with a significant difference of 1.9°/s SPV ($p = 0.035$) (Figure 2b) compared to visual fixation. The corrected horizontal SPV was higher during horizontal pursuit than under static visual fixation in 15 of 18 patients (Figure 3b). A significant difference was also found between the fixation index for steady fixation (FI_{fix}) and that during horizontal pursuit (FI_{hsp}) (median 65% ± SE 6%; Figure 4b, $p = 0.004$). In 15 of 18 patients, FI_{fix} was smaller than FI_{hsp}. The corrected SPVs of horizontal SN under visual fixation of a stationary target and during horizontal pursuit were positively correlated (Figure 3b, correlation coefficient 0.865, $p < 0.001$).

Vertical SN during horizontal pursuit

The median SPV of the vertical component of the SN in darkness (no visual fixation) at center gaze was 4.5°/s ± SE 0.6. All patients showed a significant reduction of SPV of vertical SN during visual fixation of a fixed target (median reduction of 3.4°/s SPV, $p < 0.001$) and during horizontal pursuit (median reduction of 3.4°/s SPV, $p < 0.001$). SPV between visual fixation and horizontal pursuit, however, was not significantly different ($p = 0.21$) (Figure 2c). Nevertheless, vertical SPV

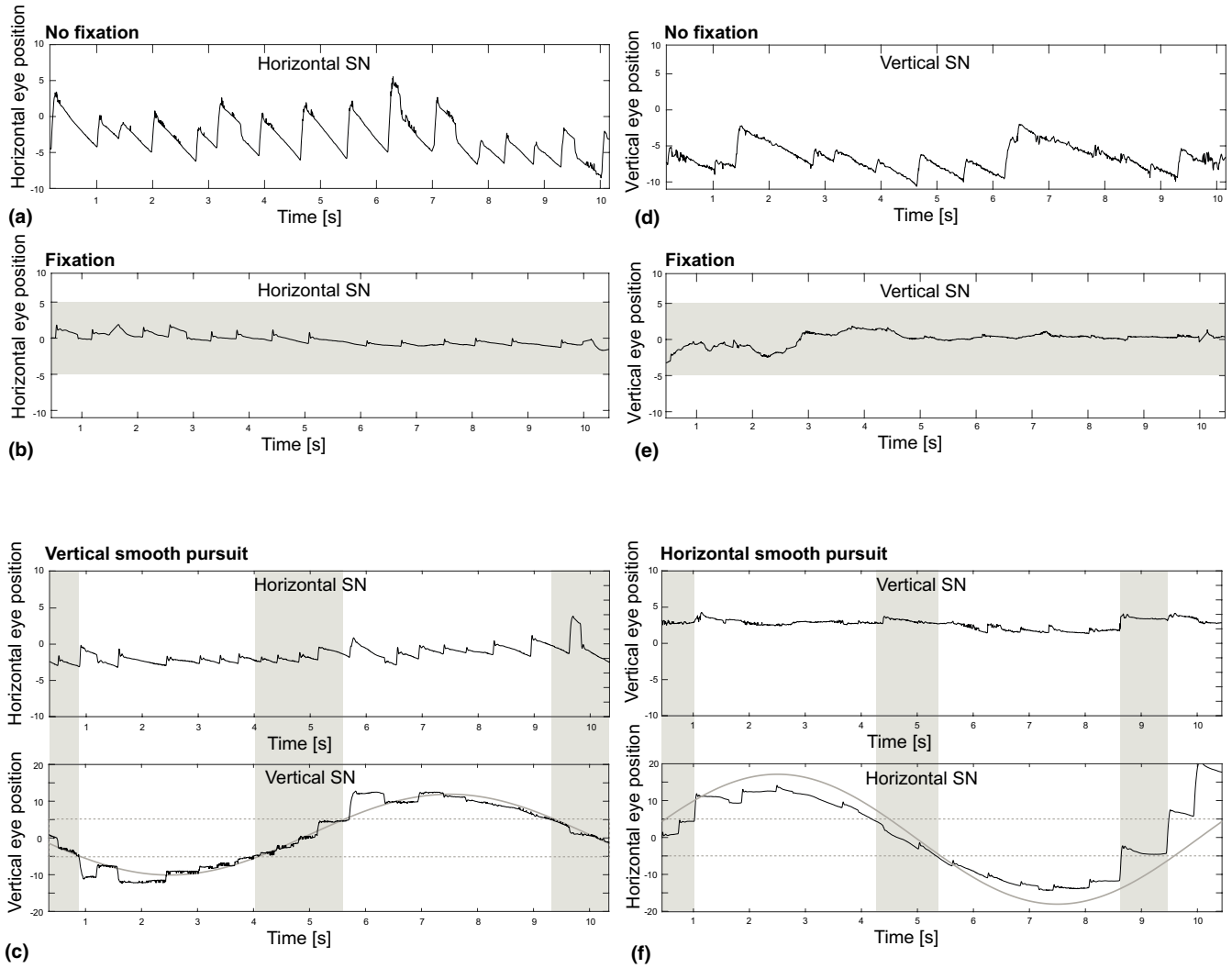

FIGURE 1 Eye position data under different conditions in darkness (a), (d), in light (b), (e) and during vertical (c) and horizontal pursuit (f). The grey zones represent the measurement time intervals for nystagmus slow-phase velocity (SPV) at straight-ahead gaze. Nystagmus SPV during pursuit was enhanced compared to nystagmus with fixation (grey zones in (c), (f) vs. (b), (e))

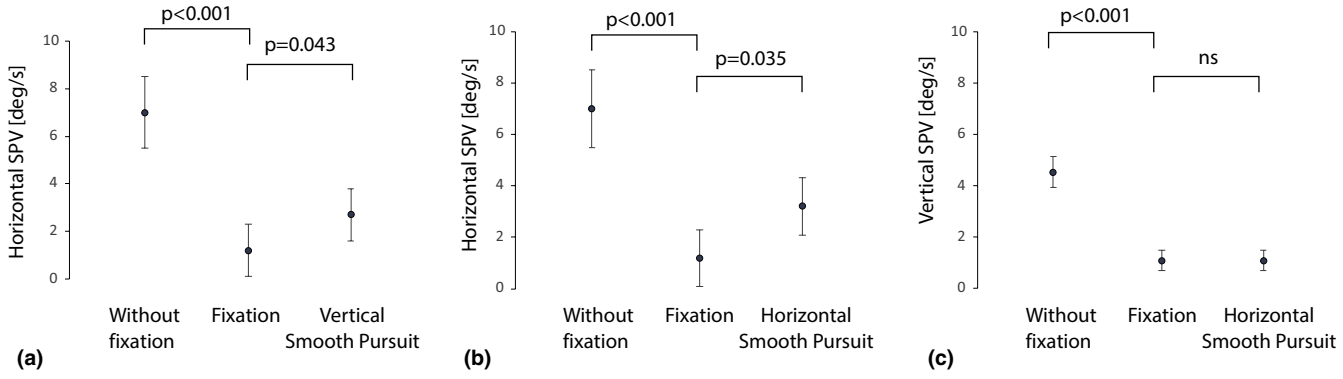

FIGURE 2 Whisker plots with median nystagmus slow-phase velocity (SPV) (°/s) and standard error for each condition (without fixation, with fixation and pursuit). Horizontal nystagmus intensity under visual fixation was compared with (a) vertical pursuit and (b) horizontal pursuit, in which the horizontal nystagmus was corrected for any bias from horizontal pursuit movements. (c) Vertical spontaneous nystagmus is compared with nystagmus during horizontal pursuit. For the comparisons, the Wilcoxon test was used and statistically significant differences were found in SPV between fixation and pursuit for horizontal spontaneous nystagmus but no significant difference for vertical spontaneous nystagmus

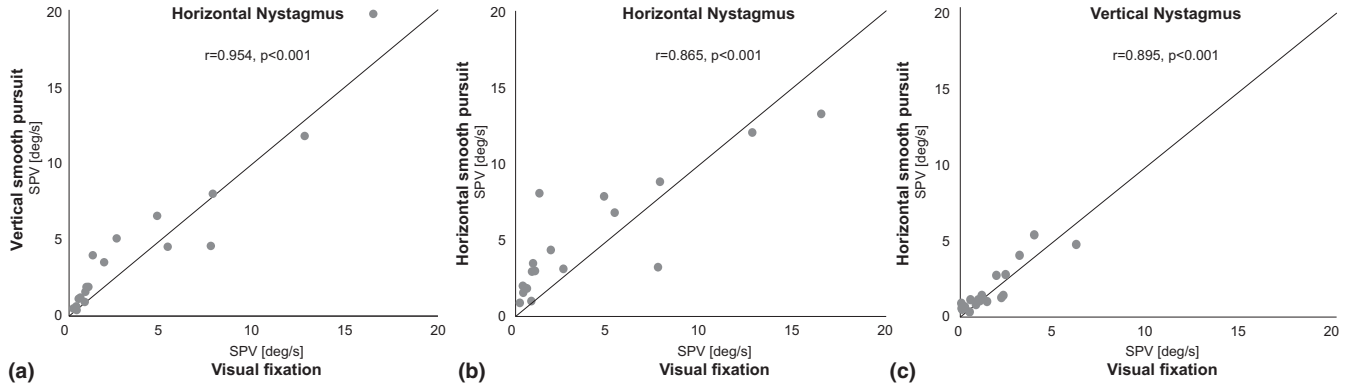

FIGURE 3 Scatter plots of slow-phase velocity (SPV) of nystagmus for individual patients under visual fixation on the *x*-axis and smooth pursuit on the *y*-axis. The graphs depict the relationship and the effect of the two tested conditions. The diagonal line represents equal nystagmus intensity with no enhancing effect during pursuit. Note that those patients who had a release of fixation effect (relatively greater SPV during pursuit) are above the diagonal. (a) Horizontal spontaneous nystagmus and vertical pursuit; (b) corrected horizontal SN and horizontal pursuit; (c) vertical SN and horizontal smooth pursuit. A positive and significant correlation (Pearson) was found for all three conditions depicted in (a) (r = 0.954, p < 0.001), (b) (r = 0.895, p < 0.001) and (c) (r = 0.865, p < 0.001)

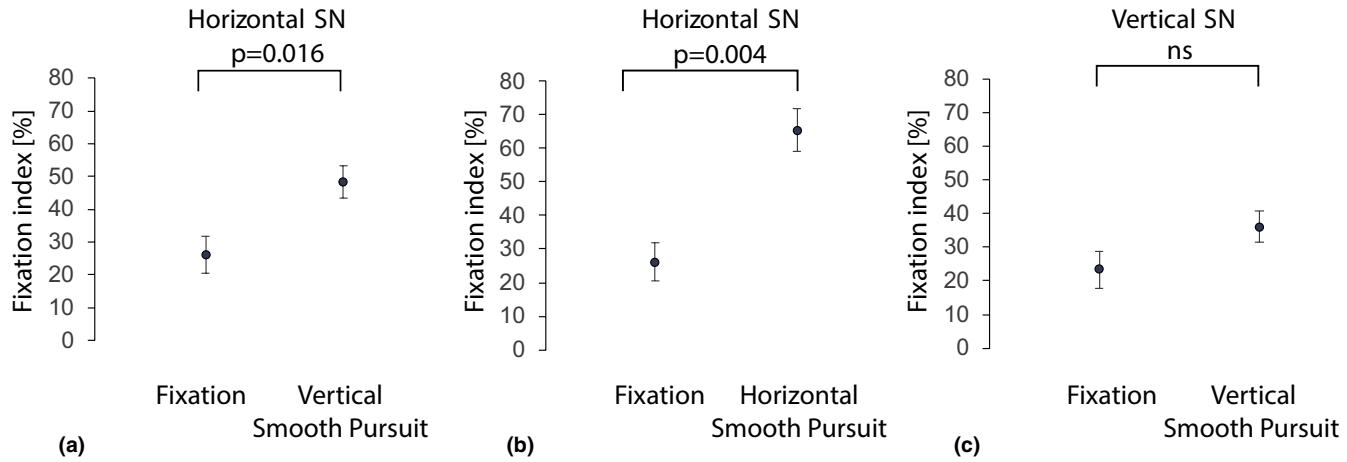

FIGURE 4 The whisker plots of median fixation index scores (± standard error) for each condition (visual fixation and smooth pursuit). (a) Horizontal spontaneous nystagmus is compared with vertical smooth pursuit; (b) the corrected horizontal spontaneous nystagmus and horizontal pursuit; (c) the vertical spontaneous nystagmus and horizontal pursuit. The Wilcoxon test was used for all statistical comparisons and statistically significant differences were found in fixation indices between fixation and pursuit for horizontal spontaneous nystagmus but no difference for vertical spontaneous nystagmus

was higher during horizontal pursuit than under static fixation SPV in 12 of 18 patients (Figure 3c). Also no significant difference was found between FI_{fix} (median 23% ± SE 6%) and FI_{hsp} (median 36% ± SE 5%) (Figure 4c, p = 0.184). In 12 of 18 patients, FI_{fix} was smaller than FI_{vsp}.

The SPVs of vertical SN under visual fixation of a stationary target and during horizontal pursuit were positively correlated (Figure 3c, correlation coefficient 0.895, p < 0.001).

DISCUSSION

The main finding of this study is that most of our patients showed better suppression of the nystagmus when fixating a stationary target than when following a pursuit stimulus. In other words, pursuit brought out the spontaneous vestibular nystagmus. This effect was most easily seen during vertical pursuit since, being orthogonal to the horizontal component of the SN, it was not contaminated by superimposed pursuit movements in the same or opposite direction as the slow phase of the SN. Quantitatively, the effect was also seen for horizontal nystagmus during horizontal pursuit, even with an inferred correction that assumed superposition of intact pursuit movements and the SN. A comparable effect of a superimposed bias by the underlying nystagmus was also seen in head impulse tests of healthy subjects during induction of a superimposed post-rotatory nystagmus [9] These findings are discussed first by considering the circuits within the brain that mediate pursuit of objects moving within the environment versus those that mediate fixation suppression of unwanted drift of the eyes such as from a pathological vestibular nystagmus, and

secondly, how this information might be used at the bedside to reveal the presence of an underlying SN without having to put the patient in the dark to eliminate fixation.

The neural circuitry underlying pursuit of a moving target versus maintaining fixation on a stationary target

Vision is best when motion of images on the fovea is minimized. Motion of images on the fovea can be from many sources including perturbations of the head during fixation of stationary objects in the environment, movement of a target of interest in the environment, and inherent drifts of the eyes from neural "noise" in the gaze-holding networks within the brain and the ocular muscles themselves. Whilst the goal of the brain is the same for each of these "threats" to vision—to detect motion of images on the fovea and to suppress it—the circuits that accomplish these tasks are widely distributed with considerable overlap [5,10]

One often expressed view is that fixation is a special case of pursuit of a target moving at a low speed, with the extreme case being tracking a target that is "moving" at zero velocity. In support of this idea is that patients with neurological disease who have deficits in pursuit usually have comparable deficits in suppression of an unwanted spontaneous vestibular nystagmus. This is typically the case in patients with chronic lesions in the cerebellum and the flocculus in particular, for example Zee et al. [11] but also in normal subjects when challenged with high-velocity pursuit targets with the head still, or tracking a target moving with the head at comparable high speeds that exceed normal capabilities [12]

On the other hand, Robinson et al. [13] and Luebke and Robinson [7] presented compelling evidence for a difference between pursuit and fixation. In normal subjects at the onset of pursuit, or when the target suddenly increased its velocity, pursuit was characterized by transient oscillations and ringing before it reached a steady-state velocity. The same happened when the target velocity suddenly decreased (e.g., from 10°/s to 5°/s). However, when the target came to a full stop, the eye quickly and smoothly glided to steady fixation without oscillations or ringing. This finding implies that fixation is a special system and is disengaged during smooth pursuit in normal subjects. Indeed, it was this observation that motivated the use of pursuit to disengage fixation in patients with nystagmus, based on the idea that a pursuit stimulus might reveal a SN that had been suppressed by a separate fixation mechanism.

Our results, in which fixation suppression of horizontal nystagmus was lessened during both vertical and horizontal pursuit, support the hypothesis of a separate fixation mechanism that, at least partially, is disengaged during attempted pursuit tracking. How might this separation be implemented? For tracking of moving targets, the pursuit system probably recreates an internal signal of target velocity by adding an internal (efference) copy of eye motion to the velocity of image motion on the retina [5] This internal estimate of target velocity, in turn, becomes the command that drives the eye. It may be that, when pursuit is not actively engaged, the fixation mechanism that suppresses motion of images on the retina, for example from a spontaneous vestibular nystagmus, does not use an efference copy of eye velocity to calculate target velocity (target velocity in the case of a SN is zero). Instead, the fixation mechanism may use the motion of images on the retina as the direct command to drive the eye to counteract the SN. Unfortunately, direct support of this idea is limited by our relative lack of knowledge of how fixation and pursuit differ in their anatomical and physiological substrates [14]

The interpretation of our results must also be tempered by the fact that the fixation effect during pursuit was not complete as there was still considerable suppression of SN during pursuit. Furthermore, the effect was present in most but not all patients, and the effect was not apparent for suppression of the vertical component of the SN. What might account for these discrepancies? The size of the fixation and pursuit targets was relatively small. If they had been larger or "full field" the dissociation between tracking and fixation might have been more complete. The amount of image motion on the retina from the SN may also influence the efficacy of the fixation system although the effect was found across the spectrum of SPVs of the SN shown by patients. How much the fixation system is released during tracking might also depend on the speed of the target (a higher target velocity might have more completely disengaged the fixation system), on how much the pursuit system is actively engaged, and on how well the pursuit system is performing. Vertical pursuit is often imperfect even in normal subjects, and in some of our patients vertical pursuit was contaminated by a vertical component of the SN, making a direct measure of pursuit capability unreliable. Similar considerations apply to knowing how well the horizontal pursuit system was functioning in the presence of a spontaneous horizontal nystagmus. The distance of the target may also be important as convergence may suppress a SN [15] Future studies should address the issues of the effects of characteristics of the target such as its speed, size and distance from the subject.

Contamination of horizontal pursuit movements by horizontal SN could not be completely avoided, which was reflected by the remaining SN asymmetry between ipsilesionally and contralesionally directed pursuit. The asymmetry of SN was smaller after the post hoc removal of the target signal but the correction was imperfect, perhaps due to an inherent underlying pursuit gain asymmetry or an asymmetrical influence of the direction of a SN on pursuit capabilities. Finally, quantification of pursuit function to compare with the fixation suppression effect might also be improved by using, for example, constant-velocity stimuli of various speeds and measuring the initial acceleration and the steady-state velocity.

Clinical applications

Fixation suppression of nystagmus is a hallmark feature of a peripheral vestibular nystagmus (the "Romberg sign" of the vestibulo-ocular

reflex) and, if not present, points to a central lesion causing the nystagmus [19] Whilst fixation suppression of a SN is not a perfect discriminator between a central and peripheral lesion, since some patients with central lesions can show fixation suppression [16,17,23] it is nevertheless useful in developing algorithms to localize lesions in patients with nystagmus. What is proposed here is that looking for a change in nystagmus during pursuit, especially horizontal nystagmus during vertical pursuit, complements other ways to reveal an effect of fixation on a SN without putting patients in the dark or using a Frenzel lens, for example, which are not always readily available. Ophthalmoscopy is another bedside test that can be used to bring out a nystagmus; one looks at the fundus of one eye with the ophthalmoscope, which is temporarily "blinded" by the ophthalmoscope light, and at the same time covers the other eye to prevent it from viewing, to see if the fundus of the eye being viewed through the ophthalmoscope shows an increase or appearance of nystagmus [18] The penlight cover test uses the same principle: by "blinding" one eye with the penlight flash and covering the other eye, one can bring out a SN [19] The challenges of evaluating patients with vestibular disorders remotely, for example during a pandemic, are considerable [20] The vertical pursuit test described here, like the penlight flash test, can be applied remotely as a test for visual suppression of SN.

Two other practical points about the bedside examination can be emphasized. Using vertical pursuit to bring out a horizontal SN may help the most when the nystagmus is minimal or not seen at all during fixation of a stationary target. It is often easier to see something new rather than to see a small change in something already present. Secondly, when evaluating pursuit one must consider that a previously suppressed SN is being uncovered and has been added to the pursuit movement, making it difficult to infer how well the pursuit system is functioning on its own. In other words, smooth pursuit in patients with a recent loss of vestibular function might show corrective saccades not because their tracking is impaired, for example by a central lesion, but because an underlying, suppressed nystagmus has been released. Since the circuits generating pursuit and the vestibular system share many structures within the brainstem and cerebellum, a vestibular imbalance might also directly affect pursuit capabilities [5]

CAVEATS

Data from patients with an acute unilateral vestibular loss were used, but these findings might not generalize to patients with compensated vestibular deficits or with other peripheral or central vestibular disorders. Whether clinicians could better detect SN using a moving rather than a stationary target was not tested; nevertheless, our video demonstration shows the effect and the difference in nystagmus intensity can be easily seen. As has been reported for the bedside head impulse test [21,22] a prospective study of the ability of physicians to detect a change in nystagmus intensity during pursuit would evaluate the practical application of this test to dizzy patients. Nevertheless, our new test of fixation suppression of vestibular nystagmus may help towards an understanding of how the brain suppresses unwanted image motion on the fovea, and how to better diagnose patients with SN.

CONCLUSION

Visual suppression of horizontal SN during vertical pursuit was less effective than during static visual fixation, implying that separate neural networks mediated visual fixation and pursuit. When horizontal pursuit appears relatively impaired, the degree may depend on how much an underlying horizontal SN is released during tracking. At the bedside, testing vertical pursuit may be a simple way to bring out or enhance a spontaneous horizontal vestibular nystagmus.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Athanasia Korda: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing—original draft (equal). **David Zee:** Conceptualization (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Thomas Wyss:** Data curation (equal); software (equal). **Ewa Zamaro:** Data curation (equal); writing—review and editing (equal). **Marco Caversaccio:** Resources (equal); writing—review and editing (equal). **Franca Wagner:** Data curation (equal); writing—review and editing (equal). Roger Kalla: Writing—original draft (equal). **Georgios Mantokoudis:** Conceptualization (equal); formal analysis (equal); funding acquisition (lead); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); visualization (equal); writing—review and editing (equal).

ETHICAL APPROVAL

The local institutional review board (KEK-Nr 047/14) approved this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (GM) upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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