

# Nystagmus characteristics of healthy controls

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## Abstract.

**BACKGROUND:** Healthy controls exhibit spontaneous and positional nystagmus which needs to be distinguished from pathological nystagmus.

**OBJECTIVE:** Define nystagmus characteristics of healthy controls using portable video-oculography.

**METHODS:** One-hundred and one asymptomatic community-dwelling adults were prospectively recruited. Participants answered questions regarding their audio-vestibular and headache history and were sub-categorized into migraine/non-migraine groups. Portable video-oculography was conducted in the upright, supine, left- and right-lateral positions, using miniature take-home video glasses.

**RESULTS:** Upright position spontaneous nystagmus was found in 30.7% of subjects (slow-phase velocity (SPV)), mean  $1.1 \pm 2.2$  degrees per second ( $^{\circ}/s$ ) (range 0.0 – 9.3). Upright position spontaneous nystagmus was horizontal, up-beating or down-beating in 16.7, 7.9 and 5.9% of subjects. Nystagmus in at least one lying position was found in 70.3% of subjects with 56.4% showing nystagmus while supine, and 63.4% in at least one lateral position. While supine, 20.8% of subjects showed up-beating nystagmus, 8.9% showed down-beating, and 26.7% had horizontal nystagmus. In the lateral positions combined, 37.1% displayed horizontal nystagmus on at least one side, while 6.4% showed up-beating, 6.4% showed down-beating. Mean nystagmus SPVs in the supine, right and left lateral positions were  $2.2 \pm 2.8$ ,  $2.7 \pm 3.4$ , and  $2.1 \pm 3.2^{\circ}/s$ . No significant difference was found between migraine and non-migraine groups for nystagmus SPVs, prevalence, vertical vs horizontal fast-phase, or low- vs high-velocity nystagmus ( $<5$  vs  $>5^{\circ}/s$ ).

**CONCLUSIONS:** Healthy controls without a history of spontaneous vertigo show low velocity spontaneous and positional nystagmus, highlighting the importance of interictal nystagmus measures when assessing the acutely symptomatic patient.

Keywords: Nystagmus, normal control, vertigo, video oculography, video nystagmography

## 1. Introduction

In the pursuit of studying, quantifying and classifying the nystagmus characteristics of common causes of vertigo, it is imperative to first distinguish what constitutes the typical spectrum of eye-movements in

healthy controls without a history of vertigo. Important findings regarding the nystagmus characteristics of known pathologies including vestibular migraine (VM), episodic ataxia, benign paroxysmal positional vertigo (BPPV) and Menière's Disease (MD) shed light on the range of possible eye movements in central and peripheral vestibular disorders [14, 29, 33, 37].

Previous studies have shown that nystagmus can occur in normal controls, observable without visual fixation [2, 20, 21, 24, 32]. Further in-depth study

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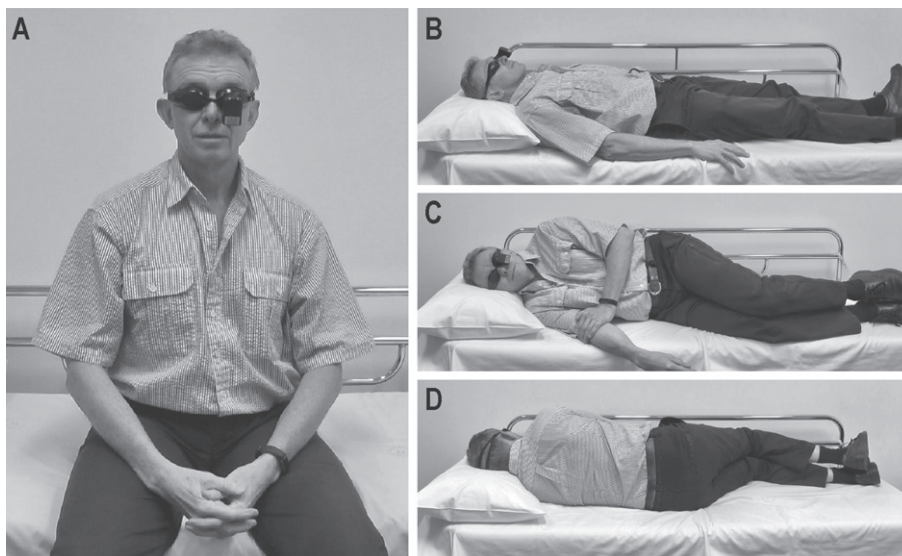


Fig. 1. Positions conducted during video-oculography; A) sitting upright, B) supine, C) right-lateral, and D) left-lateral.

on the nystagmus patterns and slow-phase velocities (SPV) will help to arrive at reasonable normative ranges that may be used to gauge whether a pattern of nystagmus fall within (or outside) the normal limits. In this study we present the nystagmus findings of 101 healthy adults without a history of recurrent vertigo lasting more than five minutes.

Novel aspects of this study include collection of video data using stand-alone portable video-goggles which could in the future be useful as a diagnostic technique for episodic vertigo. We also undertook statistical comparison of nystagmus slow-phase velocities between those with and without a migraine history and comparison of normal controls against vestibular migraine sufferers experiencing ictal episodes of vertigo, who also demonstrate low velocity nystagmus.

Community-dwelling adults  $\geq 18$  years old were prospectively recruited between June 2017 and February 2020, with informed consent (Sydney, Australia). Healthy controls were given a questionnaire regarding their vertigo and headache history. Subjects answering 'yes' to having had an episode of spontaneous vertigo lasting  $>5$  minutes in the past were excluded from the study. Participants with a previous diagnosis of BPPV (now asymptomatic) were included in the study. Based on their questionnaire answers, subjects were further sub-categorized into a *migraine* (M) or *non-migraine* (nM) group.

We used the *Headache Classification Committee of the International Headache Society* (IHS) [13]

classification for *Migraine without Aura*, to assist classification. Participants in the migraine group were those who answered 'yes' to having had a headache history including the following: B) lasting  $>4$  hours, and answered 'yes' to two of the following: C1) unilateral location, C2) pulsating or throbbing quality, C3) moderate or severe pain level, C4) aggravation by normal movement (e.g. walking or climbing stairs), and answered 'yes' to at least one of the following: D1) headache caused nausea, D2) headache caused photophobia or phonophobia. IHS Criterion A (at least five attacks of headache) and D (not better accounted for by another *International Classification of Headache Disorders* criteria) were not included in the questionnaire.

Video-oculography without visual fixation was conducted with all participants and included the following positions; 1) sitting upright, looking straight ahead for 15 seconds(s), then for 30s each; 2) lying supine, 3) lying on their right side, and 4) lying on their left side (Fig. 1). In all testing positions, participants were asked to maintain their eyes in a centre gaze position. All participants were asymptomatic from vertigo and headache at the time of testing and no visible spontaneous nystagmus could be seen with the naked eye. No adverse effects were reported.

Portable video-oculography goggles were used to record a single video for each subject, recorded at 30 Hz. The pupil was then tracked and analysed with a program using threshold-based ellipse fitting (LabVIEW, National Instruments; Austin, Texas). The

Table 1  
Nystagmus Slow-Phase Velocity ( $^{\circ}/s$ ), by Fast-Phase

	Sitting Upright				Supine				Right-Lateral				Left-Lateral			
	Horiz.	DBN	UBN	Nil.	Horiz.	DBN	UBN	Nil.	Horiz.	DBN	UBN	Nil.	Horiz.	DBN	UBN	Nil.
%	16.8	6.0	6.9	70.3	26.7	89	19.8	44.6	39.6	6.0	8.9	45.5	34.7	6.8	4.0	54.5
N	17	6	7	71	27	9	20	45	40	6	9	46	35	7	4	55
Mean	3.4	4.8	3.7	–	3.9	3.9	4.1	–	4.7	6.2	4.6	–	4.2	6.2	3.1	–
SD	2.0	3.3	2.3	–	2.5	2.5	3.3	–	2.9	5.9	3.2	–	3.0	5.4	1.7	–
Min.	0.4	0.5	0.8	–	1.0	1.4	0.7	–	1.4	1.5	1.5	–	0.8	1.3	1.2	–
Q1	1.8	1.4	1.5	–	2.0	2.1	2.0	–	2.3	2.1	2.9	–	2.1	2.0	1.4	–
Med.	3.5	5.1	4.3	–	3.0	3.3	3.4	–	3.7	2.8	3.4	–	3.1	4.1	3.1	–
Q3	4.8	7.6	5.4	–	5.3	5.4	6.4	–	6.2	13.6	5.5	–	5.1	11.0	4.7	–
Max.	7.1	9.3	7.2	–	10.8	8.9	14.1	–	11.4	14.0	12.5	–	12.7	16.0	4.9	–

Nystagmus characteristics of 101 normal controls by nystagmus fast-phase, in four positions. [RBN; Right-beating nystagmus, LBN; Left-beating nystagmus, UBN; Up-beating nystagmus, DBN; Down-beating nystagmus; Max.; Maximum, Med.; Median, Min.; Minimum, Nil.; No nystagmus, Q1; First quartile, Q3; Third quartile, SD; Standard deviation,  $^{\circ}/s$ ; Degrees per second, %; Percentage of total subjects].

pupil-analysis system was calibrated using head-fixed targets validated against manual tracing and virtual simulations. Eye-movements were analysed in both the horizontal and vertical planes, and the nystagmus slow-phase velocity (SPV) was obtained, measured in degrees per second ( $^{\circ}/s$ ). There was no lower limit placed on the nystagmus SPV reported, however a minimum of three beats of nystagmus within 15 seconds of recording was required for analysis. The nystagmus plane (vertical or horizontal) which was found to have the more significant SPV was deemed the dominant plane, and only the SPV for that plane was used for statistical analysis.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26 (Armonk, NY). Linear regression equations were used to assess the difference in nystagmus velocities between the non-migraine and the migraine groups, and the relationship between nystagmus and age. Binary regression equations were used to determine the likelihood of nystagmus presence in both groups. The SPV data is positively skewed, but the means and standard deviations are included in Tables 1 and 2 alongside non-parametric measures to facilitate comparison with previous papers.

This study received local ethics committee approval for the use of human participants (Protocol No X13-0425 & HREC/13/RPAH/591) and written informed consent was obtained from all participants in accordance with the 1964 Declaration of Helsinki and its later amendments.

## 2. Results

One hundred and one participants were included in the study with a mean age of 44.4 years ( $\pm 18.7$ ,

Table 2  
Nystagmus Slow-Phase Velocity ( $^{\circ}/s$ ) by Position

	Sitting Upright	Supine	Right-Lateral	Left-Lateral
Mean	1.1	2.2	2.6	2.0
SD	2.1	2.9	3.4	3.2
Min.	0.0	0.0	0.0	0.0
Q1	0.0	0.0	0.0	0.0
Med.	0.0	1.4	1.7	0.0
Q3	1.5	3.4	3.9	3.0
Max.	9.3	14.1	14.0	16.0

Nystagmus slow-phase velocity characteristics of 101 healthy normal controls in four positions, all fast-phase directions combined. [Max; Maximum, Med.; Median, Min; Minimum, Q1; First quartile, Q3; Third quartile, SD; Standard Deviation,  $^{\circ}/s$ ; Degrees per second].

range 18–86 years) including 55 women and 46 men. No participants reported headache or became vertiginous during the test. In all cases, the nystagmus we observed (without fixation) was persistent and lasted for the duration of the manoeuvre (sitting up, supine, lateral positions).

In total, 29.7% ( $n = 30$ ) of subjects had nystagmus in the upright position, and in at least one of the three lying positions, while 40.6% ( $n = 41$ ) had positional nystagmus only. Only 0.99% ( $n = 1$ ) of subjects had upright position nystagmus without positional nystagmus, and 28.7% ( $n = 29$ ) showed no nystagmus in any position. Detailed nystagmus results can be found in Tables 1 and 2.

When separated into three age groups (A: <40 years old, B: 40–60 years old, and C: >60 years old), there was no significant difference in overall nystagmus means between age groups A ( $1.7^{\circ}/s$ ) and B ( $2.6^{\circ}/s$ ,  $p = 0.062$ ), and between A and C ( $1.3^{\circ}/s$ ,  $p = 0.266$ ). However, there was a significant difference between age groups B and C ( $p = 0.008$ , CI: 0.338 – 0.250).

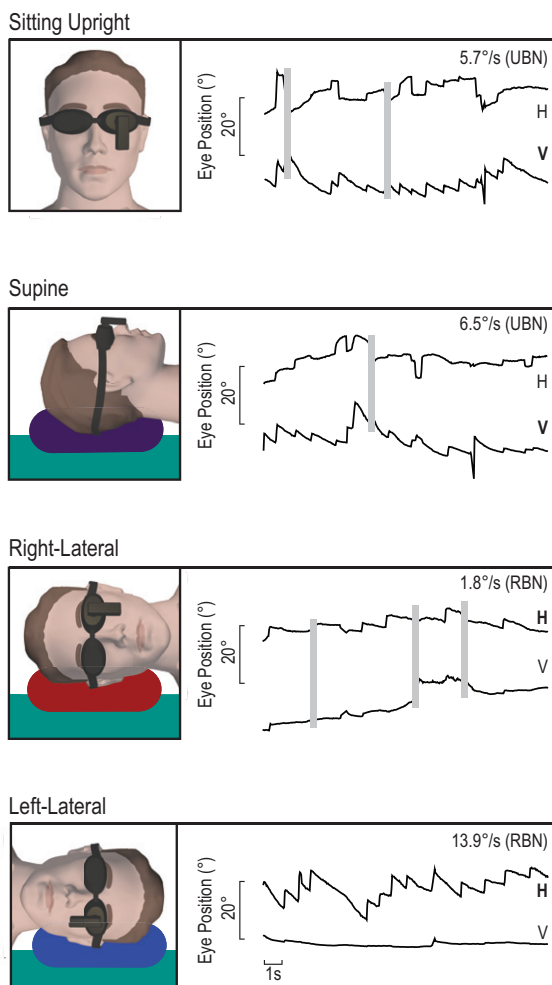


Fig. 2. Nystagmus traces in the horizontal and vertical planes in a 29-year-old normal control. In the upright and supine position there is spontaneous up-beating nystagmus, with right-beating nystagmus visible in either lateral position. [H; Horizontal (plane), RBN; Right-beating nystagmus, UBN; Up-beating nystagmus, V; Vertical (plane), °; Degrees, °/s; Degrees per second. Grey bars indicate blinking artefact.]

### 2.1. Spontaneous nystagmus: Sitting position

Spontaneous nystagmus observed while sitting was found in 30.7% of subjects with a mean SPV of 1.1 °/s ( $\pm 2.1$ , range 0 – 9.3°/s, median 0.0°/s). Nystagmus was horizontal in 16.7% and vertical in 13.7% (up-beating in 7.8%, down-beating in 5.9%) (Fig. 2, Videos 1–5). Two subjects (ages 25 and 56 years) displayed square-wave jerk eye movements in all positions. Another displayed a persistent, mild torsional nystagmus component in all positions. Comparison of M and nM groups showed no significant difference in spontaneous nystagmus SPV

( $p=0.870$ ), prevalence of nystagmus ( $p=0.335$ ) or the likelihood of demonstrating high ( $>5$  °/s) vs low ( $<5$  °/s) velocity nystagmus ( $p=0.960$ ).

### 2.2. Positional nystagmus

Nystagmus was observed in at least one of the three lying positions in 70.3% of subjects.

#### 2.2.1. Supine position

Nystagmus in the supine position was observed in 56.4% of subjects. While supine, nystagmus was horizontal (26.7%), up-beating (20.8%), or down-beating (8.9%). Mean nystagmus SPV while supine was 2.2°/s ( $\pm 2.9$ , range 0 – 14.1, median 1.4°/s). Comparison of the M and nM groups showed no significant difference in supine nystagmus SPV ( $p=0.883$ ). Eleven subjects displayed persistent positional nystagmus with velocities  $>10$ °/s, however, no vertigo was reported during assessment.

#### 2.3. Positional nystagmus: Lateral positions

In at least one lateral position, 63.4% of subjects showed nystagmus, which was horizontal (37.1%), up-beating (6.4%), or down-beating (6.4%). The difference in nystagmus SPV between the right- and left-lateral positions was not significant ( $p=0.111$ ). Ten subjects showed persistent apogeotropic nystagmus in either lateral position (one from the M group) while four showed geotropic nystagmus (two from the M group).

In comparison with nystagmus observed in the sitting position, there was a significant enhancement in nystagmus SPV in all three lying positions (supine  $p<0.001$ , CI: 0.543 – 1.655; right lateral  $p<0.001$ , CI: 0.841 – 2.127, left lateral  $p=0.002$ , CI: 0.328 – 1.459).

Subjects with non-stereotyped positional nystagmus patterns in either lateral position (such as nystagmus whilst only one side, or vertical nystagmus while one side and horizontal while on the other) totalled 34.7%. The difference in nystagmus SPV in all lateral positions between the M and nM subgroups was not significant ( $p=0.644$  and  $p=0.806$  for right- and left-lateral positions, respectively). There was no significantly increased likelihood that the M group would display nystagmus of any velocity while in a lateral position ( $p=0.213$ ) as compared with the nM group.

#### 2.4. *Nystagmus comparison between normal controls and vestibular migraine*

Using previously published data [37], spontaneous ( $6.6^\circ/\text{s}$ ) and positional ( $10.3^\circ/\text{s}$ ) nystagmus velocities in patients during episodes of vestibular migraine were statistically compared with healthy controls from the current study which showed a significant difference ( $p < 0.001$ , CI: 3.828 – 12.503,  $p < 0.001$ , CI: 3.943 – 12.656, respectively), with VM patients showing higher nystagmus velocities [37]. There was also a significantly higher likelihood of any visible spontaneous upright (65.7%) or positional (89.6%) nystagmus in the VM group during an episode of vertigo, as compared with normal controls ( $p < 0.001$ , CI: 0.120 – 0.447,  $p = 0.003$ , CI: 0.006 – 0.338, respectively).

### 3. Discussion

There has been a limited number of publications on nystagmus in normal controls with over 100 subjects, measuring both nystagmus incidence and SPVs, highlighting the importance of renewed in-depth investigation into this phenomenon. From the work of previous investigators, it is understood that healthy normal controls without vestibular or autonomic symptoms may exhibit low velocity nystagmus when examined under fixation-denied conditions, however the reported SPV ranges and spontaneous vs positional occurrence varies widely, possibly due to small study subject numbers.

Spontaneous nystagmus while sitting upright without visual fixation is reported in healthy controls with authors citing occurrences between 20 – 40% [2, 20, 21, 23, 24], while other studies cite fewer occurrences of 5 – 6.6% [11, 12, 32]. The spontaneous nystagmus was reported as horizontal in 0 – 10%, and vertical in 3.4 – 30% [2, 11, 20]. In the studies which measured nystagmus SPVs, the reported means were generally low, with ranges of  $0.7 - 5.0^\circ/\text{s}$  [2, 20, 32].

Positional nystagmus in healthy controls is described with occurrence between 22.5 – 88% [2, 11, 12, 20, 21, 23, 24, 30]. Some studies found that horizontal positional nystagmus was the most common pattern [21, 30], while other studies found vertical nystagmus was observed most frequently [2]. Previous studies agree that torsional nystagmus was either exceedingly rare or absent [20, 21]. Geotropic and

apogeotropic positional nystagmus was a common finding with reported occurrence between 8 – 32% [21, 23, 24].

Spontaneous vertical nystagmus is described in central disorders including vestibular migraine, demyelination, cerebellar disease and posterior circulation ischaemia [6, 26, 34, 35]. Down-beating nystagmus has been attributed to damaged vertical smooth-pursuit and has been reported in lesions affecting cerebellar pathways including infarction, demyelination, paraneoplastic syndrome, spinocerebellar ataxias, or Chiari Malformation [3, 15, 22, 27, 28]. Episodic Ataxia (Type II) may be associated with interictal spontaneous down-beating nystagmus [15]. Spontaneous up-beating nystagmus is rare and has been described in Wernicke's encephalopathy [16] and lesions within the paramedian medulla [8]. Lying in the supine position may also provoke or enhance nystagmus generated by Chiari malformation or posterior fossa space occupying lesions [4, 7, 17, 19, 31, 36]. In a study of patients with a diagnosis of cerebellar disease, it was found that 24% showed nystagmus while upright, 64% of which were down-beating and 15% horizontal [9]. Persistent apogeotropic positional nystagmus is reported in lateral canal cupulolithiasis which demonstrates asymmetric slow-phase velocities in either lateral position, unlike what we observed [1]. Medulloblastoma or other lesions within the vestibulocerebellum including the uvula, ventral uvula, nodulus, or tonsil regions are rare central causes of apogeotropic nystagmus [5, 15]. Although vertical positional nystagmus of peripheral origin is most commonly due to posterior canal BPPV, it is easily identified by its pattern of paroxysmal torsional/up-beating nystagmus upon provocative positional testing [33]. Studies have speculated that vertical positional nystagmus in normal controls may be at least partially due to the effect of gravity on the otolith organs [18].

Recent studies indicate that acutely symptomatic patients with vestibular migraine demonstrate low amplitude spontaneous and positional nystagmus, the slow-phase velocities of which overlap with those recorded in normal controls [34, 37]. However, our VM cohort demonstrated ictal spontaneous nystagmus in 65.7% of patients, whereas fewer than half as many (30.4%) of the normal controls in this study demonstrated this. The higher prevalence of nystagmus and the higher SPV in these acutely symptomatic patients indicates that the eye movements recorded in VM did indeed represent the ictus [37].

Our study limitations include subject convenience sampling, which may produce bias and thus the results may not be generalisable to a larger population. No formal recording was made of the subjects' eye movements with fixation. As no formal gaze-holding, saccades, pursuit, or head impulse testing was conducted on the normal controls, and without the benefit of a full medical history, neurological examination and imaging, there is a chance of the inclusion of normal subjects with sub-clinical central or peripheral vestibular disorders. These limitations should be considered when comparing oculomotor findings in neuro-otology patients to normal subjects, as these study results may overestimate the 'normal' range of nystagmus eye movement. Furthermore, substances such as alcohol and nicotine may increase nystagmus, while some medications such as benzodiazepines are known to reduce nystagmus, and were not controlled for [10, 18, 25, 27].

Thus, one third of healthy controls and two thirds of vestibular migraine sufferers show low velocity nystagmus. In the context of the interictal patient, it is important that low velocity nystagmus is interpreted with caution, since it may be unrelated to the underlying pathology. If encountered in an acutely symptomatic patient, it is best to seek a comparison with the interictal state. Rather than seeking a "cut-off" SPV value for pathological nystagmus, it is best that spontaneous nystagmus is interpreted in the context of the clinical syndrome and ictal status.

#### 4. Conclusion

Healthy normal controls without a self-reported history of spontaneous vertigo show spontaneous and positional nystagmus when observed without visual fixation. A small number of outliers demonstrate high velocity nystagmus  $> 10$  deg/s. This study highlights the importance of recording inter-ictal nystagmus when interpreting the patterns of ictal nystagmus in patients with episodic vertigo.

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#### Declaration of conflicts of interest

A Young receives scholarship funding from the University of Sydney, and reports no conflict of interest. M Welgampola receives funding from the Garnett Passe and Rodney Williams Memorial Foundation, and the National Health and Medical Research Council of Australia, and reports no conflict of interest. M D'Souza, S Rosengren and A Bradshaw report no conflict of interest.

#### Ethical standard

This study received local ethics committee approval (Protocol No X18-0087) and written informed consent was obtained in accordance with the 1964 Declaration of Helsinki and its later amendments.

#### Author contributions

A Young designed the study, collected and analysed the data, created the original figures, conducted statistical analysis, drafted and approved the final manuscript. S Rosengren edited the manuscript content, assisted with the statistical analysis and approved the final manuscript. A Bradshaw created the original figures, and approved the final manuscript. M D'Souza conducted statistical analysis, edited the manuscript content and approved the final manuscript. M Welgampola edited the manuscript content and approved the final manuscript.

**Video 1.** Fixation-denied video of a 29-year-old normal control showing mild spontaneous up-beating nystagmus in the upright position and when lying supine, and right-beating nystagmus in either lateral position.

**Video 2.** Fixation-denied video of a 61-year-old normal control showing no nystagmus in either the upright or supine position but showing apogeotropic positional nystagmus in either lateral position; left-beating nystagmus in the right lateral position, right-beating nystagmus in the left-lateral position.

**Video 3.** Fixation-denied video of a 55-year-old normal control showing spontaneous down-beating nystagmus in all positions.

**Video 4.** Fixation-denied video of a 45-year-old normal control showing no spontaneous nystagmus in the upright position, with right-beating nystagmus while supine, and geotropic nystagmus in either

lateral position; right-beating nystagmus in the right-lateral position, left-beating nystagmus in the left-lateral position.

**Video 5.** Fixation-denied video of a 40-year-old normal control showing spontaneous right-beating nystagmus in the upright position, no nystagmus while lying supine, and geotropic nystagmus in either lateral position; right-beating nystagmus in the right-lateral position, left-beating nystagmus in the left-lateral position.

### Supplementary material

The videos are available in the electronic version of this article: <https://dx.doi.org/10.3233/VES-200022>.

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