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Modeling the Interaction among Three Cerebellar Disorders of Eye Movements: Periodic Alternating, Gaze-evoked and Rebound Nystagmus

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Abstract

A woman, age 44, with a positive anti-YO paraneoplastic cerebellar syndrome and normal imaging developed an ocular motor disorder including periodic alternating nystagmus (PAN), gaze-evoked nystagmus (GEN) and rebound nystagmus (RN). During fixation there was typical PAN but changes in gaze position evoked complex, time-varying oscillations of GEN and RN. To unravel the pathophysiology of this unusual pattern of nystagmus, we developed a mathematical model of normal function of the circuits mediating the vestibular-ocular reflex and gaze-holding including their adaptive mechanisms. Simulations showed that all the findings of our patient could be explained by two, small, isolated changes in cerebellar circuits: reducing the time constant of the gaze-holding integrator, producing GEN and RN, and increasing the gain of the vestibular velocity-storage positive feedback loop, producing PAN. We conclude that the gaze- and time-varying pattern of nystagmus in our patient can be accounted for by superposition of one model that produces typical PAN and another model that produces typical GEN and RN, without requiring a new oscillator in the gaze-holding system or a more complex, nonlinear interaction between the two models. This analysis suggest a strategy for uncovering gaze-evoked and rebound nystagmus in the setting of a time-varying nystagmus such as PAN. Our results are also consistent with current ideas of compartmentalization of cerebellar functions for the control of the vestibular

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velocity-storage mechanism (nodulus and ventral uvula) and for holding horizontal gaze steady (the flocculus and tonsil).

Keywords

periodic alternating nystagmus; gaze-evoked nystagmus; rebound nystagmus; adaptation; superposition; cerebellum; paraneoplastic

2 Introduction

We report a patient with a paraneoplastic cerebellar syndrome who had a complex ocular motor disorder comprised of three types of nystagmus: periodic alternating nystagmus (PAN), gaze-evoked nystagmus (GEN) and rebound nystagmus (RN) (video shown in Online Resource 1). Each of these types of nystagmus is usually associated with dysfunction of the cerebellum (Shemesh and Zee 2019).

PAN is a spontaneous horizontal nystagmus that changes direction, usually approximately every 120 seconds (Fig. 1, first column). A disinhibited velocity-storage mechanism and a normal short-term adaptation mechanism are at the core of the current hypothesis to account for PAN (Leigh et al. 1981; Waespe et al. 1985; Furman et al. 1989, 1990). The velocity-storage mechanism is located within the vestibular nuclei and acts as an integrator that improves the ability of the vestibular system to respond to low-frequency (sustained) head motion by perseverating peripheral vestibular signals (Raphan et al. 1979). When the velocity storage circuit system is modeled as a positive feedback loop, the vestibular system can become unstable and produce an output that grows without bound if the gain of the loop is too high. When an unstable velocity storage system is combined with a normal central adaptive mechanism that tries to null any sustained nystagmus, the oscillating pattern of PAN develops (Leigh et al. 1981). Ablation of the nodulus and uvula in monkeys (Waespe et al. 1985) and isolated lesions of the cerebellar nodulus in humans (Oh et al. 2006; Jeong et al. 2007) can cause PAN. These studies suggest that a loss of (GABA-mediated) inhibition from the Purkinje cells of the nodulus/ventral uvula onto the vestibular nuclei results in a disinhibited and unstable velocity-storage mechanism that when coupled with normal adaptation can produce oscillatory behavior.

GEN is a nystagmus that occurs when the eyes cannot be held steady in eccentric positions in the orbit (Fig. 1, second column). The eyes drift centripetally towards the center and saccades take the eyes back to an eccentric position in the orbit. GEN is the signature deficit when the central neural gaze-holding network, commonly called the ocular motor integrator, becomes imperfect or “leaky”. In this case, the gaze-holding network cannot sustain a constant output (position signal) to counteract the orbital elastic forces that would make the eye drift back to the central position. A new input, such as a velocity command from the saccade system, is needed to take the eyes back toward the desired eccentric eye position. As the integrator is still “leaky” the new level of activity cannot be maintained and centripetal drift occurs again. This alternating pattern of centripetal drift and centrifugal saccades repeats itself leading to GEN. The time constant of the approximately exponential decay during the centripetal drift of the slow phase of GEN can be used to quantify the

fidelity of the ocular motor integrator. Lesions in the brainstem of monkeys suggest that an inherent, imperfect integrator for horizontal eye movements resides in the brainstem within the medial vestibular nucleus (MVN) and adjacent nucleus prepositus hypoglossi (NPH), with a time constant of decay of less than a few seconds (Cannon and Robinson 1987). Lesions in the cerebellum of monkeys suggest that the flocculus and paraflocculus (the tonsil in humans) function to improve the time constant of the brainstem neural integrator to normal values of 20 seconds or more (Zee et al. 1980, 1981).

RN is a nystagmus that occurs typically in patients with GEN after a sustained attempt to hold eccentric gaze (Fig. 1, third column). During eccentric gaze, the initial velocity of the centripetal drift of each slow phase gradually diminishes and when the eyes return to straight-ahead position, a rebound nystagmus (RN) occurs with slow phases directed towards the immediately preceding eccentric eye position (Hood et al. 1973; Hood 1981). The gradual decrease in the intensity of the GEN, and the gradual decrease in the intensity of the RB that follows on return to center gaze, reflect the action of a normal adaptation mechanism that counteracts any sustained drift away from a desired eye position in the orbit. This mechanism improves gaze stability and assures best visual acuity (Otero-Millan et al. 2019; Ritter et al. 2020). RN also occurs in monkeys that have GEN with floccular/paraflocular (tonsil) lesions (Zee et al. 1981), suggesting that the adaptation networks creating RN lie in other, unaffected areas in the cerebellum or in the brainstem.

We will first present the case history, the clinical observations of the ocular motor disorder, and the methods used to record eye movements. Then we will develop the mathematical model to test ideas about the mechanisms underlying this unusual pattern of eye movements. Finally we will discuss our analysis in the context of localization of abnormal eye movements in the cerebellum, and interpreting and recognizing complicated patterns of nystagmus at the bedside.

3 Case History and Methods

A woman, age 44, presented with nine months of increasing imbalance and one month of blurred vision. On examination she was unsteady and had slurred speech and incoordination of her limbs. Examination of eye movements showed PAN, GEN and RN. Changes in gaze position, however, evoked a complex, time-varying, oscillatory pattern of nystagmus (video shown in Online Resource 1). MRI of the brain was normal. Computed tomography of the chest and abdomen showed a mass in the right breast with enlarged axillary lymph nodes. Biopsy demonstrated invasive carcinoma. Serum levels of anti-YO antibodies were positive which are associated with Purkinje cell destruction mediated by cytotoxic T-cell against cdr2 antigen (cerebellar degeneration related protein 2). Positive anti-YO with underlying breast cancer established paraneoplastic cerebellar syndrome as the diagnosis. The patient was treated with Baclofen 20 mg daily for the nystagmus, which was begun after her first set of recordings (Experiment 1). As of December 2020, our patient is still alive but with prominent cerebellar disability. Chemotherapy and radiotherapy were the treatment of choice for stage 4 breast cancer which stabilized her condition. The disabling neurologic syndrome, however, did not respond to immunotherapy as expected from antibody targeting intracellular antigen.

Horizontal eye movements were recorded using a head-mounted video-oculography system (ICS Impulse, GN Otometrics, Taastrup, Denmark) with a sampling rate of 220 Hz. The Dokuz Eylül University Review Board approved the experimental protocol and written informed consent was obtained from the patient. All testing was in the light and in the sitting position one meter away from the central target on a wall with the head unrestrained. Rightward slow-phase velocities (from the patient's point of view) are positive and leftward negative.

Experiment 1 allowed us to demonstrate the oscillatory behavior of the vestibular system in isolation from the gaze-holding system. This data was obtained before treatment with baclofen. The patient was asked to fixate a central target for 5 min (Fig. 3). Experiments 2 and 3 were designed to elicit GEN and RN. This data was obtained after treatment with baclofen, 20 mg daily. For experiment 2 the patient was asked to alternate her gaze every 10 seconds for each pair of target stimuli (A) between center fixation and the left target, (B) between center and the right target (B) and (C) between the right and left target, for a total of three minutes (Fig. 4). Eccentric target positions were at right and left 30 degrees. For experiment 3, the patient fixated a central target for three minutes after sustained attempt to look eccentrically to right or left 40 degrees, one minute for each eccentric gaze position (Fig. 5). Experiments 2 and 3 were performed four and five months, respectively, after experiment 1.

3.1 Modeling

While we could attribute GEN and RN to malfunction in the cerebellar flocculus/parafloccullus, and PAN to malfunction in the cerebellar nodulus/ventral uvula, we asked if the time varying, oscillatory pattern of GEN/RN was due to a straight-forward superposition of PAN and GEN/RN, or to a more complex pathophysiology reflecting a nonlinear interaction between the mechanisms underlying PAN and GEN/RN, or to a separate oscillation in the gaze-holding system. This led us to develop a mathematical model (Fig. 2, Table 1) to explore potential interactions between an oscillating vestibular system (PAN) and a non-oscillatory gaze-holding system (GEN and RN). The model builds on current concepts of the normal function of the vestibulo-ocular reflex (VOR) and gaze-holding networks, and how abnormalities in these networks might lead to the pathological eye movements of our patient (Leigh et al. 1981; Otero-Millan et al. 2019). A key concept underlying the interaction between PAN, GEN, and RN relates to the dynamic properties of two adaptive networks; one that attempts to null unwanted spontaneous nystagmus in the vestibular system, and uses velocity signals, and one that attempts to stabilize gaze when the eye cannot be held steady in an eccentric position in the orbit, and uses position signals. Our main goal was to test if superposition of the two models (Fig. 2) could account for the main aspects of the complex pattern of nystagmus shown by our patient.

3.1.1 Modeling Periodic Alternating Nystagmus—

The model of the vestibular system was based on that used to simulate PAN in 1981 (Leigh et al. 1981). This model includes a positive feedback loop of integrated eye velocity signals (accomplished through a leaky integrator with time constant close to that of the cupula) for the velocity-storage circuit and negative feedback loop of eye velocity for the central adaptation circuit. Assuming

that the velocity storage time constant (τ_{VS}) is close to the cupula time constant (τ_C), the time constant of the VOR is governed by the velocity storage gain (K_{VS}) through the following relationship, $\tau_{VOR} = \frac{\tau_{VS}}{1 - K_{VS}}$. The velocity storage gain (K_{VS}) (assumed to be about 0.67 in normal individuals), is under the control of the cerebellar nodulus. A loss of GABA-mediated inhibition from the Purkinje cells of the nodulus onto the vestibular nuclei can be modeled as an increase in the feedback gain (K_{VS}). The adaptive circuit is presumed to be functioning normally. If τ_{VS} and τ_A are the time constants of the velocity storage and the adaptation circuits, respectively, when the value of K_{VS} equals $1 + \tau_{VS}/\tau_A$ oscillations develop with a cycle duration (T) of $2\pi\sqrt{\tau_{VS}\tau_A}$. For example, when τ_{VS} is 5 seconds and τ_A is 176 seconds, setting K_{VS} to a value of 1.029 drives the vestibular system into sustained oscillatory behavior with a cycle duration of 186 seconds.

For estimating the parameters of the vestibular system we first determined the the cycle duration and amplitude of PAN by fitting a sine curve to horizontal slow-phase velocity during sustained fixation of a straight-ahead target. Under this condition, the vestibular system responses could be isolated from the effects of eccentric gaze-holding system. We found that the cycle duration of PAN changed across recording sessions becoming shorter over time. The reason for this changes is unclear but we attribute them to the variable effects of baclofen (see discussion for more details). The cycle duration was 186, 183, and 160 seconds for experiments 1, 2, and 3, respectively). By rearranging terms in the cycle duration equation, the velocity storage time constant for a given period duration T is $\tau_{VS} = \frac{T^2}{4\pi^2\tau_A}$. One can see that if the value of the adaptation time constant is unchanged, the velocity-storage time constant is directly proportional to the square of the cycle duration, $\tau_{VS} \propto T^2$. This formulation allowed us to implement the simulations of experiments 2 and 3 without any change in the adaptation circuit. By using a lower value of the velocity storage time constant we accounted for the shortening in the duration of the PAN cycle (Table 1). From the point of view of pathophysiology, this seems plausible since one can conceive of the manipulations of all the parameters for simulations occurring in the one structure most important for controlling the performance of the velocity-storage circuit, the cerebellar nodulus. If we had used the same period of oscillation in all experiments the fits would not be consistent with the data, reducing the goodness of fit measured as R-squared from 0.9 to 0.2.

Note that for our patient we tuned the model to produce a peak slow-velocity of PAN to 12 deg/sec in the simulation of experiment 1 (before baclofen). In this model, the amplitude of the PAN oscillation depends on the amplitude of a constant bias that we introduced to the velocity storage circuit, following a similar strategy as Leigh and colleagues in their original PAN model (Leigh et al. 1981). The simulations of experiment 2 and 3 were implemented with a lower value of peak velocity (6 deg/sec). The differences in the time constant of the velocity storage and the amplitude of peak velocity of PAN were possibly due to baclofen or related to the underlying disease process (Halmagyi et al. 1980; Cohen et al. 1987).

3.1.2 Modeling Gaze-Evoked and Rebound Nystagmus—The brainstem neural integrator functions as a low pass filter (leaky integrator) with a time constant of 1.5 seconds or less (Robinson 1974; Cannon and Robinson 1987). The cerebellum improves the performance of the ocular motor integrator, increasing its time constant to 20 seconds or more, perhaps using positive feedback of eye position (Zee et al. 1980, 1981). Another adaptive network, also using positive feedback of eye position, improves the stability of gaze by offsetting the slow-phase velocity of GEN during attempted sustained eccentric gaze (Otero-Millan et al. 2019; Bögli et al. 2020). The positive feedback shifts the null eye position towards the sustained eccentric eye position. On return of gaze to center there is an after effect: a slowly decaying rebound nystagmus in which the eyes drift towards the shifted null position.

In our model, the neural integrator consists of a low-pass filter with the time constant reduced to about 1.7–2.5 seconds to make it “leaky”, and an adaptation positive feedback loop that creates a position bias. Note that the time constant for right gaze (τ_{RNI}) is less than left gaze (τ_{LNI}) to make gaze-holding more impaired for right than left eccentric eye positions. The positive feedback for adaptation includes a low-pass filter with a time constant of 5 seconds (τ_{PB}). This adaptation circuit integrates an efference copy of eye position and shifts the null eye position of the leaky integrator towards the previously held eccentric eye position. The adaptation network is presumed to be functioning normally. These parameters and time constants of the gaze-holding network were kept constant for all simulations.

3.1.3 Modeling the ocular plant and saccadic pulse generator—To generate eye *position* commands the model included an ocular plant, based on the mechanical properties of the extraocular muscles and other orbital tissues and a saccadic pulse generator. We used a two-pole overdamped ocular plant and a simplified saccadic system as described elsewhere (Zee et al. 1976; Optican and Zee 1984). An eye velocity signal arising from the saccadic system (“pulse”) projects directly to the ocular motoneurons to overcome orbital viscosity. The pulse also projects to the ocular motor integrator which in turn generates a position command (“step”) that also projects to the ocular motoneurons to counteract elastic restoring forces.

4 Results

In experiment 1 (Fig. 3) the recording during central fixation shows a spontaneous horizontal nystagmus with peak velocity of 12 deg/sec that reverses direction at 90 seconds intervals. This pattern is typical for PAN. With an unstable velocity storage our model based on Leigh et al. (Leigh et al. 1981) simulates the data of the patient closely.

In experiment 2 horizontal slow-phase velocity was recorded while alternating gaze positions between left and center (Fig. 4A), right and center (Fig. 4B), or left and right (Fig. 4C) for about 10 seconds each. Each time the eye moves to an eccentric position there is a nystagmus with slow drift of the eyes towards the center, GEN, i.e., a negative slow-phase velocity when looking to right and positive slow-phase velocity when looking to the left. If we also consider the adaptive mechanism that causes RN we expect slow-phase

velocity to decay between gaze shifts (Fig. 1, compare center and right columns). In Fig. 4, every gaze shift induced a different intensity of GEN and RN with a time-varying periodic pattern. A potential “bedside” interpretation of the pattern of nystagmus would suggest the gaze-holding system dynamics is also oscillatory.

Fig. 4 shows the comparison of the patient data with the simulations of our model for each type of nystagmus in isolation (PAN or GEN with or without RN) and for the model with superimposed PAN, GEN and RN working in concert. Simulations are organized from top to bottom in separate plots next to the gray profile of the slow-phase velocity of the patient. The close fit of the simulation of the complete model to the slow-phase velocity of the patient, supports our underlying assumption that there is neither a separate oscillator in the gaze-holding system nor a complicated nonlinear interaction between the vestibular and the gaze-holding networks (Fig. 4, red solid line). Note that the amplitude and period of PAN are smaller than initially shown in Fig. 3. Whether these changes were due to baclofen, inherent variability, habituation, or just the natural course of the illness is not known, but they do not interfere with the general conceptual interpretation. The model parameters were modified accordingly (Table 1).

When the eyes return to the straight-ahead position (columns A and B), a RN occasionally occurs with slow phase directed towards the previously held eccentric eye position (arrow heads). Comparing the different model simulations reveals that the relative contribution of RN (dashed line (purple) when eyes are back to center, however, is much smaller than PAN (dashdot line (green)) in these experiments. Therefore, when the eyes return to the straight ahead position (columns A and B) at the same time PAN slow-phases are directed towards the previously held eye position, the result resembles clinically observed “rebound nystagmus” – especially when gaze is held eccentrically for a short interval and the adaptation feedback loop responsible for RN is not fully charged. Note the target (eye) positions were offset for the purposes of the simulations in the first and second columns to account for a presumed small change in the patient’s position of the eye in the orbit. We attributed this offset to a small drift in the position of the head. In column C we show the effects of looking back and forth between two eccentric positions. The amplitude of the nystagmus at the onset is larger because the position bias is already charged from the prior eccentric position and its output generates centripetal drift which augments GEN at the new eccentric position. Subsequently, the adaptive circuit slowly shifts the null eye position from a position far from true “center” toward the new eccentric eye position in two phases. First, a decaying discharge of the position bias till the null reaches the “true” center (RN centripetal slow-phase drift decays to zero). Second, past the “true” center, the position bias is recharged towards the new eccentric eye position, this time offsetting the GEN. The decrement of GEN in two phases can explain why GEN slow-phase velocity decays faster (Compare dashed lines (purple) in Fig 4A, 4B with that of 4C).

In experiment 3 we focused on RN by recording slow-phase velocity during and after sustained (1 min) attempts to look eccentrically at 30 degree targets (Fig. 5). In this experiment we explored longer-term interactions between the unstable vestibular system, with its relatively long-acting, adaptive response (τ_A, several minutes) and the impaired gaze-holding system and its RN mechanism, with its relatively short-acting, adaptive

response (τ_{PB}, 5 seconds). The patient looked eccentrically to the left for 1 minute, at the center for 3 minutes, eccentrically to the right for 1 minute, at the center for 3 minutes, eccentrically to the left for 1 minute and finally looking at the center for 4 minutes. The response was a complex, time-varying pattern of horizontal slow-phase velocity suggesting a nonlinear interaction between an oscillatory gaze-holding system (GEN and RN) and an oscillatory vestibular system (PAN).

The response of the complete model during central fixation after sustained eccentric fixation is largely governed by the dynamic properties – amplitude and period – of the oscillations from the unstable vestibular system that produced PAN. In contrast, the contribution of GEN and RN is only transient because of the much faster dynamic properties of the GEN and RN adaptive mechanism. For example, RN takes the form of a brief peak in the slow-phase velocity immediately on returning to straight-ahead gaze following sustained eccentric gaze (Fig. 5, thin arrow heads). Likewise, applying a perturbation like GEN or RN to the PAN can transiently increase or decrease the PAN amplitude, depending on the direction of the GEN or RN relative to PAN (GEN transiently reverses the direction of PAN, Fig. 5, thick arrow heads). But this will not change the dynamic behavior of PAN as seen about a minute following the perturbation in the complete model response. Therefore, the overall, complex, time-varying pattern of nystagmus in this paradigm does not reflect non-linear behavior of the PAN in the presence of GEN/RN or the result of an interaction of two separate oscillators, but is consistent with simple superposition.

5 Discussion

Our patient showed a complex, time varying, oscillatory disorder of eye movements, composed of three different types of nystagmus, PAN, GEN and RN. Each of these abnormalities are commonly associated with cerebellar disease. In order to understand the pathophysiology of this complex disorder we developed a mathematical model combining the mechanisms controlling the vestibulo-ocular reflex and steady gaze-holding. Key aspects of each of these mechanisms are controlled by the cerebellum and also involve adaptive circuits that help to stabilize gaze in the face of unwanted drift of the eyes. Our simulations showed that the oscillatory pattern of the nystagmus of our patient can be due to the superposition of PAN and GEN/RN rather than to a complicated, nonlinear interaction between the vestibular and gaze-holding networks or to an additional oscillator in the gaze-holding system. Our analysis emphasizes that complex interactions between different circuits controlling movements are often better understood by using control theory to test hypotheses with explicit mathematical models. As Dr. David Robinson said:

> “As the study of eye movement control matures into an exact science, we can look forward to an increased use of the language of control theory in comprehending and describing it. Nor will these concepts remain in the laboratory, for the proper language to describe oculomotor disorders is also the language of control theory” (Robinson 1973).

5.1 Strategies for uncovering superimposed PAN, GEN and RN

While the pattern of ocular motor disorder shown by our patient was unusual, it is not the first time that patients with PAN were noted to have GEN and RB. Baloh et al reported two such patients with acquired PAN and noted that “changes in direction of gaze had a significant effect on the PAN”, and depending on when in the cycle gaze was changed, could cause the PAN to speed up, slow down or even change direction (Baloh et al. 1976). Our model explicitly addresses these possibilities and further explains how this information might be used clinically in the evaluation of patients with combinations of PAN, GEN and RN.

As we have shown, superposition of PAN, GEN, and RN can affect the “bedside” interpretation of the pattern of nystagmus. Depending on the timing of gaze shifts and the relative strength of each of these components, some may be hidden or misinterpreted. For example, an impaired integrator is expected to result in centripetal eye drift during eccentric gaze (GEN), that is, with quick-phases right beating with right gaze and left beating with left gaze. In the presence of PAN, however, with the same integrator deficit, it is possible to observe centrifugal eye drift, that is, left beating with right gaze, and right beating with left gaze. In another example, gaze shifts inducing GEN and RN could change a left beating nystagmus to right beating (or right to left) that would mask the change in direction of nystagmus due to PAN. Fig. 6 uses simulations to show how different amplitudes of PAN and different deficits of the neural integrator can interact in the “bedside” interpretation of the pattern of nystagmus and what can be a successful strategy to probe them independently.

5.1.1 Finding a small amplitude PAN in the presence of a large GEN—Fig. 6A shows a simulation of the model when the peak velocity of PAN is relatively low (6 deg/sec) and the velocity of GEN is relatively high (severely impaired oculomotor integrator, τ_{NI} 2.5 sec). In the simulation, when PAN is about to reach the null, gaze moves to an eccentric position (right 40 deg or left 40 deg) for 10 seconds (boxes 1 and 2). On returning to straight-ahead gaze, the PAN is not easily distinguishable from the RN, as both are in the same direction. This can occur at the bedside when the clinician is not aware of PAN and eccentric gaze has been directed in the same direction as the quick phases of the PAN just before the PAN reaches its null position. To avoid this misinterpretation one should always check for a reversal of a spontaneous nystagmus (boxes 3 and 4) by observing the eyes kept in the straight-ahead position for several minutes with no more than an occasional brief glance away from straight ahead gaze.

5.1.2 Finding a small GEN in the presence of a large amplitude PAN—Fig. 6B shows a simulation of the model when the peak velocity of PAN is relatively high (12 deg/sec) and the velocity of the GEN is relatively low (mildly impaired oculomotor integrator, τ_{NI} 5 sec). The simulations compare changes in gaze to an eccentric position (right 40 deg or left 40 deg) for 10 seconds when PAN is about to reach a peak (boxes 5 and 6) or a null (boxes 7 and 8). The sections highlighted in box 1 and 2 show the effect of eccentric gaze in the opposite direction to the quick phase of the PAN when PAN is at its peak. The simulations show left-beating nystagmus with right eccentric gaze (box 5) and right-beating nystagmus with left eccentric gaze (box 6). With centripetal drift being the

defining clinical characteristic of GEN, under these circumstances the absence of centripetal drift cannot be used to exclude impaired gaze-holding because of the superimposed PAN that beats in the opposite direction. Thus, with PAN it may be difficult to appreciate the component of nystagmus due to integrator failure unless one looks at or near the null period. After reaching a null, the quick phase direction of PAN has reached its point of no return – turning back to its previous direction is impossible for approximately 120 sec. This makes the null a window of opportunity for checking the gaze-holding system as any nystagmus beating in the same direction of the PAN just before its null, cannot be PAN. For instance, the patient can look eccentrically, during the null period, in the *same* direction as the quick phase of the prior PAN cycle. The reemergence of nystagmus in the same direction as the previous PAN unequivocally indicates the presence of GEN (boxes 7 and 8). This technique also identifies GN in experiment 3, see GN (thick arrow heads) in figure 5.

5.1.3 Finding a small RN in the presence of a large amplitude PAN—

Fig. 6C shows a simulation with the same parameters as Fig. 6B but with gaze shifts in the *same* direction to the quick phase of the PAN when PAN is at its peak (boxes 9 and 10). The simulations show right-beating nystagmus with right eccentric gaze and left-beating nystagmus with left eccentric gaze. The centripetal drift is the result of GEN superimposed on PAN that beats in the same direction. When the gaze is shifted to the straight-ahead position, the simulations show right-beating nystagmus following right eccentric gaze and left-beating following left eccentric gaze. Considering drift towards the previously held eye position as the defining clinical characteristic of RN, under these circumstances, the absence of drift towards previously held eye position does not exclude RN because of the superimposed PAN that beats in the opposite direction. Thus, one needs to take advantage of the null as a point of no return for the direction of the quick phases of PAN for several minutes. To detect RN it would be best to have the patient hold eccentric gaze for 10 seconds, in the direction *opposite* to the quick phase of PAN just as the PAN had entered a null. On returning to straight-ahead gaze, reemergence of nystagmus in the *same* direction of the PAN before the null indicates the presence of RN (boxes 11 and 12). This technique also identifies RN in experiment 3, see RN at ~9 sec (thin arrow head) in figure 5.

5.1.4 Changes in intensity vs. changes in direction (Alexander's law)—

One might ask how the changes in a spontaneous vestibular nystagmus associated with Alexander's law – the intensity of a jerk nystagmus increases when the eyes are moved in the orbit to a position in the direction of the quick phase – are applicable to the combination of PAN, GEN and RN. Alexander's law is commonly interpreted as arising from the superposition of a spontaneous unidirectional nystagmus with an impaired neural gaze holding network, i.e., a "leaky" neural integrator, which imposes the change in nystagmus with orbital position (Hess 1982; Robinson et al. 1984). Of course, if a gaze-evoked component (GEN) has already been identified then the spontaneous nystagmus of PAN must necessarily show the effect of Alexander's Law on its slow-phase velocity. On the other hand a mild GEN in the presence of a strong PAN might be difficult to appreciate around a brief null period. In this case Alexander's law (and a mildly impaired neural integrator) might be better appreciated by looking for a change in the intensity of nystagmus with relatively quick changes of gaze to far right and to far left, during the PAN cycle.

Note that in our simulations Alexander's law can be appreciated by looking for a change in the intensity of nystagmus with changing gaze eccentricity (Fig. 6 boxes 5, 6, 9 and 10). Changes in the intensity of nystagmus, however, are always more difficult to appreciate than changes in the direction of nystagmus.

5.2 Neurological localization

Our analysis also complemented a traditional strategy used by neurologists to arrive at a clinical and anatomical diagnosis – the law of parsimony or Occam's razor. The object is to find a common anatomical location for multiple neurological signs. By concluding that the complicated pattern of the nystagmus shown by our patient could be attributed to superposition of three well known types of nystagmus, PAN, GEN and RN that are associated with dysfunction of the cerebellum, we could further localize the lesions to two different parts of the vestibulocerebellum, the flocculus/parafloccculus (tonsil) (GEN/RN) and the nodulus/ventral uvula (PAN)(Leigh and Zee 2015; Shemesh and Zee 2019). Even in the face of a negative MRI scan, one can be confident that these areas of the brain are malfunctioning in our patient.

5.3 Adaptive mechanisms localization

Another feature of our simulation is that it required two different adaptive mechanisms both of which had to be intact. First, a short-term vestibular mechanism, with a time constant of 2–3 minutes, that develops a velocity bias to null an unwanted spontaneous nystagmus. Second, a short-term gaze-holding mechanism, with a time constant of 5 seconds, that develops a position bias to null unwanted drift of the eyes in eccentric positions of gaze. These mechanisms are examples of "set-point" adaptation, a ubiquitous strategy used by the brain to maintain a stable platform for the retina and fovea, to optimize visual acuity (Zee D. S. et al. 2017). Any instability of the eye can lead to unwanted movement of the visual world across the fovea, producing illusory movement of the environment (oscillopsia) and blurred impaired vision. Since these two adaptive mechanisms were presumed to be functioning normally, it is likely that their circuits are localized in areas apart from the vestibulocerebellum, either in other parts of the cerebellum or more likely in the brainstem.

5.4 Caveats and limitations

Our study has limitations. First, we are modeling data from a single patient and our data may not generalize to other cases. Second, the early recording was obtained before the patient took baclofen, the later recordings while on baclofen. This may have caused the decrease in the peak velocity of the slow-phases of PAN, though we cannot exclude a change in the extent or degree of malfunction of the lesion as the recordings were spaced over some months. Moreover, the period of the PAN oscillations further decreased between later recordings while on baclofen. Whether this was related to changes in plasma levels of baclofen (baclofen has maximal effect between 1 and 4 hours) or habituation is unknown (Cohen et al. 1987). Even so, we could simulate this behavior by assuming they were a result of changes in the time constant of the velocity storage circuit, and could also be attributed to malfunction in the cerebellar nodulus which controls the behavior of the velocity storage circuit. Third, there was likely some drift of the head (and consequently the eye in the orbit) during the experiments because the head was not rigidly immobilized with a bite

bar or a tight head rest. Because of this presumed drift we introduced offsets in some of simulations to match the patient's data as it was not unreasonable to assume that the eye position in the orbit could change by a small amount over the long recording periods. While our linear model of PAN well accounted for the nystagmus of our patient, simulations of patients with stronger PAN have required nonlinearities to prevent the slow-phase velocity from increasing so rapidly and to such high levels that the adaptive mechanism could not overcome it and turn it around (Leigh et al. 1981; Furman et al. 1990). But even if there were nonlinearities in the PAN system, they would not have affected the superposition of the GEN and RN on the PAN in our patient. We also did not exhaustively check many different eccentric eye positions, different durations of maintaining eccentric gaze, and different degrees of GEN or RN, to see if our simple linear model could simulate these too. This will require testing with more data from future patients with this combination of nystagmus. But even with these caveats, we suggest the main points of our analysis remain compelling. We did not require any complicated interaction or nonlinear processing to simulate the basic features of the ocular motor disorder of our patient.

5.5 Conclusions

Our results and model simulations are consistent with the idea of the compartmentalization of cerebellar functions for the control of the vestibular velocity-storage mechanism (nodulus and ventral uvula) and for holding horizontal gaze steady (the flocculus and tonsil). The effects of lesions to each of those mechanisms produce complex eye movement patterns that can be explained by the superposition of the effects of each individual lesion.

We have also designed a strategy to interrogate both systems independently at the bedside. First, to identify PAN check for a reversal of a spontaneous nystagmus by observing the eyes kept in the straight-ahead position for several minutes without an intervening sustained eccentric gaze. Second, look for GEN/RN when the quick phase direction of PAN enters its point of no return, the null. To identify GEN, have the patient directing gaze eccentrically in the same direction as the previously beating PAN and look for reemergence of nystagmus in the same direction as the previous PAN. Third, look for RN after *holding* eccentric gaze for about ten seconds during the null, in the direction opposite to the previously beating PAN. On return to the straight-ahead position, if RN is present the eyes will beat in the same direction as the previous PAN before the null.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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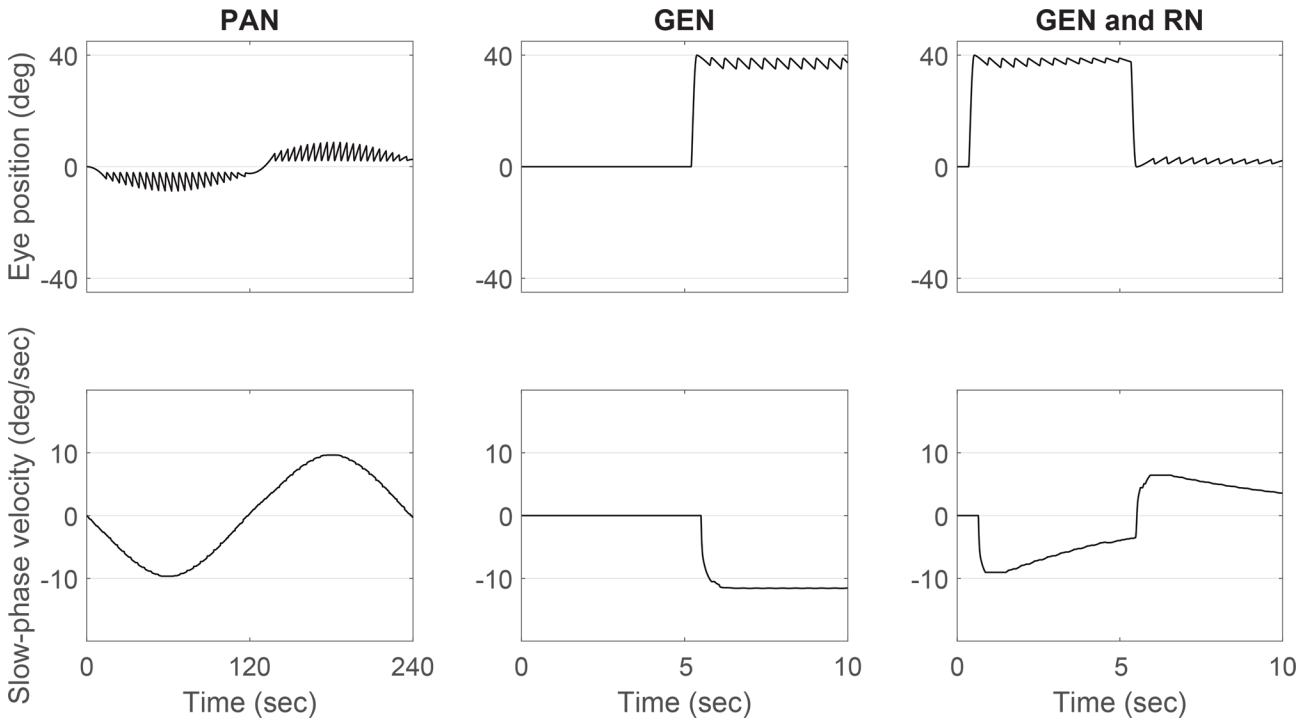

Fig. 1.

A conceptual scheme of the patterns of abnormal nystagmus that arise from isolated abnormalities in the vestibular or gaze-holding systems

Each column shows simulated eye position (top) and slow-phase velocity (bottom) plotted against time for each pattern of nystagmus. Left column: Periodic alternating nystagmus (PAN), generated by an oscillatory vestibular system. Middle column: Gaze-evoked nystagmus (GEN) generated by an impaired “leaky” gaze-holding integrator. Right column: Rebound nystagmus (RN), which decays over time after return to straight ahead following GEN. An adaptive mechanism tends to cancel the GEN over time. Note the much longer time scale for PAN.

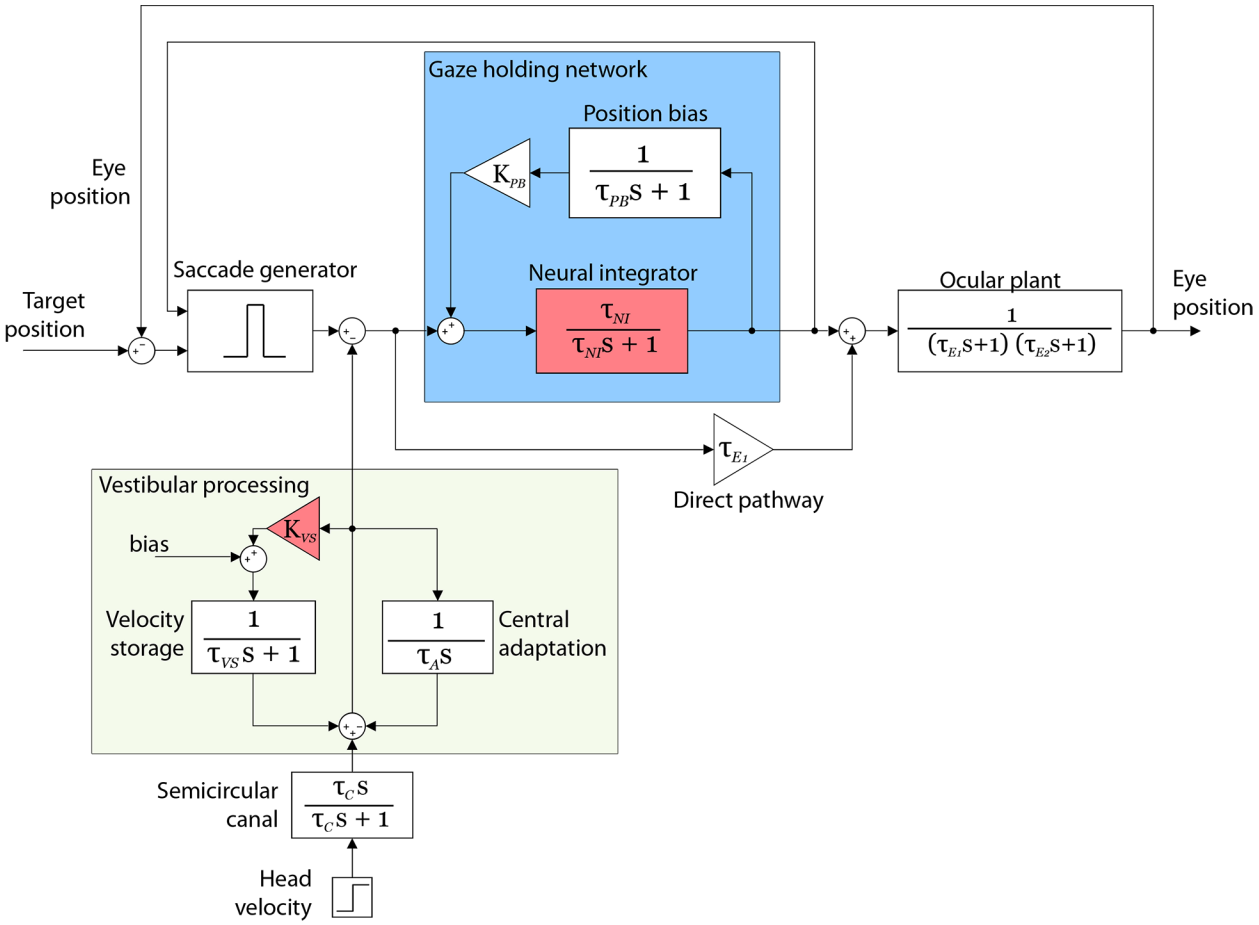

Fig. 2.

A schematic block diagram of the model. The two elements highlighted in red correspond with the two locations of the hypothetical lesions.

Block transfer functions are characterized using the Laplace transform with s, the Laplace variable. The shaded (green) segment at the bottom represents the model of the vestibulo-ocular reflex (VOR) that incorporates a positive feedback loop for velocity-storage (low-pass filter with time constant close to that of the cupula, τ_{VS}) and negative feedback loop for central adaptation (perfect integrator with time constant τ_A). The overall time constant of the VOR is governed by the feedback loop gain (K_{VS}) which under certain circumstances can drive the vestibular system into oscillatory behavior (PAN). The vestibular system responds to inputs arising from the semicircular canals, modeled as a high-pass filter with time constant τ_C. The shaded (blue) segment at the top represents the model of the gaze-holding system consisting of a low-pass filter with time constant τ_{NI} (neural integrator) with a positive feedback loop (position bias) used for adaptation and produces RN. The positive feedback includes a low-pass filter with a time constant of τ_{PB} that integrates an efference copy of eye position and shifts the null eye position slowly towards the previously held eccentric eye position. In the upper left, the saccades generator is triggered by the error signal derived by subtracting eye position from target position. An eye velocity signal arising from the saccade generator (“pulse“) projects via the direct pathway to the ocular motor neurons and ocular plant to overcome orbital viscosity (its gain equals the dominant

time constant of the plant, τ_{EI}). The pulse also projects to the ocular motor integrator which in turn generates a position command ("step") that also projects to the ocular motor neurons and ocular plant to counteract elastic restoring forces. The parameters values used in the model are listed in Table 1.

Fig. 3.

PAN during fixation of a straight-ahead target

Horizontal slow-phase velocity plotted against time. Patient data is represented by the envelope of the gray shaded area and the model simulation by dashdot line (green). Target position, which is straight ahead, is on the bottom trace. Parameter values used in the simulation are listed in Table 1. The R-squared value was 0.98.

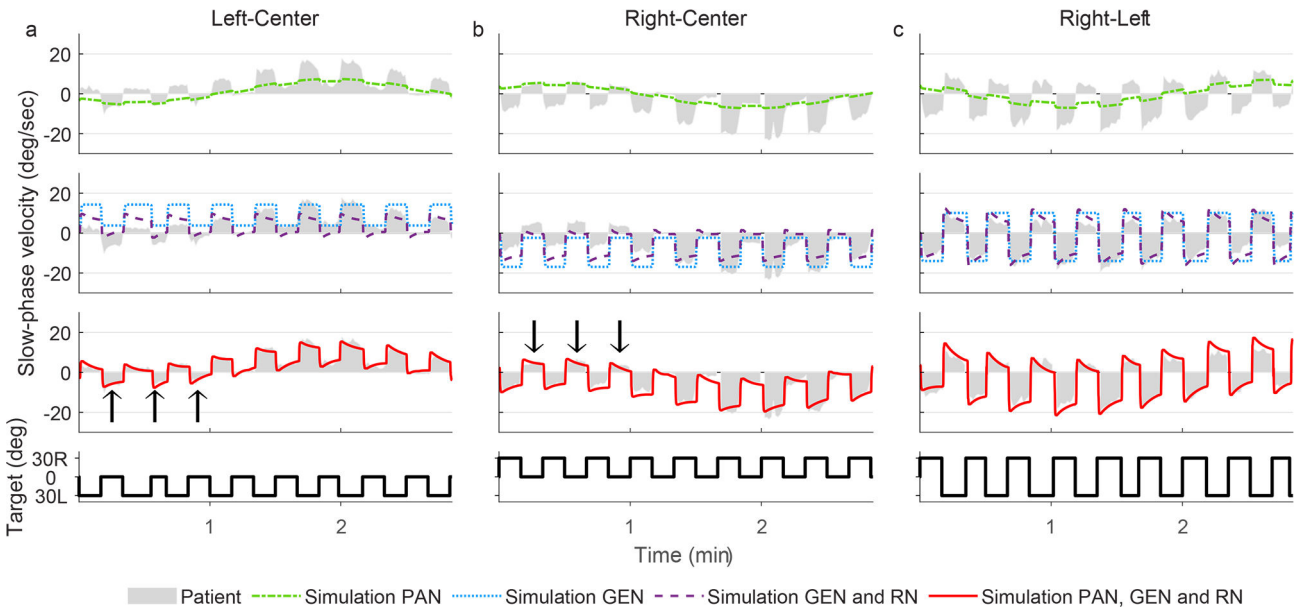

Fig. 4.

Effect of changing gaze on the pattern of nystagmus.

Slow-phase velocity is on the Y-axis, and time on the X-axis. Target position is on the bottom trace. The patient changes gaze approximately every 10 sec. Column A. Patient looks between 30 deg to the left and straight ahead. Column B. Patient looks between 30 deg to the right and straight ahead. Column C. Patient looks between 30 deg to the left and 30 deg to the right. Slow-phase velocity of the patient is represented by the envelope of the gray shaded areas. Top row. Dashdot line (green) is a simulation using changes in the vestibular velocity-storage mechanism alone to produce PAN. Second row. Dotted line (blue) is a simulation of GEN and dashed line (purple) is a simulation of GEN and RN together. Third row. The solid line (red) is a simulation of the full model to produce PAN, GEN and RN. Arrow heads show where the effect of RN can be appreciated. Parameters for simulations are shown in Table 1. By presenting the vestibular and gaze-holding components of the model in separate plots before combining them in the complete model, one can interpret how slow-phase velocity changes with time due to superposition of the three types of nystagmus. Note that some deviations between simulations and data may be due to deviations on eye position during the recordings. While we simulated perfect gaze holding the subject would sometimes change gaze or blink during the recording. The R-squared value for column A, B and C was 0.92, 0.91 and 0.91, respectively.

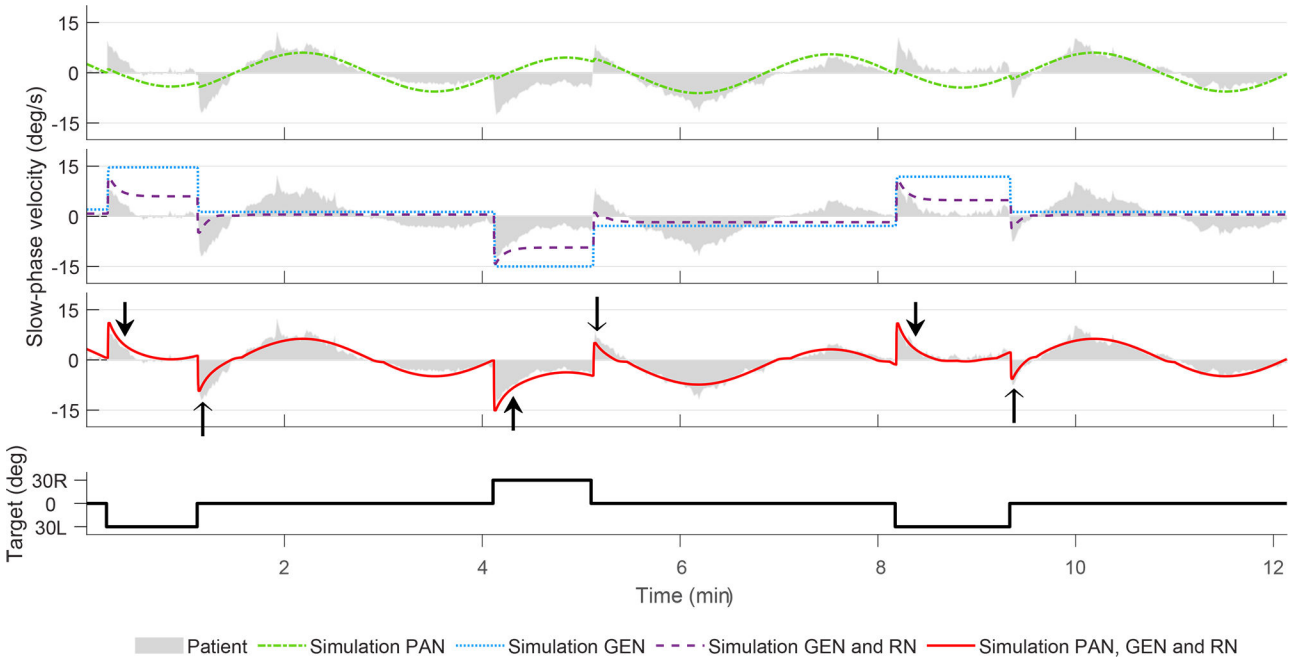

Fig. 5.

Effect of sustained eccentric fixation

Slow-phase velocity is on the Y-axis, and time on the X-axis. Target position is on the bottom trace. Periods of eccentric fixation at 30 degrees right or left are approximately one minute. Slow-phase velocity of the patient is shown by the envelope of the gray shaded areas. Dashdot line (green) is a simulation using changes in the vestibular velocity-storage mechanism alone to produce PAN. Dotted line (blue) is a simulation of GEN and dashed line (purple) is a simulation of GEN and RN together. The solid line (red) is a simulation of the full model to produce PAN, GEN and RN. Thin arrow heads indicate RN and thick arrow heads indicate GEN. Parameters for the simulations are shown in Table 1. The R-squared value was 0.89 compared with 0.24 for figure 3 PAN set of parameters.

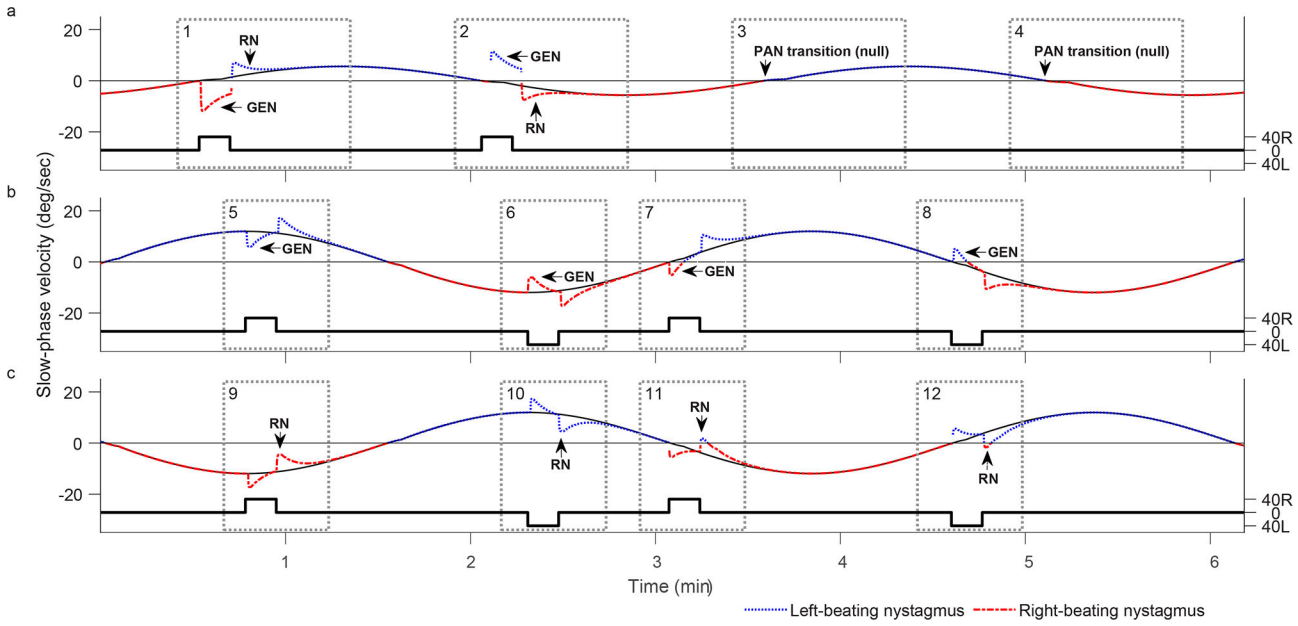

Fig. 6.

Superposition effects on different PAN amplitudes and different oculomotor integrator time constants

Slow-phase velocity is on the left Y-axis, target position is on the right Y-axis, and time on the X-axis. Slow-phase velocity is depicted as a blue dotted line for left-beating nystagmus (corresponding to rightward slow-phase velocity) and a red dashdot line for right-beating nystagmus (corresponding to leftward slow-phase velocity). Black line corresponds with the slow-phase velocity caused by PAN if gaze did not shift. Panel A shows model simulation of PAN with a small peak velocity (A_{PAN} was tuned to 6 deg/sec) and a severely impaired oculomotor integrator (τ_{NI} was set to 2.5 sec). Boxes 1 and 2 highlight the effect of gaze shifts around the time of the PAN transition or change in direction (null). Boxes 3 and 4 show the PAN transition without the interference of the gaze shifts. Panel B shows a model simulation of large peak velocity PAN (A_{PAN} was tuned to 12 deg/sec) and mildly impaired oculomotor integrator (τ_{NI} was set to 5 sec). Boxes 5 and 6 highlight how PAN at its peak can mask GEN, since it is right beating nystagmus during right gaze and left beating during left gaze. Boxes 7 and 8 show how GEN is revealed unambiguously around the time of the PAN null, with right beating nystagmus during right gaze and left beating during left gaze. Panel C shows another simulation with the same parameters of panel B but with different timing of the target jumps relative to the PAN cycle. Boxes 9 and 10 highlight how PAN at its peak can mask RN, with right-beating nystagmus after right gaze and left-beating after left gaze. Boxes 11 and 12 show how RN is revealed unambiguously around the time of the PAN null, with left-beating nystagmus after right gaze and right-beating after left gaze.

Table 1

Parameter Values Employed in the Model.

Parameter	value	description
τ_C	5 sec	Cupula time constant
τ_{VS}	3.7–5 sec	Velocity storage time constant
τ_{E1}	0.2 sec	Dominant plant time constant
τ_{E2}	0.01 sec	Small plant time constant
τ_{NI}	25 sec	Normal neural integrator time constant
τ_{RNI}	1.7 sec	Right-sided leaky neural integrator time constant
τ_{LNI}	2.5 sec	Left-sided leaky neural integrator time constant
τ_{PB}	5 sec	Position bias time constant
K_{PB}	0.25	Position bias gain
A_{PAN}	6–12 deg/sec	PAN peak amplitude
τ_A	176 sec	Central adaptation time constant
τ_{VS}	0.67 or 1 + τ_C/τ_A	Velocity storage positive feedback loop gain

The PAN peak amplitude A_{PAN} was set to 12 deg/sec for the simulation shown in Fig. 3 and 6 deg/s in all other simulations. The velocity storage time constant τ_{VS} was set to 5, 4.8, and 3.7 sec for the simulations in Fig. 3, Fig. 4, and Fig. 5, respectively. K_{VS} = 0.67 represents the value for a normal velocity-storage mechanism that does not result in PAN. When the value of K_{VS} is set to 1 + τ_C/τ_A the velocity-storage mechanism becomes unstable and results in PAN.