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ALEXANDER'S LAW: A MODEL AND RESULTING STUDY

M. J. DOSLAK, PhD
LINCOLN, NEBRASKA

L. F. DELL'OSSO, PhD
CLEVELAND, OHIO

R. B. DAROFF, MD
CLEVELAND, OHIO

Recently we developed an analog model to simulate Alexander's law in nystagmus secondary to dysfunction of a semicircular canal. Alexander's law is based on the observation that the amplitude of the nystagmus grows with increasing gaze in the direction of the fast phase and diminishes with gaze in the opposite direction. To investigate the assumptions made in the model, we conducted quantitative experimental studies on the effect of gaze on caloric-induced nystagmus in human subjects. A weak stimulus (water at 26.5°C and 240 ml/min) was administered for several minutes which caused the development of jerk nystagmus. Both the average slow phase velocity and frequency reached a steady state at about three minutes after the start of irrigation and remained stable until the flow of water was stopped. To investigate the effect of gaze, each subject was asked to hold gaze at various positions from center, to the right, to the left, and to repeat the cycle. Results indicated that the slow phase velocity of the nystagmus was greatest in the direction of the fast phase and decreased approximately linearly with gaze in the other direction in accordance with Alexander's law. Frequency was not a function of gaze. We speculate as to the biological advantages of the brainstem neural circuitry responsible for Alexander's law.

B - Central bias, EOM - Extraocular muscles, FϕS - Fast phase stimulator, G - Summed gaze and tone signals, G_r, G_l - Right gaze, left gaze, LC - Left canal, LLR - Left lateral rectus, LVN - Left vestibular nuclei, NI - Neural integraters, Θ_D - Desired angle gaze, Θ_E - Eye (gaze) angle, OMN - Ocular motor nuclei, PG - Pulse generator, RC - Right canal, RMR - Right medial rectus, RPG - Right pulse generator, RVN - Right vestibular nuclei, SSC - Semicircular canals, SϕM - Slow phase modulator, SV - Slow phase velocity, T - Central tone signals, TD - Total duration of the nystagmus beat.

INTRODUCTION

In 1912 Alexander[1] made the observation that the intensity of nystagmus grows as gaze is increased in the direction of the fast phase and diminishes with gaze in the opposite direction (Fig. 1); it later became known as Alexander's law. He categorized nystagmus into three degrees: First — present only during gaze in the direction of the fast phase; second — present during gaze straight ahead but increased in the direction of the fast phase; third — present in all fields of gaze but greatest in the direction of the fast phase.

Despite the long and almost universal recognition of Alexander's law by clinicians, there has been no serious attempt to explain the phenomenon. This prompted us to develop an analog computer model utilizing relevant brainstem anatomy and physiology in an effort to simulate Alexander's law in nystagmus secondary to dysfunction of a semicircular canal.[2] The model behaved in accordance with Alexander's law with total and partial unilateral canal dysfunction. To investigate the assumptions of the model and to quantitate the details of Alexander's law, we performed studies of variation with gaze of caloric-induced nystagmus in normal human subjects.

MODEL

The model represents the brainstem mechanisms that determine the gaze-dependent slope variation of the slow phase of vestibular nystagmus. We did not explicitly model the generation of the fast phases; they were assumed to occur with a constant frequency. A model has been proposed by other investigators for fast phase generation.[3]

A neural configuration, consistent with the known anatomy and physiology on which our model was based, is shown in Figure 2. The vestibular nuclei (right, RVN; left, LVN) transfer excitatory signals contralaterally and inhibitory signals ipsilaterally to the neural integrators (NI). Prior to synapsing with the integrators, these signals are

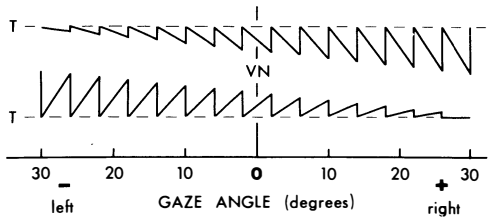

Fig. 1. Diagram of right- (upper) and left-beating (lower) vestibular nystagmus variations with gaze. T indicates target position.[2]

From the Ocular Motor Neurophysiology Laboratory, VA Medical Center, and Department of Neurology, Case Western Reserve University, School of Medicine, Cleveland. This study was supported in part by USPHS grant IT 32 EY-07021-05.

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REPRINTS — L. F. Dell'Osso, PhD, Ocular Motility (127A), VA Medical Center, Cleveland, OH 44106.

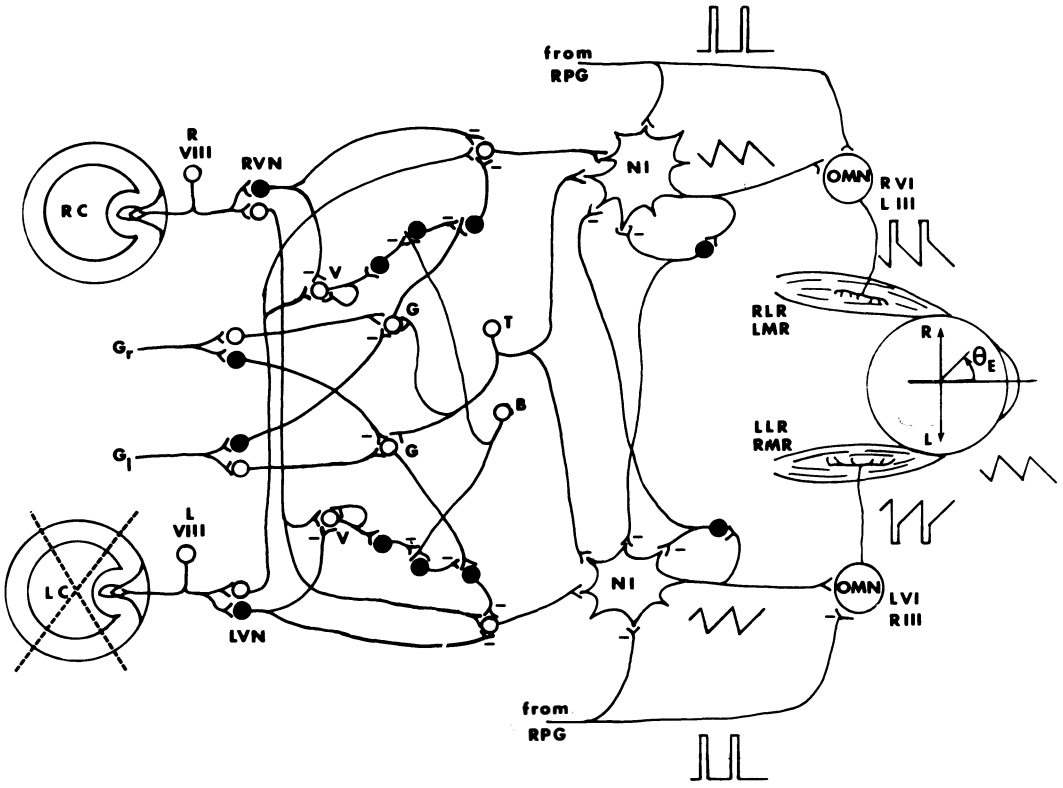

Fig. 2. A possible "wiring diagram" suggested by the model. The upper half of the diagram corresponds to the right side of the brainstem and the lower half to the left side. Open circles represent excitatory neurons; filled circles represent inhibitory neurons. Dysfunction of the left semicircular canal is signified by a large X through LC. C - Canal; R - Right; L - Left; VN - Vestibular nuclei; VIII - Eighth nerve nuclei; NI - Neural integrator; PG - Pulse generator; OMN - Ocular motor nuclei; LR - Lateral rectus; MR - Medial rectus; G - Gaze signals; T - Central tone; B - Central bias; V - Vestibular signals.[2]

modulated by desired right and left gaze (G_r, G_l) and central tone (T) signals. The evidence for a central T signal has been presented previously[2] and is related to the interconnections of the brainstem neural integrators. When no imbalance between vestibular nerve activity from each side is present, the summed gaze and tone signals (G) are prevented from influencing vestibular activity by means of the presynaptic inhibition supplied by a postulated central bias (B). When an imbalance of vestibular activity occurs, this inhibitory bias is turned off by additional presynaptic inhibition. Such inhibition of inhibitory signals is not unusual and has been documented in other areas of neurophysiology.[4] Also shown are the ocular motor nuclei (OMN) and the eye muscles. With dysfunction of the left canal (LC), the right canal (RC) provides increased stimulation of the left lateral rectus (LLR) and right medial rectus (RMR) causing the eyes (represented here as one eye) to drift to the left. Intervening saccadic pulses from the right pulse generator (RPG) move the eyes back to their predrift position. The waveforms shown represent changes in the neural firing frequencies and eye position (Θ_E).

Our model, which was implented on a Systron-Donner SD-80 analog computer, is described by the functional block diagram shown in Figure 3. Neural signals from the semicircular canals (SCC) pass to the vestibular nuclei (VN) before being integrated by the NI. The NI outputs then lead to stimulation of the extraocular eye muscles (EOM) via the OMN. The position of the eyes is represented by Θ_E.

In order to include a gaze-dependent variation, however, we added a slow phase modulator (SϕM) which modulated vestibular nuclei activity with desired gaze (Θ_D) and constant T. In this manner we

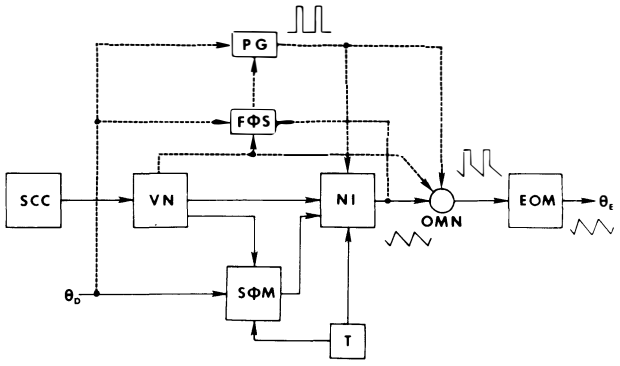

Fig. 3. Functional block diagram of the model. Solid lines represent slow phase generation; dashed lines represent fast phase aspects. SCC - Semicircular canal; VN - Vestibular nuclei; NI - Neural integrators; OMN - Ocular motor nuclei; EOM - Extraocular muscles; Θ_D - Desired gaze angle; Θ_E - Eye (gaze) angle; PG - Pulse generator; FϕS - Fast phase stimulator; SϕM - Slow phase modulator; T - Central tonic input.[2]

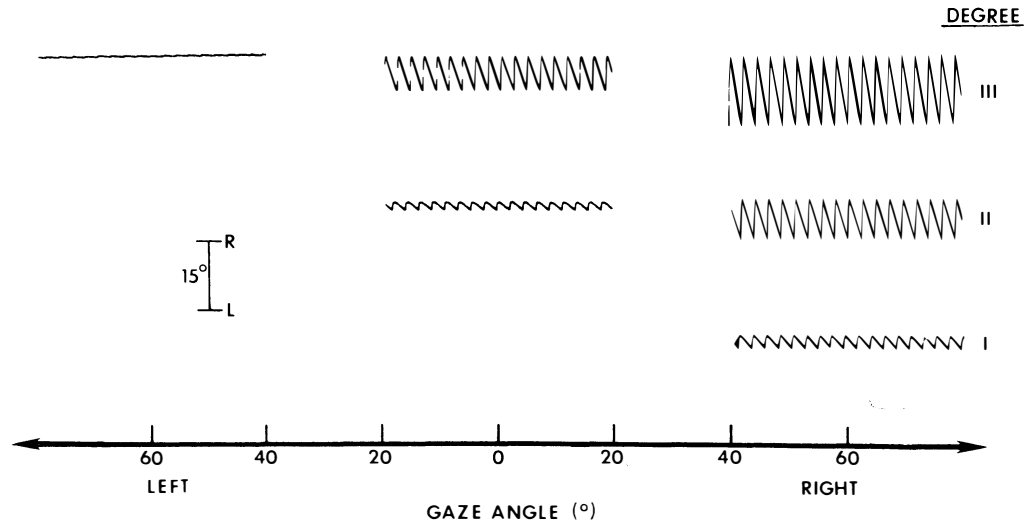

Fig. 4. Recordings of the outputs from the model with various parameter settings to stimulate three degrees of nystagmus (I-III) variation with gaze.[2]

were able to simulate the variation of slow phase velocity with canal imbalance and desired gaze. The fast phase stimulator (FΦS) and pulse generator (PG) are connected by dashed lines to illustrate that they were not *explicitly* modeled, although their role in the fast phase of the vestibular nystagmus was represented. The waveforms shown indicate both neural firing frequencies and the resulting nystagmus of the eyes.

When simulating normally functioning semicircular canals with equal spontaneous activity from the two sides, the model produced no nystagmus. When simulating total impairment of the canal on one side with gaze directed maximally in the opposite direction, the model produced large amplitude (arbitrarily chosen to be 15°) nystagmus with linear slow phases directed toward the "lesioned" side and fast phases in the opposite direction (corresponding with observed clinical phenomenology). As gaze was adjusted from far contralateral to ipsilateral, the nystagmus gradually diminished to zero. This is shown in Figure 4 as third degree nystagmus (by Alexander's classification). When one canal output was only partially reduced and the other normal, the nystagmus was smaller in amplitude and was absent in ipsilateral or in both ipsilateral and center gaze, as indicated by the second and first degree labels in Figure 4. As an initial simplifying assumption, the frequency of the nystagmus was held constant at 3.33 Hz.

Figure 5 illustrates the quantitative relationship between the amplitude of the nystagmus, the angle of desired gaze, and the amount of canal dysfunction measured as the percentage of its normal spontaneous activity. The linear property of these curves is a result of our simple interpretation of Alexander's law, ie, the amplitude of third degree nystagmus increases linearly with increasing gaze in the direction of the fast phase. The parallel property of the curves is again the result of our approximation of the linear variation of nystagmus with canal deficit (as measured above). This is not meant to imply that the vestibular function (VOR) of a canal is directly related to its spontaneous activity.

The model provoked some interesting questions: 1) Is the relationship between the amplitude of the

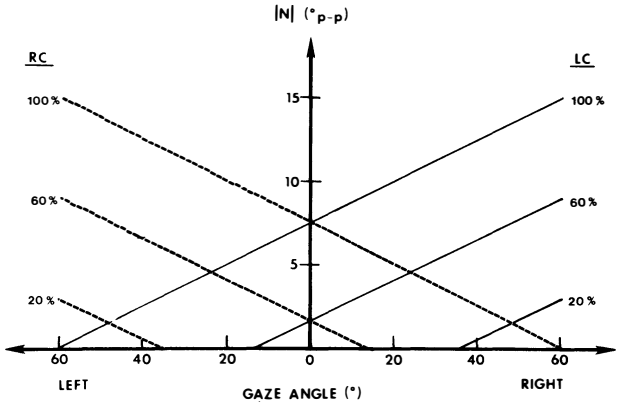

Fig. 5. Plots of variations of nystagmus amplitude as a function of gaze angle and the amount of simulated semicircular canal dysfunction. LC - Left canal; RC - Right canal.[2]

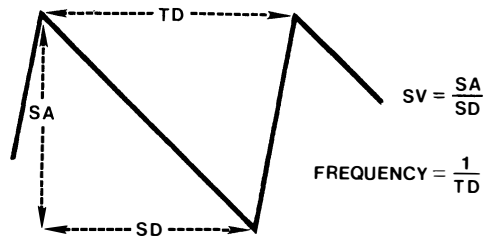

Fig. 6. Sketch of nystagmus waveform showing parameters measured. SA - Slow phase amplitude; SD - Slow phase duration; TD - Total duration of the nystagmus beat.

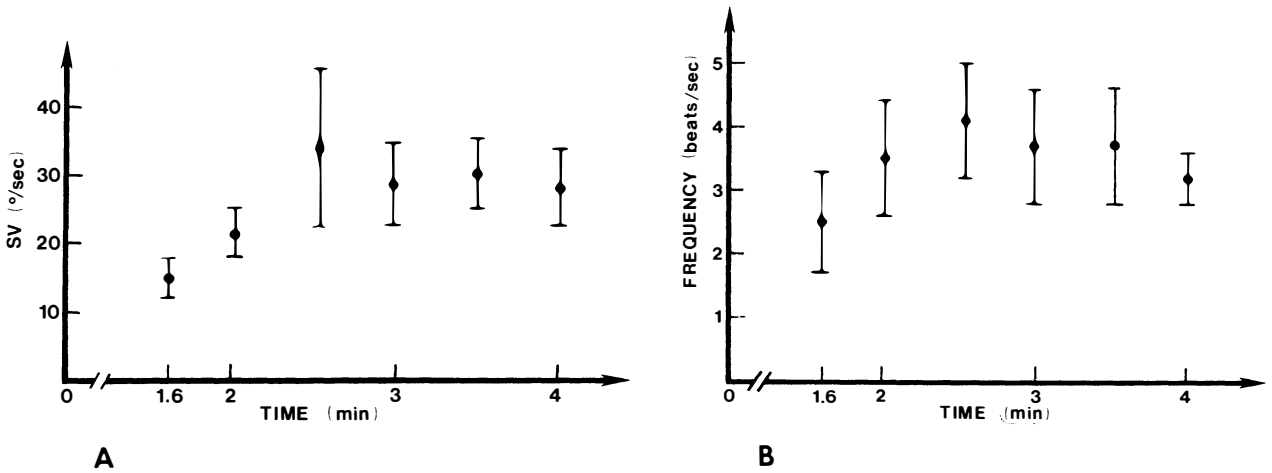

Fig. 7. (Subject 1) A) Time course of the nystagmus slow phase velocity (SV), while holding center gaze during constant irrigation. Each filled circle and error bar represents the SV mean and standard deviation, respectively, of 10 sampled beats. The position on the time axis is the mean time of occurrence of the 10 samples. B) Time course of the nystagmus frequency, while holding center gaze during constant irrigation. Each filled circle and error bar as in A.

nystagmus and the desired gaze angle actually linear? 2) For a given angle of gaze, is the nystagmus amplitude a linear function of canal deficit? 3) How does the nystagmus frequency vary with gaze? Consequently, studies of calorics on normal subjects were initiated in our laboratory to answer these questions and to provide additional direction for our modeling.

METHODS

Caloric-induced horizontal nystagmus was monitored, using an infrared technique, as a function of gaze in seven normal male subjects between the ages of 18 and 34; the infrared system was linear within ± 20°. The subjects were not patients, had no clinical ocular motor complaints, and made normal eye movements during calibration. The subjects were in complete darkness (except during calibration) and were in a reclined sitting position with the coronal plane of the head at 60° from the vertical. Blinks were detected with a vertical electro-oculographic recording of one eye. During calibration, each subject was asked to look at small spots located on the ceiling (at a distance of approximately 20 m) at gaze angles of 0°, ±20°, and ±25°.

The time courses of the slow phase velocity (SV) and frequency of one subject holding center gaze during continuous irrigation were calculated to establish when and if adaptation had occurred. The intent in this study was to first get our subjects into the adapted plateau region and then study the effect of gaze on the SV.

Cold water (26.5°C and 240 ml/min) was delivered continuously for several minutes to the external auditory meatus of the subject's left ear; right-beating linear nystagmus was thus induced. After the nystagmus reached a constant amplitude, the subject was asked to look at his best estimate (since it was dark) of various angles of right and left gaze while receiving constant corrective feedback as needed from the experimentor. Usually gaze variations originated at 20° right, proceeded to 20° left in a stepwise manner, returned to 20° right, and then the cycle was repeated at least once. In this way many beats at various gaze angles were recorded. Calibration was then rechecked after the experiment. The slow phase velocity and frequency of every third, fourth, or fifth beat, depending on the total number of beats recorded from a particular subject, were calculated (Fig. 6). The individual amplitudes and durations were determined graphically.

RESULTS

The time courses of both the SV and frequency for subject holding center gaze are shown in Figure 7A,B respectively. Notice the peak at $2^1/_2$ minutes and the subsequent plateau region in each figure.

Results from all the subjects are shown in Figure 8. The heavy solid line is the mean of the SV regression lines for subjects,[3,5-7] eliminating three special

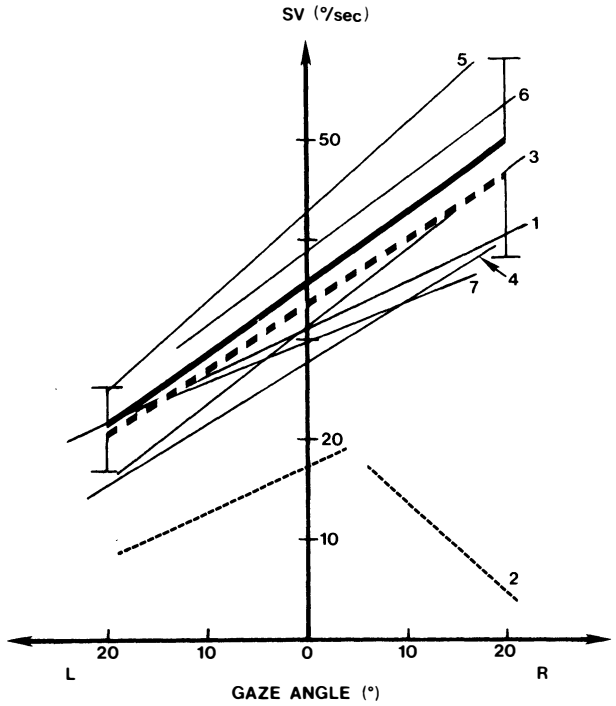

Fig. 8. Plots of nystagmus slow phase velocity (SV) versus gaze angle for each of the subjects tested. Each subject's data are represented as a linear regression. The heavy solid line is the mean of the individual curves of four subjects (3, 5-7). The heavy dashed line is the mean of the individual curves of six subjects (1, 3-7). The error bars are standard deviations.

STATISTICAL INFORMATION FOR FIGURES 9-13

Subject	Age	Sample Size	Data Starts (s)*	Data Ends (s)*	Frequency (Mean)	(SD)
1	34	53	137	290	3.80	1.41
2	18	66	120	290	1.95	0.83
3	34	52	65	138	2.91	0.62
4	30	56	180	345	3.08	1.40
5	30	69	180	350	3.34	1.10
6	27	43	180	360	3.01	0.87
7	22	51	180	450	3.05	1.41

*After the start of irrigation.

cases discussed below. The heavy dashed line is the mean of the SV regression lines for six subjects, excluding the markedly different data for subject 2. In all cases, frequency was not a function of gaze; the means were 3.08 and 3.2 beats/second corresponding to the above groupings of four and six subjects respectively. The table presents individual data for each of the subjects.

The data for subject 3 was best fit by a regression line (Fig. 9). The subject made multiple sweeps of rightward and leftward gaze during the time the nystagmus was recorded. The frequency was not a function of gaze. These results were characteristic of most of the subjects tested. The data of subjects 1, 4 and 2 are unique and will be presented separately.

Figure 10 describes data for subject 1 which were consistent with Alexander's law with one sweep of gaze from right to left (dots), but not on the return to right gaze (x's). The frequency derived from the

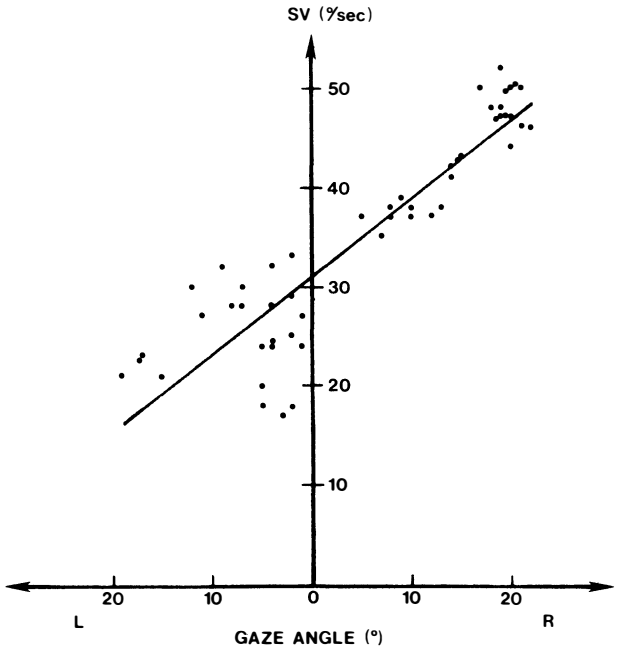

Fig. 9. Plot of slow phase velocity (SV) as a function of gaze angle (shown by dots) for the sampled nystagmus beats from subject 3 with multiple sweeps of gaze from one side to the other. The solid line is a linear regression with a = 31.25, b = 0.77, r = 0.91. In this and all subsequent figures, a and b are parameters in the equation SV = a (gaze angle) + b; r is the correlation coefficient.

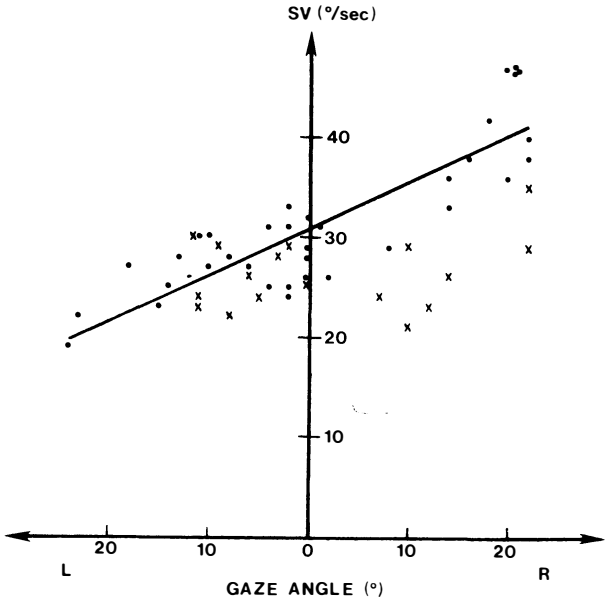

Fig. 10. Plot of slow phase velocity (SV) as a function of gaze angle for the sampled nystagmus beats from subject 1. The dots represent 36 beats occurring between 137 seconds and 242 seconds for one sweep of gaze starting at the right and ending at left gaze. The x's represent 17 beats occurring between 244 seconds and 290 seconds for the return to right gaze. The solid line is a linear regression (a = 30.95, b = 0.47, r = 0.87) of the data shown by dots. A linear regression on the other data had a value of r equal to only 0.3.

beats, referred to by the dots, was not a function of gaze.

Data for subject 4 are consistent with Alexander's law with one sweep of gaze from right to left (dots), but not for other sweeps of gaze (Fig. 11). The data shown by the dots were recorded during a time in the middle of all the data recorded. Frequency was not a function of gaze.

Subject 2 demonstrated "hemifield reciprocity"[11] (Fig. 12). With multiple rightward and leftward sweeps of gaze, results were consistent with Alexander's law at center and left gaze but *not* during right gaze where the opposite occurred. Frequency was not a function of gaze; the mean value (1.95) was the smallest of all subjects' mean frequencies (table).

DISCUSSION

For all subjects the data were obtained when we felt reasonably sure that the SV was not a function of time, ie, the system was in steady-state; this time was usually greater than 2½ minutes after the start of irrigation, based on the SV adaptation characteristic of subject 1. The frequency change also followed a similar time course. The SV time course is consistent with data in the literature.[5-8] The time course of the frequency does not appear to be documented elsewhere.

The data for subject 3 (Fig. 9) began 65 seconds after commencement of irrigation. These data,

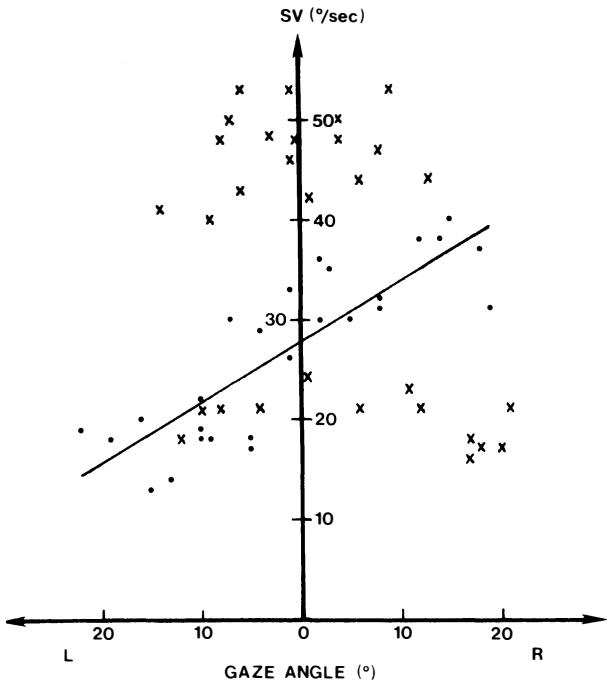

Fig. 11. Plot of slow phase velocity (SV) as a function of gaze angle for the sampled nystagmus beats from subject 4. The dots represent 26 beats occurring between 210 seconds and 300 seconds for one sweep of gaze from right to left. The x's represent 30 beats occurring from 180 seconds to 210 seconds and 300 seconds to 345 seconds. The solid line is a linear regression (a = 27.61, b = 0.61, r = 0.84) of the data shown by dots.

nonetheless, had the best fit to a linear regression line and followed Alexander's law. It is probable that the SV for this subject reached a steady state prior to the beginning of the data. Otherwise the SV would have increased as gaze was changed from the far right, to center, and to the left. Also, since the SV path was retraced with multiple right and left sweeps of gaze, and since the nystagmus first appeared much sooner than average, the subject's SV and frequency were most probably adapted.

The SV data for subject 1 (Fig. 10), on returning from left to right gaze, did not conform to the SV line established when gaze initially changed from right to left. The reduced SV on returning to right gaze was possibly due to a minor fluctuation of the SV, even when it has adapted.[5] Other possibilities are diminished attention of the subject or variation of the caloric stimulus.

The SV data for subject 4 (Fig. 11) had high values initially for variations of gaze and did not follow Alexander's law. However, for a subsequent gaze variation from right to left, Alexander's law was obeyed. With the return of gaze to the right, Alexander's law was again violated. These inconsistencies may have been due to fluctuations in the adapted state, late-occurring adaptation, fluctuations in the subject's mental state, or variation of the applied stimulus.

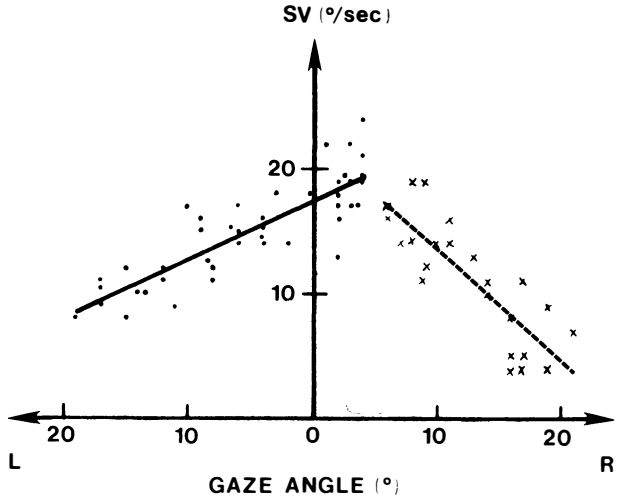

Fig. 12. Plot of slow phase velocity (SV) as a function of gaze angle for the 66 sampled nystagmus beats from subject 2 with multiple sweeps of gaze from one side to the other. The solid line is a linear regression (a = 17.46, b = 0.47, r = 0.85) of data, shown by the dots, from 43 samples. The dashed line is a linear regression (a = 22.51, b = 0.89, r = 0.84) of data, shown by x's from 23 samples.

The SV data for subject 2 (Fig. 12) were unique. In addition to being considerably smaller than for the other subjects, they were in agreement with Alexander's law for center and left gaze but *not* for right gaze. This "hemifield reciprocity" has not, to our knowledge, been reported in patients with pathological vestibular end-organ nystagmus. Interestingly, the slope of the SV versus gaze line in left gaze was similar to the slopes of the corresponding lines for all the other subjects. Since this entire SV line was followed quite well with multiple right and left sweeps of gaze, we feel that the decrease of SV with rightward gaze is a biological anomaly.

The SV data for the remaining three subjects (5-7) were quite similar to the data from subject 3. Their mean is shown by the heavy solid line in Figure 8. The SV data for two of the special cases mentioned above (subjects 1 and 4) are very similar to that of the four mentioned above (3, 5-7). In fact, the mean SV line for subjects 2, 3-7 compares very closely with the mean SV line for subjects 3, 5-7.

Figure 13 is a superposition of the mean SV line for subjects 3, 5-7 and the initial results from the model (with amplitude converted to SV). The induced vestibular nystagmus SV was linear within ± 20° of gaze, as we assumed in the model; the magnitudes of the actual and model SVs were also in close agreement. The linear extrapolations beyond ± 20° are merely to simplify comparison with the model; this region needs further investigation. It is not known what extent of canal deficit is needed to mimic the caloric-induced third degree nystagmus. In each subject, the effective degree of deficit produced was probably different as a result of biological variation and different thermal conduc-

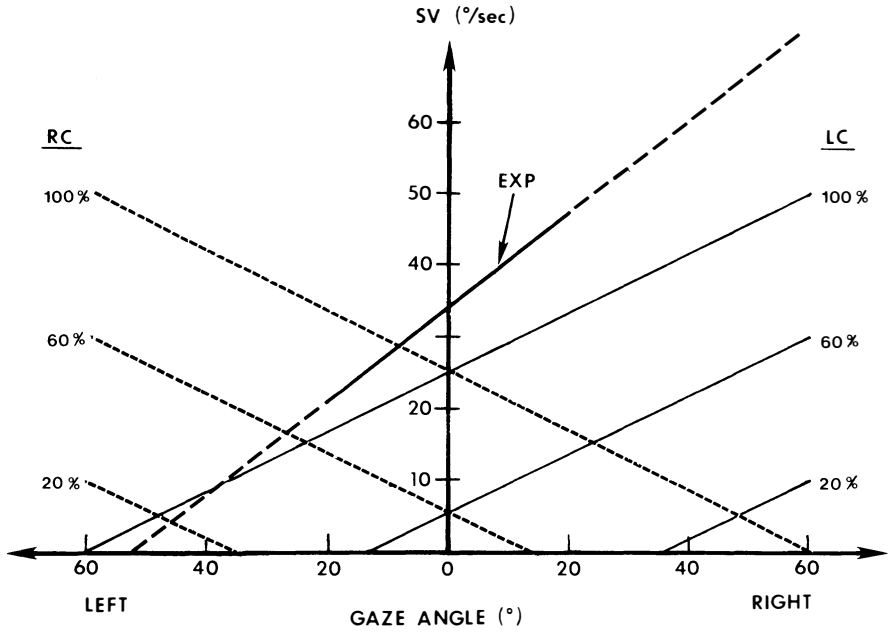

Fig. 13. Superposition of the experimental data (utilizing the heavy solid line in Fig. 8) upon the model data. The amounts of simulated semicircular canal dysfunction are indicated. LC - Left canal; RC - Right canal.

tivity properties of the meatus and petrous bone. This probably accounts for the intersubject differences in SV (Fig. 8). The fact that the slopes were quite similar and the lines were nearly parallel but separate, supports another assumption of the model. The mean frequency (3.2 Hz) of the nystagmus for all the subjects (except no. 2) tested was both constant (not a function of gaze) and also of similar magnitude to the frequency (3.33 Hz) assumed in the model. The parameters in the model can now be adjusted slightly so that the SV slopes and the frequencies are equivalent to those obtained experimentally.

The phenomenon which constitutes Alexander's law is the natural consequence of our brainstem neural circuitry. What might be the biological benefits of having a neural network so constituted? We speculate that it might be to enhance the vestibulo-ocular reflex (VOR) and, in pathological vestibular states, to minimize nystagmus. With head rotation, the eyes deviate in the direction of the fast phase.[9] The SV would therefore be greatest with the eyes deviated in that direction. Consequently, the gain of the VOR (SV/rotation velocity) would be greatest, thereby maximizing the performance of this reflex. In clinical cases of labyrinthine dysfunction, the eyes usually deviate in the direction of the affected side,[10] *away* from the fast phase of the resulting nystagmus. Thus, the SV of the nystagmus and the visual impairment would be minimized.

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