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ORIGINAL ARTICLE

Bruns' nystagmus revisited: A sign of stroke in patients with the acute vestibular syndrome

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Abstract

Objective: Gaze-evoked nystagmus (GEN) is a central sign in patients with the acute vestibular syndrome (AVS); however, discriminating between a pathological and a physiologic GEN is a challenge. Here we evaluate GEN in patients with AVS.

Methods: In this prospective cross-sectional study, we used video-oculography (VOG) to compare GEN in the light (target at 15° eccentric) in 64 healthy subjects with 47 patients seen in the emergency department (ED) who had AVS; 35 with vestibular neuritis and 12 with stroke. All patients with an initial non-diagnostic MRI received a confirmatory, delayed MRI as a reference standard in detecting stroke.

Results: Healthy subjects with GEN had a time constant of centripetal drift >18 s. VOG identified pathologic GEN (time constant ≤ 18 s) in 33% of patients with vestibular strokes, specificity was 100%, accuracy was 83%. Results were equivalent to examination by a clinical expert. As expected, since all patients with GEN had a SN in straight-ahead position, they showed the pattern of a Bruns' nystagmus.

Conclusions: One third of patients with AVS due to central vestibular strokes had a spontaneous SN in straight-ahead gaze and a pathological GEN, producing the pattern of a Bruns' nystagmus with a shift of the null position. The localization of the side of the lesion based on the null was not consistent, presumably because the circuits underlying gaze-holding are widespread in the brainstem and cerebellum. Nevertheless, automated quantification of GEN with VOG was specific, and accurately identified patients in the ED with AVS due to strokes.

KEYWORDS
acute vestibular syndrome, Bruns' nystagmus, gaze-evoked nystagmus, gaze-holding nystagmus, HINTS

INTRODUCTION

Pathologic gaze-evoked nystagmus (GEN) is a central sign in patients with acute dizziness, however, the discrimination between a pathologic and physiologic GEN is challenging. Neurology textbooks [1] suggest that physiologic GEN is not sustained and beats at a lower frequency. The direction and intensity of GEN is more difficult to discern in patients with an acute vestibular syndrome (AVS), since they have spontaneous nystagmus (SN).

We have not found a study quantifying GEN in the acute phase of patients with the AVS either from peripheral or central causes. The slow-phase velocity (SPV), frequency (beats per second), and direction of eye drift of GEN can be quantified using mobile eye tracking

devices (Video-oculography, VOG). Nystagmus can often be suppressed in light and a quantitative suppression test recorded with VOG helps to differentiate central from peripheral causes of vertigo [2, 3]. However, the nystagmus suppression test does not consider other characteristics of nystagmus and has not become a routine part of the 'HINTS' testing battery (Head impulse – *Nystagmus* – Test of skew) [4].

Quantification of the characteristics of nystagmus is an integral part of the neurootological examination and diagnostic process. Different types of nystagmus have been defined and classified [5] and quantifying nystagmus provides important information about its origin (e.g., acquired versus congenital) and in the case of a vestibular tone imbalance, the source, central versus peripheral, and the side, right verse left. A peripheral SN is characterized by unidirectional drift of the eyes (SN beating towards the healthy ear) and an increase in intensity while looking towards the healthy side. This gaze dependent and unidirectional increase of the intensity of nystagmus conforms with Alexander's law, [6] and is best seen after removal of visual fixation (in darkness or with Frenzel glasses). In contrast, patients with a pathologic GEN usually exhibit a centripetal drift while fixating an eccentric target in light. An asymmetric GEN with a SN in straight-ahead gaze was first described by Bruns [7]. Bruns' nystagmus reflects a combination of a vestibular tone imbalance, producing a SN in straight-ahead gaze and a direction-changing GEN. Bruns' nystagmus typically appears in tumors at the cerebellopontine angle [8].

Based on prior research, that central lesions close to or within the vestibular nuclei or at the root-entry zone of the vestibular nerve might also involve structures important for eccentric gaze holding, we hypothesized that an automated quantitative VOG analysis of physiological and pathological GEN might help detect strokes in patients with AVS. Such an analysis would complement the currently used three-step 'HINTS' test (nystagmus, head impulse, skew) for diagnosis of strokes in patients with AVS.

MATERIAL AND METHODS

We recorded eye movements in 64 healthy subjects between 20–70 years old (>10 subjects per decade) and compared them with adults presenting to the ED with AVS (new onset of dizziness, nausea or vomiting, motion intolerance, spontaneous nystagmus). In this prospective, cross-sectional study, data was collected in the ED during daylight hours between 07/2015 and 04/2020, which was part of a larger study (DETECT – Dizziness Evaluation Tool for Emergent Clinical Triage). Data from a large subset of this patient cohort (12/12 strokes and 32/35 vestibular neuritis) have been presented in a prior publication investigating the nystagmus suppression test [2].

Patients were enrolled if they were older than 18 years and if they were seen in the ED within 72 h after symptoms began. We included patients with a confirmed acute unilateral vestibulopathy/vestibular neuritis (unilateral hypofunction in calorics or vHIT) or vestibular stroke (Figure S1). All patients received a second MRI 3–10 days later unless their first MRI was diagnostic. The delayed neuroimaging served as our reference gold standard for detection of stroke. All images were reviewed by a blinded, experienced board-certified neuroradiologist. An experienced neurootologist assessed the eye movements and knew the patient history but not the MRI findings.

We recorded nystagmus SPV using a portable VOG device (EyeSeeCam) in room light and in the sitting position. The high-speed infrared camera (monocular, 250 Hz) was calibrated by projecting dots (6.17 Lux luminosity, 4 mm diameter dot, visual angle size of 0.8814 deg) on a TV screen or a tablet with a predefined distance of 550 mm or 260 mm correspondingly. We used three fixation lights as a target for straight-ahead gaze and for eccentric positions of 15 deg to the right and left. For analysis, we adopted a 10 deg range of eccentric gaze since some patients had considerable eye drift away from the target or the intensity of nystagmus was too strong for them to keep the eyes focused on the target. The stimulus was present for 10 s at each target position. Eye position was monitored by the tracking software to assure eccentric eye positions between 10 and 20 deg. The test was repeated if eye tracking was not accurate due to artifacts, patient inattention, or inability to fix on the targets.

Eye position signals were differentiated, and slow-phase velocity of nystagmus calculated after removing fast phases using a Matlab (Matlab R2019b, Mathworks) script. An average value was taken for all slow-phase velocities while the patient was looking at the eccentric target. We applied a linear regression through all SPV data points at the three gaze directions and calculated the slope (τau) and estimated a time constant (1/τau). The time constant was defined as the reciprocal value of the increase of slow-phase velocity (drift) per increase of degree of gaze eccentricity, and reflects the fidelity of the neural gaze-holding integrator. We calculated the intercepts on the x-axis to infer a "null point" (or rest point) where there was no eye drift (zero SPV).

Statistics

We determined thresholds of physiological eye drifts using upper cut-off values from the mean nystagmus SPV $\pm$ 2 standard deviations of the healthy subjects. We used a non-parametric test (Kruskal-Wallis-Test) to test for effect of age on physiologic GEN since the data were not normally distributed. For comparing the intensity of nystagmus between patients with central and peripheral disorders, we applied a non-parametric test (Mann-Whitney-U-Test) for several gaze positions (eccentric and straight-ahead horizontal eye position). We coded a binary variable for the automated detection of gaze-holding nystagmus based on changing nystagmus direction (positive and negative SPV) and its SPV intensity, which exceeded the physiological eye drift determined by the normative data. We cross-tabulated data to calculate the sensitivity, specificity, and accuracy of the VOG measurements in detecting stroke. We

also compared the accuracy of an expert examination in detecting gaze-evoked nystagmus. Finally, we compared characteristics of pathological with physiological gaze-evoked nystagmus (Mann-Whitney-U-Test). A cut-off value was determined using a receiver operating characteristic (ROC) curve. We used SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) for statistical analysis.

Ethics

All enrolled patients gave written consent. The local ethics committee (IRB) approved this study (KEK # 047/14).

RESULTS

Normative data from 64 healthy subjects are shown in Table 1 and Figure 1. Age did not affect test results (Table S1, results stratified by age groups). The upper limit (cut-off) for nystagmus SPV at 15° eccentric gaze was 0.86°/s (two standard deviations from the mean, Table S2). Time constants ranged from 10 s to almost infinite (mean 779 s ± SD 4797).

We present data from 47 patients with AVS (21 females, 26 males, ages between 30 and 78 years (mean 54.8 ± SD 15.2 years)) who were diagnosed with vestibular neuritis (n = 35, mean age 52.4 ± 15.5 years, 17 females, 18 males) or a stroke (n = 12, mean age 61.7 ± 12.3 years, 4 females, 8 males). We found a pathologic GEN in 8.5% (4 of 47 with AVS) based on automated nystagmus analysis (including two parameters: direction-changing on right and left gaze, and intensity >0.86°/s in both directions). There was pathologic GEN in 4 of 12 (33%) patients with a stroke. Table 1 shows means of SPV for each gaze and each group. The automated nystagmus algorithm detected four true positive patients with strokes and no false positive patients with vestibular neuritis. This corresponds to a sensitivity of 33.3% and specificity of 100% with an accuracy of 83% for detection of a stroke in patients with AVS. This accuracy was comparable to an expert assessment (sensitivity of 50%, specificity of 97.1%, accuracy 85.1%, Table 2). Considering only one single parameter such as direction- changing nystagmus, the algorithm detected 6 of 12 strokes (50% sensitivity, 97.1% specificity), however, there was one false positive result though the SPV of nystagmus was close to zero.

Panel (a) in Figure 2 shows results from patient #4 who had a SN in straight-ahead gaze, pathologic GEN, and a deviation of the null point to the left. The panels in Figure 3 show the linear regression lines of SVN versus gaze position for all normal subjects and for patients with an AVS whether with a unidirectional SN or a pathological GEN. The general pattern of nystagmus did not differ significantly between unidirectional (peripheral type) nystagmus and pathologic GEN (Table 1, Figure 3c vs 3b). The frequency (p = 0.068) and the amplitude of the quick phases (p = 0.715) of GEN were not significantly different between gaze towards the fast phase and gaze towards the

TABLE 1 Characteristics of unidirectional and pathologic gaze-evoked nystagmus

	Unidirectional nystagmus (n = 43)				Pathologic gaze-evoked nystagmus (n = 4)				
SN parameters	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**p-value[a]**
SN gaze towards fast phase (deg/s)	0.09	22.75	3.18	4.53	1.82	7.17	3.33	2.57	0.107
SN gaze towards slow phase (deg/s)	0.00	15.43	1.70	3.10	0.00	0.92	0.45	0.45	0.632
Tau	0.00	0.23	0.05	0.06	0.06	0.19	0.11	0.06	0.107
Time Constant (s)	4.39	2107.85	139.95	326.28	5.14	16.99	11.12	5.53	0.127
intercept y	0.02	17.72	2.22	3.72	0.56	2.24	1.41	0.77	0.570
intercept x (Null point)	3.29	676.91	56.69	102.76	8.09	16.90	12.78	3.83	0.127
Frequency SN gaze towards fast phase (Hz)	0.00	9.23	1.97	1.93	0.72	24.23	7.11	11.43	0.570
Frequency SN gaze towards slow phase (Hz)	0.15	15.59	2.11	2.45	0.19	9.25	3.13	4.13	0.632
Amplitude SN gaze towards fast phase (deg)	0.00	22.43	3.59	5.26	0.37	18.98	9.12	9.37	0.601
Amplitude SN gaze towards slow phase (deg)	0.16	7.69	1.77	1.77	0.68	1.99	1.14	0.60	0.601

[a]Mann-Whitney-U-Test comparing the means, SN, spontaneous nystagmus. See also Methods.

slow phase though there was a shift of the null zone in all patients with pathological GEN. This is the pattern of Bruns' nystagmus.

The locations of strokes were distributed in the dorsolateral mesencephalon, the tectum and tegmentum, the lateral medulla (but no patients had Wallenberg's syndrome), vestibular nucleus, the middle and superior cerebellar peduncle, cerebellar tonsils, inferior cerebellar vermis and cerebellar hemisphere (Figure 4). Patient # 1 (Figure 4) had lesions in the right midbrain, patient #2 lesions in the right midbrain and right superior cerebellar peduncle, patient #3 had isolated lesions of the right cerebellar hemisphere and the right middle cerebellar peduncle, patient #4 had bilateral cerebellar lesions (including the posterior vermis) and lesions in the region of the right medial and lateral vestibular nuclei. The null point (null position with no nystagmus) was deviated ipsilesionally in patients (#1,2) who had lesions in the brainstem and contralesionally in patient #3 with an isolated stroke of the cerebellum and contralesionally to the right brainstem lesion in patient #4 who also had lesions on both sides of the cerebellum.

The time constant of the exponential decay of the centripetal drift while attempting to hold an eccentric eye position was significantly lower in patients with pathologic GEN (median 11.2 s) compared to healthy subjects (median 87.3 s, $p < 0.001$, Figure 5a). We found a significant discrimination cut-off between physiologic and pathologic GEN (AUC 0.992, $p = 0.001$, CI: 0.974–1.0, Figure 5b) at a time constant threshold of 18.0 (Sensitivity 100%, specificity 84%). The frequency of nystagmus was not, however, significantly different between pathological and physiological GEN.

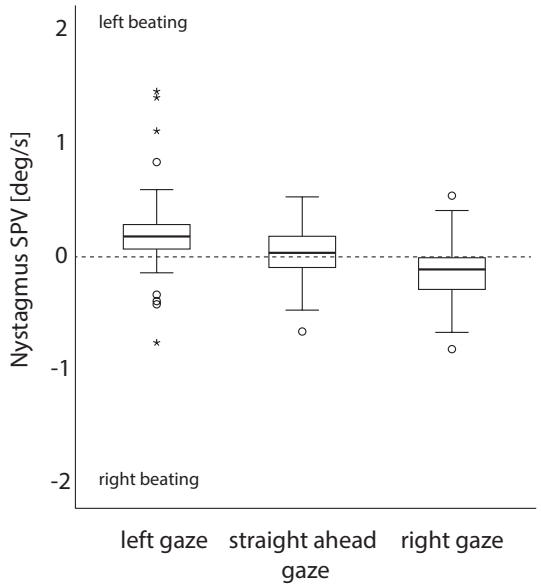

FIGURE 1 Box plots depicting the medians and the interquartile range (IQR) of physiologic GEN for left gaze (15 deg), straight ahead gaze (0 deg) and right gaze (–15 deg) in light in normal subjects. The circles and stars indicate outliers of 1.5*IQR and 3*IQR, respectively. Nystagmus slow-phase velocity (SPV) is shown on the y-axis, negative values indicate a right beating nystagmus

DISCUSSION

In our series, one third of the patients with vestibular strokes had a pathologic GEN. The accuracy of the clinical examination for detection of stroke by an expert was the same as VOG recordings with an automated assessment. The algorithm included parameters such as the velocity and direction of nystagmus. GEN was biased towards one side in all four patients with stroke. This pattern of nystagmus in which there is a SN in the straight-ahead position, a null (no nystagmus) to one side or the other of straight ahead, and a direction-changing, gaze-evoked nystagmus, is Bruns' nystagmus [7].

Gaze-evoked and Bruns' nystagmus with cerebellar lesions

Several studies have reported GEN in cerebellar lesions; however, patients with AVS have not been investigated quantitatively by VOG. In a previous study of patients with GEN and cerebellar lesions, one third showed GEN, [9] which is the same prevalence of pathologic GEN in patients with strokes found in our study. Another study reported that two thirds of patients with cerebellar or brainstem lesions with gaze-evoked nystagmus also had a smooth pursuit deficit [10]. We did not test pursuit systematically in our patients. Smooth pursuit, however, might appear abnormal because of a

TABLE 2 Gaze-evoked nystagmus (GEN) assessed by an expert and video-oculography (VOG)

		Stroke			
***N* = 47**		**No**	**Yes**	**Total**	**Test accuracy (%)**
Expert Pathologic GEN	No	34	6	40	85.1
		97.1%	50.0%	85.1%	
	Yes	1	6	7	
		2.9%	50.0%	14.9%	
VOG Pathologic GEN	No	35	8	43	83.0
		100%	66.7%	91.5%	
	Yes	0	4	4	
		0%	33.3%	8.5%	

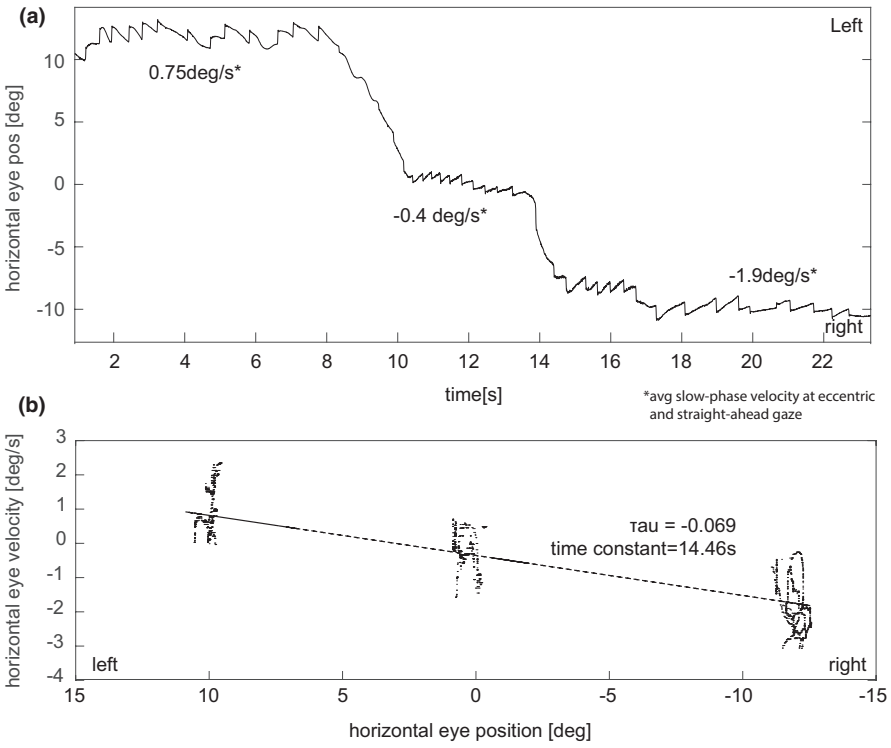

FIGURE 2 An example a pathologic GEN in a patient (#4) with a stroke involving the brainstem (right vestibular nucleus, posterior inferior medulla), both cerebellar tonsils and the inferior vermis (Figure 4, Pt. # 4). Panel (a) depicts horizontal eye positional data over time recorded with VOG. Note, left eye position is positive, right negative. The patient was first looking to the left with a left beating nystagmus (average 0.75 deg/s SPV), then he looked to the center, where nystagmus changed direction beating to the right. At right gaze (−10 deg), nystagmus intensity increased further but was still beating to the right. Panel (b) depicts the nystagmus intensity (slow-phase velocity, deg/s) at all three gaze positions: right, center and left. The dotted line illustrates the regression line and its slope τau. The time constant was derived from the reciprocal of τau

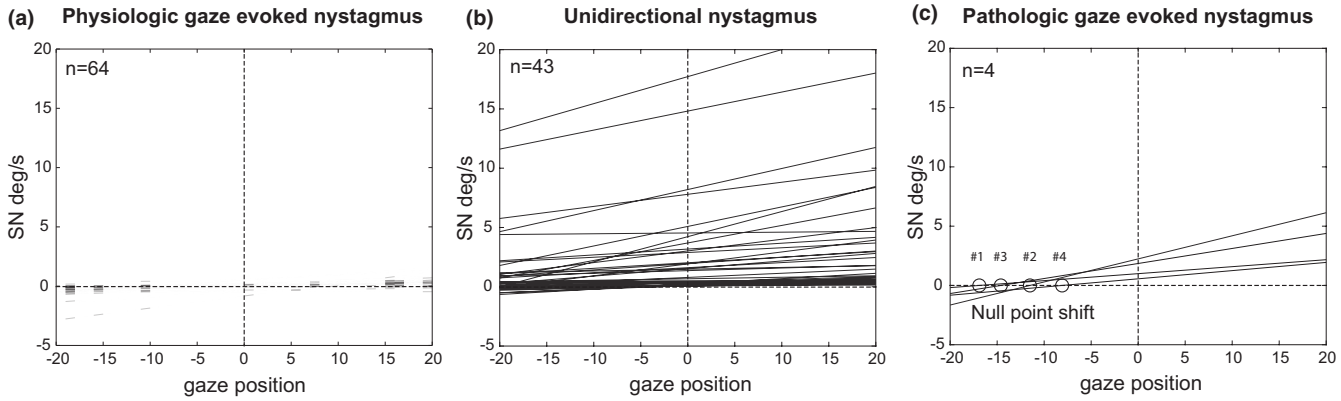

FIGURE 3 The regression lines derived from gaze position plots from each subject. We reversed all regression lines into positive slopes in order to compare data. We separated data into three groups: Healthy subjects with physiologic GEN (Panel a), AVS patients with unidirectional nystagmus regardless of the underlying cause (Panel b) and AVS patients with pathologic GEN (Panel c). Note, that the regression line crossed the x-axis defines the 'null point', at the gaze position with no nystagmus ('null' point). All four patients had an asymmetrical GEN with a shift of the null point. Note the data were mirrored for direction for comparison. Patients # 1 and 2 had shifts of the null to the right, Patient # 3 and 4# to the left

superimposed spontaneous nystagmus e.g., in patients with vestibular neuritis [11].

Holmes et al. [12] examined patients with cerebellar lesions after gunshot injury during the first world war, and described a "null point" or rest point (10° to 30°). This null point was usually shifted towards gaze to the unaffected side and thus nystagmus beat towards the side of the lesion in straight-ahead gaze. The amplitude of the quick phases of the GEN was greater when looking towards the side of the lesion. Baier and colleagues found an asymmetric GEN patients with cerebellar stroke with 5 of 7 showing a "null point" towards the unaffected side and two towards the affected side [9]. Romano et al. [13] also showed an asymmetric GEN in seven of eight patients with cerebellar lesions but opposite in direction to that of Baier et al [9]: Nystagmus was stronger with gaze towards the affected side with lesions of the caudal vermis and stronger with gaze towards the unaffected side with lesions in the cerebellar hemispheres. Most studies reporting an asymmetry of GEN did not include patients with lesions at the vestibular root entry zone at the pontomedullary junction. Pontine infarctions, however, can induce Bruns' nystagmus [14]. Some patients

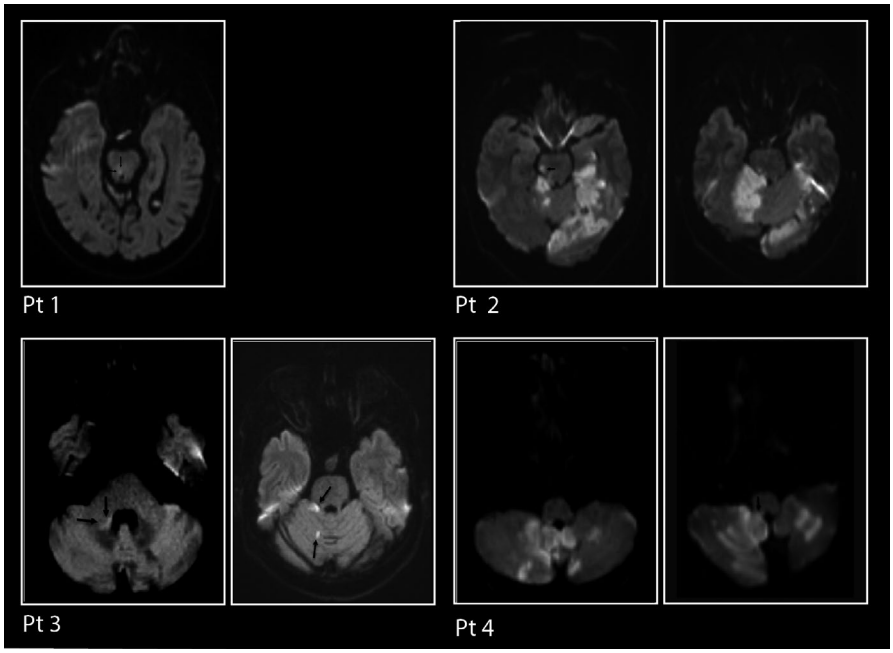

FIGURE 4 An MRI montage (axial MRI with diffusion-weighted imaging) of stroke lesions in four patients (Pt) with pathologic GEN. We chose representative image sections for each patient. Lesions were located in the right midbrain for Pt #1, in the right midbrain and right superior cerebellar peduncle, tectum and right tegmentum for Pt #2, in the right cerebellar hemisphere (lateral) and right middle cerebellar peduncle for Pt #3, and in both cerebellar hemispheres, the vermis and the right posterior inferior medulla involving the right medial and lateral vestibular nuclei for Pt #4

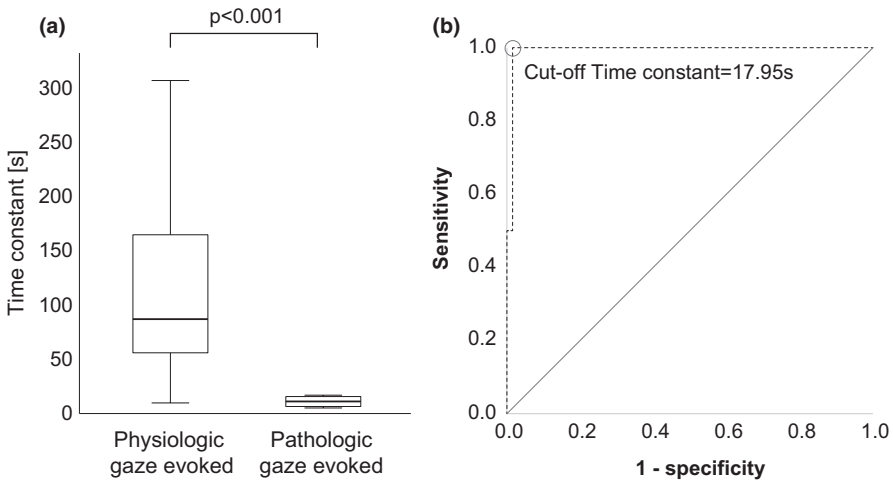

FIGURE 5 Box plots depicting the medians and the interquartile range (IQR) of the time constant (Tc) recorded with VOG in healthy subjects (physiologic GEN) and in patients with pathologic GEN (Panel a). Outliers are not shown for illustrative purposes. Panel (b) shows a receiver operating characteristics curve (ROC) using the Tc as a predictive parameter for discrimination between pathologic GEN and physiologic GEN. A cut-off value of <17.95 s favored a pathologic GEN (sensitivity 100%, specificity 84%)

with AVS and Wallenberg's syndrome may have a tonic deviation of the eye away from straight ahead gaze but only when fixation is removed [15].

Lesions inducing a pathologic, horizontal GEN are predominately located in the cerebellum (e.g. vermis, uvula, flocculus, tonsil) or the lower brainstem (vestibular nuclei, nucleus prepositus) [9, 13, 16–21]. Our results, as those in the literature, show that different lesions affect GEN and the location of the null point differently. How do we interpret this variability in the pattern of nystagmus and the location of the lesions?

Mechanisms of gaze-evoked nystagmus and shift of the null

First, we must consider the different mechanisms that might lead to a Bruns' nystagmus, i.e., a SN in straight ahead gaze and a null zone to one side or the other. One can consider two types of biases –velocity and position – that might cause this pattern. A velocity bias, such as from an imbalance in vestibular tone from a lesion in the vestibular periphery or in its central projections could account for the SN in straight-ahead gaze. However, for there to be a Bruns' nystagmus with a null zone there must be a second abnormality, such as an impaired ability of the ocular motor gaze holding networks (neural integrators) to hold eccentric eye positions. This "leaky" integrator leads to a counter drift on eccentric gaze that could null the SN when the eyes are in the orbit in the direction of the slow phase. Lesions in the horizontal gaze-holding networks in the NPH and MVN of the medulla or in the networks within the cerebellum that influence gaze-holding, can lead to impaired integration and GEN. However, if the integrator is only minimally impaired and the velocity bias is relatively strong, there would be no null but only a modulation of slow-phase velocity with orbital position, being higher when the eyes gaze in the direction of the quick phase. This behavior is the basis of Alexander's Law and an impaired integrator is one explanation for Alexander's law though

saturation of vestibular neural activity in eccentric eye positions is another [22]. In either case the effects of a change in orbital position on the SN would be similar.

Another mechanism for a Bruns' nystagmus would be a position bias, for example, in the gaze-holding integrators themselves, either in the brainstem or the cerebellum. A position bias could also arise from the adaptive networks that create rebound nystagmus [23]. Rebound nystagmus appears in straight-ahead gaze following a sustained attempt at holding eccentric gaze, and leads to a new null in the direction of prior eccentric gaze. Finally, when fixation is allowed, the ability to suppress SN by fixation could influence the null position since SN of higher speed can be more difficult to suppress than that of lower speed. In sum there are many ways that imbalances in cerebellar or brainstem circuits can lead to Bruns' nystagmus, and perhaps this is one reason it is often difficult to localize lesions solely based on the side of the null. To clarify these ideas we simulated several examples of how different biases combined with GEN might lead to a Bruns' pattern of nystagmus (Figures S2 and S3).

Localizing lesions in patients with Bruns' nystagmus

From the view of localization of lesions, based on experimental work, we would expect a null point shifted towards the affected side when there are lesions close to the vestibular nuclei, inducing a vestibular tone imbalance but also impairing gaze-holding, producing a GEN [21, 24]. To complicate matters, however, an isolated lesion of nucleus prepositus hypoglossi (NPH), which is adjacent to the vestibular nuclei, may produce a SN beating towards the side of the lesion, and a GEN with a null away from the side of the lesion [21].

With pure cerebellar lesions, as indicated above, the null point can shift either way depending on the location of the lesion, usually contralesional if the lesion is in the cerebellar hemisphere and ipsilesional, if the lesion is in the posterior vermis. Whether or not the deep nuclei are involved, may also influence the shift of the null [13].

We found Bruns' nystagmus in all our patients with pathological GEN, and their null point was between 8 and 17°. Patient #1 and #2 (Figure 4) had an ipsilesional null point and brainstem lesions; patient #2 had a second lesion in the right superior cerebellar peduncle. The null point of patient #3, who had isolated lesions of the right cerebellar hemisphere and right middle cerebellar peduncle, was contralateral. In patient #4, with a lesion involving the right brainstem but also lesions on both sides of the cerebellum (Figure 4), the null was shifted contralesionally to the brainstem lesion. These findings emphasize the difficulty in localizing lesions based on the direction of the shift of the null, and probably reflect the widespread anatomical distribution of the circuits in the cerebellum and brainstem that contribute to holding gaze studied. More patients must be studied to be confident about lateralization of a lesion based on the side of the null point.

Classically in Bruns' nystagmus the frequency of nystagmus is lower and the amplitude of the quick phases higher with gaze towards the side of a cerebellar lesion [8, 12]. Our four patients with GEN showed a frequency between zero Hz (only a slow drift without corrective saccade within 10 s) and 2 Hz. There was no consistent pattern in the differences in frequency between gaze to the affected and to the unaffected side. Our patients with AVS were measured within 72 h after the onset of symptoms, so we would not expect any bias from counterdrift (producing a Bruns like pattern) which can occur 5–20 days after an acute peripheral lesion [25].

Distinguishing physiologic from pathologic GEN

Becker and Klein reported that the time constant of drift in six healthy subjects ranged between 10 and 50 s at eccentric positions in the dark [26]. The time constant from our normative data ($n = 64$, eccentricity of ±15°) was between 10 and infinite (perfect gaze stability) in light. A recent study found physiologic GEN in only 70% of normal subjects, [27] which is in accord with the high value of the time constant in our sample (with no eye drift in some healthy subjects). In contrast, patients with a pathologic GEN had a significantly lower time constant since their gaze-holding neural integrator became imperfect (leaky). We could distinguish a pathologic from a physiologic GEN when the time constant was ≤18 s.

Strength and limitations

This is the first study assessing and quantifying GEN in acute dizzy patients with the AVS within hours after onset of symptoms. Previous studies restricted oculomotor tests to patients with specific lesions that might cause pathologic GEN, or their assessment was well after the onset of symptoms or the patient's examination, or were not related to dizziness and the acute vestibular syndrome. Since the intensity of physiologic GEN increases with eccentricity of gaze we avoided eccentric gaze of more than 20 deg to prevent any bias from a physiologic gaze-evoked nystagmus. However, examining patients in more eccentric gaze positions might lead to different values of sensitivity and specificity for stroke. Unfortunately, with too far eccentric gaze, both eye tracking by VOG may become unreliable, and a simple linear regression analysis might not be possible because of extension into a non-linear range of the gaze-holding mechanism [28]. Since we focused only on AVS patients with a stroke or vestibular neuritis, our findings may not generalize to patients with other lesions (e.g. cerebellar atrophy [29]) or metabolic, medication-related and toxic disturbances such as alcohol intoxication [30]. Likewise we had a relatively small number of patients with AVS due to central lesions with pathological GEN and their lesions were in many places. Larger-scaled studies, combined with quantification of other eye movement parameters such as pursuit, are needed to demonstrate a relation between the location of the null and lesion side. Finally, we tested always in upright, sitting position. A lying position or pitching the head back could bias the intensity or direction of gaze-evoked nystagmus [31].

CONCLUSIONS AND GUIDANCE FOR CLINICIANS

Our study has the following implications: (i) Our patients with an acute unilateral vestibulopathy had a strong vestibular bias and thus, never had any visible physiologic GEN. Any change of the direction nystagmus for left and right gaze indicated a central cause of dizziness provided that the patient had SN. (ii) The prevalence of pathologic GEN in vestibular strokes was 33%. These patients also had nystagmus at straight-ahead gaze and a null point (Bruns' nystagmus). (iii) Localization of lesions based on the null point is difficult because many circuits in the brainstem and cerebellum influence gaze-holding and vestibular tone. (iv) Physiologic GEN can be distinguished from pathologic GEN at 10–20° eccentricity by the intensity of the GEN and its time constant of drift (cut-off >18 s). (v) GEN can be reliably discerned by an expert; however, diagnostic performance of non-experts in the ED is not known. (vi) GEN can be quantitatively measured with VOG. A simple algorithm with automated analysis can identify patients with pathologic GEN. In patients with AVS, a pathological GEN with a nystagmus SPV >0.86°/s on each side is a red flag for stroke. (vii) GEN is part of the HINTS battery for diagnosing stroke but has not been previously quantified in patients with AVS. (viii) Contemporary VOG devices with fast eye tracking infrared cameras (>100 frames/s) mounted on a goggles frame can accurately record and quantify nystagmus in dizziness clinics or outpatient settings [32, 33]. VOG offers not only a more objective, automated, and examiner independent way for assessment of eye movements, but could also be a cost-effective way for a future point of care diagnosis in the ED.

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None.

CONFLICT OF INTERESTS

None of the investigators has any relevant financial interests, activities, relationships, or affiliations that represent a relevant financial conflict of interest with respect to the conduct or analysis of this study. TCS holds an endowed professorship sponsored by Touring Club Switzerland. The sponsor has no influence on the direction and content of the research conducted.

AUTHOR CONTRIBUTIONS

Georgios Mantokoudis: Conceptualization (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (supporting); Methodology (lead); Resources (equal); Software (equal); Supervision (lead); Validation (equal); Writing-original draft (lead); Writing-review & editing (lead). **Athanasia Korda:** Conceptualization (equal); Data curation (lead); Investigation (lead); Project administration (lead); Validation (equal); Writing-review & editing (equal). **David Zee:** Methodology (lead); Software (lead); Supervision (equal); Validation (equal); Writing-review & editing (equal). **Ewa Zamaro:** Data curation (equal); Investigation (equal); Project administration (equal); Validation (equal); Writing-review & editing (equal). **Thomas Sauter:** Investigation (equal); Validation (equal); Writing-review & editing (equal). **Franca Wagner:** Investigation (equal); Writing-review & editing (equal). **Marco D. Caversaccio:** Funding acquisition (lead); Project administration (equal); Resources (lead); Supervision (lead); Writing-review & editing (equal).

ETHICAL APPROVAL

The institutional review board approved this study (KEK # 047/14, approval date 04/24/2014). All patients gave written informed consent.

DATA AVAILABILITY STATEMENT

A minimal dataset is available on request to the corresponding author.

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SUPPORTING INFORMATION

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

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