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A Model of Alexander's Law of Vestibular Nystagmus

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Abstract. The observation that the amplitude of vestibular nystagmus grows as gaze is increased in the direction of the nystagmus fast phase and diminished with gaze in the opposite direction is known as "Alexander's law". We have developed an analog computer model to simulate Alexander's law in nystagmus secondary to dysfunction of a semicircular canal. The model utilizes relevant brainstem anatomy and physiology and includes gaze modulation of vestibular signals and push-pull integration to create eye positition commands. When simulating normally functioning semicircular canals, 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 a large amplitude nystagmus with linear slow phases directed toward the affected side. As gaze was changed from far contralateral to ipsilateral, the nystagmus gradually diminished to zero. When simulating partial impairment of one canal, the nystagmus was smaller in amplitude and absent in ipsilateral gaze.

1. Introduction

Nystagmus is an involuntary, rhythmical, biphasic oscillation of the eyes. Nystagmus secondary to an imbalance between the two vestibular end organs (semicircular canals) is among the most common seen in clinical practice. A pathological lesion of a semicircular canal may be mimicked by irrigation of the eardrum by water warmer or colder than body temperature (caloric-induced vestibular nystagmus). Vestibular nystagmus, either pathological or induced, consists of sequences of linear (constant velocity) slow phases which move the eyes away from the intended eye position followed by corrective fast phases (saccades) which return the eyes to the original position. The amplitude of vestibular nystagmus grows as gaze is increased in the direction of the fast phase and diminishes with gaze in the opposite direction (Fig. 1). This phenomenon was described by Alexander in 1912 and is known as "Alexander's Law". Alexander categorized vestibular nystagmus into three types:

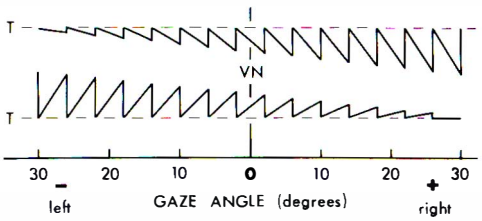

Fig. 1. Diagram of right- (upper) and left-beating (lower) vestibular nystagmus variations with gaze. *T* indicates target position

1) *First degree:* Present only during gaze in the direction of the fast phase

2) *Second degree:* Present during gaze straight ahead but increases in direction of the fast phase.

3) *Third degree:* 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 have been no serious attempts to explain the phenomenon. We have consequently developed 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. The model proved to be capable of faithfully demonstrating Alexander's law with total and partial unilateral canal dysfunction.

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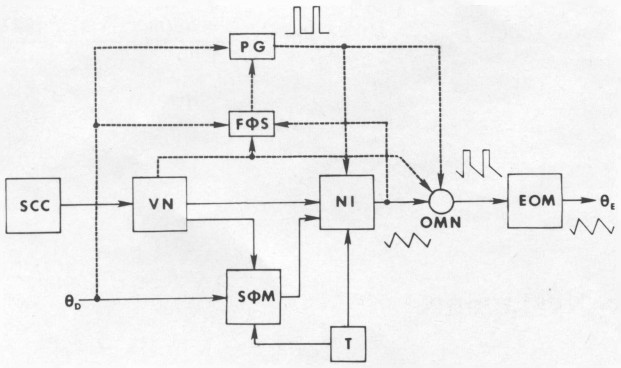

Fig. 2. Functional block diagram of the model. Solid lines represent slow phase generation; dashed lines represent fast phase aspects

2. Model

2.1. Physiological Basis

When the head is immobile, a tonic level of afferent neural activity from the semicircular canals on each side is recorded from the two vestibular nerves (Fernandez and Goldberg, 1971). The semicircular canals are transducers of angular head acceleration. The canals on the two sides are so situated that head movement in any direction will increase the neural firing frequency of a canal on one side and result in a concomitant decrease of the homologous canal on the opposite side (Young, 1974). This imbalance in neural signals from the vestibular end organs to the brainstem results in an eye movement opposite in direction and equal in velocity to the head movement; this is known as the vestibulo-ocular reflex (VOR) (Barr et al., 1976). Although the canals are responsive to head acceleration, the signals recorded in the vestibular nerves are proportional to head velocity. The integration of the signal takes place within the canal itself (Melvill Jones, 1971). The next step of integration, to produce signals proportional to head position in order to drive the vestibulo-ocular reflex, takes place within the brainstem (Robinson, 1975a; Robinson, 1975b).

When the head is passively rotated from side to side in darkness, the VOR drifts of the eyes in the opposite direction are repetitively interrupted by fast saccadic movements of the eyes in the direction of the rotation. The slow drift, induced by the head movement and consequent imbalance in neural activity from the right and left semicircular canals, is the initiating movement of this rotation-induced vestibular nystagmus.

Inner ear disease of a variety of causes induces an imbalance between the two sides which is responsible for pathological vestibular nystagmus. The diseased end organ almost always has a decreased rate of tonic firing. The slow phase of the nystagmus drifts toward the abnormal side and the fast phase beats in the opposite direction (i.e., toward the normal ear). Warm or cold caloric stimulation induces convection flows of the endolymph of the semicircular canal on the side of irrigation. The direction of flow depends upon the temperature of the water. Warm water results in an increase in tonic firing frequency whereas cold water induces a decreased frequency and therein mimics the effect of a diseased semicircular canal. In either instance, however, an imbalance between the two sides is created, the eyes drift to one side, and nystagmus is induced.

Thus, vestibular nystagmus, whether pathological or induced (head rotation or caloric stimulation) is secondary to an imbalance between the semicircular canals on the two sides. This imbalance is superimposed upon a steady-state tone present at the output of both agonist and antagonist motoneurons of the extraocular muscles. With the eyes in primary position (straight ahead), all the muscles are equally innervated so that the net torque on each globe is zero. The position commands from each side of the brainstem are equal.

2.2. Operation

The model represents the brainstem mechanisms that determine the gaze-dependent slope variation of the slow phase of vestibular nystagmus. Therefore, it was not necessary to explicitly model the generation of the fast phases; they were assumed to occur with a constant frequency. A model has been proposed for fast phase generation (Chun and Robinson, 1978).

Our model, which was implemented on a Systron-Donner SD-80 analog computer, is described by the functional block diagram shown in Fig. 2. Neural signals from the semicircular canals (SCC) pass to the vestibular nuclei (VN) before being integrated by the neural integrators (NI). The NI outputs then lead to stimulation of the extraocular eye muscles (EOM) via the ocular motor nuclei (OMN). The position of the eyes is represented by θ_E. The net effect is an idealized VOR.

In order to include a gaze-dependent variation, however, we added a slow phase modulator ($S\phi M$) which modulates vestibular nuclei activity with desired gaze (θ_D) and a constant tone signal (T). In this manner we were able to simulate the variation of slow phase velocity with canal imbalance and desired gaze. The fast phase stimulator ($F\phi S$) and pulse generator (PG) are connected by dashed lines to illustrate that they were not *explicitly* modelled, although their role in the fast phase of the vestibular nystagmus was represented. The waveforms shown indicate neural firing frequencies and the resulting nystagmus of the eyes.

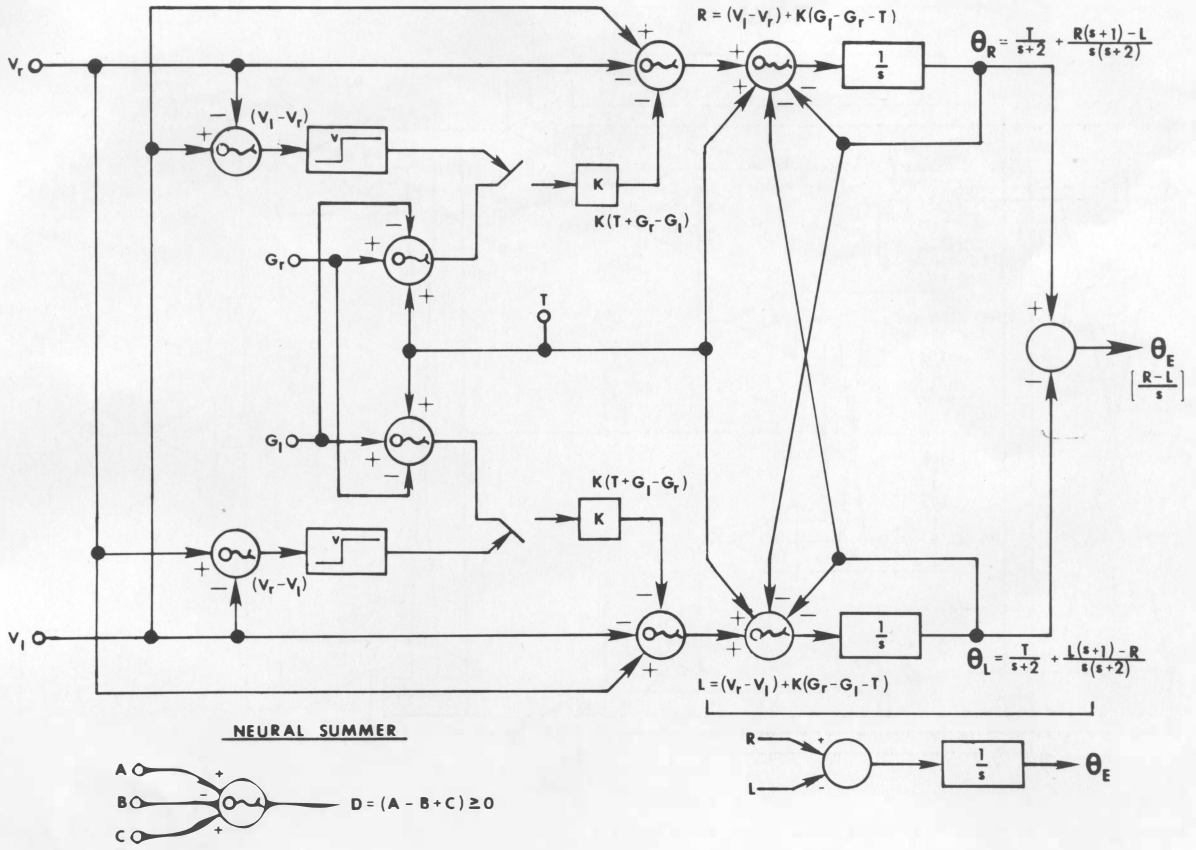

Fig. 3. Signal flow diagram of the model containing the necessary quantitative interaction among signals. Mathematical relationships utilize Laplace notation where applicable

The signal flow diagram of the model is shown in Fig. 3. The terminology *Neural Summer* is utilized to emphasize the true correspondence with actual neurons which fire with positive frequency only when the net input stimulation is excitatory.

Several characteristics were required of this brainstem model: a) equal and opposite neural tone from each side should exist when the eyes are in primary position; b) when a vestibular imbalance is present, a gaze angle signal should modulate the value of the drift velocity produced by the imbalance; c) the gaze angle signal must not induce a drift velocity when no vestibular imbalance existed; and d) the modulated imbalance must result in a constant-velocity, linear drift of the eyes.

These considerations resulted in specific model characteristics. The constant tone output requirements from each of the eye position integrators and the necessity for the integrator outputs to track each other in a push-pull fashion about that steady-state tonic level, gave rise to the push-pull connection of first-order lag elements shown in Fig. 3. This solution was taken from an earlier, more complete, model of brainstem circuitry developed by Dell'Osso in 1974 (unpublished). It has the unique characteristics that yield a constant output for equal innervation to each of the integrators and an integrated output for a differential input. Satisfaction of requirements b and c resulted in a gated modulation which was present only when a vestibular imbalance exceeded a threshold. To maintain linear slow phases, desired gaze signals, rather than feedback of the output of the integrators (actual gaze commands), had to be used, as the latter would result in non-linear slow phases.

To help in understanding the operation of the model, consider what happens when input from the right vestibular nucleus exceeds that from the left ($V_r > V_1$). This imbalance triggers a gating voltage, V, which activates a switch allowing desired gaze and tone signals (G_r, G_1, and T to pass through an attenuator (K) and summate with vestibular signals. Note that desired gaze signals are allowed to pass to only one side (depending on which of V_r or V_1 is greater). The modulated signal is then integrated by the push-pull integrators and differentially added (simulating the agonist and antagonist muscle function)

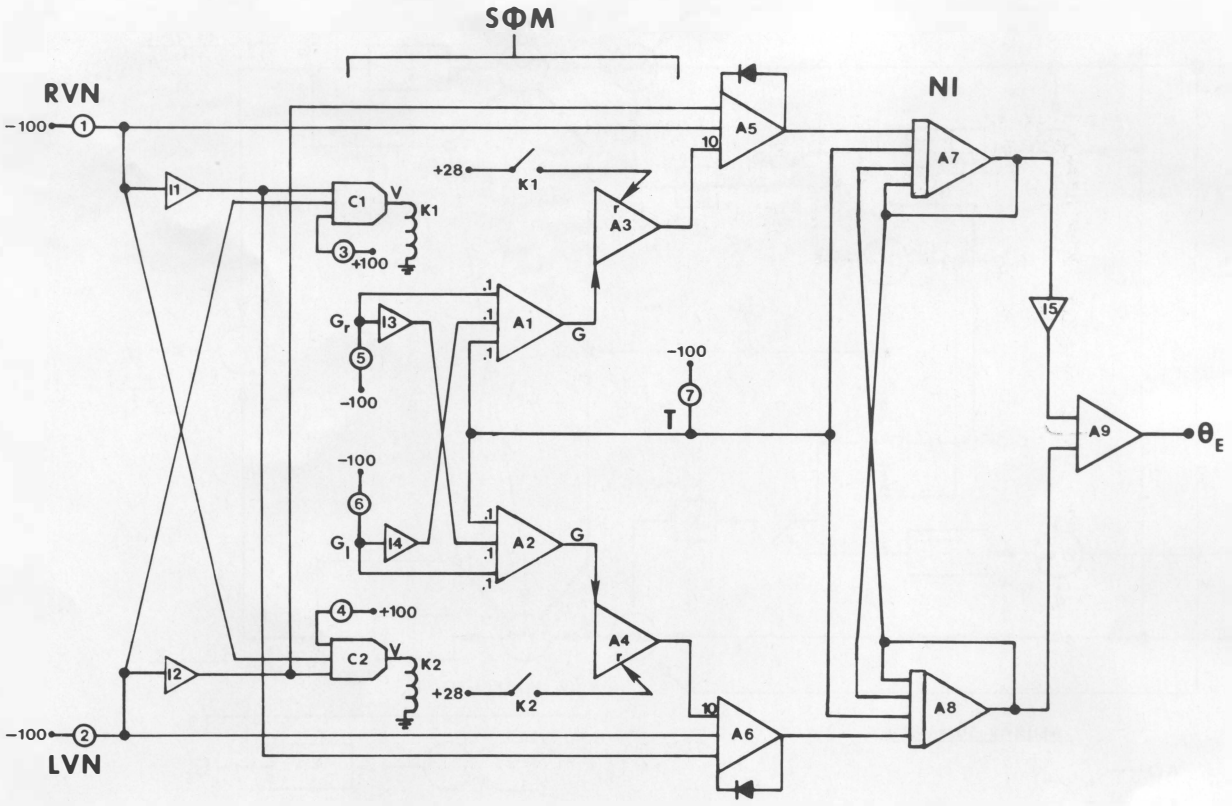

Fig. 4. Schematic diagram of the analog computer realization of the model

to give an output proportional to eye position. The whole push-pull configuration can be represented as an ideal differential integrator with inputs from the right (R) and left (L) sides, as shown at the bottom of Fig. 3. The mathematical relationships of the pertinent variables in the complex frequency domain, s , are indicated in the figure.

3. Results

A schematic diagram of the model is illustrated in Fig. 4. Signals from the right and left semicircular canals, via the vestibular nuclei (RVN and LVN), are represented by potentiometers 1 and 2. Desired gaze signals (G_r and G_l) are simulated by the potentiometers 5 and 6. A constant tone signal (T) is provided by potentiometer 7. When an imbalance between the vestibular input signals occurs, either comparator C1 or C2 activates relay K1 or K2, respectively. Thus, only one half of the slow phase modulation network is turned on, and summed gaze and tone signals, G, are allowed to pass via A3 or A4 to summers A5 or A6, respectively. It is here that the gaze and tone signals are summed with the vestibular signals to produce a modulated signal. The neural integrators (A7 and A8) are connected in a push-pull configuration and have the property of producing a constant output from simultaneous equal inputs and an integrated output from unbalanced inputs, in accordance with principles discussed above. The output of A7, after inversion by I5, is summed with the output of A8 by A9. A negative ramp output from A9 represents slow eye movement in the leftward direction caused by excitation of the agonists (left lateral and right medial recti), with subsequent jerk right nystagmus. The model primarily simulates the slow drift in vestibular nystagmus; the saccades were simulated by running the computer in the Rep-Op mode which automatically resets the integrator outputs to zero at a predetermined rate.

When simulating normally functioning semicircular canals with equal tonic innervation 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 Fig. 5 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 Fig. 5.

Figure 6 illustrates the quantitative relationship between the amplitude of the nystagmus, the angle of desired gaze, and the amount of canal dysfunction. The linear property of these curves is a result of our simple interpretation of Alexander's law, i.e., 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 a result of our linear approximation of the variation of nystagmus with canal deficit.

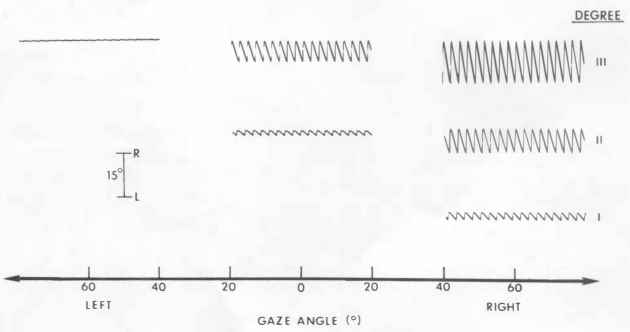

Fig. 5. Recordings of the outputs from the model with various parameter settings to simulate three degrees of nystagmus (I–III) variation with gaze. Blank areas imply no nystagmus

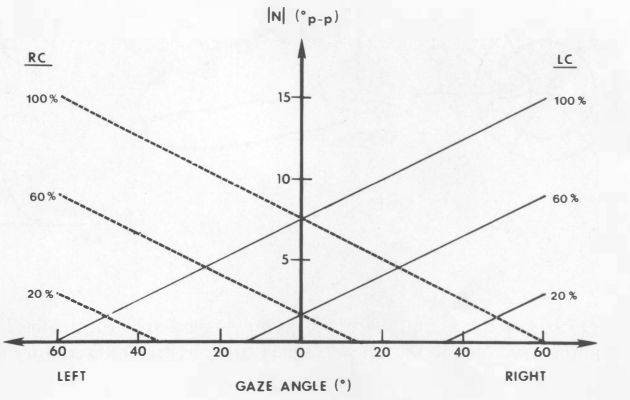

Fig. 6. Plots of variations of nystagmus amplitude as a function of gaze angle and the amount of simulated semicircular canal dysfunction. *LC*: left canal, *RC*: right canal

4. Discussion

We have developed an analog computer model that simulates the gaze-dependent variation of the slow phase of vestibular nystagmus in accordance with Alexander's law. The model incorporated current anatomical and physiological concepts of the vestibulo-ocular arc and version eye movements. As an initial simplifying assumption the frequency of the nystagmus was held constant (at 3.33 Hz). The computer was adjusted to automatically zero its output approximately every 0.30 s, thereby simulating the action of the fast phases of nystagmus. During this time the slow phase drift increased at a rate determined by the model output. The results from the model suggest a quantitative relationship between nystagmus amplitude, vestibular imbalance, and desired gaze. The model provoked some interesting questions: 1) Is the relationship between the amplitude of the nystagmus and the desired gaze angle actually linear? 2) For a given angle of gaze, is the change in nystagmus amplitude a linear function of canal deficit? 3) How does the nystagmus frequency vary with gaze? 4) Is the present definition of intensity (frequency times amplitude) the best dependent variable to measure? Consequently, studies of calorics on normal subjects have been initiated in our laboratory to answer these questions and to provide additional direction for our modelling.

Two crucial aspects of the model are the slow phase modulator ($S\phi M$) and the push-pull configuration of the neural integrators. The $S\phi M$ allowed desired gaze signals to modulate vestibular imbalances. The resulting signal needed to be integrated in a way which would produce a linear movement of the eyes by an increase in muscle agonist force and a decrease in antagonist force. The rather simple push-pull feedback network accomplished this. Integration is performed in the paramedian pontine reticular formation (Robinson, 1975a; Robinson, 1975b) and slow phase modulation presumably occurs in the same region.

The model suggested a possible neural configuration, shown in Fig. 7, which would produce nystagmus from vestibular imbalance which varied with gaze. The vestibular nuclei (RVN, LVN) transfer excitatory signals contralaterally and inhibitory signals ipsilaterally to the neural integrators (NI). Prior to synapsing with the integrators, these signals are modulated by desired gaze (G_r, G_1) and tone (T) signals. When no imbalance between vestibular nerve activity from each side is present, the summed gaze and tone signals (G) are prevented from passing by means of the presynaptic inhibition supplied by a postulated 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 in other areas of neurophysiology (Eccles, 1964; Davidoff, 1978). Also shown are the

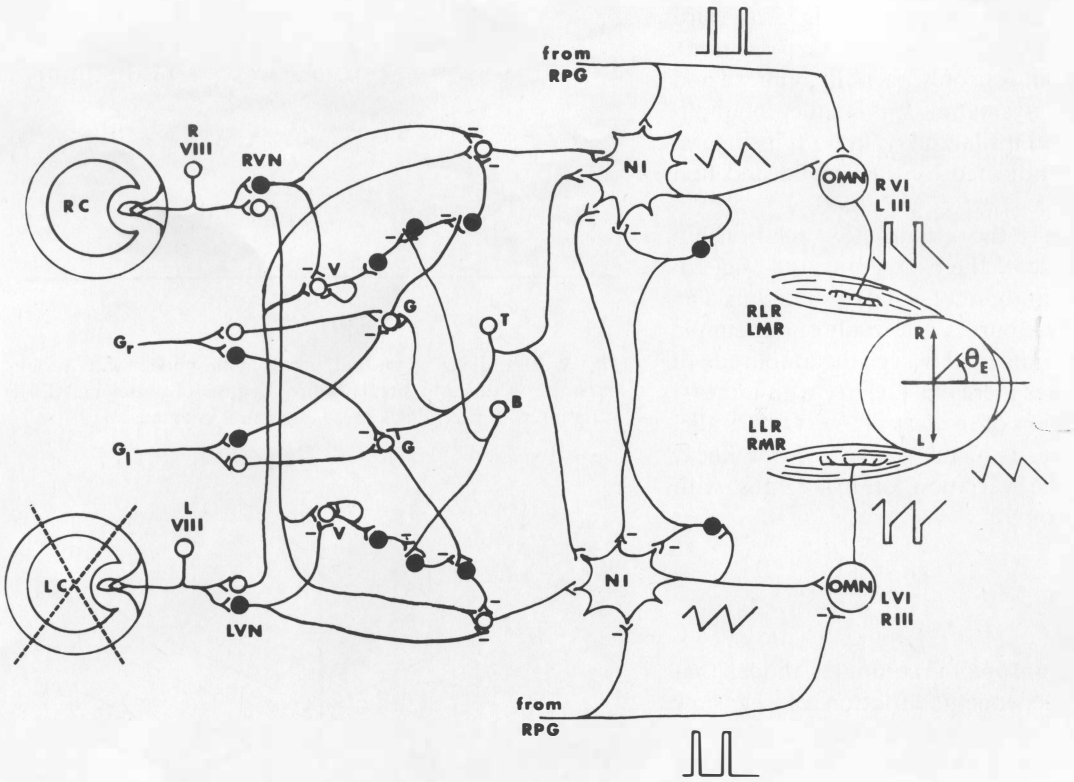

Fig. 7. A possible neural "wiring diagram" suggested by the model. The upper half of the diagram corresponds to the right side of the brainstem and the lower half to the left side. Open circles represent excitatory neurons; filled circles represent inhibitory neurons. Dysfunction of the left semicircular canal is signified by a large *X* through *LC*

ocular motor nuclei (OMN) and the eye muscles. With dysfunction of the left canal (LC), the right canal (RC) leads to 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 pre-drift position. The waveforms shown represent changes in the neural firing frequencies and eye position (θ_E).

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