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Spontaneous Nystagmus Violating the Alexander's Law: Neural Substrates and Mechanisms

Jae-Hwan Choi
Pusan National University School of Medicine, Pusan National University Yangsan Hospital
Eun Hye Oh
Pusan National University School of Medicine, Pusan National University Yangsan Hospital
Hyun Sung Kim
Gyeongsan National University School of Medicine and Gyeongsang National University Changwon Hospital
Ji-Yun Park
Ulsan University Hospital, University of Ulsan College of Medicine
Suk-Min Lee
Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute
Seo Young Choi
Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute
Hyo Jung Kim
Seoul National University Bundang Hospital
Jeong-Yoon Choi
Seoul National University Bundang Hospital
Ji-Soo Kim
Seoul National University Bundang Hospital
Jorge Otero-Millan
University of California, Berkeley
Kwang-Dong Choi
kdchoi@pusan.ac.kr

Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute

Research Article

Keywords: Nystagmus, Alexander's law, Neural integrator, Lateral medullary infarction, Cerebellum

Posted Date: August 6th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4722547/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at The Cerebellum on January 20th, 2025. See the published version at https://doi.org/10.1007/s12311-025-01788-0.

Abstract

Alexander's law states that spontaneous nystagmus increases when looking in the direction of fast-phase and decreases during gaze in slow-phase direction. Disobedience to Alexander's law is occasionally observed in central nystagmus, but the underlying neural circuit mechanisms are poorly understood. We found a violation of Alexander's law in one or both directions of lateral gaze in lesions of unilateral lateral medulla affecting the vestibular nucleus. When Alexander's law is violated, the time constant (Tc) was larger than that in the controls (median [interquartile range, IQR]: 14.4 s [6.4–38.9] vs 9.0 s [IQR 5.5–12.6], $p = 0.036$) while the Tc did not differ between the groups when Alexander' law is obeyed (9.6 s [3.6–16.1] vs 9.0 s [5.5–12.6], $p = 0.924$). To test the study hypothesis that an unstable neural integrator may generate nystagmus violating Alexander's law, we primarily utilized the gaze-holding neural integrator computational model, incorporating lesion-induced changes. With normal integrator function, the false rotational cue generates nystagmus following Alexander's law. The first lesion, which changes the brainstem neural integrator, and the second lesion, which causes the Purkinje synapse to exert excitatory input, both lead to nystagmus that violates Alexander's law. We propose that when the neural integrator is unstable with lesions in the brainstem neural integrator itself or the neural synapse between Purkinje cells and the brainstem vestibular nucleus, nystagmus violates Alexander's law.

Introduction

Alexander's law refer to the phenomenon that spontaneous nystagmus increases during the gaze in the fast-phase direction and decreases during the gaze in the opposite slow-phase direction [1]. This law applies to most nystagmus from either peripheral or central lesions [2, 3]. A few hypotheses have been proposed to explain this behavior, which include adaptive changes in the function of velocity-to-position neural integrator [4, 5] and inherent physiological properties of the brainstem nuclei that process information both for the vestibulo-ocular reflex (VOR) and normal gaze holding [6, 7].

Previously, spontaneous nystagmus that contravenes the Alexander's law has been described in a patient with upbeat nystagmus associated with Wernicke's encephalopathy [8]. Although the exact mechanism behind this phenomenon remains uncertain, one plausible explanation is an unstable neural integrator, as suggested by the slow phases of nystagmus with an exponentially increasing velocity [8]. In this context, we hypothesized that coalescence of unstable neural integrator with direction-fixed spontaneous nystagmus may give rise to violation of the Alexander's law.

This study aimed to define the characteristics and anatomical substrates of spontaneous nystagmus that violates the Alexander's law, and elucidate the mechanism using quantitative oculographic analyses and a mathematical model of an unstable neural integrator.

Materials and Methods

Subjects

We reviewed the medical records 2,652 patients with posterior circulations stroke (PCS) in the stroke registry at two University Hospitals in South Korea, Pusan National University and Pusan National University Yangsan Hospitals during a 13-year period.

We found 17 patients having presented spontaneous horizontal or mixed horizontal and torsional nystagmus that disobeyed the Alexander's law, i.e., decrease of nystagmus when looking in the direction of fast-phases and/or increase of nystagmus during the gaze in the direction of slow-phases (Video 1). The patients included nine men with the age ranging from 31 to 87 years (mean ± SD = 62 ± 13). For comparison, 20 patients with acute vestibular neuritis (VN, 13 men, 56 ± 10 years) served as a control. The demographic and clinical characteristics of the subjects are summarized in Table 1.

Table 1
Demographic and Clinical Characteristics of the Patients

	Patients with nystagmus violating Alexander's law (n = 17)	Patients with vestibular neuritis (n = 20)	*p*
Male sex, n (%)	9 (53)	13 (65)	0.272
Age, y, mean (SD)	62 (13)	56 (10)	0.149
Lesion side, right, n (%)	9 (53)	14 (70)	0.286
Onset to evaluation, day, median (IQR)	1 (0.5–2.5)	1 (1–1)	0.478
SN, °/s, median (IQR)	3.3 (2.0-7.8)	4.8 (2.5–6.5)	0.557
Abnormal vHITs, n (%)	6 (43)	20 (100)	< 0.001

vHITs video head impulse tests, *IQR* interquartile range, *SN* spontaneous nystagmus, *Tc* time constant

Clinical and Radiological Evaluation

All patients received structured neurological and neuro-otological examination by the authors (J-H.C., K.D.C). Bedside neuro-otological evaluation included 4-item HINTS plus (Head Impulse, Nystagmus, Test of Skew, and acute hearing loss detected by finger rubbing) [9]. All patients had evaluation within 7 days from symptom onset. Patients received stroke protocol MRIs including axial T2, fluid-attenuated inversion recovery image, DWI, and angiography.

Eye Movement Recording and Analyses

Eye movements were recorded using three-dimensional video-oculography (VOG, SLVNG, SLMED, Seoul, South Korea) with the patients seated upright. The VOG device was calibrated for horizontal and vertical eye positions using its calibration system with laser projections on the screen at a distance of 1.5m. After calibration, we recorded nystagmus by instructing the patients to look at a target straight-ahead and displaced ± 20° horizontally. The target was present for 20 seconds at each position.

We analyzed the nystagmus at three gaze positions: the primary and each eccentric gaze. The horizontal eye position was coded positive when looking in the fast-phase direction of spontaneous nystagmus. The slow-phase velocities (SPVs) of nystagmus were calculated using a MATLAB by differentiating eye positions. An average value of all SPVs was measured at each gaze position by applying a linear regression of the velocity versus position [3, 10, 11]. Then, we measured the slope of SPVs between the primary and eccentric gaze positions to determine an obedience of Alexander's law. When the slopes of the fast and slow phases were both positive, we defined that the nystagmus obeyed the Alexander's law. In contrast, we defined that the nystagmus violated the

Alexander's law when at least one of the slopes was negative. We also calculated the time constant (Tc) of nystagmus at each eccentric gaze position as follows [2, 3, 10, 11].

$Tc = \Delta E_{pos}/\Delta E_{vel}$

ΔE_{pos}: difference of eye position between the two positions

ΔE_{vel}: difference of slow-phase velocity between the two positions

We also recorded spontaneous nystagmus without visual fixation, and positional nystagmus induced by various positional maneuvers including lying down from sitting, head turning to either side while supine, straight-head hanging, and Dix-Hallpike maneuver to each side.

Laboratory Evaluation

The VOR during head impulses was quantitatively assessed in 14 patients using a video-based equipment (SLMED, Seoul, Korea) as described previously [12]. The VOR gain was calculated as the ratio of the area under the entire eye-velocity relative to the area under the entire head-velocity. Reference data were obtained from 31 normal controls. The subjective visual vertical (SVV) tilt was measured in 13 patients by seating them upright in a dark room and asking to align a rod (80 cm long and 0.3 cm wide) vertically. The rod was presented randomly at various angles from the vertical at a distance of 130 cm from the patient's eyes. The SVV tilt was determined by calculating the average deviation from the earth vertical during five adjustments. The SVV tilt was considered abnormal when it exceeded the normal values obtained from healthy controls (-3.0° to 3.0° in both eyes; a negative value indicates a counterclockwise rotation) [12].

Statistical Analysis

All analyses were performed with SPSS (version 22.0, Chicago, IL, USA). Continuous variables were compared using the t test or Mann–Whitney U test, and nominal variables were compared with the $\chi 2$ or Fisher exact tests. The significance level was set at $p < 0.05$.

Results

Clinical and Radiological Characteristics

During visual fixation, patients had mixed horizontal-torsional-upbeat (n = 11), pure horizontal (n = 4), and mixed horizontal-torsional (n = 2) nystagmus (Table 2). The direction of horizontal nystagmus was contralesional in all. Without visual fixation, all patients showed mainly horizontal nystagmus with or without a vertical or torsional component. One patient (Pt 4) showed right and clockwise torsional (from the patient's perspective) beating nystagmus with an upbeat component that was irregularly interposed by left and counterclockwise torsional beating nystagmus with an upbeat component (aperiodic alternating nystagmus).

Table 2
Clinical and Radiological Characteristics of Patients with Spontaneous Nystagmus Violating Alexander's Law

Patients	Sex/age	Lesion side	Involved lesions	SN with fixation		Waveforms change during horizontal gazes	SN without fixation	
				Direction	Slow phase waveforms		Direction	Slow phase waveforms
1	F/82	L	LM, CB	R	C	D in slow-phase direction in only right eye	R = U	C
2	F/74	R	LM	L	C	(-)	L	C
3	M/72	L	LM, CB	R	mixed (D + C)	(-)	R	C
4	F/54	L	LM	R > U > CW	mixed (D + I or D + C)	(-)	R > U > CW (aPAN)	C
5	F/62	L	LM	R	mixed (D + C)	(-)	R = CW	C
6	M/31	R	LM	L > CCW > U	C	(-)	L > CCW > U	C
7	F/63	R	LM	L > CCW > U	C	(-)	L > CCW > U	C
8	F/56	L	LM	R > CW > U	mixed (D or D + I or D + C)	(-)	R > CW > U	C
9	F/87	L	LM	R > CW	C	(-)	R > CW	C
10	F/63	R	LM, CB	L > U > CCW	C	(-)	L > U > CCW	C
11	M/67	R	LM, CB	CCW > L > U	C	(-)	L > CCW > U	C
12	M/66	L	LM, CB	CW > R > U	C	mixed (D or D + C) in slow-phase direction	R > CW > U	C
13	M/61	R	LM	CCW > L > U	C	(-)	L > U > CCW	C
14	F/43	R	LM	CCW > L > U	C	(-)	L > CCW > U	C

C constant-velocity, *CB* cerebellum, *CCW* counterclockwise, *CW* clockwise, *D* decreasing-velocity, *F* female, *I* increasing-velocity, *L* left, *LM* lateral medulla, *M* male, *aPAN* aperiodic alternating nystagmus, *R* right, *SN* spontaneous nystagmus, *U* upbeat

Patients	Sex/age	Lesion side	Involved lesions	SN with fixation		Waveforms change during horizontal gazes	SN without fixation	
				Direction	Slow phase waveforms		Direction	Slow phase waveforms
15	M/57	R	LM	CCW > L	C	(-)	L > CCW > U	C
16	M/62	L	LM	R > CW > U	C	(-)	R = U > CW	C
17	M/52	R	LM	L = U > CCW	I	D in slow-phase direction, C in fast-phase direction	L = U > CCW	I

C constant-velocity, *CB* cerebellum, *CCW* counterclockwise, *CW* clockwise, *D* decreasing-velocity, *F* female, *I* increasing-velocity, *L* left, *LM* lateral medulla, *M* male, *aPAN* aperiodic alternating nystagmus, *R* right, *SN* spontaneous nystagmus, *U* upbeat

Direction-changing apogeotropic and geotropic nystagmus were induced during supine roll test in each patient (Pt 13 and 16, respectively). Seven patients showed ocular ipsipulsion with ipsilesional saccadic hypermetria while 11 had impaired horizontal smooth pursuit in one (n = 4) or both directions (n = 7). Accompanying neurological signs included ataxia (n = 17), sensory changes (n = 11), Horner syndrome (n = 6). dysphagia (n = 5), dysarthria (n = 4), and hoarseness (n = 2).

The head impulse VOR gains for the horizontal semicircular canals were abnormal in six patients (6/14, 43%); slightly decreased ipsilesionally (n = 2) or bilaterally (n = 1), and increased contralesionally (n = 2) or bilaterally (n = 1). Most of the patients tested exhibited ipsilesional SVV tilt (13/14, 93%).

All patients had an acute infarction involving unilateral lateral medulla, and five showed an additional infarction in the ipsilateral cerebellum (Fig. 1).

Oculographic Analyses

Slow-phase Waveforms of Spontaneous Nystagmus

Patients showed various slow-phase waveforms of spontaneous nystagmus during visual fixation that included linear- (n = 12), exponentially increasing- (n = 1), and mixed forms (n = 4). The mixed-velocity waveforms mostly comprised an initial decreasing-velocity followed by a constant or increasing-velocity even in a single beat. On elimination of visual fixation, the slow phase of spontaneous nystagmus became linear in 16 patients regardless of the waveforms observed during visual fixation while the slow phase velocity remained increasing in one (Pt 17). In three patients (Pt 1, 12 and 17), the patterns of slow-phases were changed by lateral gazes in a various way (Table 2).

Patterns Violating the Alexander's Law

Spontaneous nystagmus violated the Alexander's law during the gazes in both directions (n = 5, 29%) or during the gaze only in one direction (n = 12, 71%) (Table 3). Of the five patients with a violation in both directions, one (Pt 4) showed centripetal nystagmus (beating toward the primary position during the gaze in the direction of nystagmus). All five patients showed a negative slope for gaze both in the slow- and fast-phase directions (Table 3 and Fig. 2A), and the median slopes were − 0.027 (IQR − 0.009 ~ -0.156) and − 0.103 (IQR − 0.032 ~ -0.143), respectively. In these patients, spontaneous nystagmus had a linear- (n = 2, Fig. 2A) or mixed-velocity (n = 3) slow-phase waveforms.

Table 3

Oculographic Analysis of Spontaneous Nystagmus as a Function of Horizontal Eye Positions

Patient	Slow-phase direction			Primary position	Fast-phase direction		
	Velocity (mean ± SD, °/s)	Slope (°/s/°)	Tc (ΔE_{pos}/ ΔE_{vel}, s)	Velocity (mean ± SD, °/s)	Velocity (mean ± SD, °/s)	Slope (°/s/°)	Tc (ΔE_{pos}/ ΔE_{vel}, s)
Complete violation of AL							
1	7.24 ± 2.73	-0.012	83.3	7.00 ± 2.14	3.75 ± 1.80	-0.163	6.2
2	14.21 ± 5.14	-0.279	3.6	8.63 ± 8.21	6.58 ± 1.27	-0.103	9.8
3	2.94 ± 0.80	-0.027	37.7	2.41 ± 1.12	2.00 ± 0.82	-0.021	48.8
4	1.59 ± 0.36	-0.033	30.8	0.94 ± 0.47	-1.52 ± 0.32†	-0.123	8.1
5	1.78 ± 0.54	-0.006	166.7	1.66 ± 0.54	0.82 ± 0.37	-0.042	23.8
Partial violation of AL in the slow-phase direction							
6	4.90 ± 1.47	-0.024	42.6	4.43 ± 1.32	7.14 ± 1.76	0.136	7.4
Partial violation of AL in the fast-phase direction							
7	9.94 ± 2.06	0.085	11.8	11.63 ± 2.29	9.37 ± 2.41	-0.113	8.9
8	1.34 ± 0.23	0.027	37.7	1.87 ± 0.76	0	-0.094	10.7
9	3.20 ± 0.73	0.033	30.8	3.85 ± 0.98	2.46 ± 1.11	-0.070	14.4
10	3.29 ± 0.70	0.060	16.8	4.48 ± 2.00	0	-0.224	4.5
11	7.71 ± 3.46	0.513	2.0	17.96 ± 4.05	8.30 ± 2.44	-0.483	2.1
12	1.36 ± 0.31	0.085	11.8	3.06 ± 0.66	0	-0.153	6.5
13	-2.68 ± 1.29†	0.300	3.3	3.31 ± 1.42	2.66 ± 0.87	-0.033	30.8
14	-2.94 ± 1.15†	0.237	4.2	1.79 ± 0.72	1.15 ± 0.13	-0.032	31.3

† Negative value indicates that horizontal nystagmus reverses the direction during eccentric position.

AL Alexander's law, *Tc* time constant, ΔE_{pos} difference of eye position between the two targets, ΔE_{vel} difference of slow-phase velocity between the two targets

Video legends

Video. Patient 1 with infarctions in the left lateral medulla and cerebellum shows spontaneous right-beating nystagmus of which the intensities increase during leftward gaze (slow-phase direction) while decrease during rightward gaze (fast-phase direction).

Patient	Slow-phase direction			Primary position	Fast-phase direction		
15	-1.41 ± 0.43†	0.181	5.5	2.20 ± 0.54	1.76 ± 0.54	-0.022	45.5
16	1.39 ± 0.33	0.073	13.8	2.84 ± 0.62	1.46 ± 0.33	-0.069	14.5
17	5.19 ± 2.64	0.506	2.0	15.30 ± 2.57	9.97 ± 1.93	-0.267	3.8

† Negative value indicates that horizontal nystagmus reverses the direction during eccentric position.

AL Alexander's law, *Tc* time constant, ΔE_{pos} difference of eye position between the two targets, ΔE_{vel} difference of slow-phase velocity between the two targets

Video legends

Video. Patient 1 with infarctions in the left lateral medulla and cerebellum shows spontaneous right-beating nystagmus of which the intensities increase during leftward gaze (slow-phase direction) while decrease during rightward gaze (fast-phase direction).

Of the 12 patients with a violation of the Alexander's law only in one direction of gaze, one showed an increase of nystagmus during the gaze in the opposite direction of nystagmus (Pt 6). In this patient, the slow phase was linear, and the slope was − 0.024 during the gaze in the opposite direction of spontaneous nystagmus (Table 3 and Fig. 2B). In the remaining 11 patients (Pt 7–17), spontaneous nystagmus decreased when looking in the direction of spontaneous nystagmus with a median slope at -0.094 (IQR − 0.033~ -0.224) (Table 3 and Fig. 2C). The slow phases were mostly linear (n = 9), but accelerating or mixed in each patient (Fig. 3).

Comparison of the Time Constant between the Controls (patients with VN) and Patients with Spontaneous Nystagmus Violating the Alexander's Law

In the controls, the spontaneous nystagmus invariably obeyed the Alexander's law with a positive slope during the lateral gazes in both directions. The median slopes were 0.100 (IQR 0.070 ~ 0.156) during the gaze in the direction of spontaneous nystagmus and 0.099 (IQR 0.063 ~ 0.188) during the gaze in the opposite direction. The median Tc was 9.0 s (IQR 5.5 ~ 12.6 s).

In 17 patients with spontaneous nystagmus violating the Alexander's law, the median Tc was measured at 14.4 s (IQR 6.4 ~ 38.9 s) when the Alexander's law was violated and at 9.6 s (IQR 3.6 ~ 16.1 s) when the Alexander's law was obeyed. The median Tc was higher when the Alexander's was violated than that observed in the controls (14.4 s [IQR 6.4–38.9] vs 9.0 s [IQR 5.5–12.6], $p = 0.036$), whereas the Tc when the Alexander's law was obeyed in the patients did not differ from the Tc observed in the controls (9.6 s [IQR 3.6–16.1] vs 9.0 s [IQR 5.5–12.6], $p = 0.924$) (Fig. 4).

Modeling

Neural Integration Model

To test the study hypothesis that an unstable neural integrator can generate nystagmus violating Alexander's law, we primarily utilized the gaze-holding neural integrator model [13], incorporating lesion-induced changes. Based on the neural activities being proportional to eye position, the burst-tonic neurons within the vestibular nucleus and nucleus prepositus hypoglossi are believed to be the primary neural integrator, converting eye velocity into

position information. However, this process is not perfect and is known as 'leakiness,' which might offer advantages in counteracting the accumulation of biological noise. This leakiness was herein modeled as a low-pass filter with a time constant of 2 seconds [13]. The flocculus and paraflocculus then play an important role in compensating for the leakiness of the brainstem neural integrator. They can be modeled either through positive feedback or negative feedback. In the positive feedback model, the eye position signals generated in the brainstem neural integrator are fed back to the neural integrator itself via the pathway through the cerebellum (Fig. 5A) [2, 14]. Meanwhile, the negative feedback model provides feedback to the vestibular nucleus and uses velocity information based on the difference between predicted and estimated eye velocities (Fig. 5B) [13]. The details of each model have been introduced elsewhere [13, 14], but herein we adopted the negative feedback model, assumed to be more physiological.

Lesion-induced Changes

Because the lesions observed for the violation of Alexander's law were commonly located in the lateral medulla, these lesions could directly affect the brainstem neural integrator itself or the neural synapse between Purkinje cells and the brainstem vestibular nucleus. Therefore, we set the lesion-induced change such that a hyperexcitable brainstem neural integrator abnormally accumulates neural signals, replacing leakiness, or the cerebellar input exerts a positive, instead of a negative, effect on the vestibular nucleus (site-1 in Fig. 5B and 5C). The basis of these changes is as follows: For the direct neural integrator lesions, increased intracellular Ca2 + concentration can cause neuronal hyperexcitability [15]. For the cerebellar positive feedback, it has been suggested that GABA, the inhibitory neurotransmitter utilized by Purkinje cells, can paradoxically exert an excitatory effect (site-2 in Fig. 5B and 5C) [16]. Lastly, we implemented false constant rotational cues to induce lesion-induced spontaneous nystagmus.

Simulation

The results show that with normal integrator functions, the false rotational cue generates nystagmus following Alexander's law (first row in Fig. 5C). The first lesion, which changes the brainstem neural integrator, and the second lesion, which causes the Purkinje synapse to exert excitatory input, both lead to nystagmus that violates Alexander's law (second and third rows in Fig. 5C). This successfully visualizes our hypothesis.

Discussion

This study demonstrates that violation of the Alexander's law is an occasional finding in patients with Wallenberg syndrome and an unstable neural integrator would be an underlying mechanism of the phenomenon. We provide evidence to support this hypothesis using a gaze-holding neural integrator model that incorporates lesion-induced changes.

An explanation for Alexander's law is adaptive changes in the velocity-to-position neural integrator to reduce spontaneous vestibular nystagmus during the gaze in the slow-phase direction to bring about improvement of vision [2–5, 17]. The neural integrator is responsible for holding the eyes in eccentric position by mathematically integrating the eye velocity commands [2, 18, 19]. Impaired gaze holding and resultant gaze-evoked nystagmus (GEN) may be observed in lesions involving the nucleus prepositus hypoglossi (NPH) and medial vestibular nucleus (MVN) that play a crucial role in horizontal neural integration [20–23]. If the neural integrator becomes leaky in patients with direction-fixed vestibular nystagmus, the drift velocity of nystagmus increases during the

gaze in the fast-phase direction and decreases during gaze in the slow-phase direction, conforming to the Alexander's law.

When the neural integrator becomes unstable, the eyes drift away from the central position, causing centripetal nystagmus [2, 24–28]. Theoretically, when an unstable neural integrator is combined with direction-fixed vestibular nystagmus, the drift velocity may increase during the gaze in the slow-phase direction and decrease during the gaze in the fast-phase direction, thereby violating the Alexander's law. In support of this hypothesis, our patients with Wallenberg syndrome and violation of the Alexander's law showed that the Tc of nystagmus is increased only during the gaze where the Alexander's law was disobeyed. In addition, some patients exhibited the nystagmus with an accelerating (increasing velocity) slow phase or centripetal nystagmus. Our patients with the violation of Alexander's law had invariable lesions in the lateral medulla. These lesions could directly affect the brainstem neural integrator itself or the neural synapse between Purkinje cells and the brainstem vestibular nucleus [29, 30]. The neural integration for horizontal eye movements depends on a distributed network of neurons lying in the brainstem and cerebellum [2, 20–23]. The flocculus and paraflocculus enhance the performance of an inherently leaky neural integrator in the brainstem either through positive or negative feedback [14, 31–33]. Our gaze-holding neural integrator model, incorporating lesion-induced changes showed that when the neural integrator becomes unstable, nystagmus violates Alexander's law. Under normal integrator function, the false rotational cue generates nystagmus following Alexander's law. In contrast, the lesion-induced change such that a hyperexcitable brainstem neural integrator abnormally accumulates neural signals, replacing leakiness, or that the cerebellar input exerts a positive, instead of a negative, effect on the vestibular nucleus, produces nystagmus that violates Alexander's law. Increased intracellular Ca2 + concentration may cause neuronal hyperexcitability for the direct neural integrator lesions [15], while for the cerebellar positive feedback, it has been suggested that GABA, the inhibitory neurotransmitter utilized by Purkinje cells, may paradoxically exert an excitatory effect [16]. Consistent with our results, previous experimental studies also showed that injection of either bicuculline or muscimol into the MVN caused instability of gaze holding, in which the eye drifts away from the central position with increasing-velocity waveforms, implying an unstable neural integrator [34, 35]. These effects may be related to inactivation either of neurons within NPH-MVN or the cerebellar projections to them that control the fidelity of neural integration.

Patients with a lesion restricted to the vestibular nuclei may show diverse signs of both peripheral vestibulopathy (spontaneous nystagmus, caloric paresis, and positive head impulse tests) and central vestibular dysfunction (GEN) [30, 36–38]. Our study disclosed that lesions in the area of the vestibular nuclei can lead to diverse patterns of spontaneous nystagmus and its modulation by visual fixation and gaze. These findings may be explained by significant divergence of excitatory projections from the peripheral vestibular structures and brainstem neural integrators, along with inhibitory inputs from the cerebellum (Fig. 6) [2, 13, 29, 30].

Some patients exhibited a mixed pattern of slow-phase velocity of spontaneous nystagmus with a beat-to-beat and intrabeat variability. Even in a single beat, the nystagmus consisted of an initial decelerating and following linear or accelerating slow phases. Similar waveforms have been reported in vertical nystagmus observed in lesions involving the paramedian tract (PMT) [39] or in patients with ankylosing spondylitis [40]. According to a mathematical model, these unusual waveforms may occur due to the pulse-step mismatch creating the initially decreasing-velocity waveforms due to leaky neural integrators, and subsequent disruption of the cerebellar feedback for gaze holding through PMT, resulting in unstable neural integrators and nystagmus with an increasing-velocity waveform [39, 40]. GEN and superimposed pendular nystagmus observed in patients with multiple sclerosis also imply that the neural integrator can be simultaneously leaky and unstable [41].

Our patients more frequently showed a violation of the Alexander's law only in one direction. This indicates that dysfunction of the neural integration depends on gaze direction. Thus, the neural integrators may become unstable in one direction while they become leaky in other directions of gaze [42–44]. Indeed, asymmetrical GEN has been described in patients with unilateral lesions of the NPH or MVN [30, 37, 38, 45]. In unilateral lesion of the NPH, the neural integration is more severely impaired with a decrease in the Tc of postsaccadic drift after ipsilesional eccentric gaze [45].

Conclusion

Spontaneous nystagmus in patients with Wallenberg's syndrome can violate Alexander's law, which permit a differentiation from acute peripheral vestibular syndrome. The violation of the Alexander's law may be attributed to unstable neural integrator and can be simulated by lesions affecting the brainstem neural integrator itself or the neural synapse between Purkinje cells and the brainstem vestibular nucleus.

Declarations

Author contributions J-HC and E-HO analyzed and interpreted the data and wrote the manuscript. H-SK, J-YP, S-ML, S-YC, H-JK, J-YC, J-SK and JOM analyzed and interpreted the data. K-DC designed and conceptualized the study, interpreted the data, and revised the manuscript. All authors reviewed and approved the final version of the manuscript. K-DC is responsible for the overall content as guarantor, and obtained funding.

Funding This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (NRF-2023R1A2C1004810).

Data availability Anonymized data will be shared upon request from any qualified investigator.

Conflict of interest Drs. JH Choi, EH Oh, HS Kim, JY Park, SM Lee, SY Choi, HJ Kim, JY Choi, J Otero-Millan, and KD Choi report no disclosures. Dr. JS Kim serves as an Associate Editor of Frontiers in Neuro-otology and on the editorial boards of the Journal of Clinical Neurology, Frontiers in Neuro-ophthalmology, Journal of Neuro-ophthalmology, and Journal of Vestibular Research, and Clinical and Translational Neurology.

Ethical approval All the experiments performed in this study followed the tenets of the Declaration of Helsinki. Informed consents were obtained from the participants (including technicians in supplementary video) after the nature and possible consequences of this study had been explained to them. This study was approved by the Institutional Review Board of Pusan National University (2308-031-130) and Pusan National University Yangsan Hospitals (05-2023-180).

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Figures

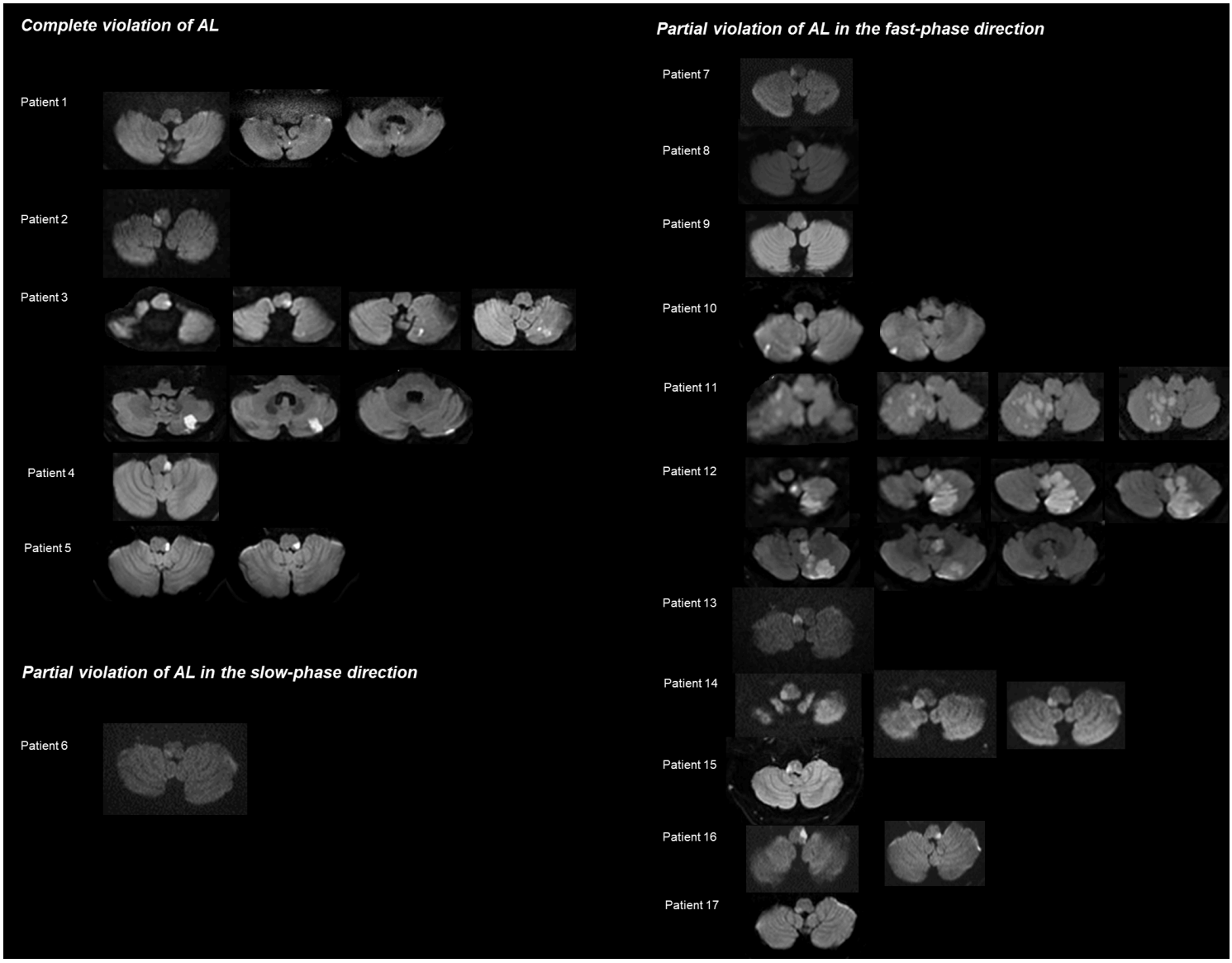


Figure 1

Involved lesions in 17 patients with spontaneous nystagmus violating the Alexander's law. Diffusion-weighted images show the lesions mostly affecting unilateral lateral medulla. Five patients (patients 1, 3, and 10-12) have additional infarctions in the ipsilesional cerebellum.

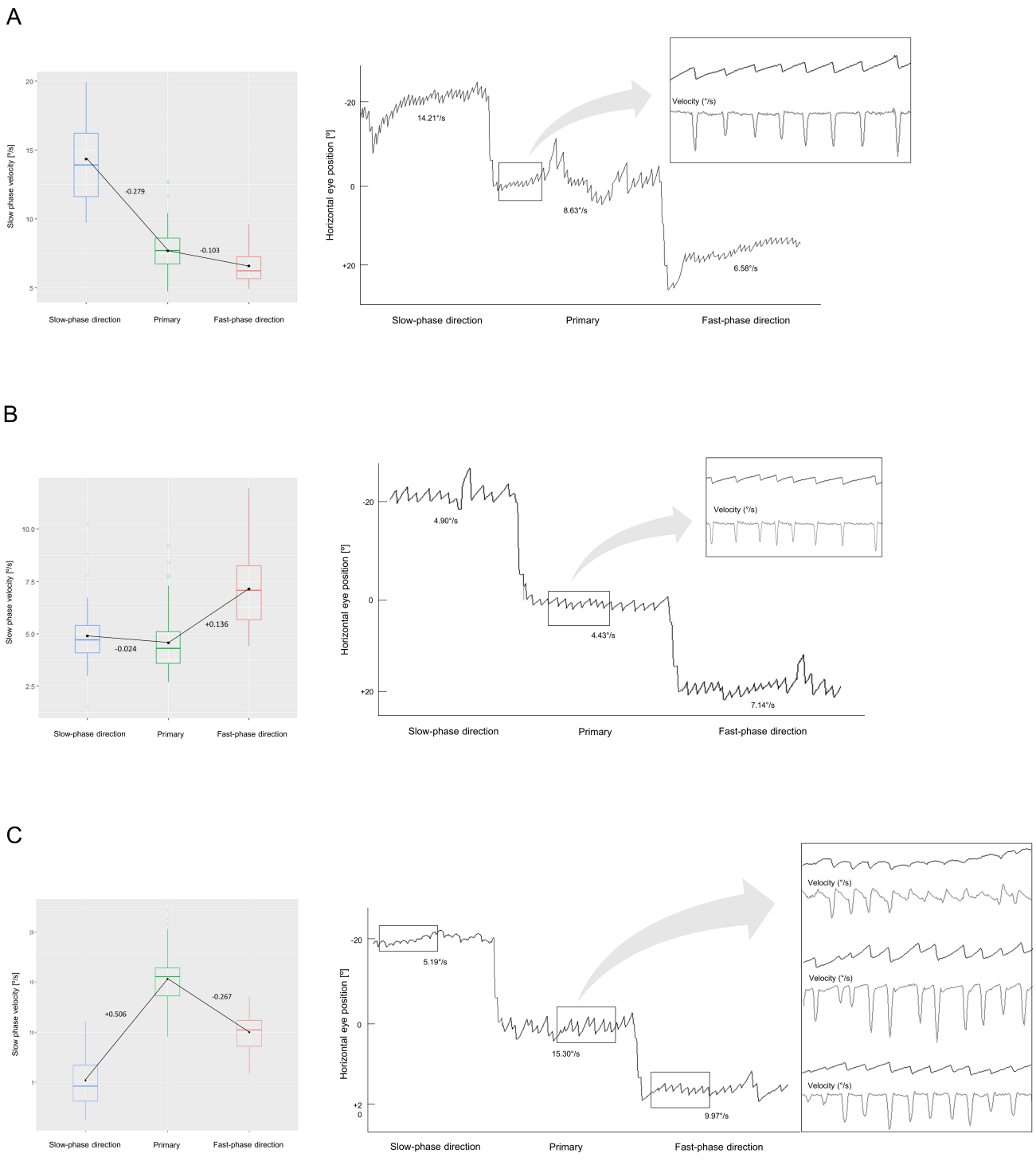


Figure 2

The patterns violating the Alexander's law. (**A**) In patient 2, the slow-phase velocities (SPVs) of nystagmus increase when looking in the slow-phase direction while decrease when looking in the fast-phase direction. As a result, both slopes for gazes in the slow- and the fast-phase directions have negative values. The slow-phase waveforms of the nystagmus have a linear velocity during the primary and eccentric gazes (inside the rectangle). (**B**) In patient 6, the nystagmus increases during the gaze in both directions. The slow phases are linear (inside the rectangle). (**C**) In patient 17, the nystagmus decreases during the gaze in both directions, thus the slope is

negative in the fast-phase direction. The slow phase waveforms are variable, showing an increasing-velocity at the primary position, and then changing into a decreasing velocity during the gaze in the slow-phase direction and a constant velocity during the gaze in the fast-phase direction (inside the rectangle).

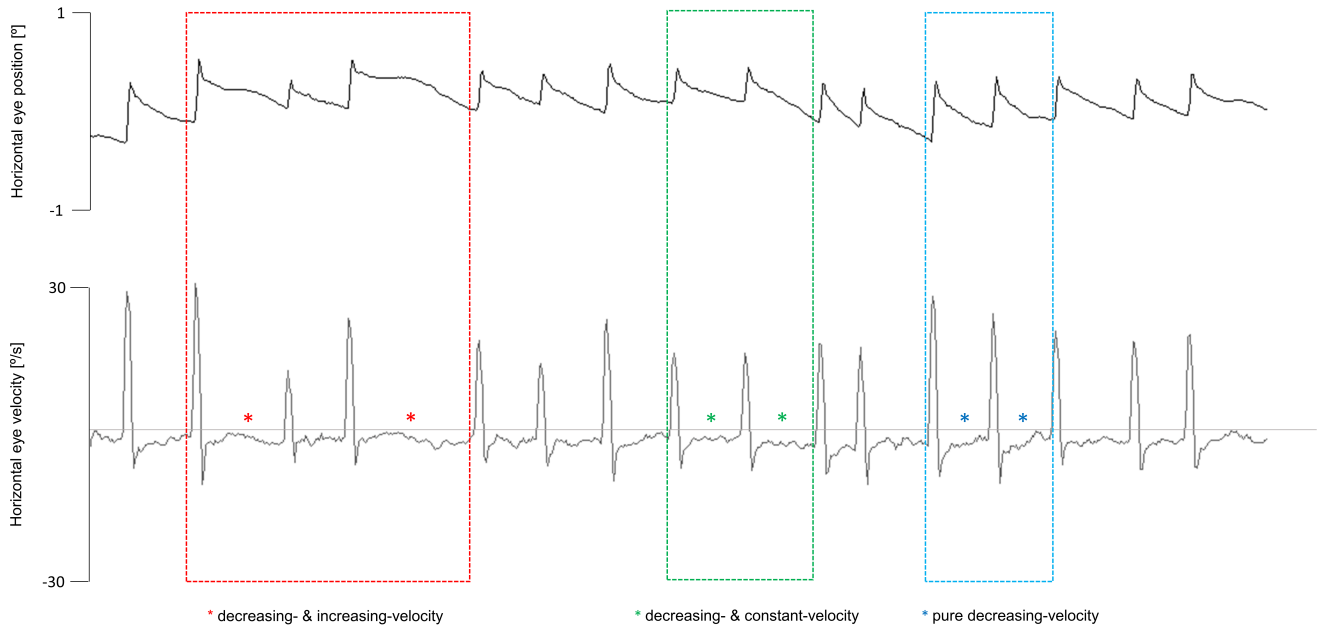


Figure 3

The slow-phase waveform of spontaneous nystagmus with a mixed-velocity in patient 8. The slow phase starts with a rapid drift with a deceleration, which is then followed by an acceleration (red asterisks) or constant velocity (green asterisks). Some waveforms show a pure decreasing velocity (blue asterisks).

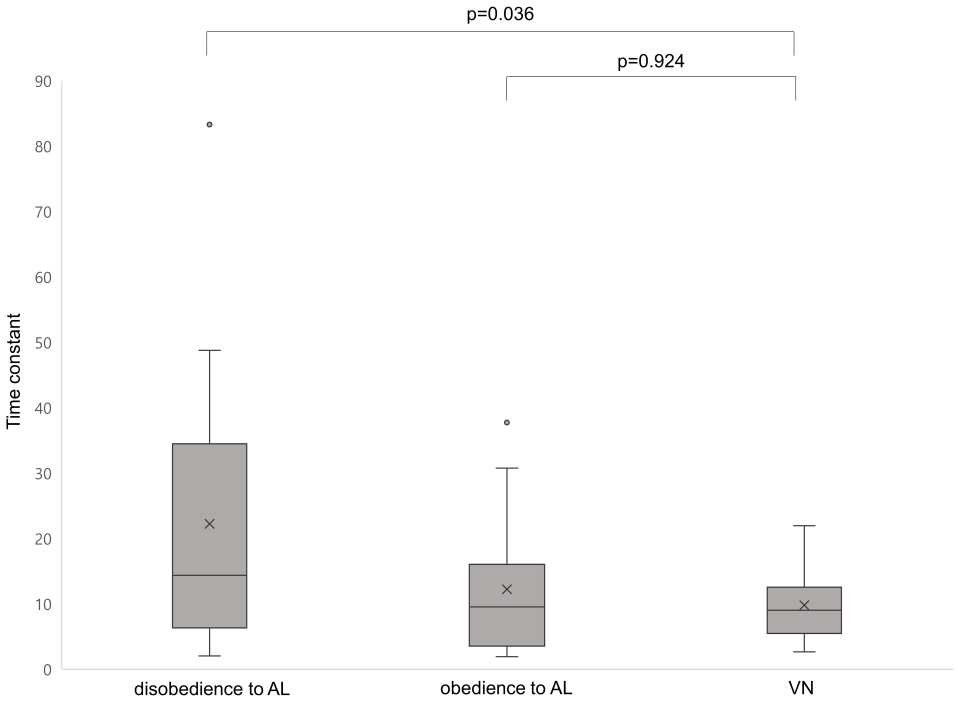


Figure 4

Comparison of the time constants between patients with spontaneous nystagmus violating the Alexander's law and vestibular neuritis. The median Tc is higher when the Alexander's is violated than that observed in the controls (14.4 s [interquartile range, IQR 6.4-38.9] vs 9.0 s [IQR 5.5-12.6]), whereas the Tc when the Alexander's law is obeyed in the patients does not differ from the Tc observed in the controls (9.6 s [IQR 3.6-16.1] vs 9.0 s [IQR 5.5-12.6]).

AL=Alexander's law, VN=vestibular neuritis

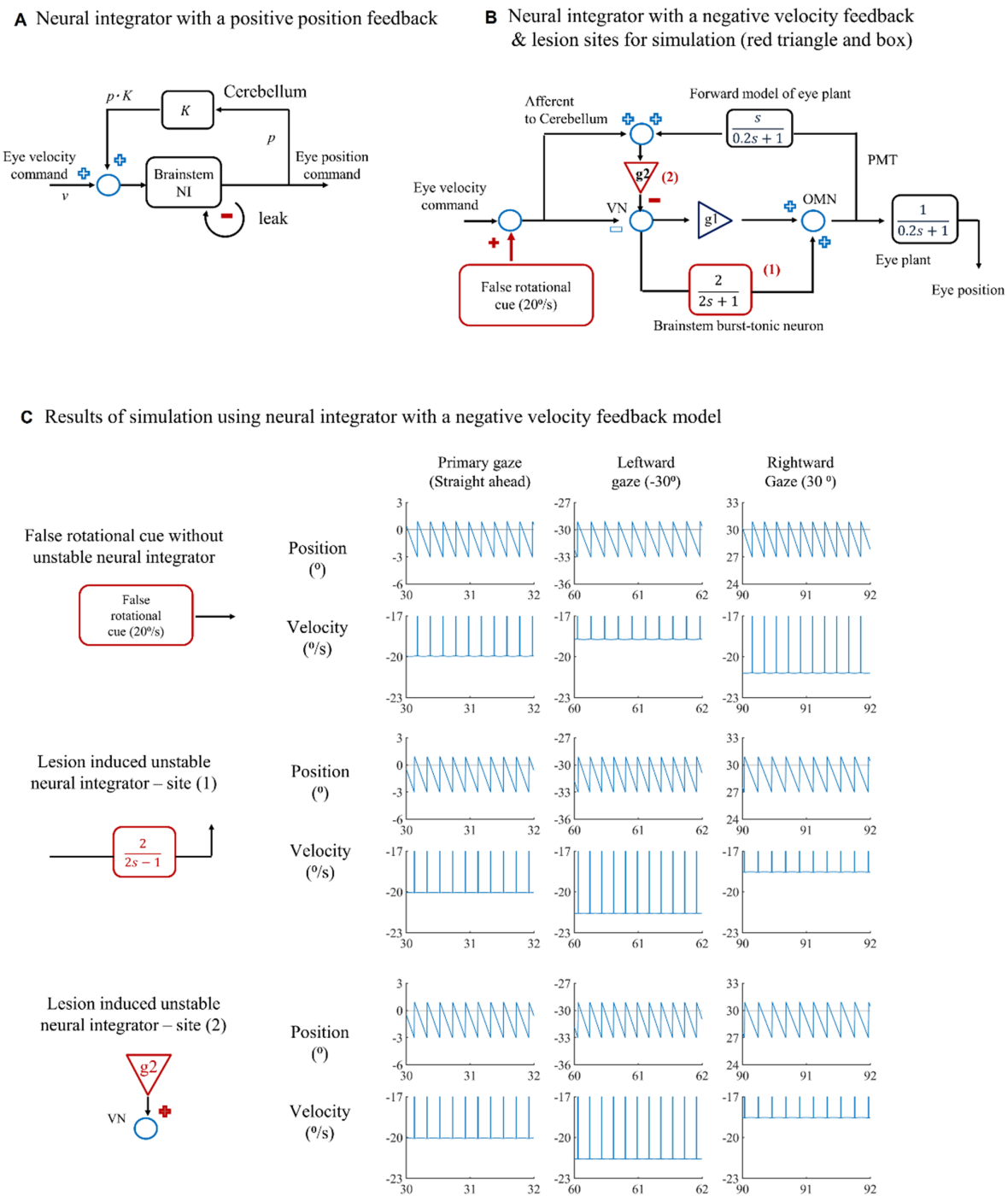


Figure 5

Schematics of neural integrator models and the result of simulations. (**A**) In the positive feedback model, the cerebellum compensates for the leakiness of the neural integrator with position information. (**B**) The model of negative velocity feedback. The vestibular signals primarily reach the vestibular nucleus (VN). These signals are then sent to the ocular motor nucleus (OMN) via both the direct and the neural integrator pathways, which in turn send signals to the eye plant. The cerebellum receives predicted eye velocity signals using a forward model of the eye plant, as well as desired eye velocity information through primary vestibular afferents. The difference between

these signals is sent to the negative feedback pathway. (**C**) For the simulation, three changes were made. One is the introduction of a false rotational cue (20 degrees/s clockwise in the yaw axis), simulating lesion-induced vestibular bias. This results in spontaneous nystagmus directed rightward. With normal integrator function, the gaze direction during the quick phase of nystagmus increases eye velocity, while gaze in the opposite direction decreases it. However, lesions at sites 1 and 2 alter the function of the neural integrator, making it unstable. These changes generate spontaneous nystagmus that does not comply with Alexander's law during lateral gaze movements.

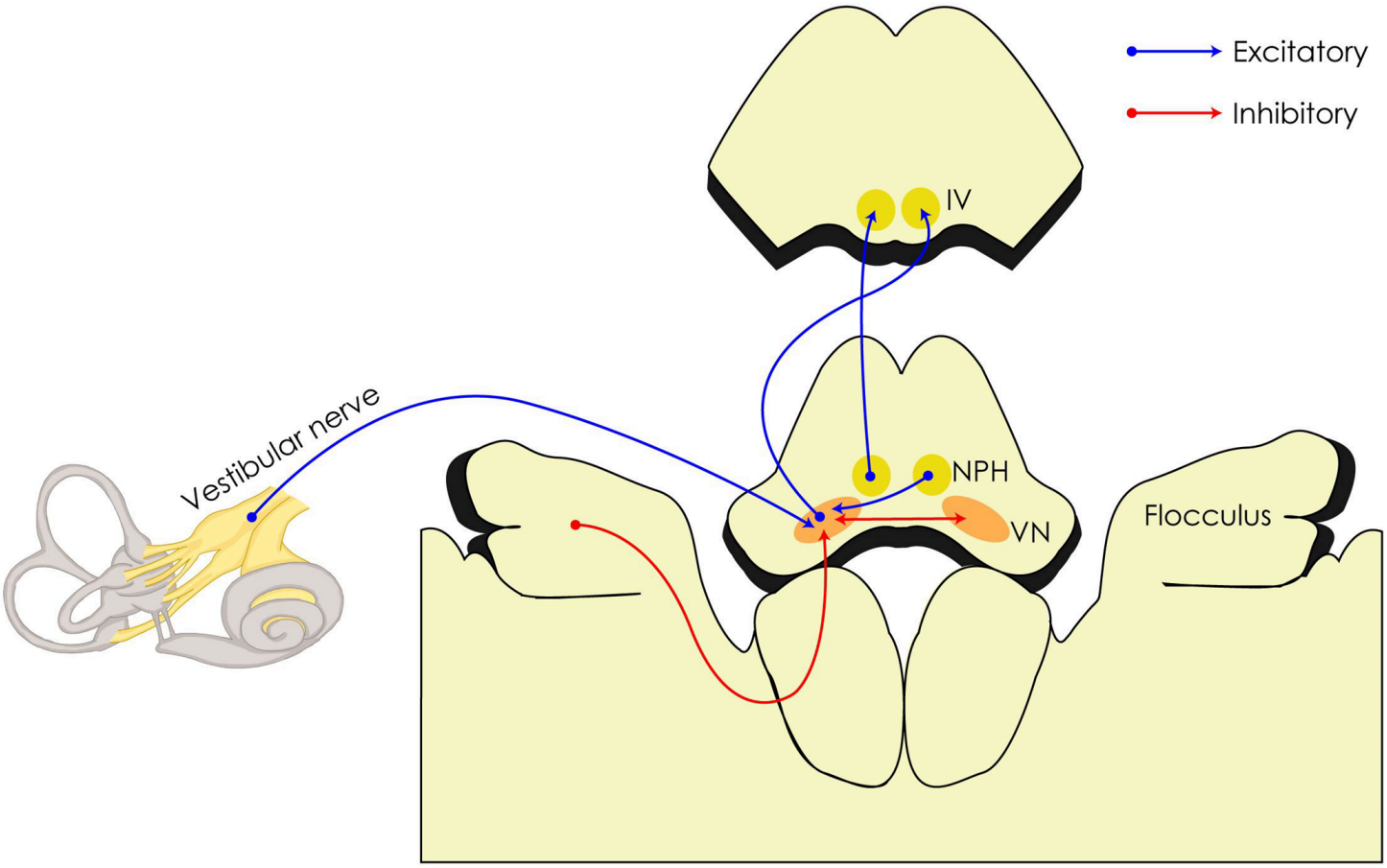


Figure 6

Schematic illustration of the anatomical connections among the VN, NPH, vestibular nerve, and cerebellum. The VN receives excitatory projections from the ipsilateral vestibular nerve and contralateral NPH while it receives inhibitory projections from the ipsilateral cerebellum and its contralateral partner via the commissural connections.

IV=abducens nucleus, NPH=nucleus prepositus hypoglossi, VN=vestibular nucleus

Supplementary Files

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- video.mp4