POINT PROCESS ANALYSIS IN THE PHYSIOLOGICAL STUDY OF HUMAN NYSTAGMUS

by

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ABSTRACT

This work is concerned with the application of signal analysis techniques and computer methods to the study of human vestibular and optokinetic nystagmus. It is comprised of essentially two parts.

In the first part the rhythmic nature of the occurrence of the saccadic components during nystagmus is analyzed in terms of the intervals between saccades. The technique of point process analysis is used. It is found that there is a striking similarity between the interval statistics of the two types of nystagmus, and there is a characteristic change in the rhythm of nystagmus with intensity.

The second part is concerned with the study of the mechanism of optokinetic nystagmus with emphasis on, (1) the retinal contribution, (2) the effects of volition and (3) some considerations on the validity of classifying optokinetic nystagmus into several distinct entities as proposed in the literature. A major finding is that an area on the central portion of the retina subtending approximately 20 degrees of the visual field is normally responsive to optokinetic stimulus. Stimuli outside this area produce no optokinetic nystagmus unless they are facilitated by attention.

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CHAPTER 1

INTRODUCTION

Types of nystagmus considered in this thesis are involuntary eye movements resulting from stimulation of either the vestibular or the visual system. These eye movements are produced by physiological reflexes which serve the function of stabilising the visual image on the retina. When the head is rotated relative to the environment, the motion sensors within the vestibular organ are stimulated, which in turn causes vestibular nystagmus. When the visual environment is moved relative to an observer, the moving image on the retina produces an optokinetic stimulation, which in turn evokes optokinetic nystagmus. In both cases, the eyes move involuntarily relative to the skull so that the visual image remains relatively fixed on the retina, this movement is called the compensatory eye movement. The compensatory eye movement is interrupted by another involuntary flick (or saccade) in the opposite direction to fixate on a new image. These compensatory and saccadic movements occur repetitively resulting in ocular nystagmus.

The record of eye movements during vestibular or optokinetic nystagmus show typical tracings of saw-tooth like waveshapes. The compensatory eye movement is often referred to as the slow component or slow phase of nystagmus while the saccadic component in the opposite direction is called the quick component

(or phase) or the fast component (or phase).

Early interest in nystagmus was mainly aroused by its clinical diagnostic significance. For example, absence of nystagmus under adequate stimulation or the presence of spontaneous nystagmus without stimulation are often signs of pathological conditions. More recently, there has been a strong desire to develop the potentials of these diagnostic tools. The study on nystagmus has also been accelerated by man's venture into the unnatural environments of the outer space and the deep sea, and by the advent of sophisticated machinery and high speed vehicles which often dictate the consideration of man as an integral part of the system design. All these conditions require the detailed understanding of man's sensory reflexes. Thus the vestibular and the visual systems have been subjected to intensive studies by workers from different disciplines.

However, from published work on vestibular and optokinetic nystagmus, it is apparent that the mechanism of the slow component is considerably better understood than that of the saccadic component. In particular, the occurrence of the saccadic components is known to be somewhat random, but the nature of which has not been studied in depth. Past work further indicates that a great deal more is known about the pathways of the vestibular nystagmus compared with those of the optokinetic nystagmus, and that there exist several unresolved controversies concerning the mechanism of optokinetic nystagmus. The study of the occurrence of the saccadic components during nystagmus, and the enquiry into

some aspects of the mechanism of optokinetic nystagmus constitute two principal themes of this thesis.

It is useful to consider briefly the factors which appear to have contributed to a better understanding of the vestibular system compared with the visual-oculomotor system. In the past 15 years, special attention has been placed on the vestibular system study mainly because of the space exploration programs. Vestibular nystagmus has been widely used as an objective measure of vestibular response resulting in its increased understanding. Furthermore, the basic vestibulo-ocular reflex involves a comparatively simple pathway which is phylogenetically very old and does not have great variation in different species. Thus, more direct inference to man can be made from animal experiments. At present, the mechanism of the saccadic component in vestibular nystagmus is still not well understood, but considerable knowledge has been gained on the slow component.

In the visual-oculomotor system, the evolutionary process of increasing encephalisation among higher animals seems to have resulted in different visual-oculomotor pathways in different animals. This makes it difficult to make direct inferences to man from animal experimental results. Oculomotor system research is further complicated by voluntary and involuntary eye movements. Most of the basic research so far has emphasised voluntary movements, both saccades and smooth pursuits. Although the physical characteristics of these eye movements and the overall operating characteristic of the voluntary visual tracking system are now

quite well understood, their neural pathways remain to be explored. Optokinetic nystagmus research has been largely confined to the clinical environment, and apart from the uncertainty of its neural pathway, it is complicated by volition and the different parts of the retina which can be optokinetically stimulated. Several different types of optokinetic nystagmus have been proposed in the literature.

In this thesis the technique of point process analysis is applied to analyze the occurrence of the saccadic components in terms of the time intervals between successive saccadic components (the inter-saccadic intervals). Vestibular and optokinetic nystagmus recordings were converted into point processes, in which each point corresponds to the position in time at which the saccadic component occurs. A characteristic pattern of variation in the statistics of inter-saccadic intervals is demonstrated which may open an avenue for future studies on nystagmus. Multimodal interval distribution occurs under certain conditions and this reveals a significant feature of the nystagmus rhythm generating mechanism.

The second theme of this thesis is the study of some aspects of the optokinetic nystagmus mechanism, in particular the effect of volition, and contribution to optokinetic nystagmus from different parts of the retina. The experimental results disagree with the findings of several authors and this leads to the suggestion that the different classifications of optokinetic nystagmus proposed in the literature should perhaps be reconsidered.

The thesis is organised into four main parts. The technique of point process analysis is described in Chapter 2 with emphasis on presenting the basic concepts and in developing terminology, statistical measures and procedures which are later used in the thesis.

Chapter 3 concerns vestibular nystagmus. Introductory materials and critical reviews are described in Section 3.1. Section 3.2 analyses the inter-saccadic interval characteristics of vestibular nystagmus. Section 3.3 describes a stochastic model which simulates the generation of saccadic components and compares the results with the clinical and experimental results. Although the results simulated were based on those of vestibular nystagmus, it became clear later that the model could be readily applied also to optokinetic nystagmus.

Chapter 4 concerns optokinetic nystagmus. The first two sections are organised in a manner parallel to those in Chapter 3. However, Section 4.3 is devoted to the study of retinal contribution to optokinetic nystagmus.

Chapter 5 recapitulates, discusses and correlates the main experimental results of the thesis. Some speculations and recommendations for further investigations are also given.

The major contributions of this thesis are presented in the Summary.

In Appendix 1, a useful contribution to instrumentation in nystagmus recording is described. The nystagmus waveform is idealised and mathematically formulated. A method is introduced

to estimate the percentage harmonic power transmitted for a given bandwidth of recording. The theoretical prediction was confirmed by a digital computer spectral analysis of a clinical record.

Finally, Appendices 2,3 and 4 describe background materials for the thesis.

CHAPTER 2

POINT PROCESS ANALYSIS IN BIOLOGICAL RESEARCH

2.1 INTRODUCTION

A point process is a sequence of events occurring in time or space. The events are assumed to be indistinguishable except for their time or space of occurrence. From a statistical point of view, the only point processes of interest are those which exhibit at least some degree of randomness in their occurrence, and these are called stochastic point processes. Typical examples are the emission of particles from a radioactive source, the passing of vehicles at a point on the road, the series of failures of a computer, the arrival of patients at an emergency department, or the occurrence of impulses in some nerve fibers. A point process may also be derived from a continuous waveform, such as the occurrence of waveform maxima, or the axis or threshold crossings of a signal. The occurrence of saccadic components in a nystagmus recording is another example which will be analysed in this thesis.

The analysis of point processes can enter different levels depending upon the purpose of the investigator. One investigator might be interested in obtaining some convenient statistical parameters as a means of data reduction to describe, compare, or classify the processes. Another might want to study the nature of the process generating the sequence. That is,

to find out whether the process is truly random with successive events independently generated, and if so by what probability law these events are likely to be governed, and if not, then what are the correlations among the events. Examples of these uses in general are given by Cox and Lewis (1966). Many biological applications can be found in Moore et al (1965).

2.2 BASIC CONCEPTS AND TERMINOLOGY

In general, two types of statistics are available to describe a point process (Cox and Lewis, 1966; Sayers 1970). The studies of the times between events leads to interval statistics, and the study of the occurrence of events as a function of time (times to events) leads to event statistics They are equivalent only in their complete descriptions of the point process, and if a statistical analysis is based only on first and second order properties, the two sets of statistics provide different information about the process. The following description will be based on interval statistics, and the useful event statistical measure, namely the expectation density will be calculated from interval data.

The intervals between events of a stochastic point process are regarded as being drawn, not necessarily independently from a population which obeys some probability distribution such as a Poisson, Gaussian, or Gamma distribution. If that

distribution, together with all its parameters such as mean, variance and all higher moments do not vary with time of observation, the stochastic point process is stationary. If the distribution itself, or any of its parameters varies with time, then the process is non-stationary. For example, in neural spike processes, non-stationarity could result from a change in firing rate caused by stimulation or any other disturbances. A non-stationary process is often a process with a trend. The investigation of stationarity is usually the first step of analysis because the majority of statistical methods are based on the assumption of stationarity. Confusing conclusions may result if the effects of non-stationarity are not taken into account.

Order-dependence between successive intervals is a very important consideration in point process analysis. The question often asked is: Has each interval been independently drawn, in a statistical sense, from the probability distribution of the process, or have the preceeding intervals affected the lengths of the following intervals ? If the latter is the case, the point process sequence is said to be order-dependent or serially correlated or non-recurrent, Otherwise, it is said to be order-independent, (serially uncorrelated, recurrent).

If the process is found to be stationary and also order-independent, it is called a renewal process. This term originated during the early development of point process analysis for the study of component replacement in industrial plants

(Cox, 1962). The attractive feature of a renewal process is that the interval distribution completely characterizes the process. The order dependence between the inter-saccadic intervals of a spontaneous nystagmus recording will be examined in some detail in this thesis.

When successive intervals are not independent, then much more complicated descriptions are needed. The elaborate statistical measures which are required for a reasonably complete description may themselves be too complicated to analyse or compute, and their practical utility becomes questionable. Thus, in practise, analysis is often limited to a few low order statistics.

2.3. SOME STATISTICAL MEASURES

Let each event of a point process be represented by an impulse occurring at a position in time corresponding to t_k as shown in Fig.2.1.

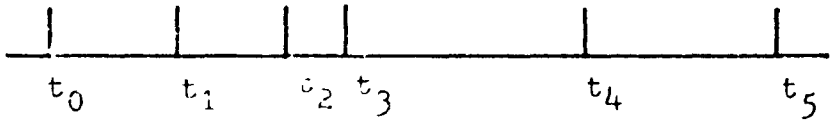


Fig.2.1

This can be mathematically represented by

$$f(t) = \sum_{k=0}^{N} \delta(t-t_k)$$

where $\delta(t)$ is defined as: $\delta(t) = 1$ for $t = 0$; $\delta(t) = 0$ for $t \neq 0$. N is the total number of events in a record. Some useful statistical measures of the process will be described below.

The Interval Histogram of the intervals between successive events can be written as

$$I(T) = \sum_{k=1}^{N} \delta(t_k - t_{k-1} - T)$$

where T is the interval duration and I(T) serves as a finite sample estimator of the probability density function of the intervals between successive events. I(T) is of paramount importance in characterizing the point process.

In practice, T is assigned discrete time dunation $T_b = b\Delta$ where b= 1, 2, 3....., and $\Delta = T_{b+1} - T_b$ determines the resolution of the interval histogram. Tb is often referred to as the bin b . All interval measured between T_{b+1} and T_b is counted in bin b. The total number of counts in bin b are added together to give the height of the bth bar in a histogram. It should be noticed that the time ordering of the intervals is necessarily lost in an interval histogram. Interval histograms of higher orders may also be constructed. This will be discussed later with the expectation density.

The Scatter Diagram is a two-dimensional plot of the three-dimensional joint interval histogram. The joint interval histogram between two successive time intervals can be written as

$$I(T_1, T_2) = \sum_{k=2}^{N} \delta(t_{k-1} - t_{k-2} - T_1)\, \delta(t_k - t_{k-1} - T_2)$$

where $I(T_1, T_2)$ serves as a finite sample estimator of the probability density function which describes the probability of finding an interval T_1 followed by an interval T_2. The definition of a T_1, T_2 pair between adjacent intervals is illustrated in Fig.2.2

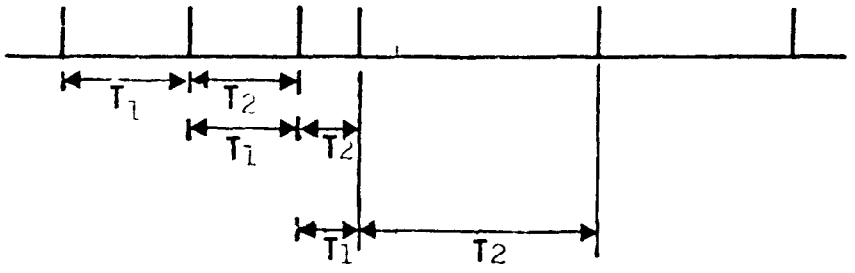


Fig. 2.2

In practice, the joint interval histogram is often called a scatter diagram. The abscissa represents the duration of T_1, while the ordinate represents T_2. Thus each point on the diagram represents a pair of adjacent intervals. In an oscilloscope display, the point is produced by intensifying the corresponding coordinate position.

The scatter diagram can be used to examine certain types of recurring time patterns in the interval sequence. For example, if there is a tendency for short intervals to be followed by long intervals, the display will show a cluster in the upper left region. If the tendency is for long intervals to be followed by short ones, the display will show a cluster in the lower right region. An overall upward trend of 45^0 indicates positive correlation between successive intervals; that is, short intervals tend to be followed by short ones, and long ones by long ones. If successive intervals are independent, the joint interval histogram will be symmetric about a 45^0 line through the origin. This symmetry test is a necessary but not sufficient condition for statistical independence of successive intervals.

It must be noted that, as in the ordinary interval histogram, time information is lost in such a plot unless the order in which a joint interval histogram is filled is observed.

Plot of Row and Column Means of the scatter diagram provides another method of testing independence of successive intervals. Each column or row of the scatter diagram represents a conditional interval histogram. The statistical independence of successive intervals requires that the probability density of all the intervals preceeded or succeeded by an interval of a particular duration be independent of the duration of that interval. Thus, the test of independence is reduced to the

problem of comparing the conditional interval histogram represented by the rows and columns of the scatter diagram. It is known that two probability densities are the same if they have the same mean, variance, and all higher moments. In the case here, the column and row means represent the means of the corresponding conditional interval histograms, and for these histograms to remain identical, it is essential that their means must be the same. Thus, for statistical independence, the row and column means should fall on two straight lines parallel to the coordinate axes. Again, this is a necessary but not a sufficient condition.

The Serial Correlogram is a plot of the serial correlation coefficients as a function of order or lag. The serial correlation coefficient is defined as

$$\varphi_j = \frac{\frac{1}{(N-j)}\sum_{i=1}^{N-j}(T_i - \bar{T})(T_{i+j} - \bar{T})}{\frac{1}{(N-1)}\sum_{i=1}^{N}(T_i - \bar{T})^2}$$

where φ_j is the serial correlation coefficient of order j

j = ...-1,0,1,.....is the order or lag

$\bar{T}$ is the estimated mean interval

T_i is the i th interval

The values of the serial correlation coefficients range between -1 and 1, and provide quantitative measures

of the correlation between intervals. If all the intervals were independent, then the coefficients of all orders would be zero. A constant value of the coefficients usually indicates a long term trend in the interval data.

The serial correlogram may also show characteristic patterns which could indicate the nature of departure from independence among the intervals. This has been demonstrated by Perkel et al (1967) using data from computer simulated neuronal spike trains with known characteristics. They found that cyclic variations in firing rate produced a damped oscillation in the serial correlogram. Alternation between long and short intervals resulted in persistent alternation in sign of the coefficient. Irregular bursts of spikes are characterized by negative serial correlation coefficients for low order, followed by slightly positive and then zero correlation coefficients.

The Expectation Density E(T) specifies the probability of encountering any event as a function of time after a given event. Since any event encountered must be either the first, second, third event after the event at time zero, the expectation density is actually the sum of the interval histograms of all orders. Thus

$$E(T) = \sum_{k=1}^{\infty} I_k(T)$$

where $I_k(T)$ is the interval histogram of k th order: the first order interval is the time elapsed from an event to the next following event; the second order interval is the time elapsed between an event and the second following event. An n th order interval is the sum of n consecutive first order intervals and is spanned by (n+1) consecutive events

Given a sequence of interval data, a computer construction of the expectation density is done by forming all possible higher order intervals = T_1+T_2 , T_2+T_3....., $T_1+T_2+T_3$, $T_2+T_3+T_4$....., $T_1+T_2+T_3+T_4$, $T_2+T_3+T_4+T_5$..... up to a selected upper order. These intervals are then collected into time bins of incremental width to compile the histograms of different orders which are added together to form the expectation density. Instead of combining them to produce the expectation density, some authors use the higher order interval histograms directly for analysis (Rodieck et al 1962, Sayers 1970).

A useful role of the expectation density is to resolve an event sequence into one or more separate periodic or quasi-periodic components which might be present. In neural spike train analysis, a plot of the spike interval histogram revealing Poisson-like distribution may lead one to falsely conclude that the process is that of Poisson and is therefore completely random; however, an examination of the expectation density of the sequence may reveal periodic components, suggesting that the sequence may be the pooled result of several spike trains

including some with periodic firing (ten Hooper and Reuver, 1966). The period of occurrence may not show up in the interval histogram at all due to the 'splitting of intervals' as a result of the pooling process. For example, in foetal electrocardiogram recordings, the foetal R peak, besides being buried more or less in muscle 'noise' activities, is also obscured by the maternal QRS complex. The expectation density function has been used to resolve the separate components (ten Hoopen, 1967).

It should be pointed out that the expectation density is actually an auto-correlation of the event sequence. It is sometimes called the autocorrelation (Yagiwara, 1954) whereas it should be precisely called the event autocorrelation (Sayers, 1970). There is much confusion between this and the serial correlogram. The event autocorrelation is a function of time, while the serial correlogram is a function of the sequence number, which is an integer, of the intervals. The two functions need not correspond at all. For example, a pace maker cell that fires at nearly uniform intervals will have a strongly oscillating autocorrelation, whereas the serial correlogram may be positive, negative, oscillatory or zero depending on the order-dependence of the process.

2.4 DISCUSSION

In using point process analysis, the investigator is often faced with two basic questions, namely, what pattern of variation should one expect to see from the different statistical measures, and what variations in the experimental results are significant. Several practical approaches to these problems are discussed below.

If certain characteristics are suspected to be contained within experimental data, then it is often possible to simulate these characteristics as a model on a computer and analyse the model results for salient features which can be used as references in analysing the experimental data. This technique has been used by Perkel et al (1967), and ten Hoopen and Reuver (1966).

In assessing the significance of variations in the experimental results, if the sample distribution of the statistics is known, then standard statistical methods of testing significance can be used. On the other hand, the sample distributions are often not known, and other more empirical methods have to be used. Here again computer model results may be useful; with the use of non-parametric statistics the experimental results can be tested against the model results.

In testing the significance of the order-dependence among data, one useful approach would be to subject the

original data sequence to random shuffling, which destroys any order-dependence among the samples and then converts the sample to one from the corresponding renewal process. The recomputed statistical measures provide the control cases in which any residual dependence among data are in fact due to statistical fluctuation; a convenient visual comparison can then be made with results from the corresponding unshuffled data. The use of this technique will be applied in section 3.3.

Finally, it is noted that there is a lack of universal and powerful statistical measures. For example, the results from the scatter diagram, and its row and column means plots each provide a necessary but not sufficient test for order-dependence; the serial correlogram and to some extent the expectation density, must be used to supplement the finding. Further, the sensitivity of a statistical measure may be process dependent. For example Perkel et al (1967) showed that ±10% variation in the mean interval in a 'noisy' pacemaker, which arises from a Gaussian process with a narrow spread, was reflected quite clearly in the serial correlogram. However, for the same percentage mean interval variation in a Poisson process, the serial correlogram hardly showed any difference from that of the original process without the variation. On the other hand, the same authors showed that the expectation density was more sensitive to change in a Poisson process than the serial correlogram. All these point to the fact that each statistical measure may contribute a part of the entire

picture about the process and many different measures must be used to analyse a process to obtain a better understanding.

CHAPTER 3

VESTIBULAR NYSTAGMUS

3.1 INTRODUCTION

3.1.1 Gross Anatomy and Physiology of the Vestibular System

(Ref. Brodal et al (1962), Outeridge (1969))

The bony labyrinth is a system of cavities and canals in the petrous portion of each temporal bone. It contains a clear fluid, the perilymph. Submerged in the perilymph is a membranous labyrinth consisting of three parts, cochlea, vestibula, and semicircular canals. All parts of the membranous labyrinth are filled with endolymph and are in communication with one another.

The cochlea is the sensory organ of the auditory system while the vestibule and semicircular canals contain receptors of the vestibular system (Fig. 3.1). The vestibule consists of the utricle and the saccule. A small patch of sensory epithelium called the macula is found on the wall of the utricle and also on the wall of the saccule. Projecting from the macula surface are otolithic receptors, which are cilia covered with a cap of jellylike substance embedding crystals of calcium carbonate (otoconia). The otolithic receptors respond to gravity and linear acceleration, being especially sensitive to tangential shearing forces because the otoconia are more dense than the surrounding endolymph. In the saccule, the macula is oriented in the sagittal plane, and the cilia are directed laterally. In the utricle the macula lies in the horizontal plane with the cilia directed

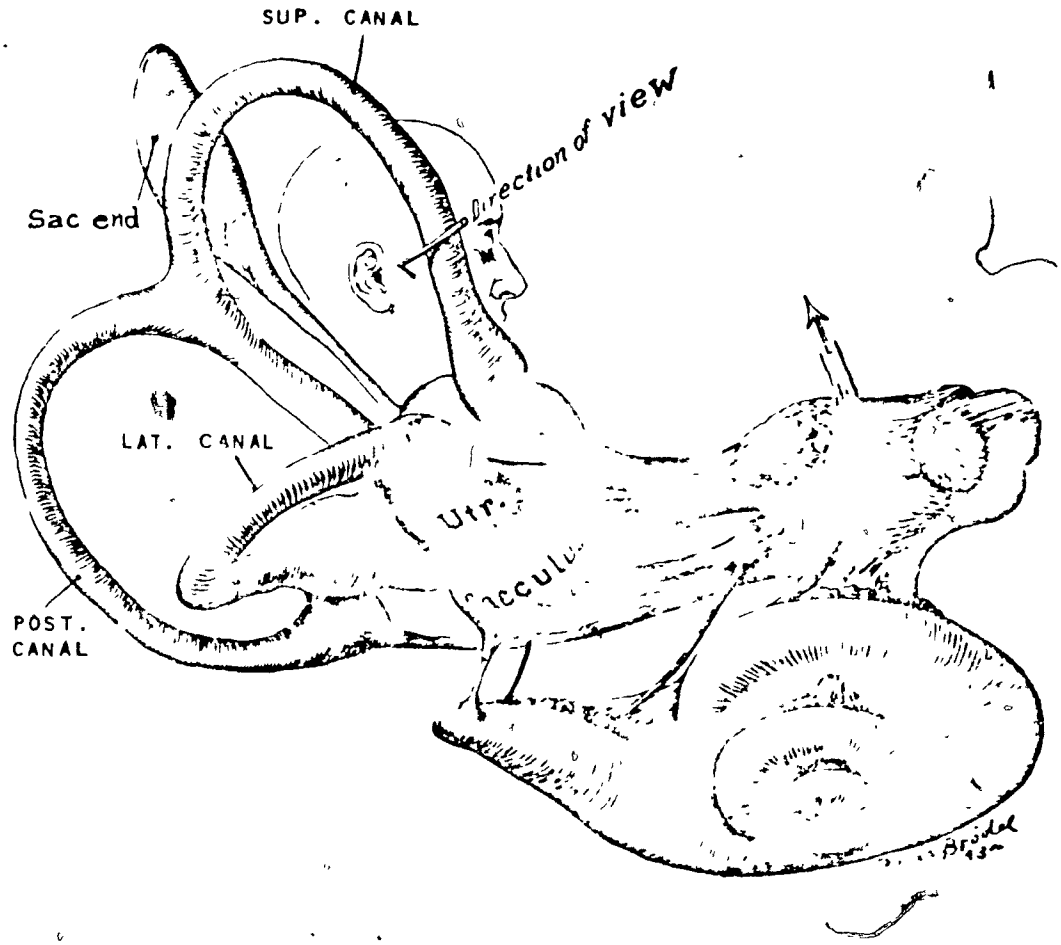


Fig. 3·1 SEMI-DIAGRAMATIC DRAWING OF THE HUMAN VESTIBULAR APPARATUS (From M. Hardy, Anat. Rec., 59:412, 1934

upward. In both locations, the maculae are prolonged slightly onto the curved surface of their respective receptacles, both prolongations being predominantly directed in the frontal plane. Thus, macular surfaces are provided for each of the three planes of space.

The three semicircular canals lie in three planes approximately orthogonal to each other, with the lateral (or horizontal) semicircular canals tilted backwards in man about 30° from the classical anatomical horizontal plane of the skull. Each canal describes about two-thirds of a circle and terminates on an enlarged portion of the duct called the ampulla. The ampulla contains two structures, the cupula and its base, the crista. The cupula containing sensory cilia projected from the crista, is a gelatinous structure which acts as a fluid-tight elastic valve across the path of canal endolymph. When the canal is subjected to angular acceleration, the inertial reaction of the endolymph moves the cupula which in turn stimulates the sensory cilia of the crista. The two sets of semicircular canals on each side of the head sense angular head movement in the three dimensional space.

The primary afferent neurons from the cristae and maculae combine to form the vestibular portion of the eighth nerve. They enter the internal auditory meatus within which is located the vestibular ganglion. Axons of the ganglion pass through the internal auditory canal and reach the upper medulla. Most of these fibers end in four vestibular nuclei which are clustered in the lateral part of the floor of the fourth ventricle. Afferents from

the semicircular canals terminate in superior, medial and inferior vestibular nuclei while the macular afferents connect the lateral and inferior vestibular nuclei. Some primary afferent fibers are distributed to the vestibula portion of the cerebellum. In addition to the afferent fibers, there are also efferent fibers in the vestibular nerve. Extensive references are cited by Outerbridge (1969).

From the vestibular nuclei, the lateral vestibulo-spinal tract descends (uncrossed) from the lateral vestibular nucleus: the medial tract (with both crossed and uncrossed fibers) descends mainly from the medial and spinal vestibular nuclei. The vestibular nuclei also have extensive reciprocal connections with the cerebellum. The vestibulo-spinal and vestibulo-cerebellar connections are responsible for postural coordination. The precise nature and termination of ascending fibers from the vestibular nuclei is not completely known. However, it is believed that the majority of ascending fibers travel in the medial longitudinal fasciculus (Brodal et al, 1962). Connections to the thalamus (Carpenter and Strominger, 1965; Deecke et al, 1971) and the cortex (Kornhuber and da Fonseca, 1964; Schwarz et al,1971) have been reported. Connections from vestibular to oculomotor nuclei have been extensively investigated, particularly in connection with horizontal conjugate eye movements. This will be described in the next section together with a consideration of the mechanism of nystagmus.

3.1.2 The Vestibulo-Ocular Reflex Arc

The simplest form of neural reflex arc consists of two neurons, the sensory afferent and the motor efferent (Lorente de No, 1933). However, in most reflex arcs, the connection between the afferent and the efferent is relayed by one or more internuncial neurons. In certain reflex mechanisms, in addition to internuncial chains, there is a special group of connecting neurons between the sensory termination nucleus and the motor neurons, and the system works as a functional unit (Lorente de No, 1933, Szentagothai, 1950).

The vestibulo-ocular reflex arc comprises at least two kinds of circuits (Szentagothai, 1950, 1964; Brodal et al, 1962). The elementary three neuron arcs were described by Szentagothai. The internuncial neuron lies in the medial longitudinal fasciculus, which relays the afferent signals from the vestibular nuclei to the oculomotor, trochlea, and abducens nuclei. Szentagothai inferred from experimental observations that the elementary three neuron arc established the predominant correlation between a given crista of the semi-circular canals and two of the six extra-ocular muscles in each eye. The crista of the superior semicircular duct has a predominant connection with the ipsilateral superior rectus and the contralateral inferior oblique: the crista of the posterior duct with the ipsilateral superior oblique and the contralateral inferior rectus: the crista of the horizontal duct with the ipsilateral medial rectus and the contralateral lateral rectus.

Besides the basic three-neuron arc, Lorente de No had demonstrated earlier that numerous internuncial pathways passed through the reticular formation. The exact connections are not known but they most probably involve chains or even groups of neurons (Lorente de No, 1933: Duensing and Schaefer 1957, 1958: Gernandt, 1964). Lorente de No proposed that the rhythmic bursts of impulses to the extra-ocular muscles, which produce the saccadic components during nystagmus, originated from this area. The different views on the anatomical origin of this rhythmic activity will be considered in the next section.

There are also vestibulo-ocular pathways through the cerebellum as is evident from the fibers branching from the primary vestibular nerve to enter the cerebellum and the extensive reciprocal connections between the vestibular nuclei and the cerebellum. Reports on cerebellar influence of eye movement have been given by Cohen et al (1965), Collewijn (1970) and Kornhuber (1971).

3.1.3 A Survey and Discussion of the Mechanism of Vestibular Nystagmus

The mechanism of vestibular nystagmus has been a subject of extensive study. It is now well established that the slow component is initiated from the labyrinth while the saccadic component is entirely central. The elementary three-neuron arc via the medial longitudinal fasciculons described by Szentagothai forms the basic skeleton pathway for the slow component. In addition, Lorente de No (1933) demonstrated that the reticular formation also contained pathways mediating the slow component. The origin and

pathways of the saccadic component, on the other hand, are still not well understood, and before considering different views on this subject, the basic mechanism for the slow component during horizontal vestibular nystagmus based on the elementary three-neuron arc will be described.

With reference to Figure 3.2, a clockwise rotation of the head causes the endolymph of the left lateral semicircular canal to flow toward the ampulla (ampullo-petal flow) and the endolymph of the right lateral semicircular canal to flow away from the ampulla (ampullo-fugal flow). These in turn cause the firing rate of the left vestibular nerve to increase and that in the right vestibular nerve to decrease (Jones, Barry and Kowalsky, 1964; Lowenstein, 1966). The change in firing is relayed to the oculomotor and abducens nerves causing conjugate compensatory eye movement in a counter-clockwise direction which serves the function of retinal image stabilization. The angular velocity of this compensatory eye movement is approximately proportional to the angular velocity of the head over the frequency range of head rotation from 0.1 to 5 Herz (Jones and Milsum, 1965: Outerbridge, 1969). This slow component of eye movement is interrupted by a rapid saccadic component in the opposite direction, and the two components repeat themselves, resulting in ocular nystagmus. The views concerning the saccadic component are considered below.

Evidence seems to suggest that the saccadic component is mediated mainly via a more complicated pathway than the

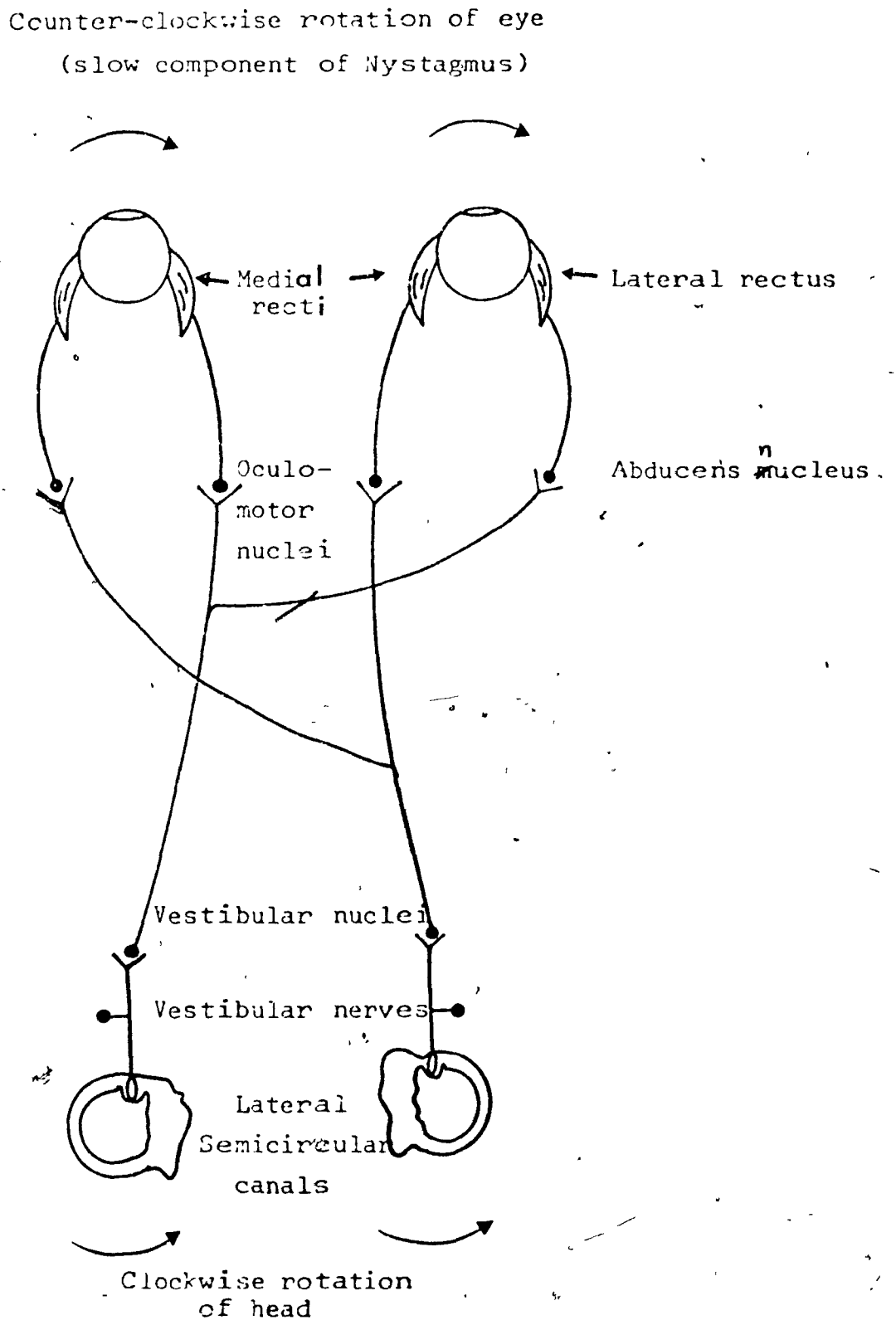


Fig. 3.2 Basic mechanism of vestibular nystagmus

elementary three-neuron arc. It was found that certain drug intoxication, such as ether (McIntyre, 1939) or barbiturate (Nathanson and Bergman, 1958; Bjegvod, 1962) converted nystagmus into tonic deviation of the eyes in the direction of the slow component during vestibular stimulation. The deviation of the eyes would last for a period of time in which nystagmus would normally occur if drugs were not given. The interpretation of this was that tonic eye deviation was 'nystagmus' without the saccadic components, and since drugs acting on the nervous system generally have a relative specificity of areas, that is, affecting some areas or neuron systems more profoundly than other areas or neuron systems, the finding of selective abolition of the saccadic component by drug suggested a disruption of the more complex vestibulo-ocular pathways presumably through the reticular formation. More direct evidence was provided by Barany (1907, cited by Lorente de No), who observed in a patient with a lesion in the pons close to the abducens nucleus that the saccadic components in nystagmus as well as voluntary eye movements were absent. In experiments Lorente de No (1933) induced extensive lesions in the reticular formation of rabbits, and upon vestibular stimulation he found tonic eye deviation in the direction of the slow component for the same duration as the nystagmus produced in normal animals.

The anatomical location originating the neural signals for the saccadic components during nystagmus has been for a long time a subject of controversy. The old proposal

(Wald, 1902, cited by Crape, 1965) that they were triggered by proprioceptive signals from the extra-ocular muscles during the slow component when the eye turned as far as possible from the mid-position was strongly contradicted by experimental evidence. During nystagmus the saccadic component could actually occur at any position of the eyes even when the saccade would place the eyes further away from its neutral mid-position. Further, after cutting all the nerve connections to the extra-ocular muscles on both eyes of cats to eliminate the different proprioceptive signals, McIntyre (1939) still recorded from nerve ends impulses characteristic of normal nystagmus; he demonstrated beyond doubt that the saccadic components were not triggered by proprioceptive signals from the extra-ocular muscles. Other areas eliminated as essential sites originating the saccadic components included levels above the oculomotor nuclei and below the vestibular nuclei (Lorente de No, 1933), the cerebellum (Brodal et al, 1962), the labyrinth (Spiegel, 1926, cited by Spiegel and Price, 1939: Dohlman, 1938), and the oculomotor nuclei (Spiegel, 1929, cited by Spiegel and Price, 1939). The remaining unresolved areas are the vestibular nuclei and the reticular formation.

The inability of the remaining mechanism to produce saccadic components in nystagmus after lesions in the reticular formation led Lorente de No (1933, p. 285: 1938, p. 236) to conclude that the impulse activity

created in the vestibular nuclei was a constant one, and that the rhythm center must be located in the reticular formation. The lack of sophisticated equipment in those days to perform intracellular experiments must have forced Lorente de No to rely on gross experimental observations. In proposing a neural mechanism in the reticular formation for generating the saccadic components of nystagmus Lorente de No (1938) stated among other things, that:the impulse activity in the vestibular nuclei was a constant one; the relaxation of the agonist (the extra-ocular muscle which contracts during the slow nystagmus component) is not attributable to an active inhibitory process but only to a lack of excitatory impulses (Lorente de No, 1933b); the turning points in the antagonist are not synchronised with those of the agonist (Lorente de No, 1935). The latter was taken to suggest that in generating the saccadic impulses to the antagonist, there was a time delay circuit through the reticular formation. On the other hand, Spiegel and Price(1939) pointed out that Lorente de No's experimental results were obtained during the acute stage after the operation. In Spiegel's own experiments, results similar to those obtained by Lorente de No were obtained soon after lesion was induced in the reticular formation, but after a few days, nystagmus with saccadic components returned. Spiegel stated that the saccadic components of nystagmus must be originating in the vestibular nuclei.

More recently, Lachmann and Bergmann (1961) recorded rhythmic activities in the vestibular nuclei

synchronised with nystagmic eye movements. They felt that the vestibular nuclei must, at least in part, be responsible for the nystagmic rhythm. McCabe (1965), however, found that the lesions induced on different vestibular nuclei reduced the speed of the slow component but did not alter the speed of the saccadic, whereas saccadic components which returned one or two weeks after extensive lesions in the reticular formation "were seldom normal in speed, frequency and amplitude." McCabe supports the theory that the saccadic component must be generated in the reticular formation.

The most recent work with modern techniques of intra- and extra-cellular recording was reported by Maeda, Shimazu and Shinoda (1972). In addition to recording rhythmic activities in vestibular nucleus neurons synchronised with rhythmic ocular motorneurons during nystagmus, they also found active inhibition from the vestibular nucleus neurons to the ocular motorneurons. Further, the inhibition and facilitation of the agonists and the antagonists occurred almost simultaneously. Maeda et al refuted Lorente de No's assumption described earlier and supported the proposal that the nystagmic rhythm originated in the vestibular nuclei. They hypothesized that mutual inhibitions of the vestibular nuclei on the two sides of the brain, reported by Ladpli and Brodal (1968) and earlier workers, might lead to the rhythm production. Such a mechanism had been suggested to be responsible for rhythmic activities in many other biological systems; an electronic model simulation

by Harmon (1964), and Barron and Lewis (1966) had produced similar results to experimental findings. However, it remains to be investigated if such a mechanism can also simulate the characteristic pattern of variation in the rhythm of vestibular and optokinetic nystagmus demonstrated by the analysis results of this thesis. This question will be further discussed in section 5.1.

All the above experimental findings and controversial claims may point to the possibility that in reality a more complicated mechanism is at work, and perhaps other possible interpretation of the results should be considered. The presence of rhythmic activities in the vestibular nuclei may not necessarily imply that the vestibular nuclei are the generating center. It is possible that the rhythm is a result of modulation originating elsewhere. Hornhuber and da Fonseca (1964) reported neurons in the vestibular cortex showing modulation of discharge in the rhythm of vesticular nystagmus. The modulation disappeared when the eyes are closed. Further, modulation of firing rate in the efferent fibers of vestibular nerves before saccadic eye movements was reported by Dichgans (1972), who found that approximately 10% of the units recorded from the peripheral vestibular nerve of relaxed, unanaesthetized rabbits and goldfish displayed a characteristic modulation of their resting discharge beginning 10 to 100 milliseconds before a saccadic eye movement or the fast phase of nystagmus.

It is difficult to accept the view that the vestibular

nuclei alone originate the rhythmic activity and the reticular formation serves only as a pathway transmitting the activity to the oculomotor nuclei (a possibility proposed by Maeda et al, 1972). It is well known that nystagmus is strongly affected by arousal level of the subject (Collins, 1962; Crampton, 1964), and it is also generally known that the reticular formation is closely associated with arousal (Henry Ford Hospital Symposium, 1958; Guyton, 1966). In collecting nystagmus records for this thesis, it was frequently observed that mental activity of the subjects clearly altered the rhythm of both vestibular and optokinetic nystagmus (see section 4.2.3). If the reticular formation served only as a pathway, it might affect the magnitude (or gain) of the signals being transmitted, but would be unlikely to alter the rhythm.

It is possible that the vestibular nuclei and the reticular formation are each capable of generating an independent rhythm, and when they are connected together to function as a unit, their individual rhythm will be entrained (or synchronised) to a common rhythm. A good example for the concept is that in the heart the sinus node and the atrio-ventricular node are each capable of initiating an independent rhythm of contraction. However, the heart as a whole beats at a common stable rhythm. Simulation of their interaction by a system of coupled electronic relaxation oscillators was carried out by Roberge and Nadeau (1966, 1967). They found that a steady state of synchronised

rhythm was achieved with a frequency intermediate between the free-running rates of the two oscillators and determined by the relative amounts of direct and feedback coupling. Several experimental results were explained in terms of this model.

The role of the cerebellum in the saccadic component generation should perhaps be more closely investigated. From his experiments on cerebellectomised rabbits, Collewijn (1970) concluded that the cerebellum was indispensable for correct programming of the saccadic components in optokinetic nystagmus of that animal. It is quite probable that the rhythmic generation in the reticular formation is not localised in a small area, but distributed over a region so that arousal and connections from other inputs such as cortical influences and visual-oculomotor pathways may modify the rhythm. The idea that multiple rhythmic areas are entrained to produce the resultant nystagmus rhythm is very attractive when it is considered that a common central mechanism may exist to serve both vestibular and optokinetic nystagmus. It will be demonstrated in this thesis that there are striking similarities in the inter-saccadic interval statistics of vestibular and optokinetic nystagmus. These findings provide a powerful support for the hypothesis of a common generating mechanism.

A characteristic pattern of change in the nystagmic rhythm shown by this thesis may also be used to aid neurophysiological experiments in determining the anatomical areas

which are involved in the rhythmic generation. For example, in the experiments by Maeda et al (1972), it would be informative to observe the effect on rhythmic activities recorded from the vestibular nuclei when lesions of various size are introduced into the reticular formation. Conversely, the effect may be observed from the reticular formation when lesions are introduced in the vestibular nuclei or the cerebellum. It is important that the observation should be made not just on the presence or absence of the saccadic components, but also on the deviation in the saccadic rhythm when compared with the normal characteristic pattern of change. Any area which causes a deviation in the characteristic change must be regarded as an integral part of the rhythm generating mechanism.

3.1.4 Methods of Inducing Vestibular Nystagmus

Vestibular nystagmus are commonly induced by rotatory, caloric and galvanic stimulations. Rotation of the head is the most natural form of stimulation, semicircular canals on both sides of the head are simultaneously stimulated and the mechanism of nystagmus production has been described in the preceeding section. Galvanic and caloric stimulations are less natural but have the advantage that semicircular canals in each ear can be separately stimulated. Galvanic stimulation is produced by passing an electric current through the inner ear, by means of skin electrodes. However, its mechanism is not yet well

understood, and some research is concentrated in this area (Weiss and Tole, 1971; Coates 1971).

Caloric stimulation has been widely used in the clinical environment, where nystagmus recording is referred to as ENG (electronystagmography). Responses from separately stimulated ears are compared to yield diagnostic information. Caloric stimulation is produced by water or air irrigation into the ear canal . The temperature change conducted into the semicircular canals causes a convection current flow of the endolymph which in turn deflects the cupula receptors. In a clinical test the patient normally lies supine with the head tilted 30 degrees above the horizon thus bringing the plane of the lateral semicircular canals to a vertical position. If the middle ear is irrigated with cold water, the cooling will result in a downward convection current in the endolymph (ampullopetal flow), which will induce nystagmus with the slow component in the direction of the endolymph motion, or the saccadic component beating towards the unirrigated ear. By convention, nystagmus direction is defined in the direction of the saccadic component. Thus, cold water irrigation to the left ear results in a right beating nystagmus. If hot water is used in the same ear, endolymphatic flow and hence nystagmus direction will be reversed.

Generally, nystagmus in the horizontal, vertical, diagonal or circular direction can be induced, depending on which semicircular canal or groups of semicircular canals are stimulated. In this thesis, only the horizontal nystagmus will be considered.

Four types of nystagmus in the horizontal position will be included, namely, spontaneous, positional, caloric, and alcoholic nystagmus. Only caloric nystagmus as introduced above is definitely of vestibular origin; the origins of the other three types are not sure. Spontaneous and positional nystagmus are usually caused by pathological conditions and their inclusion here under the category of vestibular nystagmus is because the patients from whom the records were obtained were suspected of vestibular lesions, but the final diagnosis has not been confirmed. Alcoholic nystagmus is induced by consumption of alcohol, and the site of alcoholic action in the central nervous system is not clearly understood, although it has been reported that bilateral labyrinthectomy resulted in cessation of alcoholic nystagmus (Cooney, Johnson and Corlett, 1965).

The advantage offered by spontaneous, positional and alcoholic nystagmus is that relatively long recordings can be made which are desirable for statistical analysis.

3.2 INTER-SACCADIC INTERVAL ANALYSIS OF VESTIBULAR NYSTAGMUS

3.2.1 Introduction

Vestibular nystagmus recording has been widely used both in the research laboratories and clinical diagnosis. The main parameters of interest were frequency and duration of nystagmus, and the speed of the slow component. Recently, emphasis has been placed on the speed of the slow component because its mechanism is now quite well understood. (frequency and duration are still used by some clinicians when nystagmus is not recorded but directly observed). In contrast to the slow component, the study of the saccadic component during nystagmus has lagged. The occurrence of the saccadic components during nystagmus has been described in the literature as rhythmic or periodic, and it is generally agreed that a certain degree of randomness exists in the time of their occurrence, however the random properties have so far not been studied in depth.

The study of random occurrence of events require special techniques. The definite onset of each saccadic component makes a nystagmus recording well suited to be converted into a point process, in which each point corresponds to the position in time at which the saccadic component occurs.

The techniques of point process analysis and its application to neuronal research have been reviewed in chapter 2. In the work to be described in this chapter, nystagmus recordings were converted into point processes and their stochastic properties were analysed with the use of digital computers.

Some preliminary graphical displays of the gross characteristics of the inter-saccadic intervals of a spontaneous nystagmus record are presented in section 3.2.4, and a hypothesis that such an interval sequence was generated by a Poisson process was tested and the results rejected the hypothesis.

A technique using dot displays on a compressed scale was found to present a sensitive visual depiction of the variations of inter-saccadic interval pattern and this resulted in the finding of a phenomenon of multi-modal interval histograms in many records. The results led to the consideration in section 3.3 of a possible explanation of this phenomenon as resulting from a simple interaction between the basic physiological processes of neural excitation and inhibition.

3.2.2 Method of Nystagmus Recording

All nystagmus recordings in this thesis were done by the electro-oculography (EOG) method (Shackel, 1967). Bitemporally placed Ag-AgCl skin electrodes (Beckman type 3503) having an electrode area of about 8 mm^2 each were used for the recording. Electrode jelly was applied between the electrode

and the skin. The signal from the electrode amplified by an A.C. coupled differential amplifier with a three-second time constant, except for experiments described in section 4.3 where a D.C. coupled amplifier was used. The differential amplifier (Burr-Brown, type 3061/25) having a differential input impedance of about 50 mega-ohms and the high frequency bandwidth was set at 20 Hz. This bandwidth was found to be satisfactory both by a theoretical and digital computer spectral analysis of nystagmus signals described in Appendix 1. Following amplification, signals were recorded on an FM tape recorder (Hewlett Packard model 3917B) having a bandwidth of 0 to 625 Hz. Computer analysis was later performed on the playback signal from the tape recorder.

3.2.3 Computer Measurement of Inter-saccadic Intervals

Two methods were used to measure the inter-saccadic intervals of nystagmus records. In one method the detection of the onset of a saccadic component was done by a digital computer while in the other the onset of a saccadic component was visually determined and manually marked before measurement by the digital computer.

In the first method, the tape recorded nystagmus record was differentiated by an analogue differentiator resulting in a series of sharp pulses corresponding to each saccadic component (Fig. 3.3) The differentiated signal was fed into an analogue input channel of the LINC-8 computer,

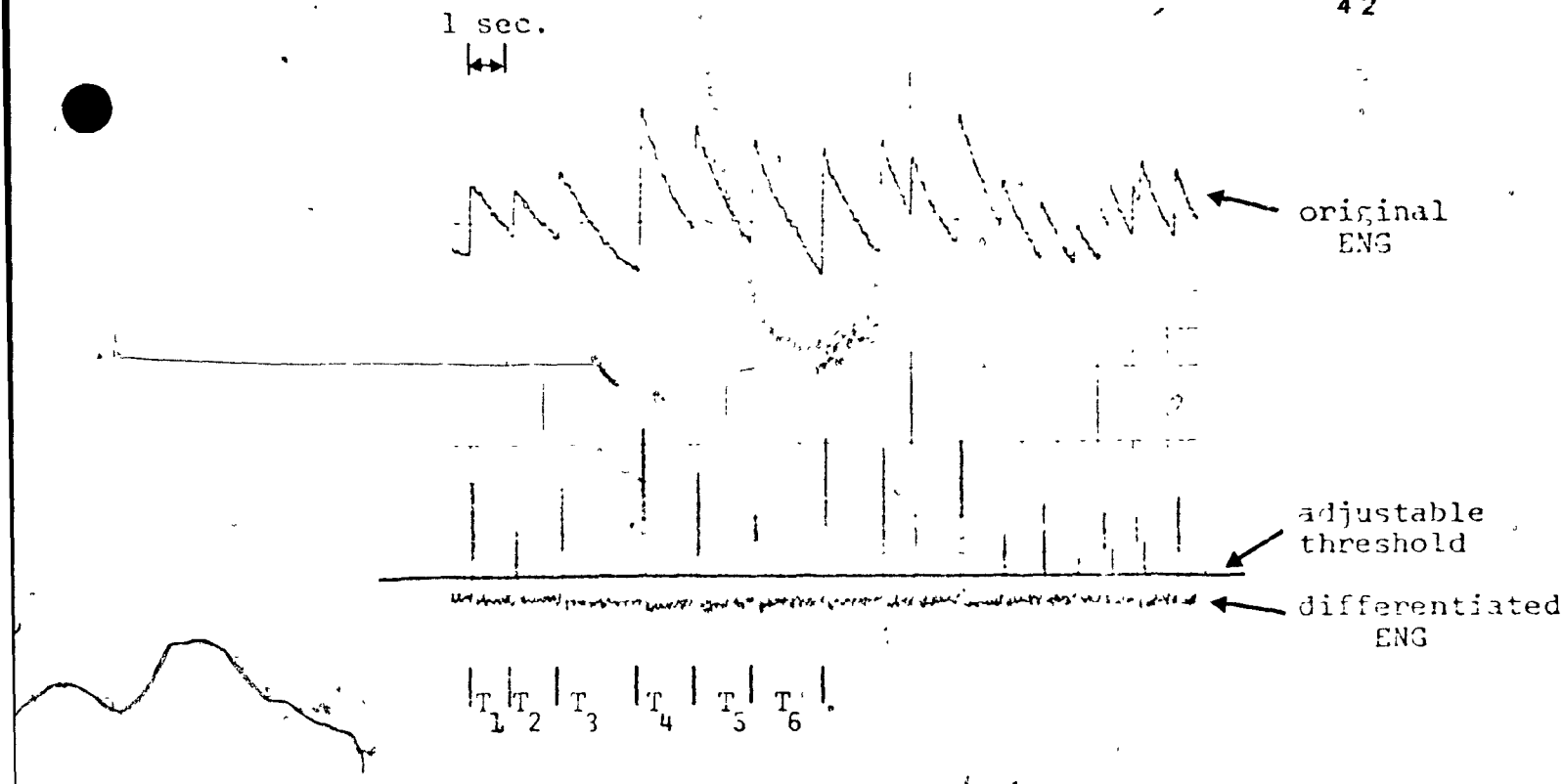


Fig. 3.3 Computer determination of saccadic occurrence times

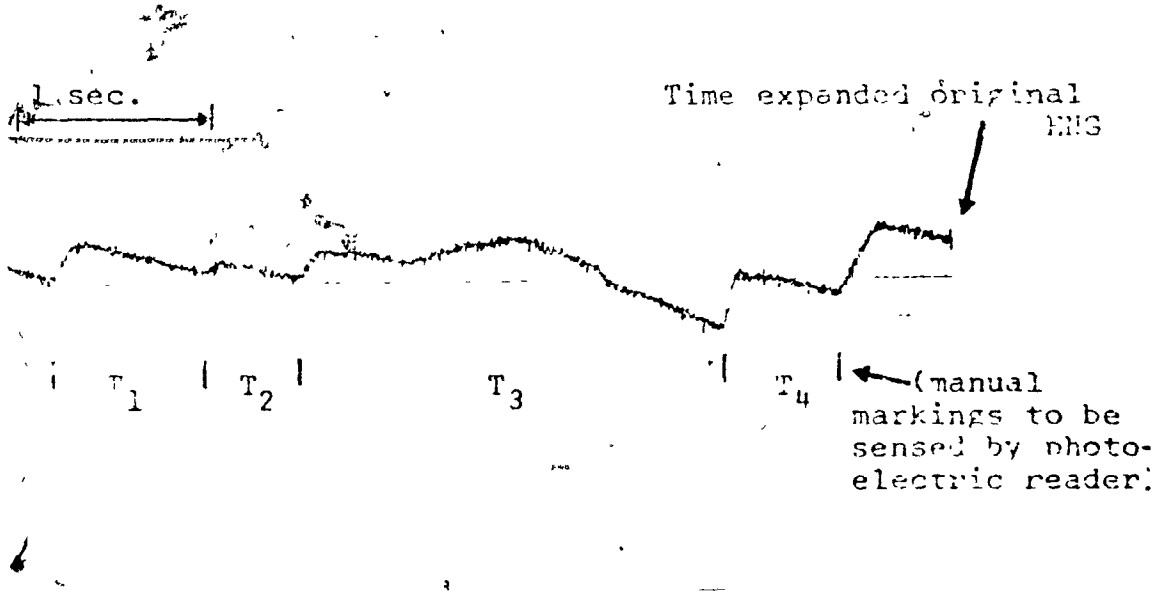


Fig. 3.4 Manual determination of saccadic occurrence times

which digitized and displayed the signal on the LINCSCOPE. An adjustable threshold level was also monitored on the display (Fig. 3.3) and when the differentiated signal rose above the threshold level, the computer would recognize the occurrence of a saccadic component.

The computer then measured the consecutive intervals T_1, T_2, T_3... as shown in Fig. 3.3. The resolution of the interval measurement was one millisecond. The measured interval sequence was stored on magnetic data tape. Before analysis, the interval data was plotted out on a CALCOMP digital plotter, with time scales matched to the original nystagmus recording on a strip chart so that the two could be compared to detect any errors in the measurement (see Fig. 3.5).

In cases of low intensity nystagmus, the saccadic components after differentiation did not always rise above the noise level. This would result in error in the computer recognition of the saccadic components. In such cases the nystagmus recordings were traced out on strip charts with expanded time scales and the corresponding saccadic components marked by visual inspection as shown in Fig. 3.4. The marked strip chart was run through a chart drive on which a photo-electric sensor was installed to detect the occurrence of a mark. Each detection of a mark resulted in a pulse output from the photo-electric sensor which was fed into the LINC-8 computer to signify the occurrence of a saccadic component. The successive intervals between pulses were measured in the same manner as before. Again, the data was checked against the strip chart marking

before analysis. The intervals were measured between saccadic components in the direction opposite to the slow component, and occasional saccades in the same direction as the slow component were ignored. Records analysed were selected from recordings in which saccadic components could be unambiguously observed.

3.2.4 Preliminary Analysis and Testing of the Poisson Hypothesis

In analysing the point process for the first time, graphical methods are convenient for finding quickly the gross features of the data and also in suggesting more formal methods of analysis later. Four graphical displays were used in the preliminary examination of the inter-saccadic intervals derived from nystagmus recordings. Examples of these graphical displays of intervals obtained from spontaneous nystagmus records are shown in figures 3.5 through 3.8.(This patient was suspected to have a labyrinthine lesion).

Fig. 3.5 is a display of the actual point process derived from the nystagmus record. It gives an overall view of the frequency of the occurrence of the saccadic components.

In Fig. 3.6, the relative interval duration represented by the vertical length of the bar was plotted against the interval sequence number. This plot aids in the detection of regularity and trends of the interval. In Fig 3.6 long intervals

Fig. 3.5 Point process derived from a spontaneous nystagmus record. Each impulse represents the on-set of a saccadic component. Scale 1 cm = 5 sec. 512 samples of intervals

Fig. 3.6 Sequential display of interval magnitude
Ordinate scale 1 cm = 0.5 sec.

are observed to occur only occasionally, and no significant trends are evident. Fig 3.7 is a plot of the total number of saccades (ordinate) occurring in the time from the beginning of the process (abscissa). At each saccade, the plot jumps one unit upwards. An important property is that the slope of a line joining any two points on the plot gives the average number of events per unit time for that period. The plot in Fig. 3.7 shows that the average number of events was slightly higher at the beginning of the record but there seemed to be no significant change in the rest of the record.

Fig. 3.8 (a) shows the interval histogram which estimates the probability of occurrence of a particular interval duration between saccades.

The combined overall impressions from these graphical displays was that the saccadic components occurred in a rather random manner. Short intervals tended to predominate at the beginning of the record but no other significant trend could be observed. The interval histogram in Fig. 3.8 (a) shows a sharp peak near the shortest intervals, and a rapid, followed by a more gradual decrease in longer interval suggesting the possibility of an exponential tail.

The next consideration is what stochastic process could possibly generate such intervals? The simplest stochastic process of all is the Poisson process (see Appendix 2). Only one parameter, the mean rate of occurrence, is needed to describe the process in mathematical terms. To satisfy a Poisson process,

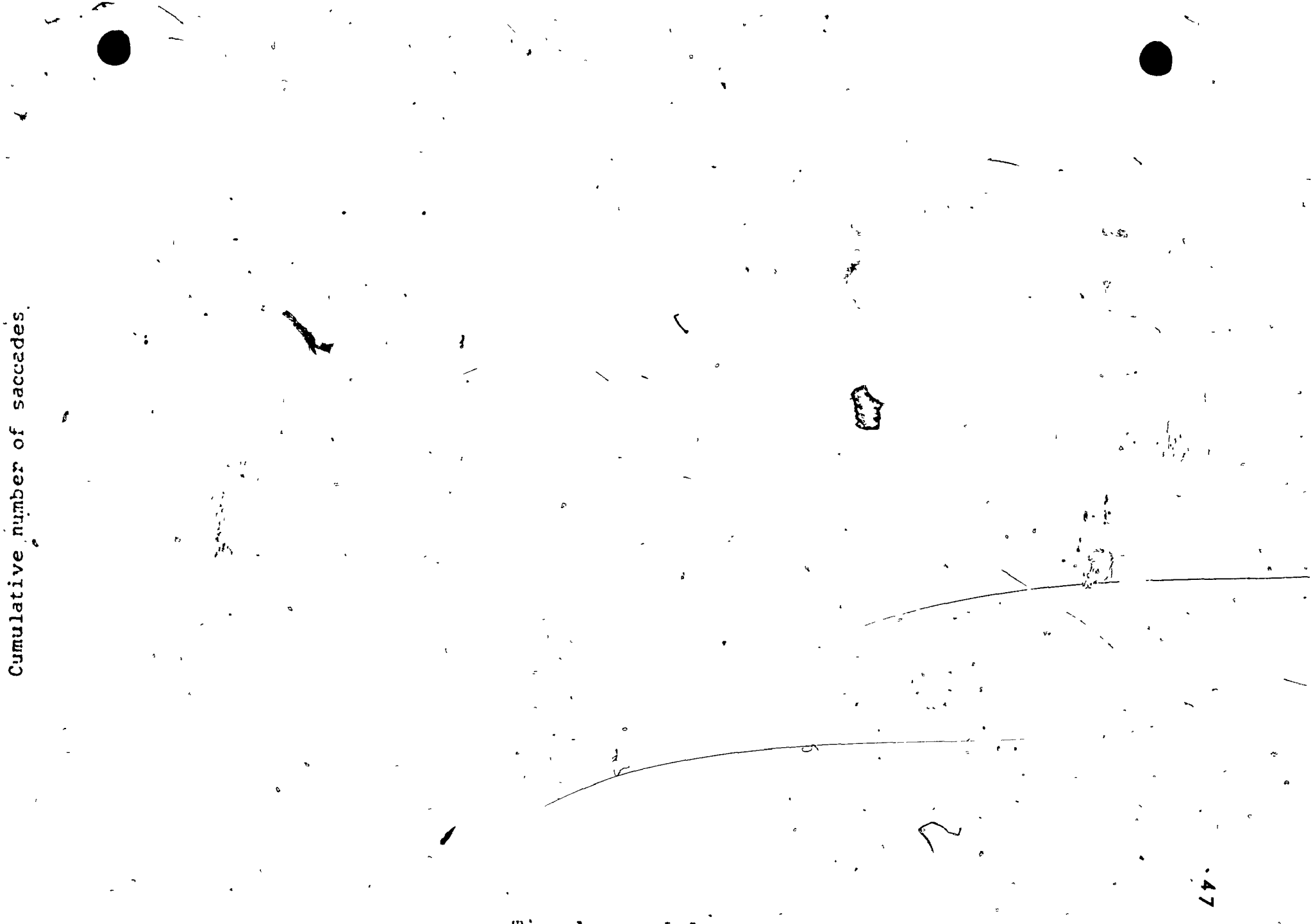
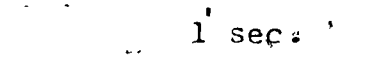


Fig. 3.7 Cumulative plot of saccadic occurence (beginning 256 samples)



(a) From the same data set as shown in Figs. 3.5 through 3.7
512 samples

(b) Data from a different subject. (used in Appendix 3)
398 samples

Fig. 3.8 Interval Histograms
Abscissa = interval duration
Ordinate = relative frequency of occurrence

each interval must be independent, that is, there must be no correlations or trends in the interval sequence, and the intervals must be exponentially distributed. Spike trains from different types of neurons have been reported to satisfy a Poisson hypothesis (Griffith and Horn, 1966; Moore et al, 1966). From the impressions gathered from the graphical displays of the inter saccadic intervals, a test of the Poisson hypothesis for the underlying mechanisms seemed reasonable.

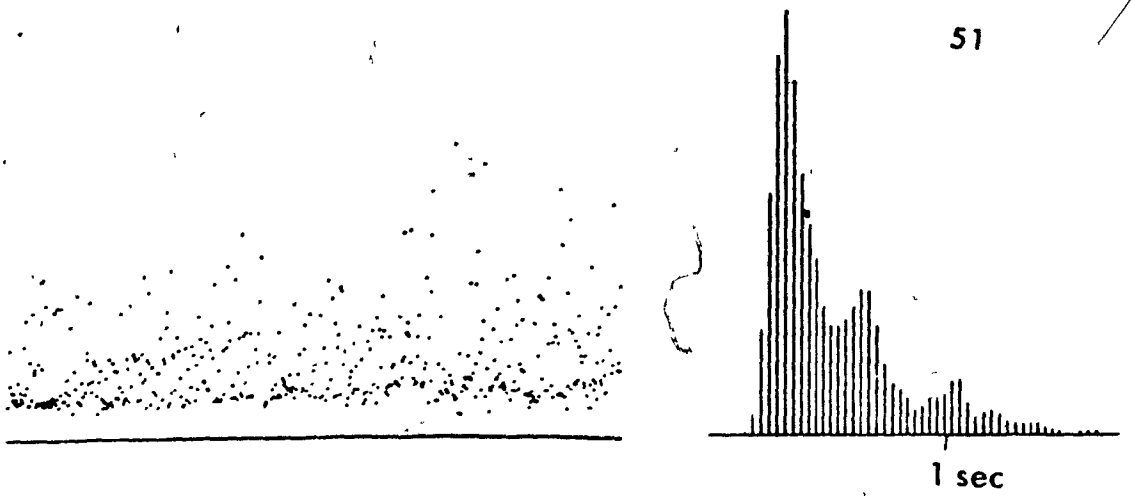
The testing of the Poisson hypothesis was carried out using a digital computer program "[illegible] IV" provided by the IBM Research Center, and the program, which required 252 K bytes of storage, was run on an IBM 360/75 model computer. The procedure and results of the test are summarized in Appendix 3. The conclusion was that the Poisson hypothesis was strongly rejected, and a trend in the data was indicated just passing the five percent significance level. Therefore, different data display methods using the LINC-8 digital computer were developed to examine more closely the pattern of trends and other variations in interval characteristics. This will be described in the next section.

3.2.5 Investigation into Multi-modality in Interval Histograms

Most of the statistical measures for point process analysis as described in section 2.3 are based on the assumption of a stationary process. Confusing conclusions may arise if they

are used to analyse data with trends whose nature is not understood. The detection of a weak trend by the statistical test in the preceeding section calls for a more revealing analysis method to examine the pattern of trend. This is particularly important in analysing records of positional and caloric nystagmus which are accompanied by strong trends. In this section two additional techniques of analysis will be introduced: a 'compressed' display of the interval magnitudes represented by dots on an oscilloscope photo, and the use of a digital filter to smooth the interval histograms which were plotted from segmented data from a larger data sequence. It will be shown that an interesting phenomenon of multi-modal interval histograms was detected. Selected records will be used to illustrate this phenomenon in four types of nystagmus.

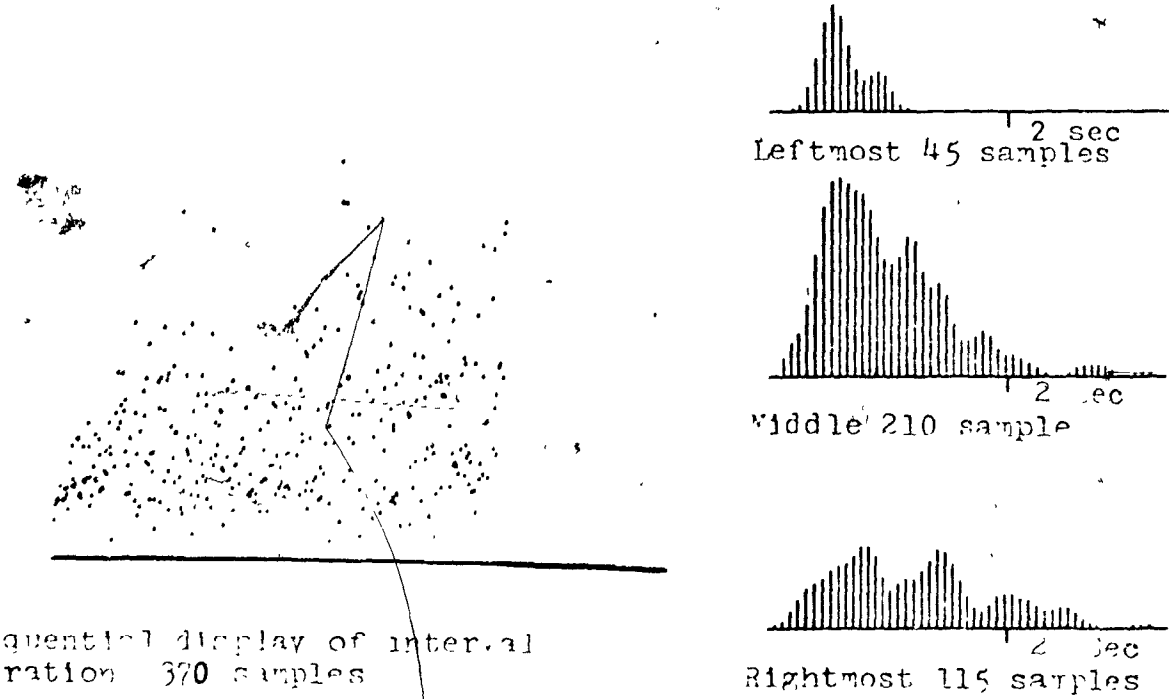
It was found that by representing the relative magnitude of an interval by the vertical position of a dot on the LINCSCOPE, (an oscilloscope display on the LINC-8 computer), and by displaying the sequence of intervals in a compressed space, the variation patterns of the inter-saccadic intervals were more clearly shown. This is illustrated in Fig. 3.9(a) which was plotted from data used in the four graphical displays in the preceeding section; here the tendency for shorter intervals to occur more frequently at the beginning of the record is shown more clearly. Further, the dots have a tendency to cluster into two layers, especially in the left half of the photo; this resulted in multi-modal interval histograms to be described



(a) Sequential display of interval duration 512 samples

(b) Interval histogram of leftmost 256 samples of Fig. 3.9 (a)

Fig. 3.9 Data from spontaneous nystagmus



(a) Sequential display of interval duration 370 samples

(b) Interval histograms of segmented data of Fig. 3.10(a)

Left side : Sequential displays
Abscissa = sequence number
Ordinate= relative time duration
Right side: Interval histograms
Abscissa = interval duration
Ordinate= relative frequency

Fig. 3.10 Data from positional nystagmus

below. It should be noted that the dot display of intervals is based on the same principle as the bar display in Fig. 3.6, but the substitution of the dots for bars and the compression of the horizontal scale produce a much more informative display. For example, the layering effect is not so readily observable in a bar display.

Fig. 3.10(a) shows the result from another patient having a positional nystagmus. The positional nystagmus was suspected to be due to a previous brain trauma affecting the vestibular system. The trend in this record is quite pronounced especially at the beginning of the record. It reflects the fact that the nystagmus was quite rapid when the head was first turned to the 30 right position, but gradually settled to a lower frequency. The corresponding nystagmus record was observed to show a corresponding decline in intensity.

Because of trends, the interval sequence was segmented into portions within which trends were relatively small. The interval histogram of these segmented data were computed and smoothed by a digital filter function to reduce the effect of statistical variation before the histogram was plotted. The smoothing function used was in the form:

$$b_n' = \tfrac{1}{4}b_{n-1} + \tfrac{1}{2}b_n + \tfrac{1}{4}b_{n+1}$$

where b_n' is the smoothed value of the nth bin

b_n is the unsmoothed value of the nth bin

b_{n-1} is the unsmoothed value of (n - 1)th bin

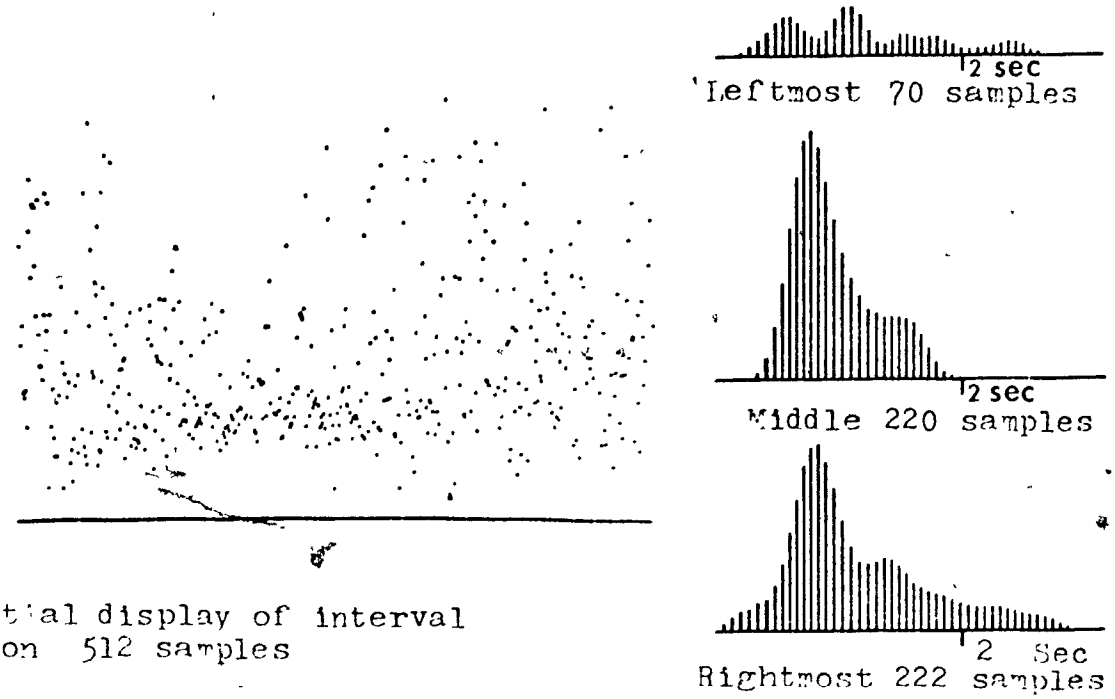
b_{n+1} is the unsmooth value of the (n+1)th bin

The properties of such a function have been described by Wilcock and Kirsner (1969). The resulting smoothed interval histogram of the left half (256 samples) of Fig. 3.9(a) is shown in Fig. 3.9(b); a distinct tri-modal histogram was revealed.

Fig. 3.10(b) contains the multi-modal histograms of the segmented data from the positional nystagmus recording. In all these histograms, the location of the high order modes on the time axis are approximately integral multiples of the location of the basic mode. Furthermore, when there was a strong trend, as in Fig. 3.10 the basic mode of the histogram increased and the higher order modes appeared to increase proportionately. The multi-modal phenomena are reflected by the gross layering effect in the sequential display of interval durations (Figs. 3.9(a) and 3.10(a)). Fig. 3.11 is another record from a patient suspected of a central lesion in the vestibular pathway. This patient had a mild spontaneous nystagmus resulting in relatively large saccadic intervals.

It is clear from these records that if the entire record without segmentation of data were used to plot the interval histograms, multi-modality would be masked by trends.

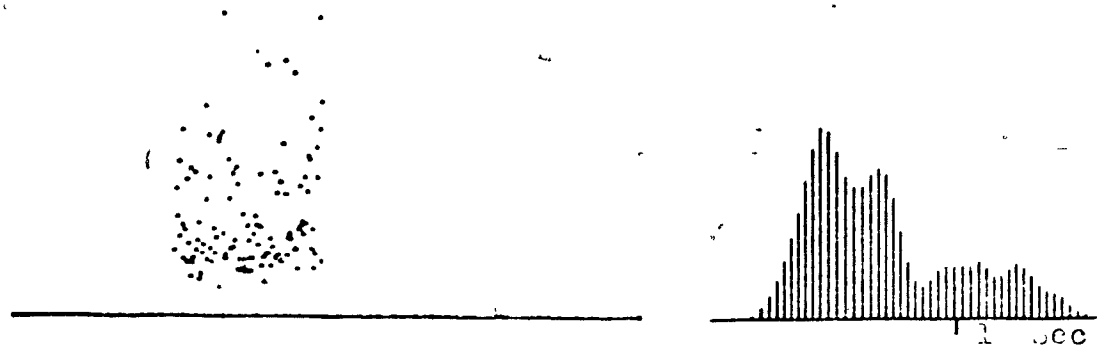
Fig. 3.12 was obtained from the results of an induced alcoholic positional nystagmus. The subject, who weighed 150 pounds, was tested, and found to be free from spontaneous, positional or gaze nystagmus before the experiment. Six ounces of 80° proof whisky was drunk by the subject within three minutes.



(a) Sequential display of interval duration 512 samples

(b) Interval histogram of segmented data

Fig. 3.11 Data from spontaneous nystagram



(a) Sequential display of interval duration 135 samples

(b) Interval histogram (ordinate scale expanded)

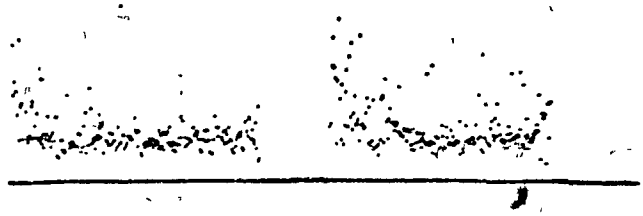
Fig. 3.12 Data from alcoholic nystagmus

He then lay on a couch and 30 minutes later, head-turning to left and right side resulted in left and right beating nystagmus which were recorded and analysed. Nystagmus was not so intense as that found in the above clinical case of spontaneous and positional nystagmus, and perhaps a larger dosage of alcohol would have resulted in more intense nystagmus. Fig. 3.12 shows a selected segment of the recording where multi-modality effect was observed.

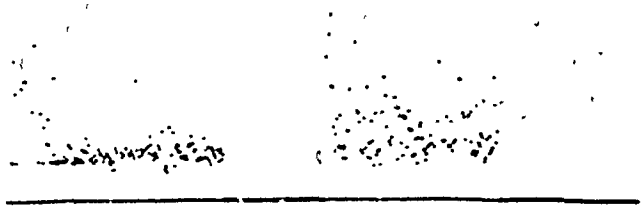
In caloric nystagmus, due to a rapid change in intensity of the nystagmus, the multi-modal phenomena in interval distribution could only be seen at the beginning and end of the oscilloscope photograph as observed by the layering effect of the dots. Fig. 3.13 shows the results from four routine irrigations to a patient suspected of a central lesion. The layering effect at the beginning of the first three records can clearly be observed. The top layers are at approximately twice the vertical distance of the bottom layer. Fig. 3.14 shows the results from two cold water irrigations to a normal subject. The subject was free from spontaneous, positional, or gaze nystagmus. Again, layering effects at the beginning and end of the records are observed.

3.2.6 Discussions

In the preceeding section, efforts were concentrated on illustrating the occurrence of multi-modal histogram, and selected records were used. Therefore, statements concerning

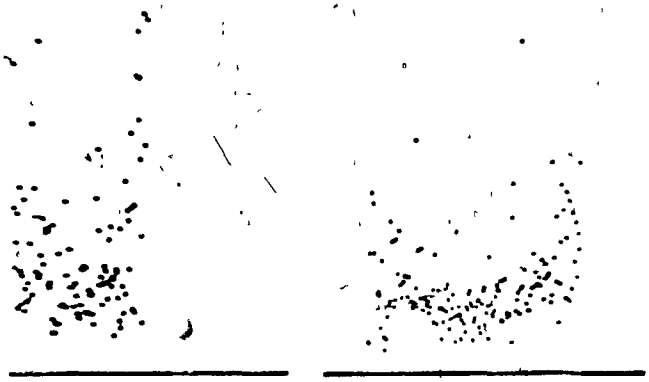


Left 30 degrees Right 30 degrees



Left 44 degrees Right 44 degrees

Fig. 3.13 Data from caloric nystagmus of patient



Left 30 degrees Right 30 degrees

Fig. 3.14 Data from caloric nystagmus of normal subject

Sequential display of interval duration
Abscissa = sequence number
Ordinate = relative interval duration

the frequency of occurrence and variations in the results are presented here.

Of five patients examined for spontaneous nystagmus, all produced multi-modal inter-saccadic interval histograms in all or parts of the records. The two cases presented in the preceeding section were entire records from two patients. In the other three, multi-modality occurred only in parts of the records, and in the remainder, the interval histogram usually showed 'long tail' with a wide spread towards the longer interval.

One patient was examined for positional nystagmus. The result shown in the preceeding section was the entire record from one position of the head (30R). In eight other positions, multi-modality was occasionally observed from the dot-displays but the records were not long enough for meaningful histogram plots.

Two normal subjects were used in experiments in alcoholic nystagmus. Nystagmus intensity was low and frequently interrupted by random eye movements. Multi-modality was observed in short segments, about one-tenth of the long experimental records. Other places produced long tailed interval histograms.

The phenomena of layering in the dots at the beginning and sometimes also at the end of caloric records were observed in results from three patients among ten patients examined.

It will be demonstrated in the remainder of this thesis that symmetric mono-modal interval histogram, long-tailed

interval histogram and multi-modal interval histogram each can occur in both vestibular and optokinetic nystagmus, and the conditions under which one interval histogram changes into another will be examined by a stochastic model in the next section and by the optokinetic nystagmus experiments in the next chapter.

3.3 FURTHER INTERVAL ANALYSIS AND COMPARISONS OF RESULTS FROM A STOCHASTIC MODEL

3.3.1 Introduction

This section serves two purposes. The stochastic properties of the inter-saccadic intervals of some of the results obtained in the previous section will be further analysed and, at the same time, the results from a model simulating the generation of the inter-saccadic interval sequence will be compared.

The model to be considered in the following will concern only the inter-saccadic interval characteristics during nystagmus. The basic requirement of the model is that it should have the capability of producing the multi-modal interval distribution of the types found in the previous section. The higher order modes should be at multiple integral values of the basic mode. Such an interval distribution has been found to exist in many biological systems. Boyd and Martin (1956) found a multi-modal distribution of end-plate potentials in mammalian muscles. Poggio and Viernstein (1964) found bi-modal interval histograms for spikes of spontaneously active lemniscal neurons. Herz, Creutzfeldt and Fuster (1964) found bi and tri-modal spike interval histograms from cells in the visual system. Bishop, Levick and Williams (1964) found for a class of geniculate body neurons a spike interval histogram which showed up to nine peaks. Bishop et al suggested that this multi peak

phenomenon was a result of interaction between excitatory and inhibitory afferents. They proposed that there was a single excitatory afferent fiber forming a synapse with the geniculate neurons, and that there were also one or more inhibitory fibers present. The geniculate neuron was assumed to trigger whenever an impulse arrived along the excitatory fiber, provided that it was not blocked by an impulse arriving along an inhibitory fiber. If the impulse arrivals of the excitatory afferent were quasi-periodic, and if inhibitory impulses arrived in a random manner, then the train of output impulses from the geniculate neuron would contain intervals which were the sum of varying members of adjacent intervals in the excitatory afferent, resulting in multi-modal interval distributions. With computer simulation, they demonstrated that this phenomenon occurred. Subsequently, ten Hooper and Reuver (1965) formulated the model in mathematical terms and derived the interval probability density function for the output. The concept of this model is adapted here for the saccadic component generation.

It must be emphasized that the model used here is not meant to represent the actual structure of the real system. The possible complexity of the nystagmus mechanism has been discussed in section 3.1.3, and the saccadic component which requires a much more complex burst of impulses (Robinson, 1964) is only replaced by a single impulse here. The purpose of the model, however, is to see if the overall behavior of the nystagmic saccades could be explained in terms of the simple

excitatory and inhibitory processes.

In order to compare the model and experimental results in a stringent manner, all statistical measures described in section 2.3 plus the sequential displays of the interval duration were used to analyse and compare the results: in addition the technique of random shuffling the original interval sequence was used in compiling the serial correlograms for comparison with those of the unshuffled data.

3.3.2 The Stochastic Model

The model proposed for the generation of saccadic components during nystagmus is shown in Fig. 3.15. The excitatory impulses are quasi-periodic. The intervals between pulses are independent of each other and are distributed according to the gamma distribution:

$$f(t) = \frac{m^r (t-t_1)^{r-1}}{(r-1)!} e^{-m(t-t_1)} \qquad \text{for } t>t_1$$

$$= 0 \qquad \text{for } t \leq t_1$$

where t is the interval duration between impulses

t_1 is the 'dead time' of the Gamma process or the period of the external clock signal (see section 3.3.3)

m, r are parameters of the distribution and m/r gives the mean rate of the impulse arrival. It is known that the greater the parameter value r, the more symmetrical

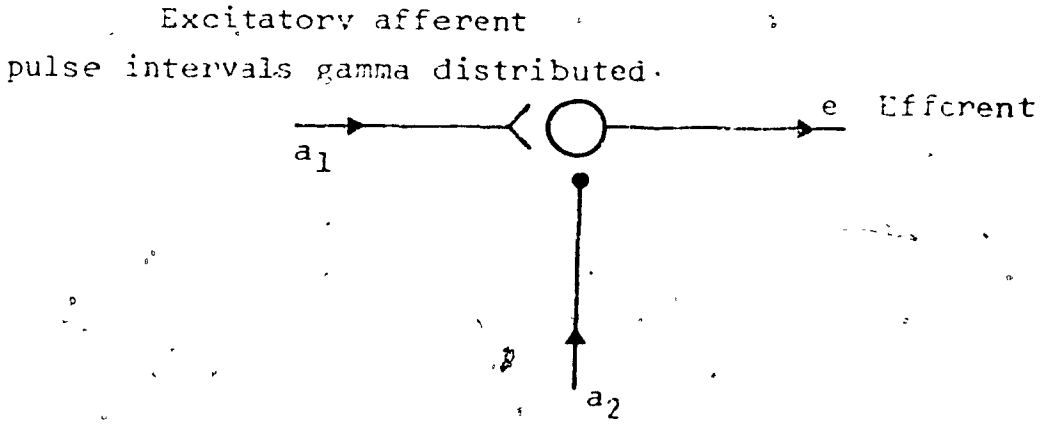


Fig. 3.15 The stochastic model

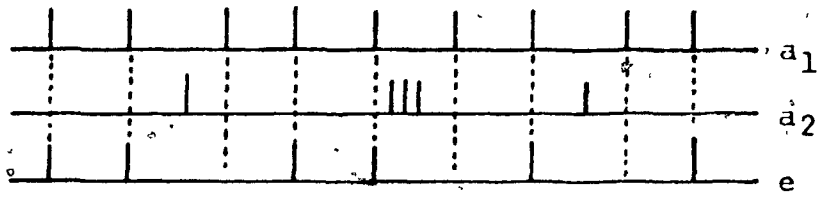


Fig. 3.16 Mode of synaptic action of the proposed model impulse series a_1 inhibited by impulse series a_2 resulting in impulse series e

is the distribution about its mean and the smaller is its variance (Kendall and Stuart, 1967).

The inhibitory impulses are arriving in a random manner which constitutes a Poisson process. The intervals between pulses are independent of each other and are distributed according to the exponential distribution:

$$f(t) = \mu e^{-\mu(t-t_2)} \qquad \text{for } t>t_2$$

$$= 0 \qquad \text{for } t \leq t_2$$

where t is the interval duration between pulses

t_2 is the 'dead time' for the Poisson process, or the period of the external clock signal (see section 3.3.3)

μ is the mean rate of Poisson impulse arrival.

The 'synaptic interaction' is such that every excitatory impulse provokes an output impulse, provided it has not been blocked by an inhibitory impulse occurring at some time since the last excitatory impulse. If there are two (or more) inhibitory impulses without an excitatory impulse, only one subsequent excitatory impulse is inhibited. This action is illustrated in Fig. 3.16.

3.3.3 Computer Simulation of the Model

The model was simulated on a hybrid computer. Two independent binary noise generators (Burr-Brown model 3000/25)

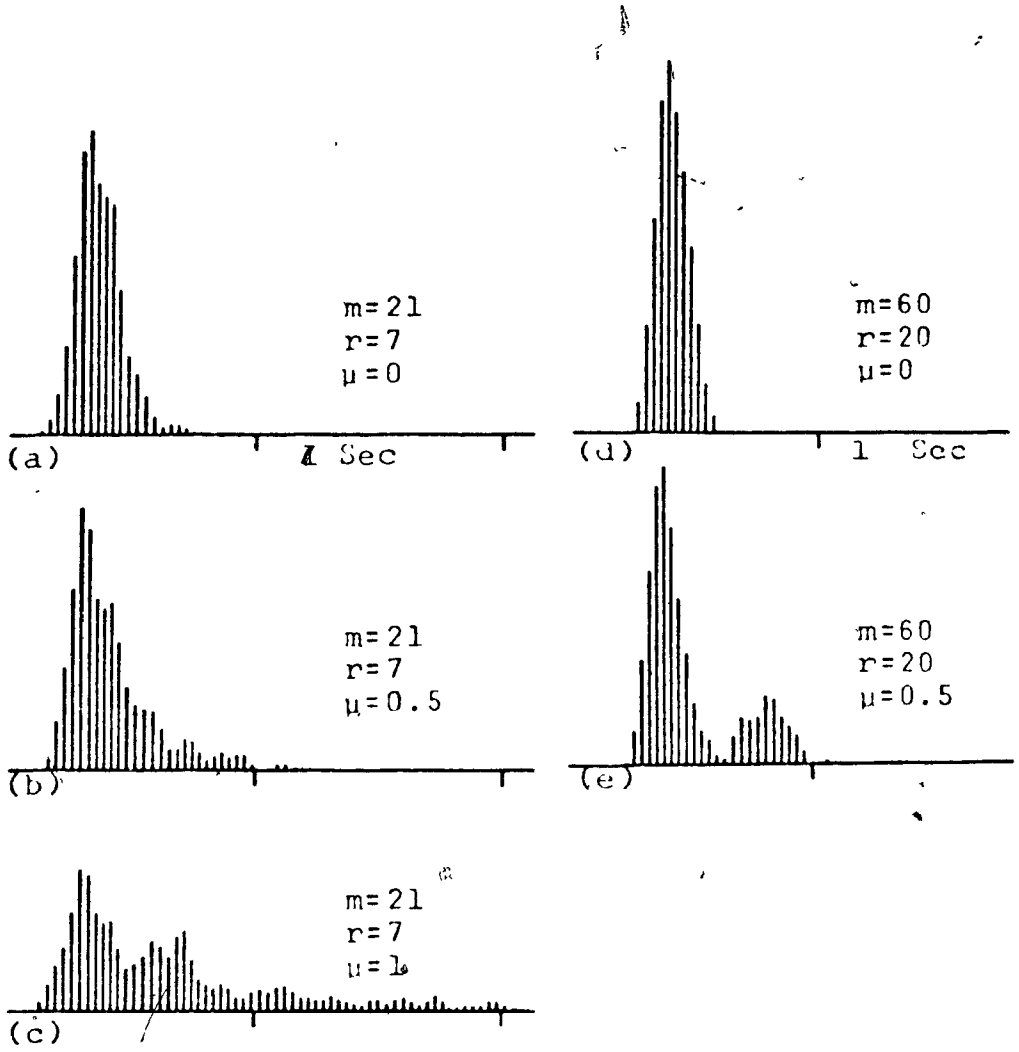
were used to simulate the two inputs. The output of this type of generator is always at one or the other of its stable states ($\pm$ 5 volts) and the state changes are approximately Poisson distributed. The rate of state changes can be continuously altered by an external clock signal. The outputs of these noise generators were differentiated and conditioned to give a pulse of 10 milliseconds long. One output was directly used as the inhibitory input. The gamma distributed excitatory pulses with parameter r were obtained by counting every rth pulse (see Appendix 2) from the other noise generator before an excitatory pulse was emitted to the 'synapse'. The two inputs were fed into a LINC-8 digital computer where the synaptic action was programmed according to the rules specified in the previous section (see Fig. 3.16). The digital computer served to detect when a legitimate output impulse occurred. The intervals between consecutive output impulses were subsequently measured by the computer and displayed on the LINCSCOPE in sequential order. Thus the temporal pattern of the simulated inter-saccadic interval could be observed on-line. Any change in input parameters was reflected immediately by the interval display. At any time, the simulation process could be interrupted to calculate and display the interval histogram of the accumulated interval data from the model.

During simulation, the input parameters μ, m, r were first estimated, and then refined by trial and error adjustment to simulate the experimental results. Observations were based on the sequential display of interval duration and

the interval histogram.

The effects of changes in the parameters of the input processes on the results are shown in Fig.3.17. Fig.3.17(a) shows the interval histogram of the gamma distributed excitatory input. The parameter r was set at 7 and the mean rate of pulses was 3 per second. The mean rate μ of the inhibitory input was set at zero (i.e. no inhibitory pulses). In Fig. 3.17(b), the parameters of the excitatory input were not changed, while the inhibitory input μ was set at a rate of 0.5 per second. A 'long tail' in the interval histogram resulted. In Fig. 3.17(c), the parameters of the excitatory input remained unchanged while the mean rate μ of inhibitory input was increased to 1 per second. Multi-modality in the interval histogram was produced.

Figs. 3.17(d) and (e) show the effect of narrowing the spread of the gamma distribution of the excitatory input pulses. The parameter r was increased to 20 while the mean rate of the excitatory pulses was kept approximately the same at 3 per second as in Fig. 3.17(a) (by increasing the rate of the external clock signal). With no inhibitory input, Fig. 3.17(d) shows the resulting interval histogram which became more symmetrical with a narrower spread. When the inhibitory input was set to have a mean rate of 0.5 per second, distinct bimodal interval histogram was obtained (Fig.3.17(e)).



Each histogram has 100 samples

Fig. 3.17 Effects of changing model input parmeters on output pulse interval histograms. (See text)

The results demonstrated that mono-modal, long-tailed and multi-modal interval histograms can be obtained depending on the rate of the inhibitory input and the spread or variance of the excitatory input. The following section describes attempts made to simulate some of the clinical results obtained in the previous section.

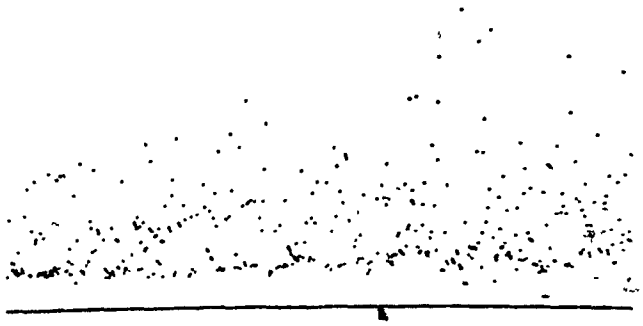
3.3.4 Comparison of Experimental and Model Results

The model was used to simulate some experimental results shown in the previous section. These include spontaneous, alcoholic and caloric nystagmus. The experimental and simulated spontaneous nystagmus results were analyzed and compared for six different statistical measures. The theory and methods of calculating these statistical measures are described in Section 2.3.

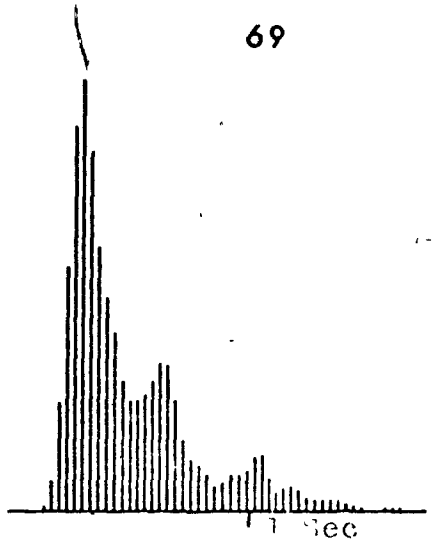
Spontaneous Nystagmus. Fig. 3.18(b) is a simulated result of a spontaneous nystagmus to be compared with the clinical result shown in Fig. 3.18(a). (Fig. 3.18(a) is the same as Fig. 3.9 in the previous section, re-inserted here for convenience). Data of Fig. 3.18(b) was obtained from the model with a mean rate of 3 per second and the parameter $r = 14$ for the excitatory gamma process. The inhibitory process had a mean rate of 0.5 per second. The simulation was run for five minutes. In the last two minutes, the mean rate of the excitatory input was gradually decreased from 3 to 2.6 per second. Attention is drawn to the gross similarity between the two results, especially the clustering effect at the left end of the records and the effect of layering in the overall records. However, more similarities between the results are demonstrated in other statistical measures.

Figs. 3.18(c) and (d) are the interval histograms of the left hand halves of Figs. 3.18 (a) and (b) respectively. Similarities between the two histograms are quite clear. Fig. 3.19 through 3.22 are further analyses of the same full 512 data samples displayed in Fig. 3.18.

Figs. 3.19(a) and (b) are the scatter diagrams between adjacent intervals for the clinical and simulated data. They are very similar and both show a symmetry about the 45 degree line indicating reasonable independence between adjacent intervals. There is a concentration of points in the lower left hand corner signifying the basic mode of the interval



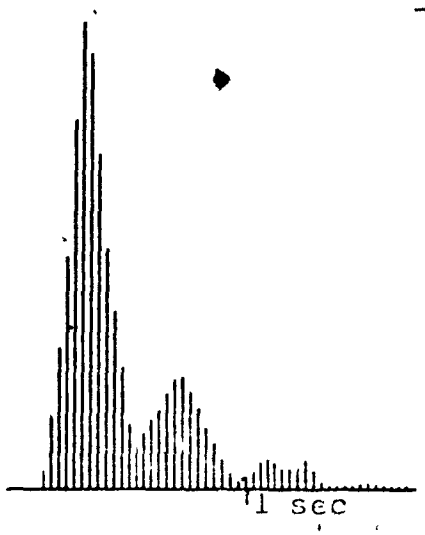
(a) Sequential display of interval duration



(c) Interval histogram of leftmost 256 samples of (a)

SIMULATED DATA

(b) Sequential display of interval duration



(d) Interval histogram of leftmost of 256 samples of (b)

Left side : Sequential displays
Abscissa = sequence number
Ordinate= relative time duration
Right side: Interval histograms
Abscissa = interval duration
Ordinate= relative frequency

Fig.3.18 Simulation of spontaneus nystagmus

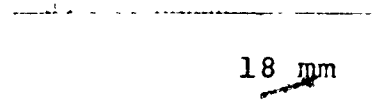
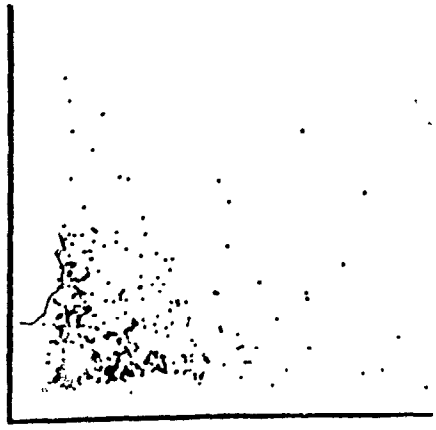
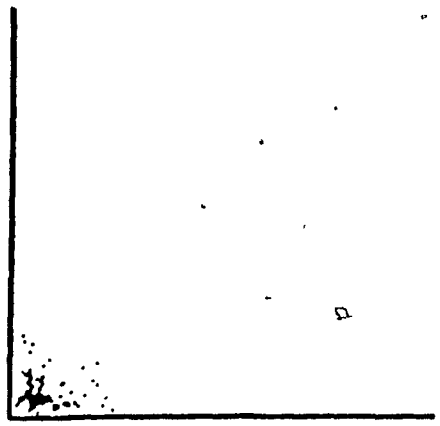


Fig. 3.18(e) Amplitude distribution of saccadic components measured from strip chart records of clinical spontaneous nystagmus, the inter-saccadic interval characteristic of which is shown in Figs. 3.18(a) and (c). This figure will be needed for the discussion in section 3.3.5.

CLINICAL DATA

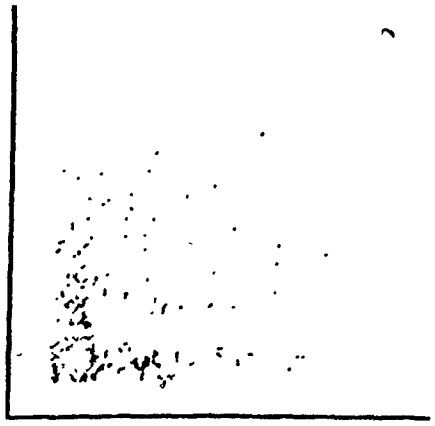


(a) Scatter diagram between adjacent intervals

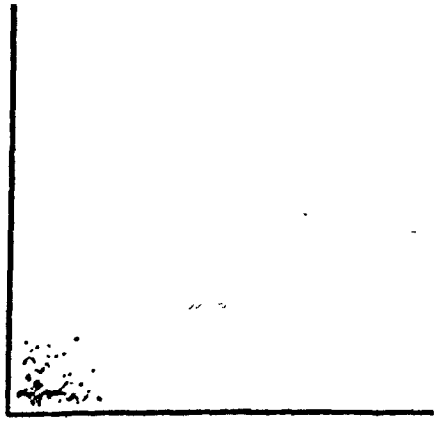


(c) Rows and columns means of (a) (scale contracted)

SIMULATED DATA



(b) Scatter diagram between adjacent intervals



(d) Rows and columns means of (b) (scale contracted)

Abscissa and ordinate = relative interval duration

Fig.3.19 Scatter diagrams (further analysis and comparson of clinical and simulated spontaneous nystagmus)

histogram. The tendency for the points to cluster paralled to the two axes, forming the letter 'L', reveals an important characteristic of the generating mechanism, namely that whenever long intervals occur, they tend to be preceeded and succeeded by short intervals. This is explained by the fact that inhibition occurs only occasionally.

Figs. 3.19(c) and (d) are plots of the row and column means corresponding to Figs. 3.19(a) and (b) respectively. The means lie approximately on two straight lines parallel to the coordinate axes, again indicating a reasonable independence between adjacent intervals.

Figs. 3.20(a) and (b) show the expectation density plots. The approximate periodicity indicates that out of the random intervals, there is a preferred interval of about 0.35 second which occurs with a higher probability throughout the record length. This statistical finding may seem trivial in view of the fact that the interval histograms show peaks at this interval duration indicating its higher probability of occurrence. However, it is not possible to infer from the interval histogram alone that this preferred interval occurs consistently throughout the record length, because information about the temporal pattern is necessarily lost in the interval histogram.

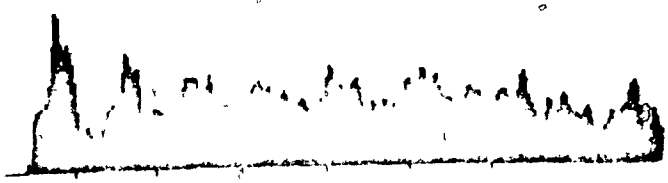
Fig. 3.21(a) shows the serial correlogram of the clinical data. It is seen that the serial correlation coefficients up to an order of 64 fluctuate within ±0.15, indicating a low correlation between intervals. Fig. 3.21(b) shows no significant change in the result after the same set of

CLINICAL DATA

.5 1.0 1.5 2.0 2.5 3.0 3.5
sec.

(a)

SIMULATED DATA



.5 1.0 1.5 2.0 2.5 3.0 3.5
sec.

(b)

Abscissa = time
Ordinate = relative frequency

Fig. 3.20 Expectation densities (further analysis and comparison of clinical and simulated spontaneous nystagmus)

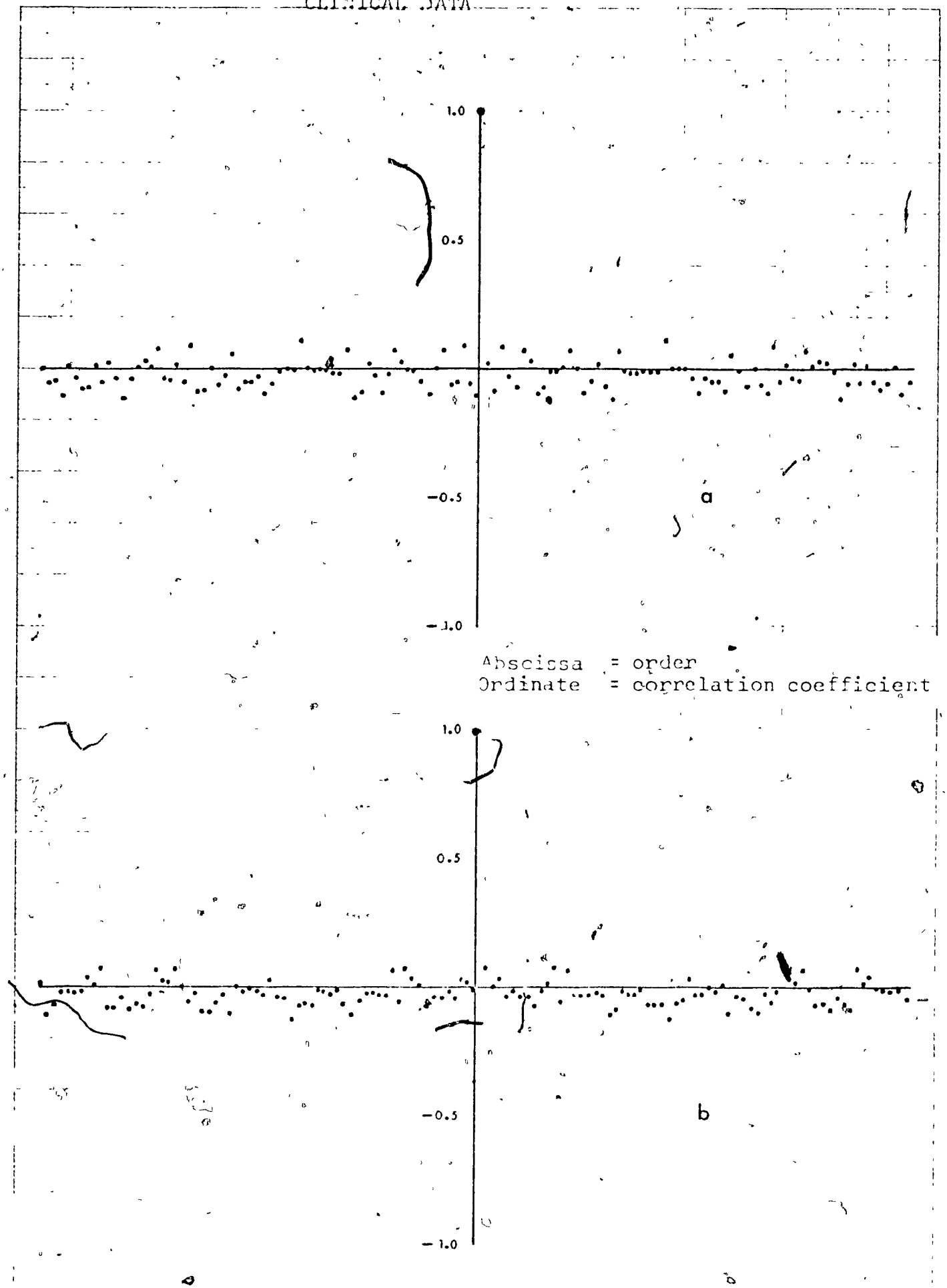


Fig. 3.21 Serial correlograms
(a) original clinical data (b) randomly shuffled clinical data

clinical data was randomly shuffled (see section 2.4) before the serial correlogram was compiled. This serves as a control case of independent intervals. The correlation coefficients again fluctuate within the ±0.15 limits suggesting that the result in Fig. 3.21(a) could well be ascribed to statistical fluctuation.

Fig. 3.22(a) and (b) show the serial correlograms for the simulated data and for the corresponding randomly shuffled sequence respectively. Again theyare similar to the clinical results.

Alcoholic Nystagmus. Figs. 3.23(b) and (d) show an attempt to explain the troughs which were found in the main peaks of the interval histogram of alcoholic nystagmus shown in Fig. 3.23(c). The results were simulated by a wider spread of the gamma distribution of the excitatory impulses. In this case the parameter r = 6 and the mean rate was 2.5 impulses per second. Thus a wider spread in the excitatory impulses could give rise to troughs within the main modes. The comparatively small number of samples also contibute to this effect.

Caloric Nystagmus. Fig. 3.24(b) is a simulation of the caloric nystagmus result shown in Fig. 3.24(a). The simulation was achieved by continuously varying the input parameters. At the beginning, the mean rate for the gamma distributed excitatory input was 1.5 per second and r = 14. Inhibitory input rate was 1 per second. In approximately 20 seconds, the mean rate was increased gradually to 2 per second while the inhibitory

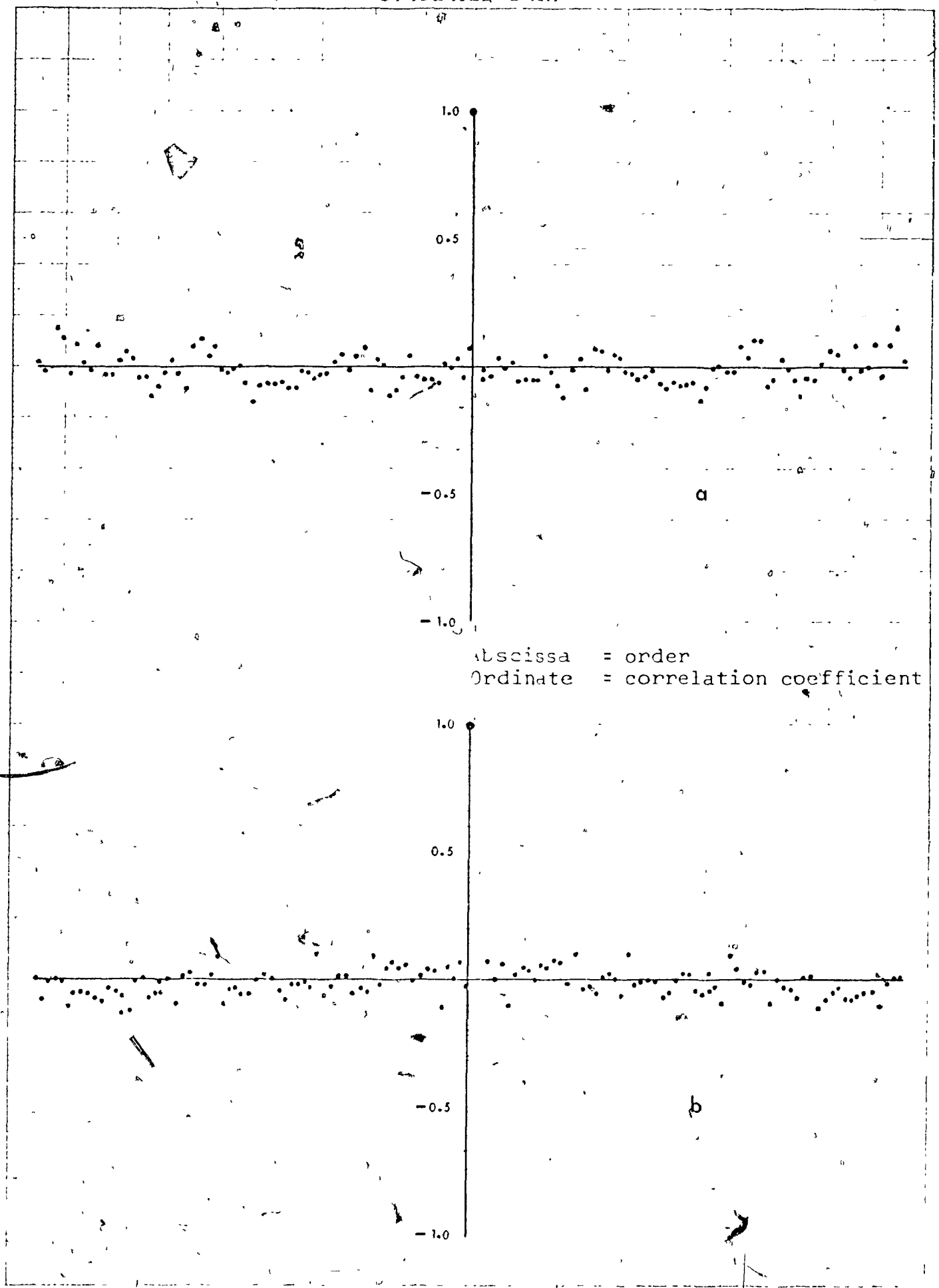
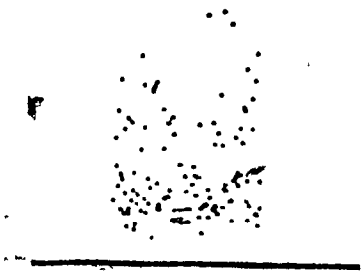
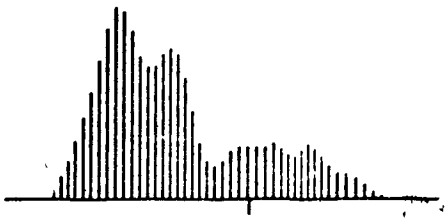


Fig. 3.22 Serial correlograms
(a) original simulated data (b) randomly shuffled simulated data

EXPERIMENTAL DATA





1 sec.

(a) Sequential display of interval duration 135 samples

(c) Interval histogram

SIMULATED DATA

(b) Sequential display of interval duration 135 samples

1 sec.

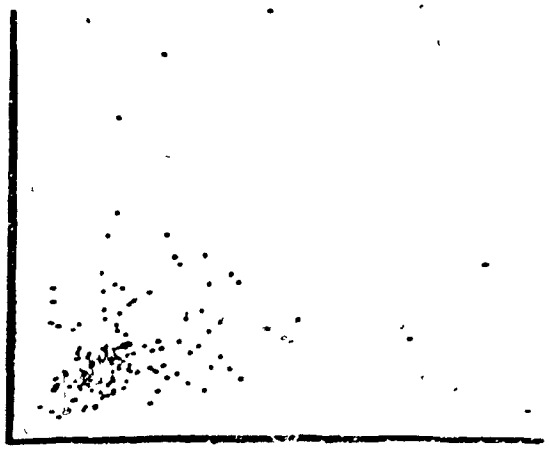
(d) Interval histogram

Left side : Sequential displays
Abscissa = sequence number
Ordinate= relative time duration
Right side: Interval histograms
Abscissa = interval duration
Ordinate= relative frequency

Fig. 3.23 Simulation of alconolic nystagmus

EXPERIMENTAL DATA

(a) Sequential display of interval duration



(c) Scatter diagram

SIMULATED DATA

(b) Sequential display of interval duration

(d) Scatter diagram

Fig. 3.24 Simulation of caloric nystagmus

input was decreased to zero. No change was introduced for the next 10 seconds. After that, for the next approximately 35 seconds, r was changed to 7: the mean rate of excitatory pulses was decreased gradually to one per second and the mean rate of inhibitory input was increased from zero to 0.7 per second.

From fig. 3.24(b) the layering effect in the dots at the beginning of the simulated record is demonstrated and the gross appearance of trends is similar to those in the clinical data.

3.3.5 Comments

The work in this section has demonstrated that multimodal interval distribution could be explained by a model in which the saccadic components which normally occur in a quasi-periodic manner are occasionally inhibited. Another possible explanation is that the inhibition does not actually take place but that, instead some of the saccadic components were of such small amplitude that they were not detected while the records were analysed. This concept can be checked by constructing the amplitude histogram for the saccadic components. Fig. 3.18(e) shows the saccadic amplitude histogram from the record, the inter-saccadic interval histogram of which is shown in fig. 3.18(c). It is seen that the smallest saccadic component observed was represented by about two millimeters on the record and the

frequency of occurrence at this value is greatly decreased. If follows that the chance of missing many small saccades both by the computer and by visual analysis is very small.

It must be emphasized that, in the present model, although the excitatory input is represented by a quasi-periodic signal. This is not meant to indicate that there is a free running stochastic oscillator in the brain. In fact is is more likely that this quasi-periodic signal is produced by vestibular inputs. Further, the parameters of both excitatory and inhibitory inputs such as means and spreads are controlled by inputs to the system in a deterministic way. The deterministic element in the model is manifested by trends and is clearly demonstrated by the simulation of caloric nystagmus in Fig. 3.24.

3.3.6 Summary of Stochastic Properties of Inter-Saccadic Intervals

In a case of spontaneous nystagmus with a weak trend, the inter-saccadic intervals show insignificant correlation among each other. There is a higher probability of occurrence of a basic interval. Long intervals occur intermittently and tend to be followed immediately by short intervals. These long intervals have the tendency to be at multiple integral value of the basic interval thus creating a multi-model interval histogram.

Strong tends exist in positional and caloric nystagmus which make it difficult to interpret the stochastic

properties from the present analysis. However, in view of the fact that the gross features of spontaneous, alcoholic and caloric nystagmus have been simulated by the stochastic model the general stochastic properties of nystagmus may be described by this model which has been mathematically formulated and analysed by ten Hoopen and Reuver (1965). The model consists of an input of quasi-periodic excitatory impulses randomly inhibited by a Poisson process. As demonstrated by simulation in Section 3.3.3, the interaction can produce output impulses occurring at intervals having different distributions depending on the parameters of the input processes. In particular it may produce a mono-modal and symmetrical, a mono-modal but skewed (long-tailed), or a multi-modal interval distribution.

The pattern of inter-saccadic intervals and the hypotheses of the model will be further examined using results from optokinetic nystagmus in the next chapter.

CHAPTER 4

OPTOKINETIC NYSTAGMUS

4.1 INTRODUCTION

4.1.1 Gross Anatomy and Physiology of the Visual System (Ref. Yarbus (1967), House and Pansky (1967), Walsh and Hoyt (1969))

The retina consists of a complicated neural structure which is often regarded as an extension of the brain. The brief description below is a simplified picture of the real system. There are two types of photo-receptors within the retina, the rods and the cones. The rods are the most numerous and are estimated to range from 100 to 130 million in each eye. They are absent from the center region of the retina subtending a visual angle of one to two degrees (Oesterberg, 1935; Polyak, 1941; Yarbus, 1967). The distribution of the rods and cones in the retina is given in Fig. 4.1. The rods react to low intensity illumination and are known to subserve twilight and night vision. The photosensitive pigments of the rods have a maximum spectral sensitivity at a wavelength of 510 mμ. The cone receptors number six to seven million in each eye, and are most concentrated on the center of the retina which is rod free. They have a higher threshold to photo-excitation and are known to be responsible for day light clear vision and colour determination. The cones contain three photosensitive

Fig. 4.1 Distribution of rods and cones in the retina. Abscissa—the distance (in mm) from the middle of the fovea centralis (the foveola) along the horizontal section of the right eye. Ordinate—the number of hundreds of rods and cones per mm². The broken line represents rods and the solid line cones (Oesterberg, 1935).

(From Yarbus,1967)

Table 4·1 Subdivision of the Retina into Regions (from Polyak, 1941)

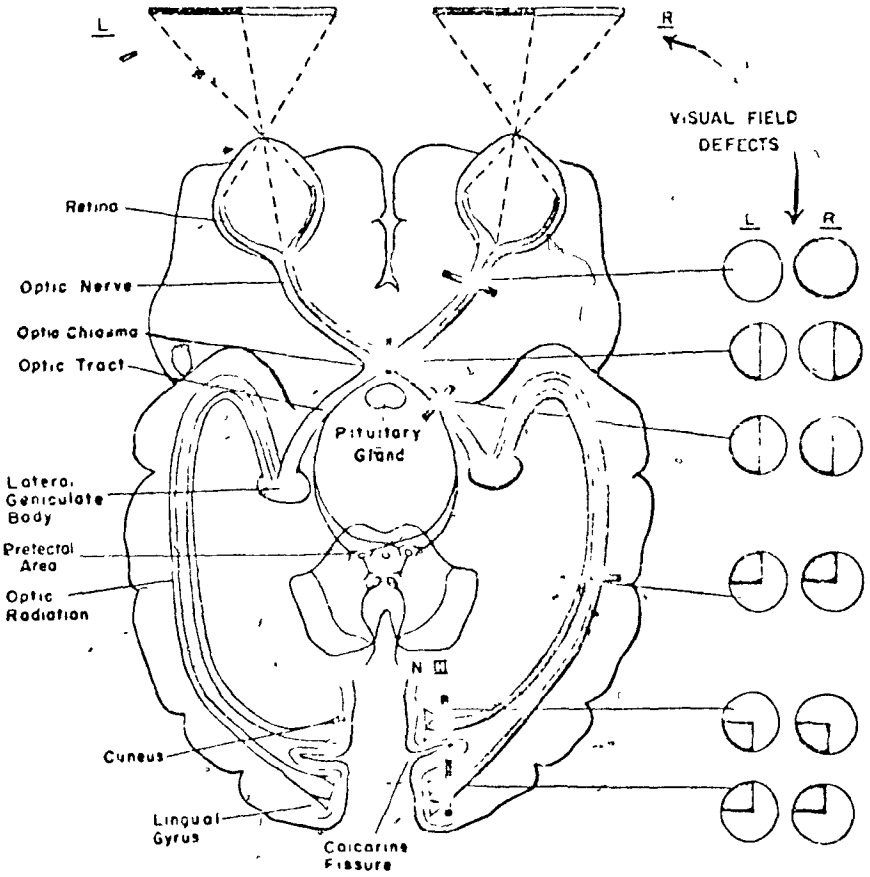
Retinal Region		Approximate Outer Diameter on Retina	Corresponding Angular Diameter in External Field
Central area			
I. *Fovea*	This corresponds to a pit or depression in the retina-vitreous surface (internal limiting membrane) and to a thinning toward the center of layers 5 to 9, at the same time layers 2 and 4 become thicker (see Fig. 2.3)	1,500 μ	5.2°
	The nearly flat central area of the foveal pit where layers 5 to 9 are almost absent is called the *foveola*. There are no blood vessels here	400 μ	1.4°
	In a *central island* within the foveola the cones have maximum length. There are no rods here	50–75 μ	0.17–0.24°
II *Parafovea*	Roughly circular belt of width about 500 μ. In this the thickness of layer 2 has dropped to the value it retains throughout the remainder of the retina	2,500 μ	8.6°
III *Perifovea*	Circular belt of approximate width 1500 μ, marked by the progressive reduction in thickness of the ganglion-cell layer from about 4 cells to about 1 cell thick.	5,500 μ	19.0°
Peripheral area			
IV. *Near periphery*	Approximate width 1500 μ	8,500 μ	29.0°
V *Middle periphery*	Approximate width 3000 μ	14,500 μ	50.0°
VI *Far periphery*	Approximate width 10,000 μ (temporal side) Approximate width 10,000 μ (nasal side)	40,000 μ (horizontal)	
VII *Ora serrata* (extreme periphery)	Approximate width 2100 μ (temporal side) Approximate width 700–800 μ (nasal side) [For the special characteristics distinguishing regions IV to VII, see Polyak (1941).]	44,000 μ (horizontal)	
VIII *Yellow spot*	The yellow pigment penetrates diffusely all layers from 4 to 9. This pigmentation is very slight in the foveola, intense on the slopes and margin of the fovea, and gradually fades out beyond. However it is visible in some preparations nearly up to the papilla (Polyak, 1941)	3,000 μ (intense) 5,000 μ (total)	10° 17°
	The yellow spot is more extended in the horizontal than in the vertical meridian		
IX *Rod-free area*	Diameter	500–600 μ	1.7–2.0° (Polyak) 1.0° (Oesterberg)
	[Oesterberg's data (1935) correspond to a smaller value]		
X *Avascular area*	Diameter	400–660 μ	1.4–2.3°

(From Wyszecki and Stiles,1967)

pigments with spectral sensitivity maxima at wavelengths of 440, 540, and 590mμ.

Since the contribution to optokinetic nystagmus from different parts of the retina is a major topic of this thesis, a table showing the subdivision of the retina into regions based on data provided by Polyak (1941) is included in Table 4.1 for later reference . In the following, a brief description of the visual pathway with reference to Fig.4.2 will be given.

Light falling on the rods and cones triggers a photochemical reaction which in turn generates nerve impulses which are relayed to the ganglion cells via the bipolar cells; each ganglion cell may receive signals from several rod and cone receptors. Axons of the ganglion cells converge towards the optic disc where they perforate the scleral coat to form the optic nerve. The optic nerve fibers pass directly to the optic chiasm anterior to the pituitary gland. A partial decussation takes place in the chiasm. Fibers from the nasal half of each retina cross while those from the temporal half of each retina approach the chiasm and leave it without crossing. Proximal to the chiasm the fibers form two optic tracts. The majority of the optic tract fibers go to the lateral geniculate bodies of the thalamus, while some go to the superior colliculus, pretectal area and the reticular formation. Cells of the lateral geniculate bodies give rise to new fibers which form the optic radiations to the visual cortex in the



The visual pathway. On the right are maps of the visual fields with areas of blindness darkened to show the effects of injuries in various locations

Fig.4.2 The Visual Pathway
(From J.Gatz, 1966)

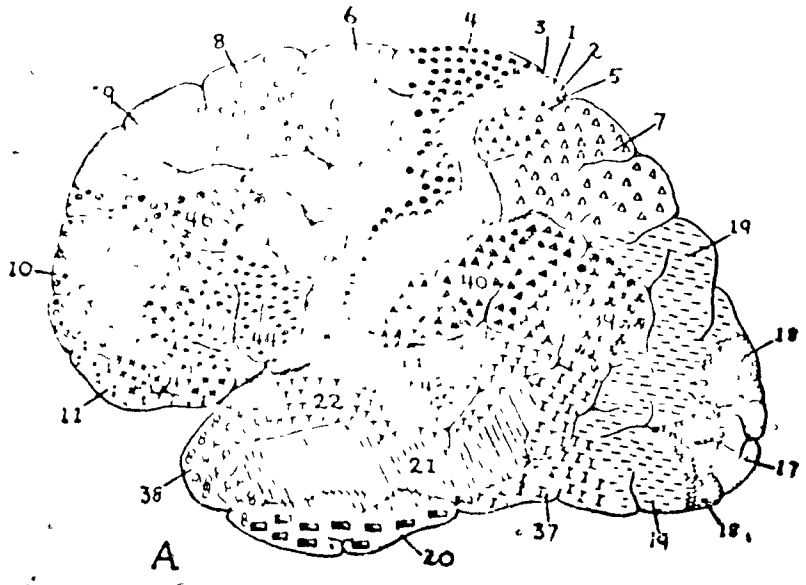


Fig.4.3 Areas of the human cerebral cortex according to Brodmann (From Ranson and Clark, 1959)

occipital lobes, and in this region there exists a hierarchy of visual information processing centers that serve the function of visual perception.

4.1.2 The Visual-oculomotor Pathway

In contrast to the visual pathway, the centers and efferent pathways from the cortex giving rise to oculomotor functions are rather poorly understood. In summarising the present knowledge, an area map of the human cerebral cortex according to Brodmann as shown in Fig.4.3 will be referred to.

From experimental and clinical evidence (Holmes, 1938; Robinson, 1968; Walsh and Hoyt, 1969; Fuchs, 1971; Hoyt and Daroff, 1971.), it seems generally accepted that the frontal eye fields (area 8 of Fig.4.3) are associated with voluntary saccadic eye movements and the occipital eye fields (area 17, 18 and 19) with smooth pursuit movements.

How the occipital eye fields communicate with the frontal eye fields is not known. On the other hand, fibers are known to descend via the corticobulbar tract into midbrain tegmentum (Crosby, Yoss and Henderson, 1952) and mesencephalic reticular formation (Brucher, 1966). Fibers from areas 18 and 19 descend via the internal corticotectal tract into the tegmentum, superior colliculus, mesencephalic and pontine reticular formation (Crosby and Henderson, 1948). The exact integration of these descending fibers with the oculomotor, trochlear and abducens nuclei are not clearly understood and at present is a topic of

intensive study.

In lower animals such as fish, there is no visual cortex and all visual and visual-oculomotor functions are served by the subcortical optic tectum. In land animals such as rabbits, pigeons, cats, dogs and monkeys, optokinetic nystagmus can be elicited even in decorticated animals (Rademaker and ter Braak 1948). Thus the subcortical pathways are known to serve definite visual-oculomotor functions. In human, however, the functional significance of subcortical pathways is not certain.

The subject of the pathways governing the involuntary eye movements of optokinetic nystagmus is confusing; this will be discussed in the next section in conjunction with different types of optokinetic nystagmus proposed in the literature.

4.1.2 A Survey and Discussion on the Types of Optokinetic Nystagmus

Optokinetic nystagmus, commonly abbreviated as OKN, occurs in normal persons when a part or the entire visual field of that person is moved, or conversely, when a person is moved past a series of stationary objects. For example, a person sitting in a railway coach or a bus watching the outside scenery go by develops this type of ocular nystagmus, which was originally called train nystagmus by Barany (1907). As the eyes fixate and track upon one scene, a pursuit eye movement is produced which is the slow component of nystagmus, and in a similar manner to vestibular nystagmus this slow eye movement is interrupted by

the saccadic component in the opposite direction to fixate on the next scene. These eye movement patterns occur repetitively resulting in a sawtooth-like nystagmus waveform.

The phenomenon of optokinetic nystagmus was first reported by Purkinje (1825) while watching a crowd at a cavalry parade. Around the turn of the century, Barany (1907) began to realise the importance of this form of nystagmus and to study it in patients. Other names used by early workers to refer to the same phenomenon were "optomotor nystagmus" (Cords, 1926), "optical turning nystagmus" (Ohm, 1922), "optic nystagmus" (Dodge and Fox, 1928; Rademaker and ter Braak, 1948), "optical-kinetic nystagmus" (Rademaker and ter Braak, 1948) and others. The term optokinetic nystagmus, proposed by Borries (1926) was agreed upon at the International Ophthalmological Congress at Amsterdam in 1929.

In recent literature , there appear many classifications of optokinetic nystagmus. The types described by different authors are first listed and later explained in three groups. The types are: following, stare, and fixated types (Nelson and Stark, 1962; Stark, 1971); look, and stare types (Roelofs, 1954; Honrubia, Downey, Mitchell and Ward, 1968); cortical, and subcortical types (Rademaker and ter Braak, 1948; de Klyn, 1948; Monnier, 1967); foveal and retinal types (ter Braak, 1935); foveal and peripheral types (Hood, 1967; Dix and Hood, 1971). From the survey, it is apparent that different factors were taken as a basis for classification by different authors. The principal factors which affect optokinetic nystagmus and which might be used as a basis

for classification appear to be the following: (1) Mental set of the subject under test, in particular his voluntary influence, (2) contribution to optokinetic nystagmus from different parts of the retina, and (3) pathways and centers for optokinetic nystagmus in the central nervous system. For convenience, the findings leading to the different classifications of optokinetic nystagmus listed above will be explained under these three headings

Mental Set of the Subject. Following, stare, fixated, and look types are included under this heading. Under experimental or clinical conditions, optokinetic nystagmus is elicited by asking the subject to view a rotating drum or moving belt which has on its surface vertical black stripes on a white background. The subject is instructed either to voluntarily follow the moving stripes as far as possible without turning his head (Honrubia et al, 1968) or to relax his eyes and let involuntary mechanisms take control. In the first case, the tracking actions of the eyes produce relatively large smooth pursuit movements followed by saccades in the opposite direction to fixate on a new target. Honrubia et al (1968) called this the "look" type optokinetic nystagmus, and Nelson and Stark (1962) and Stark (1971) called it the "following" type. For convenience, the term "voluntary following" will be used in this thesis to refer to eye movements produced under this kind of experimental condition. In the second case, if the subject retains his attention on the moving

stripes but makes no voluntary effort to follow these movements, reflex action will cause his eyes to follow the stripes for a comparatively short distance and to make saccades in the opposite direction, thus producing nystagmus. This is called the "stare type" both by Honrubia et al, and Nelson and Stark. They reported that the voluntary following type had a higher average tracking speed for a given speed of the optokinetic stimulus (the moving stripes) and also could track the optokinetic stimulus to a higher speed than stare type. The "voluntary following type" also had larger and more uniform amplitude, and was of lower frequency and more regular.

The fixated type was described by Nelson and Stark (1962) and Stark (1971). They provided a stationary point target superimposed on the moving stripe background and asked the subject to fixate on the point. They found nystagmus of a fraction of a degree amplitude and called it the fixated type. However, many other authors (Roelofs, 1954, Jung and Kornhuber, 1964; Hood, 1967 and others) reported cessation of nystagmus if a stationary fixating point was provided in addition to the moving stimuli, and this is also my experience. In the same report, Nelson and Stark found that the slow component eye velocity of the stare type optokinetic nystagmus remained less than 5 degrees per second while the stimulus velocity was increased from 5 to over 40 degrees per second. This again is contrary to findings of most other authors. Thus Nelson and Stark's findings seem to be special to their experimental conditions.

Under the condition of voluntary following of optokinetic stimulus, it seems probable that the extended target following movements are resulting from voluntary suppression of the saccadic components and augmentation of the slow components of the basic reflex. This concept is suggested by some experimental results of this thesis and it will be further discussed in Chapter 5 when evidences are available for illustration.

The experimental condition which minimised voluntary influences on eye movements produced the so called 'stare type' optokinetic nystagmus. The majority of experiments described in this thesis were conducted under this condition. However, the term 'stare' will not be used since it may convey the unintended impression of inattentive gaze, or on the other hand, of voluntary suppression of reflex movements.

Retinal Contribution to optokinetic nystagmus is the basis for distinguishing foveal, retinal and peripheral types. The retina can be divided functionally into central and peripheral portions; central vision has been also loosely referred to as foveal vision or macular vision. However, there is no general agreement on the extent of these subdivisions of the visual field. Since an optokinetic stimulus may be presented so that the image falls on different regions of the retina, the interest naturally arises concerning the ocular response to the different stimuli.

Dodge and Fox (1928) studied a patient with central scotoma, with a loss of central vision about 10 degrees above, below and to the temperal side, and about 15 degrees to the nasal side. Optokinetic nystagmus was elicited upon presentation of an optokinetic stimulus to the peripheral vision. However, no data was available to be compared with nystagmus from central vision,

Ter Braak (1935) referred to cortical nystagmus as 'foveal nystagmus', and the subcortical type as 'retinal nystagmus', but he did not emphasize these terms in later publications.

More recent work was done by Hood (1967), and by Dix and Hood (1971) who reported obtaining quite different kinds of optokinetic nystagmus from foveal and peripheral vision, and postulated that these were served by two separate and distinct mechanisms. In Hood's experiment, the subject sat inside a large drum; the interior drum wall was of black material with white vertical stripes at 15 degree intervals and the drum could be made to rotate at any angular velocity up to 120 degrees per second. Two experimental conditions were described: (1) Provision was made for good illumination of the interior so that the whole of the visual fields was excited by the movement of the drum. (2) To exclude macular vision, he illuminated the interior with ultra-violet light. Following a prolonged period of dark adaptation the intensity of the ultra-violet was increased until the faintly fluorescent white stripes could just be perceived peripherally.

Hood reported that nystagmus of entirely different

character was obtained in each case. He stated: "Whereas in good illumination the eyes deviate in the direction of the fast component, in liminal illumination they deviate in the direction of the slow. Furthermore, in the case of good illumination, the change in direction always begins with a fast component, while in the case of liminal illumination it begins with a slow component". Hood (1967 discussion) emphasized that these two types of optokinetic nystagmus were not to be identified with the cortical and subcortical types of ter Braak, and later Dix and Hood (1971) suggested that the two types were mediated by quite different cortical mechanisms.

Retinal contribution to optokinetic nystagmus is a major topic of study in this thesis; experiments concerning this are described in Section 4.3. The results disagree with the findings of Hood and Dix.

Neural Pathways and Centers for optokinetic nystagmus are the basis for distinguishing cortical and subcortical types.

Opinions expressed in the literature concerning the neural pathways and centers for optokinetic nystagmus reflex are conflicting, especially in the clinical literature. There are many different schools of thought based on clinical and experimental findings and, not infrequently, on unsupported hypothesis. Nearly all experimental work was performed on animals, and direct inferences were often made as to the situation in man. The validity of such inferences in the case of optokinetic nystagmus is questionable because of the possible difference in visual-oculomotor pathways between different species as a result of

increasing encephalisation among higher animals. Data for human were mostly based on clinical studies, often unsupported by appropriate pathological investigation, and thus contradictory results were often reported.

The proposal that a distinction can be made between 'cortical' and 'subcortical' optokinetic nystagmus seems to have originated from de Kleyn and Rademaker (1923), ter Braak (1935), and Rademaker and ter Braak (1948). The findings of these authors are summarised below.

It was observed that when a black and white striped drum was rotated in the field of vision of a waking dog, nystagmus did not occur. However, when a revolving platform with a number of rabbits placed along the border was placed in the dog's field of vision, nystagmus would result in those animals which became excited by the rabbits and snapped at them. Nystagmus did not occur if, instead of rabbits, other objects were placed along the border of the revolving platform. They concluded that the production of this nystagmus required 'a very special and complicated stimulation which excites the instinctive interest, and thereby it was established that in dogs a cerebral optic nystagmus occurs.' When a decorticated animal was placed inside a rotating vertical cylinder with alternating black and white stripes on the inside, nystagmus occurred. From these observations, it was concluded that in dogs, two forms of optokinetic nystagmus can be distinguished: (1) cortical optokinetic nystagmus which occurs when successive moving objects, which arouse the instinctive

'interest' traverse the field of vision, (2)subcortical optokinetic nystagmus which occurs when all parts of the visual environment are moving in the same direction. Similar phenomena were observed in rabbits, cats, pigeons and monkeys, except that in rabbits, attempts to excite the cortical type of optokinetic nystagmus all failed.

A question naturally arose whether the two forms of optokinetic nystagmus described above could be distinguished in human. As described in Section 4.1.2, some fibers from the optic tract enter subcortically into the pretectal area, the superior colliculus and the reticular formation. Whether these subcortical pathways would incite optokinetic nystagmus or not is not known, and this, at least in part, might have led to many controversial claims.

Rademaker and ter Braak (1948) reported that in patients with extreme idiocy nystagmus occurred when they were examined while the whole visual environment was rotating, but nystagmus did not occur in response to the to-and-fro movement of a string of beads or of a series of coloured prints at some distance from the eyes. De Klyn (1949, cited by Kestenbaum, 1957) reported that in a five-year-old child with both visual cortices presumed blinded by gas intoxication, the cortical optokinetic nystagmus, elicited by a series of moving targets against a stationary background, was absent, while the subcortical optokinetic nystagmus, elicited by rotating the entire surrounding, was present. These findings led de Klyn to accept the existence of subcortical optokinetic nystagmus in human.

On the other hand, Vetzeboer (1952) found in a sixty-year-old man with sudden bilateral cortical hemianopsia, no nystagmus was incited by revolving the whole environment. Later light perception returned in the left half of the visual field and a weak nystagmus appeared when the drum was rotated to the right. Vetzeboer denied the existence of a subcortical optokinetic nystagmus in human.

Clinical findings concerning this complicated mechanism, however, may not be interpreted with certainty. For example, optokinetic nystagmus can be inhibited by defocussing (converging or diverging) or fixating on stationary objects. Rademaker and ter Braak 's findings in patients with extreme idiocy and de Klyn's finding in a five-year-old child that a series of moving objects in the visual field did not incite optokinetic nystagmus in these patients might simply be because the patients were not looking at the moving objects, and when all parts of the visual field were rotated, it eliminated stationary fixation and hence nystagmus resulted.

The only conclusive evidence about the existence of a subcortical optokinetic pathway in human would be from studies of a de-cerebrated human, but such a case has not been reported. Thus the problem remains unresolved.

Attention is now turned to the actual anatomical locations in the central nervous system which are concerned with optokinetic nystagmus. From clinicopathological correlations, Kestenbaum (1948), Smith and Cogan (1960), and Smith (1963)

supported the notion that the cortical centers for optokinetic nystagmus are localised in circumscribed regions of the parietal lobe. Jung and Kornhuber (1964) suggested that the centers are in the peristriate cortex. Carmichael, Dix and Hallpike (1954) proposed that the cortical centers are situated in the angular and supra-marginal gyri, while the lower centers are found in the superior colliculi whose functions during optokinetic nystagmus are, according to these authors, similar to those of the vestibular nuclei during vestibular nystagmus. On the other hand, Krieger and Bender (1957), Pasik and Pasik (1964) denied the existence of specific centers for induced nystagmus in the cerebral cortex and suggested that oculomotor function is widely distributed over the entire cortex, and no particular region is indispensable for the function of another. In addition, Pasik and Pasik (1964) found that two weeks after bilateral destruction of the superior colliculi in monkeys, optokinetic nystagmus had recovered. They concluded that there were no centers for optokinetic nystagmus in the superior colliculi. More recently, Dix and Hood (1971) proposed two cortical optokinetic nystagmus centers: the frontal eye fields governing nystagmus from foveal vision and the occipital visual cortex governing nystagmus from peripheral vision.

However, in many cases, it is not clear what the authors exactly meant by 'centers', in particular, whether these are

essential pathways leading to a more complicated nystagmus generating mechanism or whether these 'centers' actually generate impulses which are directly transmitted to the oculomotor nerves to cause nystagmus. This problem will be further considered in Chapter 5 where a common central mechanism for optokinetic and vestibular nystagmus will be discussed. Meanwhile, further considerations of pathways will be informative.

In considering optokinetic nystagmus, as in vestibular nystagmus, two separate components must be recognized. Experimental and clinical evidence suggest that the two components are served by two different pathways although this does not imply that the two components are independent. Holmes (1938) reported that human with damage to area 8 in the frontal cortex or its projection fibers were unable to make voluntary saccades. Mackensen and Schumacher (1960), and Goto, Tokumasu and Cohen (1968) have shown that the saccadic components of nystagmus have the same characteristics of voluntary saccades. Hoyt and Daroff (1971) reported that a patient with right-side frontal lobe lesion was unable to make voluntary saccades to the left; also, optokinetic testing with targets turning towards the right side only produced smooth tonic deviation of the eyes to that side without saccadic components to the left. Further, they reported that in patients with deep posterior hemispheric lesions (involving the occipital and the parietal lobes), voluntary pursuit to the side of lesion and optokinetic nystagmus with slow components to the side of lesion were both defective, but were intact when voluntary pursuit and optokinetic stimulus direction were reversed.

These evidences suggest that reflex saccadic and pursuit eye movements may be dependent upon the same anatomic substrate as voluntary saccadic and pursuit eye movements whose pathways were introduced in Section 4.1.2, and that at least two cortical areas namely, the frontal eye fields and the occipito-parietal areas, must remain intact to generate a normal optokinetic nystagmus. Opinions expressed by Jung and Kornhuber (1964), Robinson (1968), Fuchs (1971) also indicate that these areas are not nystagmus centers but function as essential mediating pathways or facilitating and inhibitory centers and that the nystagmus center is more likely to be in the brainstem. This concept will be supported by the experimental results of this thesis in which the inter-saccadic interval characteristics of optokinetic nystagmus will be shown to be very similar to those from vestibular nystagmus, and the vestibular nystagmus center, with its possible complex organisation as described in Section 3.1.3, is known to be located at the brainstem level. An overall discussion on the optokinetic nystagmus mechanisms will be presented in Chapter 5.

4.1.4 Methods of Inducing Optokinetic Nystagmus and Outlines of Experiments

In contrast to many methods of inducing vestibular nystagmus, optokinetic nystagmus is invariably induced by moving the image in either a part of or the entire visual field of the subject. Clinically, it is common to use a small rotating drum on which vertical lines are marked, as originally devised by Barany (1921).

For the experiments of this thesis, in order to have a great feasibility in providing different images as optokinetic stimuli, a computer was used to generate the images. Furthermore, a unique feature of the computer method that is difficult to match by any other method is that eye movement signals can be fed back into the computer to control the generation of the image so that a portion of the central vision is effectively deleted. This was used to study the retinal contributions to optokinetic nystagmus. These methods will be described in more detail in the corresponding experimental sections.

Experiments will be divided into two major sections: In Section 4.2, the inter-saccadic interval characteristics of optokinetic nystagmus will be analyzed in the same manner as vestibular nystagmus. In addition, the effects of various parameters of the optokinetic stimulus and that of voluntary following the stimulus will be examined. In Section 4.3, experiments will be described which examined the retinal contribution to optokinetic nystagmus.

Normal subjects were tested in all experiments. Instructions were given to minimise voluntary influence on eye movements, except in one experiment of Section 4.2, where the effect of voluntary following of optokinetic stimulus at various speeds was tested.

In describing the experimental results, it should be pointed out that in some cases an immediate interpretation of the result was not possible because of interaction from other

factors which could only be understood after later experiments. Therefore, in places where immediate explanation can not be given, only brief comments will be made. An overall discussion of the results is given in Chapter 5 where cross references to all experimental results will be freely made.

The results seem to suggest that the different proposed types of optokinetic nystagmus described in the preceeding sections are actually variants of a basic type generated by a mechanism in common with that of vestibular nystagmus.

4.2 INTER-SACCADIC INTERVAL ANALYSIS OF OPTOKINETIC NYSTAGMUS

4.2.1 Introduction

In the preceding chapter, evidence of multi-modality in the inter-saccadic interval histogram was shown to occur in spontaneous, positional, caloric and alcoholic nystagmus. Optokinetic nystagmus has the same saw-tooth like waveform as these vestibular types of nystagmus and its inter-saccadic interval characteristics will be considered in this chapter. Naturally, one main interest will be to see if multi-modality in interval histograms of the type found in vestibular nystagmus can also occur in optokinetic nystagmus. Because optokinetic nystagmus can be more easily induced and maintained at an approximately constant level of response, the inter-saccadic interval characteristics can be investigated in a relatively more controlled manner. A comparison of the results with those obtained from vestibular nystagmus may also serve to check on the proposal of a common neural mechanism generating the two types of nystagmus.

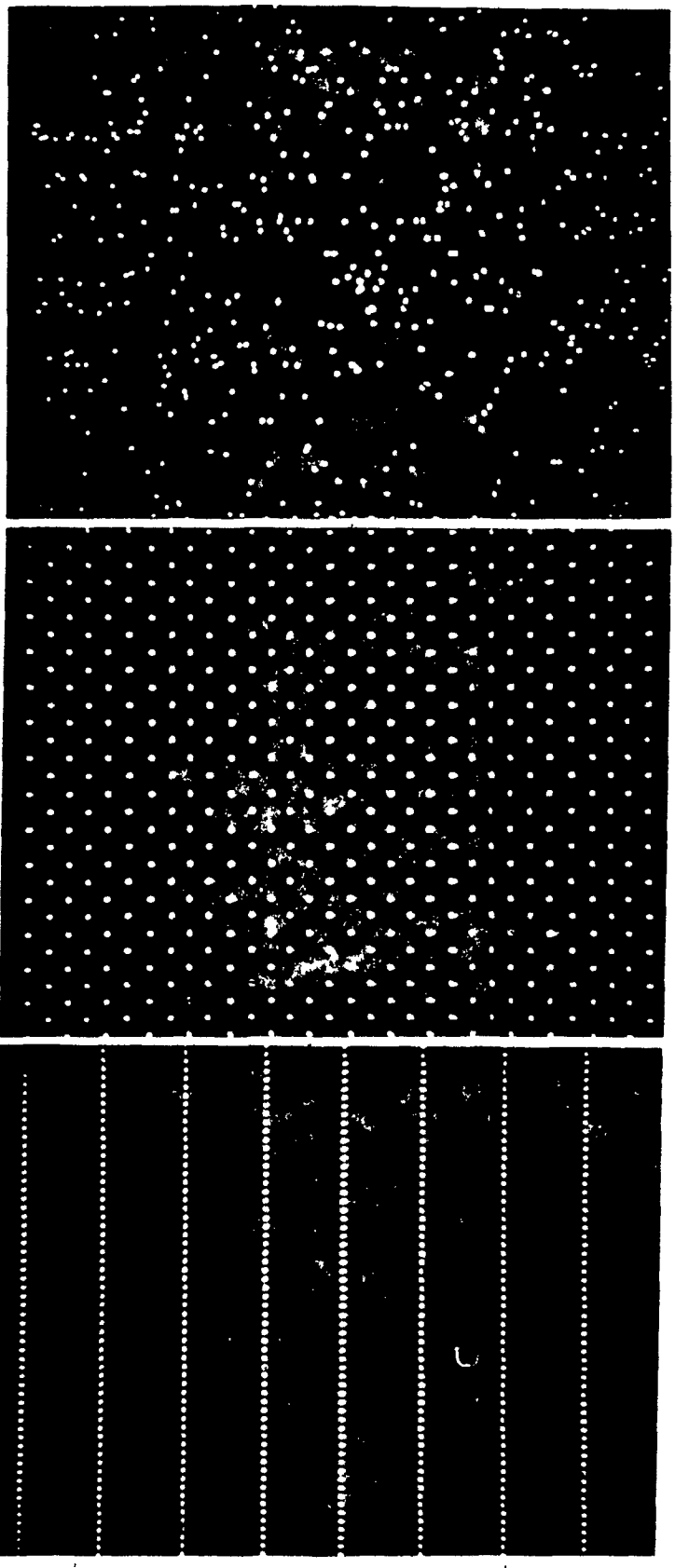
Computer generation of optokinetic stimulus also makes it possible to readily change the stimulus parameters. The effects of changes in image speed, pattern, density and brightness of the optokinetic stimulus on the inter-saccadic interval characteristics will be examined.

It should be pointed out that although optokinetic nystagmus can be induced at a given speed for a rather long period of time, arousal and mental activity, which are known to strongly affect the vestibular nystagmus, also affect optokinetic nystagmus. It will be demonstrated that mental arithmetic changes the inter-saccadic interval characteristics of optokinetic nystagmus significantly. Therefore, to avoid a significant change in mental state of the subject caused by fatigue, the experimental periods were kept short. Also, in analysing the results, only major changes were considered, and subtle changes were not pursued.

4.2.2 Method

Computer Generation of Optokinetic Stimuli

The computer used to generate the optokinetic stimuli was the Digital Equipment Corporation LINC-8. This computer has an oscilloscope (LINCSCOPE) capable of displaying a matrix of 512 x 512 points. In the experiments of this section, 512 points were programmed to form three basic patterns as shown in Fig. 4.4. These patterns were (1) non-repeating random dots, (2) dots arranged in a checker-board pattern, and (3) dots arranged to form eight vertical stripes. A pattern was projected onto a screen 38 inches in front of the seated subject by an oscilloscope (Tektronix type 561B with P31 phosphor) fitted with a camera lens (NIKKOR-S 1:1.4, f=5.8 cm) and located above



Random dots

Checker Board

Stripes

Fig. 4.4 Patterns of computer generated optokinetic stimuli

the subject's head (Fig. 4.5). The full 512 point display formed a rectangular image subtending 80 degrees horizontally and 60 degrees vertically at the subject's eyes. When projected on the screen, each dot of the display was approximately 0.6 degree in diameter.

The random pattern was obtained by taking the vertical height of successive dots a random number. The random numbers were approximately uniformly distributed in the range of 0 to 512 and were generated by a congruential method described by Connelly (1970). 512 such random numbers were stored as a reservoir in the core memory and they were randomly shuffled after each one of them had been used. The method provided fast computer accessibility to a non-repeating sequence of random numbers within the duration of the experiment.

The horizontal spacing between dots of the checkerboard pattern was about 4.8 degrees and that between the vertical stripes was about 12 degrees.

Each frame of 512 points took about 15 milliseconds to display. The pattern was programmed to move in one or the other horizontal directions by either a left or a right shift of the data in the pattern memory between each 'frame' of display, and the time taken for a shifting operation was about 6 milliseconds. The shifting of one data location corresponded to about 0.15 degree increment in the projected image. Due to this relatively small increment compared with the dot size and the speed of the computer display, the incremental

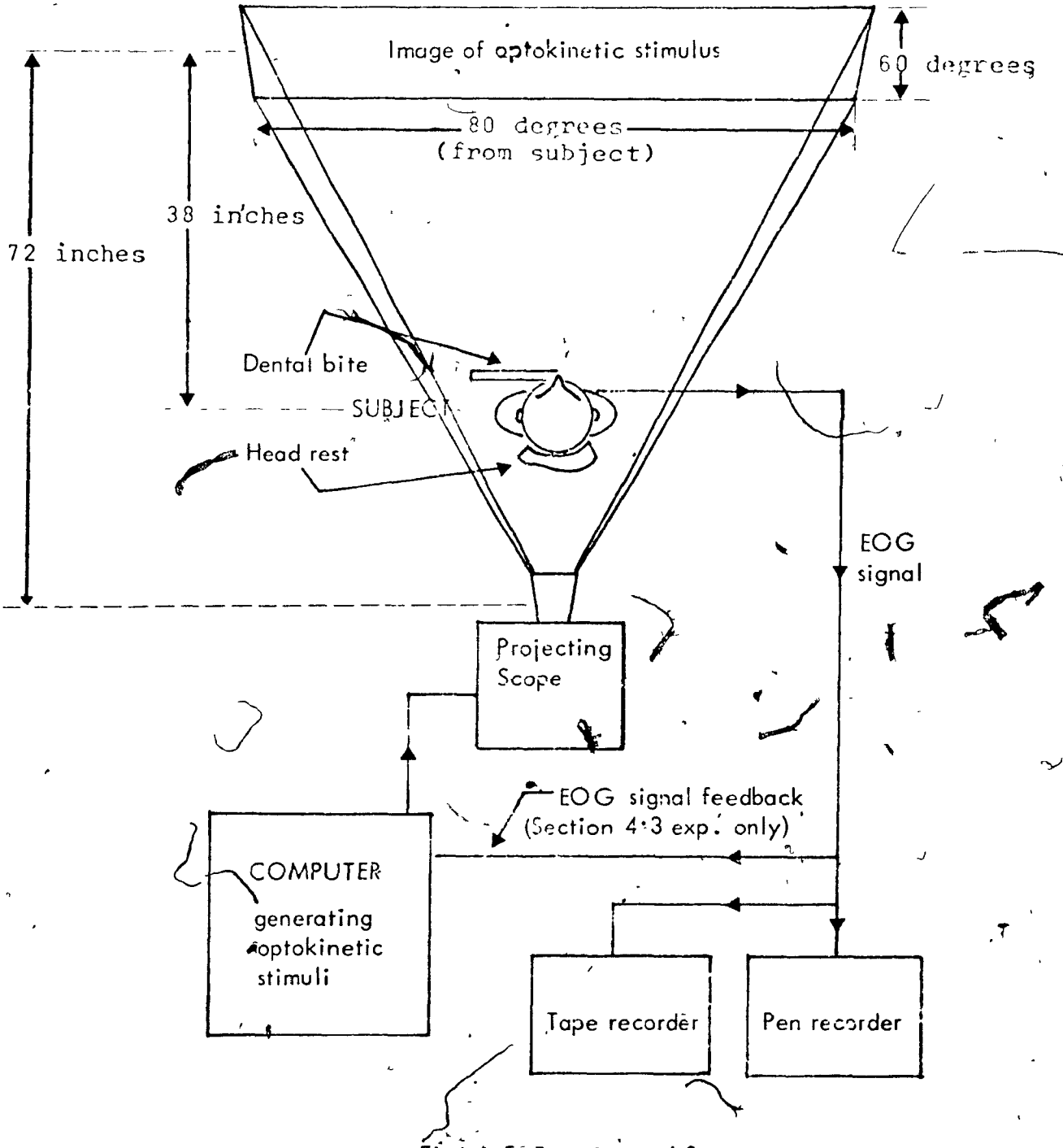


Fig. 4.5 Experimental Setup

movement effect of the projected image was not perceptible up to 50 degrees per second. Also the movement of the image could be reversed in about 6 milliseconds.

Experimental Setup and Procedure

The essential setup for the experiment is shown in Fig. 4.5. The subject sat on a comfortable chair which could be adjusted to suit individual physiques. A comfortable head rest was provided and a dental bite was used to prevent head movements. The eyes of the subject were 38 inches from the image screen whose center was coincident with the position of central gaze.

Eye movements were recorded by skin electrodes according to methods described in section 2.1; the eye movement signal was traced by a polygraph (Beckman type 3 II) and recorded by an FM tape recorder (Hewlett Packard 3917B) for later analysis.

Because of the limited intensity of the projecting oscilloscope, the experiments were conducted in a completely dark room to increase the contrast of the optokinetic stimulus; this also serves to exclude the subject's possible vision of the stationary surroundings during the experiment. The subject was dark adapted for at least ten minutes before each experiment and at that time, a clear vision of the green coloured moving stimulus was always reported by the subject.

Only normal subjects were tested, both male and

female with age ranging from 17 to 40. The subjects were asked to focus their vision forward on the screen while allowing reflex action to take complete control of any eye movements. No instructions were given to control mental activities.

Under these experimental conditions, a preliminary test showed that nystagmus always resulted, and the response could not be suppressed except by defocussing the vision on the screen or by fixating on a stationary target provided. The response at a given speed of stimulus in each direction also showed symmetry in both the appearance of the nystagmus tracings and in the inter-saccadic interval histograms.

Methods of Data Analysis

The emphasis on data analysis in this section will again be the inter-saccadic intervals. The methods of interval measurement were described in section 3.2.3. Results were mainly examined by the interval histogram shapes aided by observations of the corresponding sequential displays of interval magnitude; the interval histograms were smoothed by the function described in section 3.2.5.

In comparing different sets of results, the Kolmogarov-Smirnov two-tailed test (Seigel, 1956) was used to aid deciding whether the two given samples were drawn from the same population, and in this test, no smoothing was applied to the data. The test concerns the agreement between the two cumulative distributions and is very sensitive to any kind of difference in the distribution

such as location, dispersion, and skewness (Seigel, 1956; Kendall and Stuart, 1967). The null hypothesis will be that the two samples under test were from the same population. The probability of making an error resulting from rejecting the null hypothesis will be indicated by the parameter PROB, and a five percent significance level will be set so that if PROB is less than 0.05 , the null hypothesis that the two samples are from the same population will be rejected. PROB will be quoted with the results wherever it is desirable. It should be pointed out that this test was used only as an aid and not as a deciding figure. Individual variation in saccadic pattern sometimes could be considerable even under identical experimental conditions: experience showed that this was caused mainly by attention levels, mental activity and some unintentional voluntary tracking or random eye movements which happened more readily at lower stimulus speeds. A difference in results was recognized only when a consistent difference was obtained in at least three different subjects.

The actual experimental data collected was quite voluminous, but only representative results will be included in this thesis

4.2.3 Experimental Results

a. Effect of Mental Arithmetic

Arousal and mental activity in general were observed

to affect vestibular and optokinetic nystagmus. The purpose of this experiment was to give a specific demonstration of the effect of mental arithmetic on the rhythm of optokinetic nystagmus.

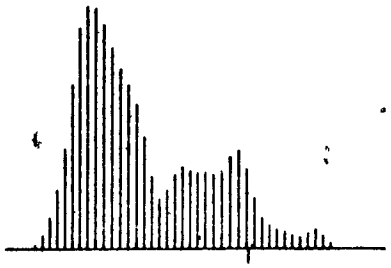
The experiment was conducted with the random pattern first at the speed of 50 degrees per second and later at 5 degrees per second. Four subjects were tested. For a given speed the random pattern was presented for 60 seconds without mental arithmetic, then for the next 60 seconds, the subject was asked to perform mental arithmetic of a simple type.

Typical results in Fig. 4.6 clearly show that mental arithmetic has the effect of randomising the inter-saccadic interval duration. The low PROB values from the Kolmogarov-Smirnov (K-S) test indicate a strong rejection of the hypothesis that interval characteristics during mental arithmetic are the same as those without mental arithmetic.

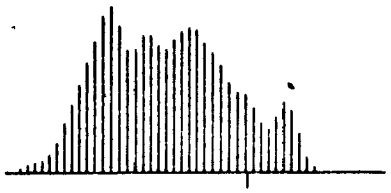
These results demonstrate that mental activity has considerable influence on the inter-saccadic interval characteristics, and can be expected to lead to non-stationarity. For this reason caution is required in the interpretation of experiments investigating the effects of other factors on the interval statistics.

b. Effect of Changing Optokinetic Stimulus Parameters

Image Speed. The experiment was conducted on seven subjects using the random pattern. An exception was the



(1) No ment.arith. 1 sec



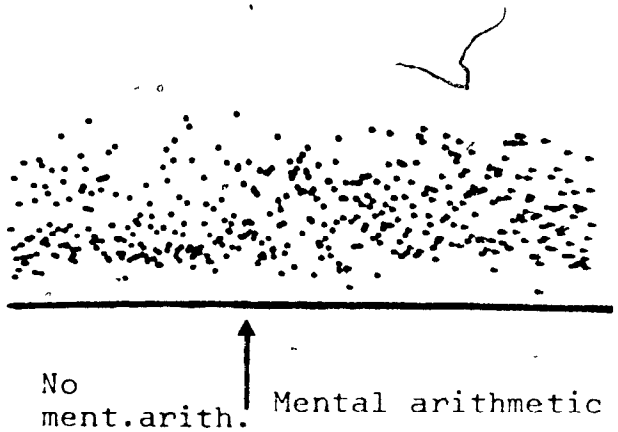
(2) Ment. arith. 1 sec

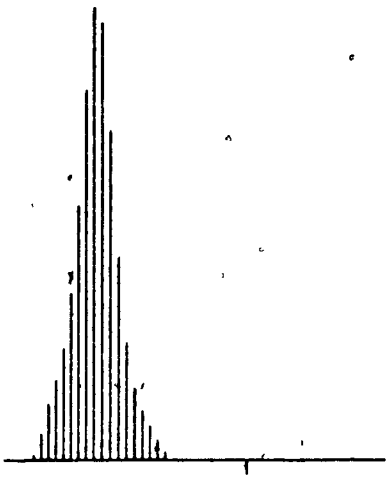
1,2 each has 230 samples

Subject VC, results 1,2
Image speed = 5°/sec

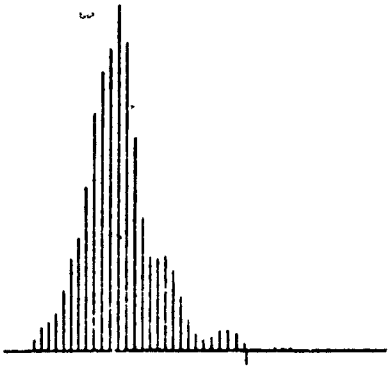
K-S Test

Compare	PROB
1,2	0.00





(3) No ment.arith. 1 sec



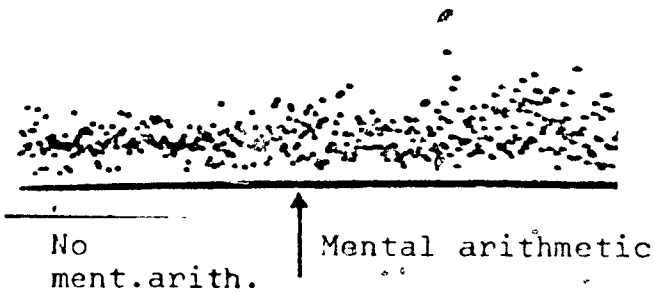
(4) Ment. arith. 1 sec

3,4 each has 180 samples

Subject SR, results 3,4
Image speed = 30°/sec

K-S Test

Compare	PROB
3,4	0.00



(a) Left side: Interval histograms
Abscissa = interval duration
Ordinate= relative frequency

(b) Right side: Sequential display of interval duration
Abscissa = sequence number
Ordinate= interval duration

Fig.4.6 Effect of mental arithmetic on inter-saccadic intervals

case of G.L., Fig. 4.8, in which a stripe pattern was used. Speeds ranged from 2.5 degrees per second to 50 degrees per second. A given constant-speed stimulus was presented to the subject for a period of about 90 seconds during which the nystagmic response was recorded. The subject then closed his eyes to rest for at least 30 seconds before the next stimulus at a different speed.

Fig. 4.7 shows a typical set of results from this experiment. At high speed the inter-saccadic interval is rather narrowly and symmetrically distributed signifying a fairly regular nystagmus beat which can also be observed from the corresponding nystagmus record in Fig. 4.7(b). As the stimulus speed decreases, the spread of the interval histogram increases and the distribution of intervals becomes skewed towards longer durations. With a further decrease in speed, multi-modal histograms appear. The corresponding nystagmus tracings in Fig. 4.7(b) at lower speeds are more irregular. Fig. 4.8 shows results from three other subjects. It is seen that in many of the multi-modal histograms, the second mode occurs at approximately twice the basic mode duration. Therefore, multi-modal histograms of the type found in vestibular nystagmus also occur in optokinetic nystagmus at lower stimulus speed.

Fig. 4.9 shows some sequential displays of interval duration and their corresponding scatter diagrams and an example of an expectation density display of data from the set of results shown in Fig. 4.7. These are for the convenience of comparison with the results of vestibular nystagmus.

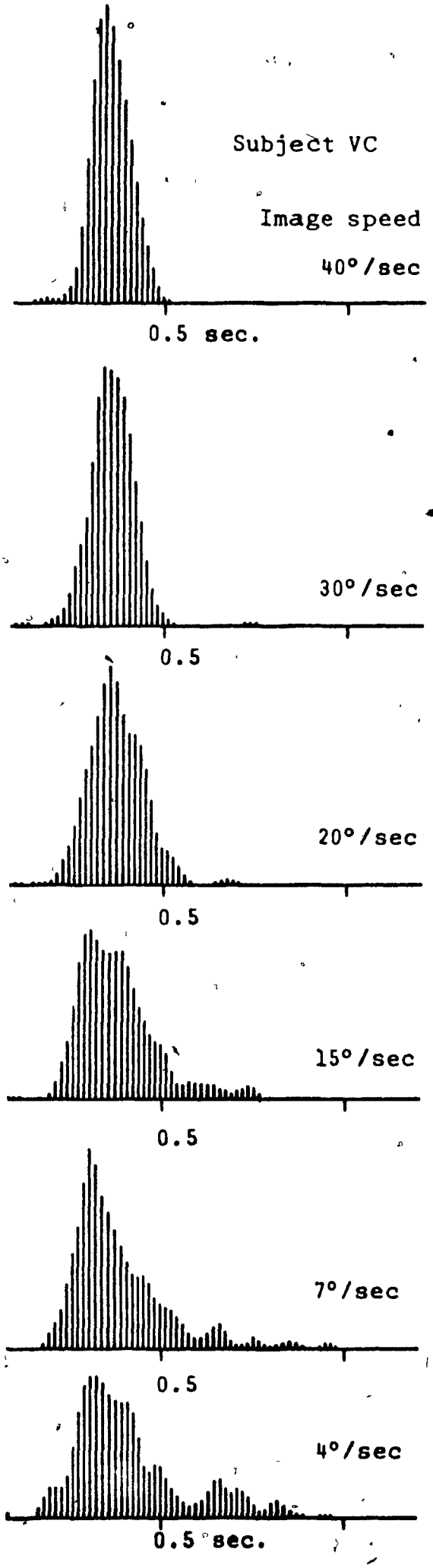


Fig.4.7 Effect of changing optokinetic stimulus speed

Left: Interval histograms
(a) Abscissa = interval duration
Ordinate= relative freguency
Each histogram has 197 samples

Right: Waveform tracing
(b) Chart speed = 0.5 cm/sec

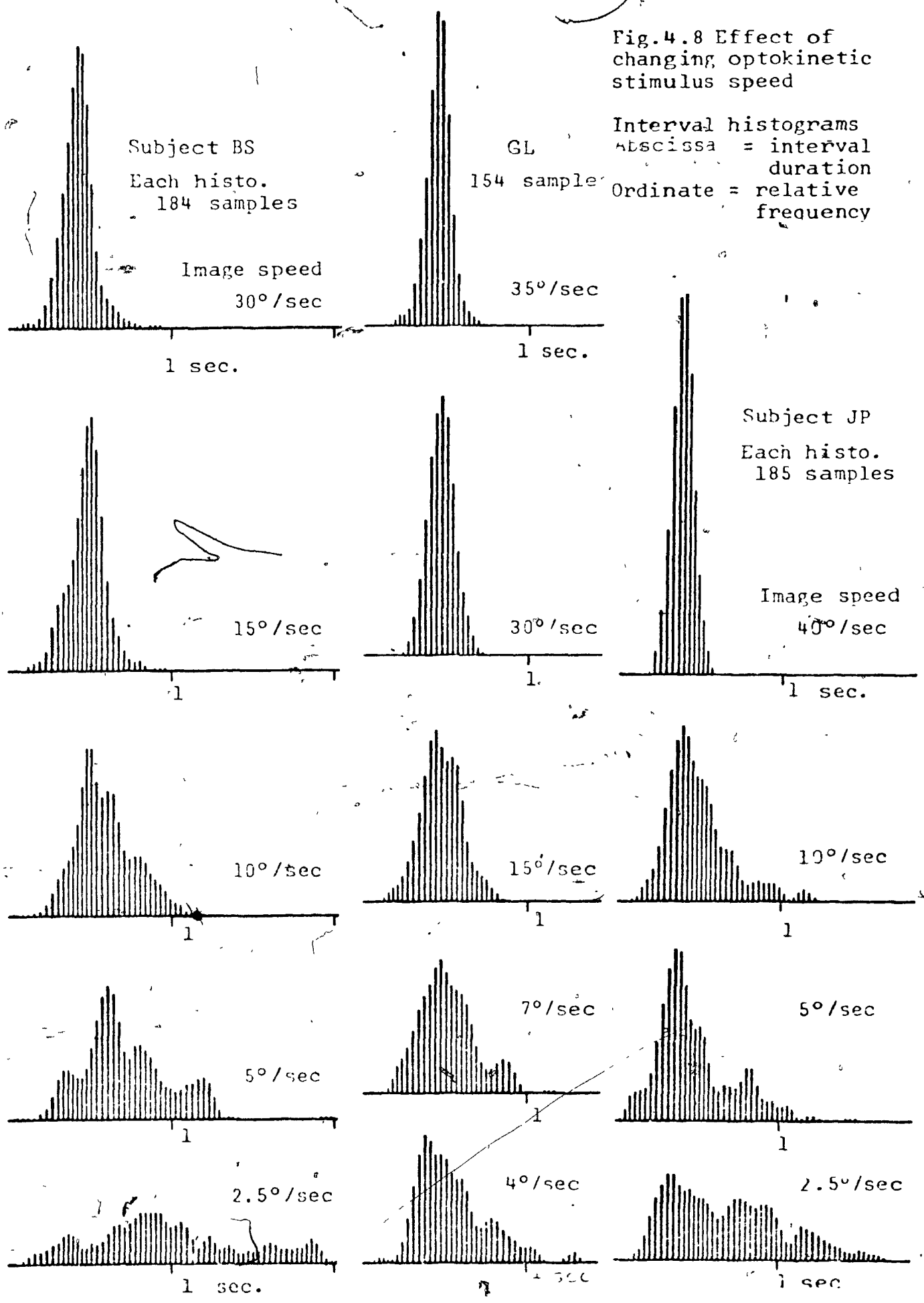
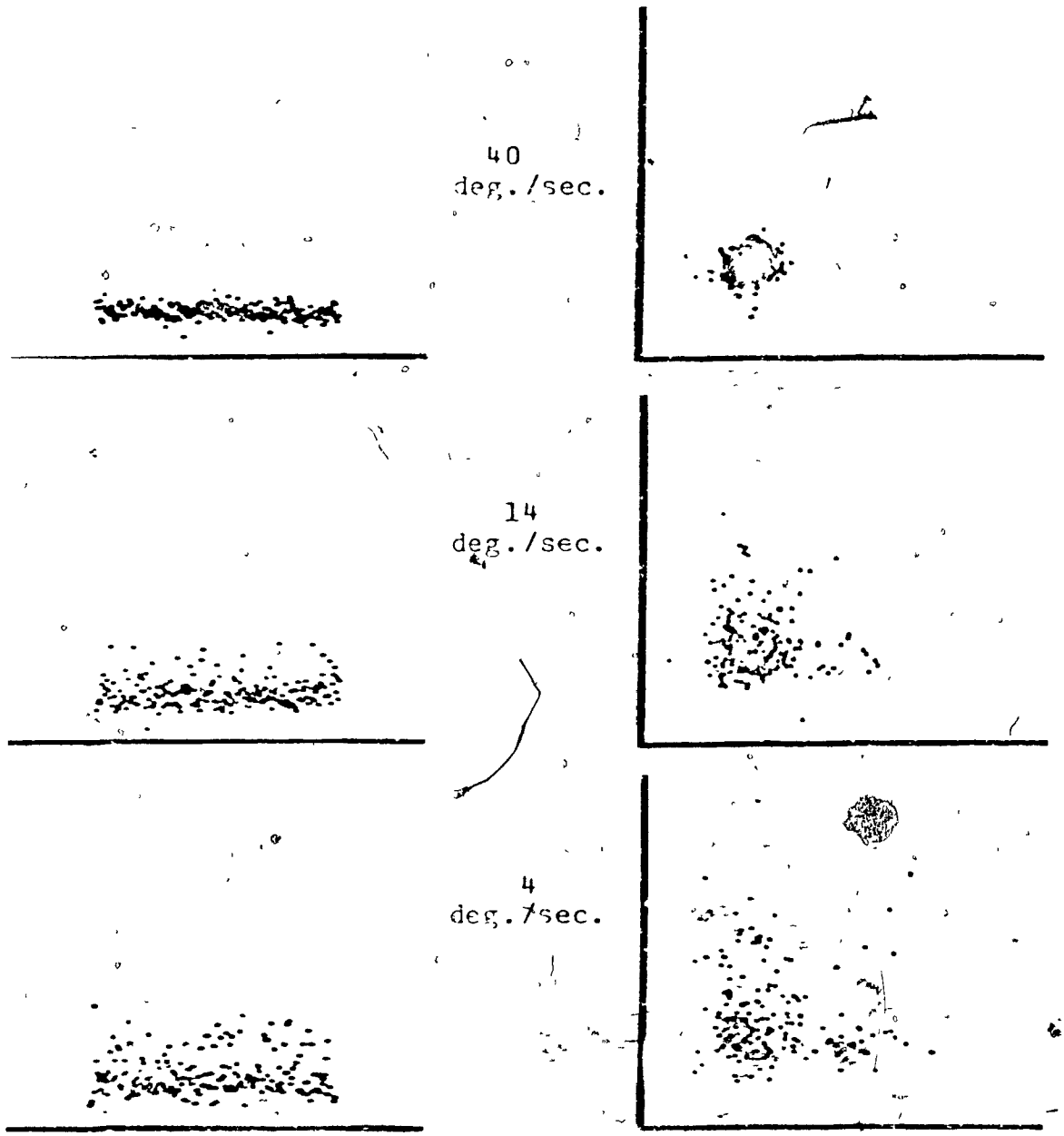


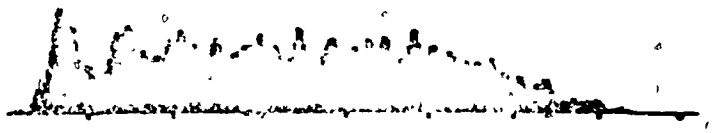
Fig.4.8 Effect of changing optokinetic stimulus speed

Interval histograms
Abscissa = interval duration
Ordinate = relative frequency



(a) Sequential point of
nterval duration
bscissa = sequence no.
rdinate = relative time
uration

(b) Scatter diagram
Both axes = relative time
duration



(c) Expectation density
Abscissa = time, each mark = 1/2 sec.
Ordinate = relative frequency

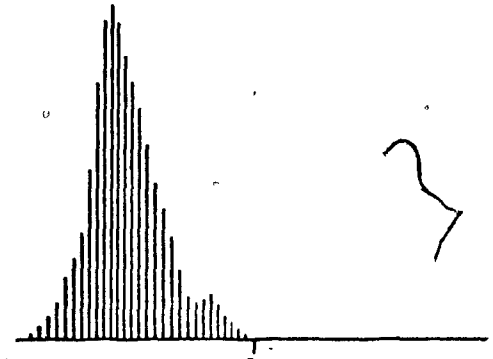
Fig. 4.9 Further analysis of some results in Fig. 4.7

It is seen that the scatter diagram and the expectation density at 4 degrees per second have characteristics similar to those resulting from spontaneous nystagmus and from the stochastic model simulation, both of which are shown in Fig. 3.19 and Fig. 3.20.

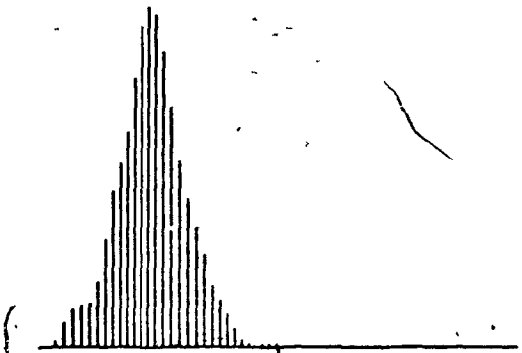
It is clear that the variations in inter-saccadic interval statistics of optokinetic nystagmus obtained so far can all be readily simulated by the stochastic model described in Section 3.3, as Fig. 3.17 in that section demonstrates. It will be shown that no other pattern of variation is obtained: thus the model can be applied to optokinetic nystagmus as well as to vesticular nystagmus.

Image Pattern. The experiment was conducted on six subjects. The random, checker-board and stripe patterns, each formed by 512 dots as shown in Fig. 4.4 all were moving at 25 degrees per second. Each pattern was displayed for a duration of about one minute so that the duration of the experiment was three minutes. The order of presenting the pattern was randomly chosen. The results from one subject are shown in Fig. 4.10. In this subject, the interval histogram resulting from stimulation with the stripe pattern appears to have a narrower spread and a smaller mean value, however, results from the other five subjects did not yield a consistent finding, as demonstrated by the results of two other subjects in Figs. 4.11(a) and (b).

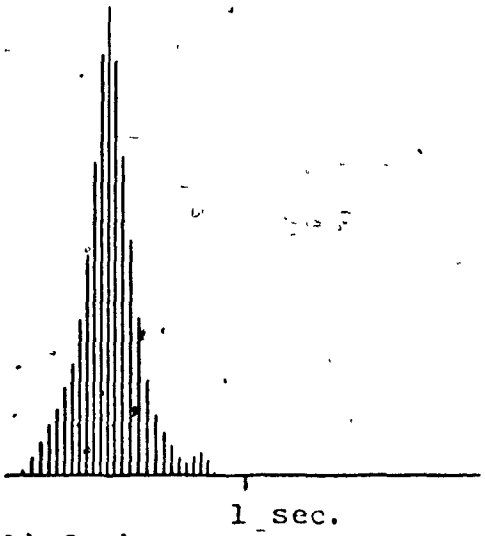
It was concluded that no major change in inter-



(1) Random dots



(2) Checker Board



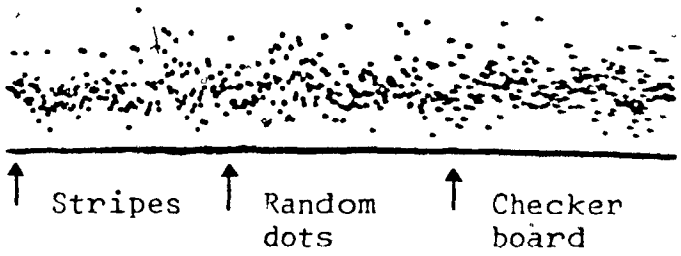
(3) Stripes

(a) Interval histograms
Each has 223 samples

Subject BS
Image speed = 25°/sec

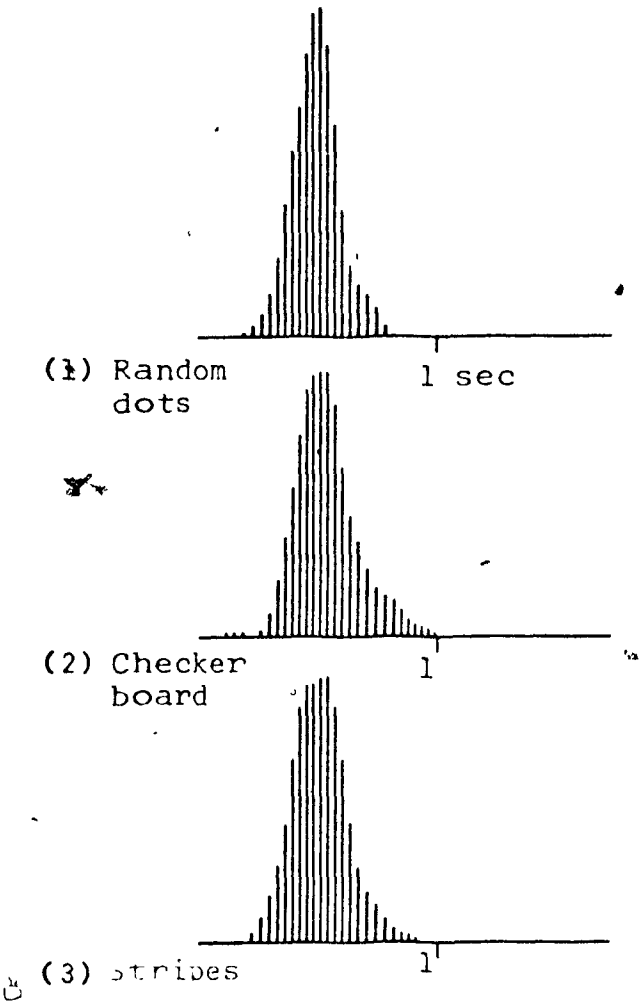
K-S Test

Compare	PROB
1,2	0.12
1,3	0.00
2,3	0.00



(b) Sequential display of interval duration

Fig.4.10 Effect of changing optokinetic stimulus pattern

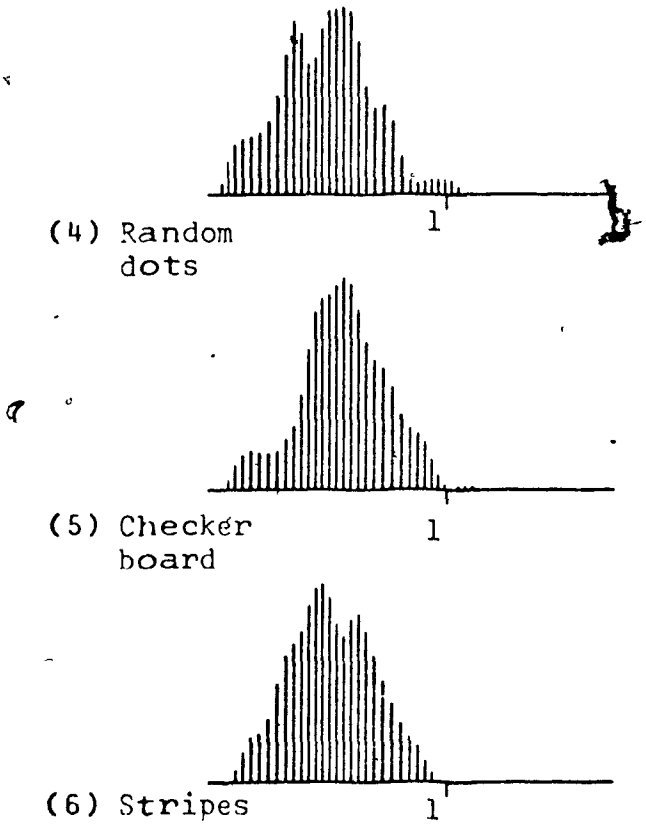


1,2,3 each has 161 samples

Subject CC
Results 1,2,3
Image speed = 25°/sec

K-S Test

Compare	PROB
1,2	0.02
1,3	0.33
2,3	0.57



4,5,6 each has 179 samples

Subject HK
Results 4,5,6
Image speed = 25°/sec

K-S Test

Compare	PROB
4,5	0.00
4,6	0.21
5,6	0.02

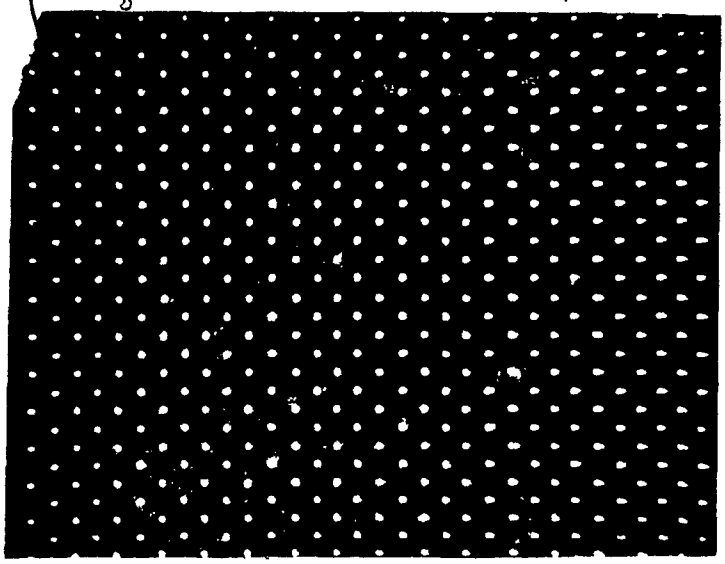
Fig.4.11 Effect of changing optokinetic stimulus pattern

Interval histograms

saccadic interval characteristics resulted by changing the pattern of stimulus under the present condition of a relatively brief experiment. However, it is conceivable that if each pattern were presented over a longer period, the oculomotor system might become adapted to the regular patterns and then produce more regular inter-saccadic intervals. In other words, predictive abilities of the human oculomotor system (reviewed by Robinson, 1968) may play a role here. It may also be conceivable that the spacing of the stripe pattern could affect the inter-saccadic interval regularity, especially when the stripe spacings are at the mean value of the saccadic amplitudes of the nystagmus at the given stimulus speed. Thus, if these subtle differences in results were questioned, further experimentation would be required.

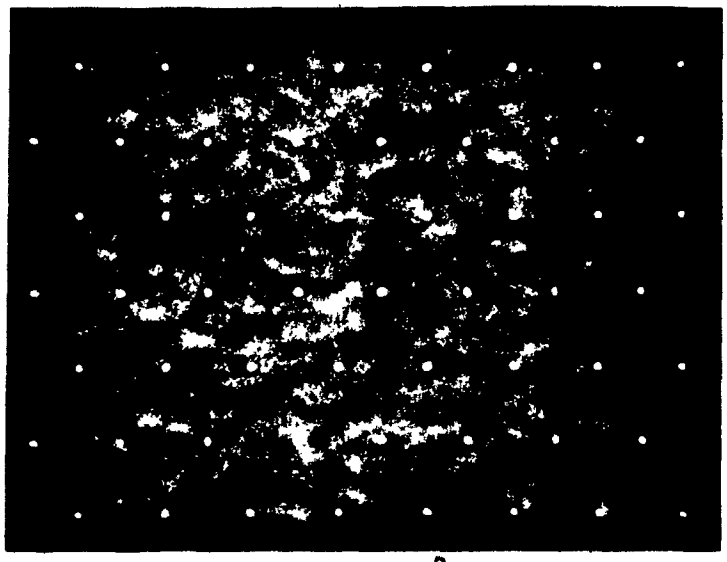
Image Density. The checker-board pattern in these experiments was used because it was the most suitable pattern for changing the image density evenly. Three densities of the checker-board were used (Fig. 4.12), with horizontal spacing between dots of 4.5, 9, and 19 degrees. Each pattern was presented to the subject for 60 seconds, followed by a 30 second rest before the next experiment. The order of presentation of the patterns was randomly chosen, and in each case the pattern was moving at 25 degrees per second. Nine subjects were tested.

Under these experimental conditions, no consistent difference in the results was observed. The results from two subjects which are shown in Fig. 4.13 and Fig. 4.14. Subsequent



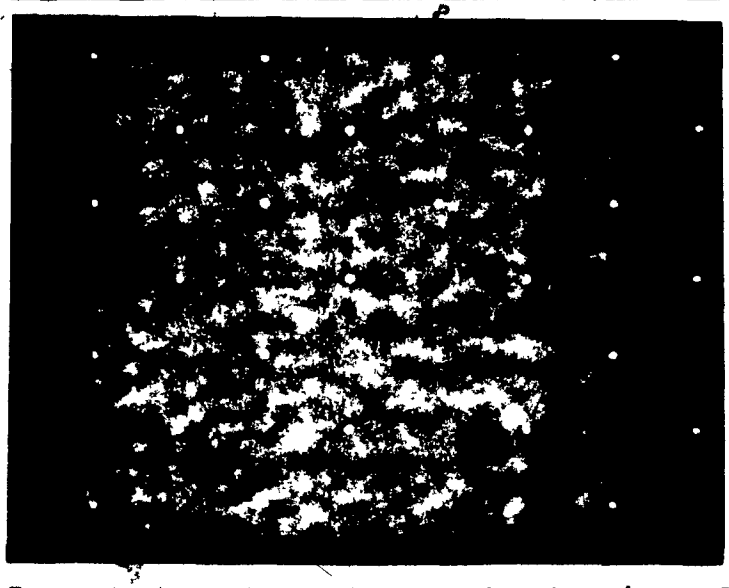
Horizontal spacing between dots

4.5 degrees



Horizontal spacing between dots

9 degrees

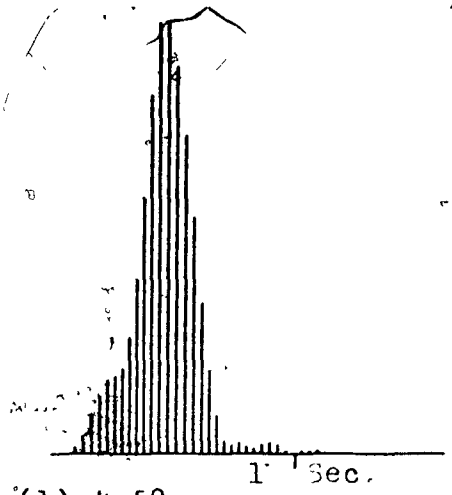


Horizontal spacing between dots

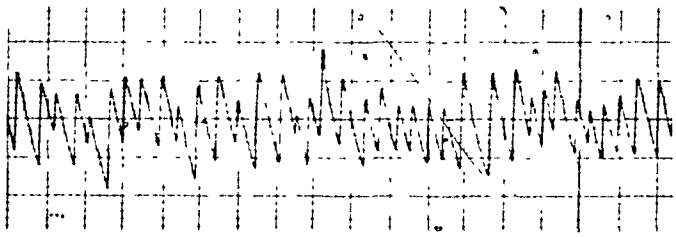
19 degrees

Fig. 4.12 Patterns used to change the density of optokinetic stimulus

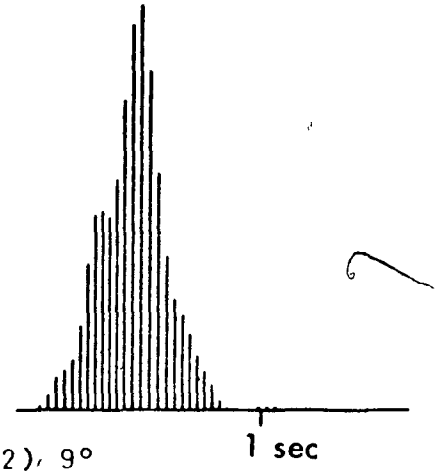
Subject BS
Image speed = 25°/sec



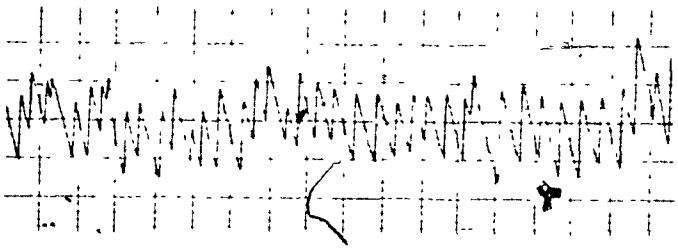
(1) 4.5°



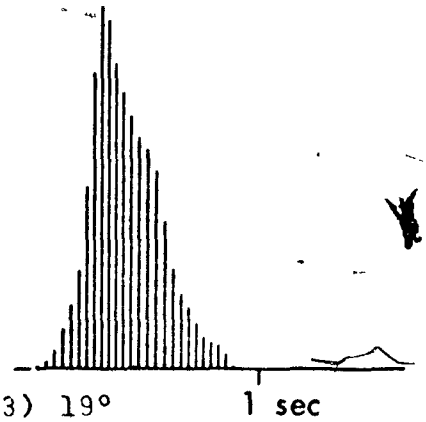
Dot spacing 4.5 degrees



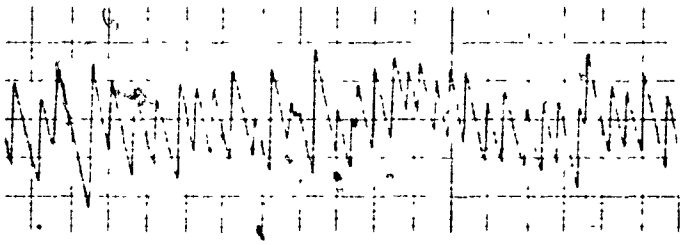
(2) 9°



Dot spacing 9 degrees



(3) 19°



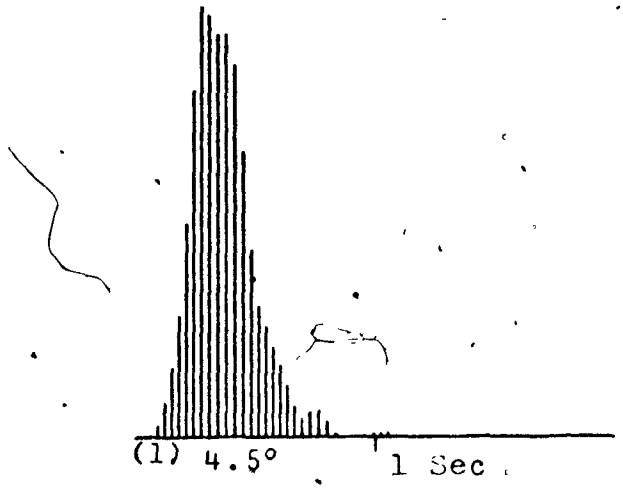
Dot spacing 19 degrees

Interval histograms
Each has 223 samples

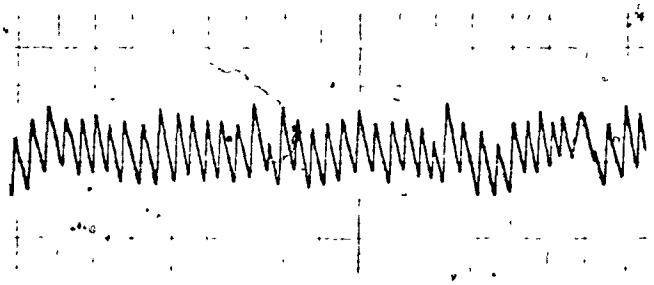
K-S Test

Compare	PROB
1,2	0.17
1,3	0.00
2,3	0.00

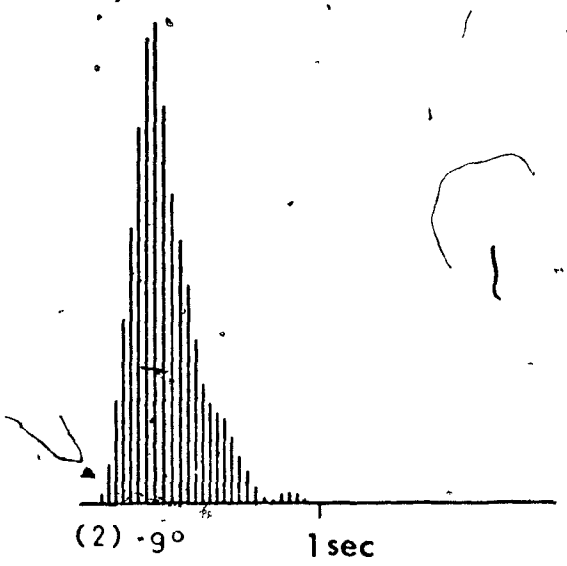
Fig. 4.13 Effect of changing optokinetic stimulus density

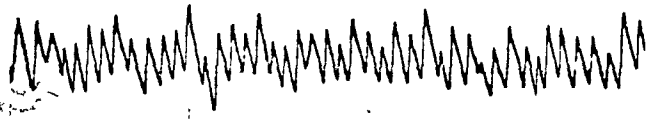


Subject JP
Image speed = 25°/sec

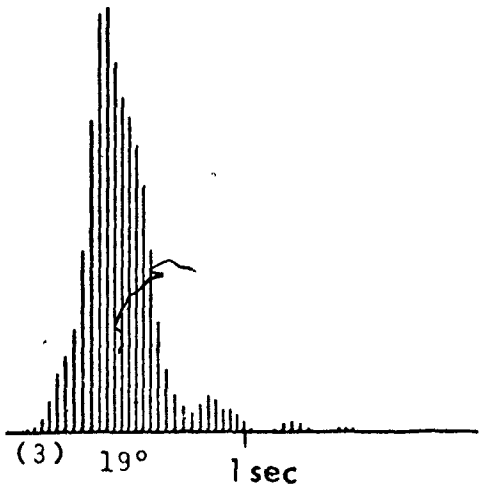


Dot spacing 4.5 degrees

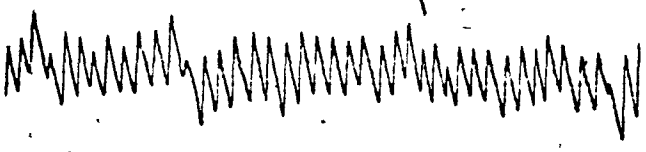




Dot spacing 9 degrees



Interval histograms
Each has 254 samples



Dot spacing 19 degrees

K-S Test

Compare	PROB
1,2	0.13
1,3	0.17
2,3	0.47

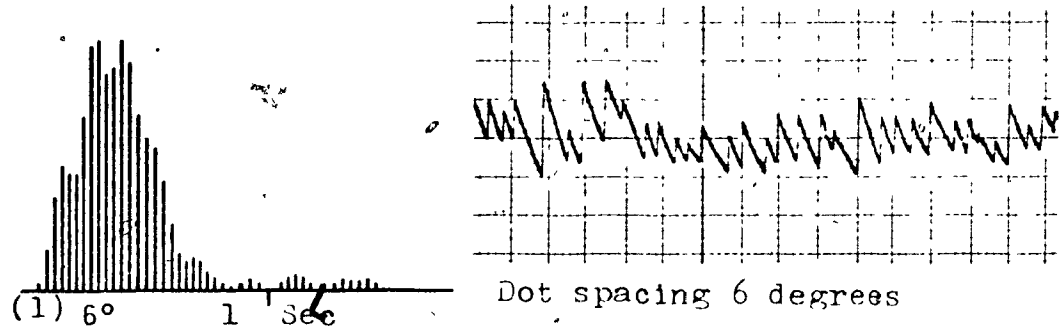
Fig. 4.14 Effect of changing optokinetic stimulus density

work, to be described in section 4.3, suggested that the character of optokinetic nystagmus should change if the horizontal spacing between successive points in the display were greater than about 20 degrees. A brief study was therefore made, on two subjects, using a similar sequence of three checkerboard patterns, but with horizontal dot spacings of 6, 12.5 and 25 degrees.

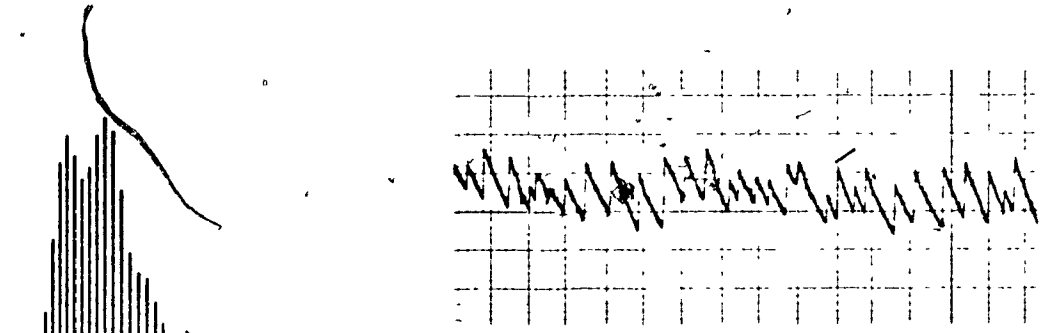
In both subjects there was a marked difference in the interval histogram resulting from stimulation with the least dense pattern (25 degrees spacing). This is illustrated in Fig. 4.15; the corresponding nystagmus tracing for the least dense pattern shows irregular beats and intermittent nystagmus. The explanation for this, according to the finding of this thesis, is that the horizontal spacing of the optokinetic stimulus in the least dense pattern in this case had exceeded the normally sensitive region for optokinetic nystagmus on the retina. This effect will be appreciated after results of section 4.3 are interpreted. Further discussion on this will be found in section 5.3.5.

Image Brightness. The purpose of this experiment was to investigate the effect of changing the image brightness; no dark adaptation period was used. The experiment was performed in 90 seconds. Three subjects were tested with the random pattern at 25 degrees per second. The image brightness was varied by changing the aperture setting of the projecting lens from 1.4 to 4, which corresponded to an eightfold reduction

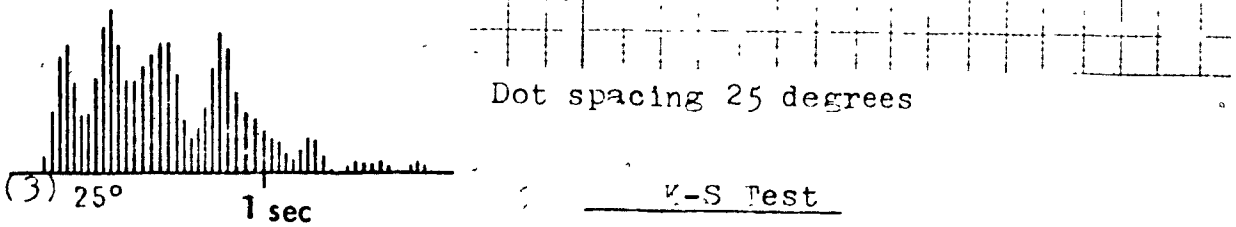
Subject JP
Image speed = 25°/sec



Dot spacing 6 degrees



Dot spacing 12.5 degrees



Dot spacing 25 degrees

Interval histograms
Each has 97 samples
Ordinate scale expanded

K-S Test

Compare	PROB
1,2	0.35
1,3	0.00
2,3	0.00

Fig. 4.15 Effect of changing optokinetic stimulus density

in image intensity. The aperture setting at 4 was used for 45 seconds and then it was changed to 1.4 for the remaining 45 seconds.

No consistent change in the results was observed in the three subjects. The results of one subject are shown in Fig. 4.16.

c. Effect of Voluntary Following of the Optokinetic Stimulus

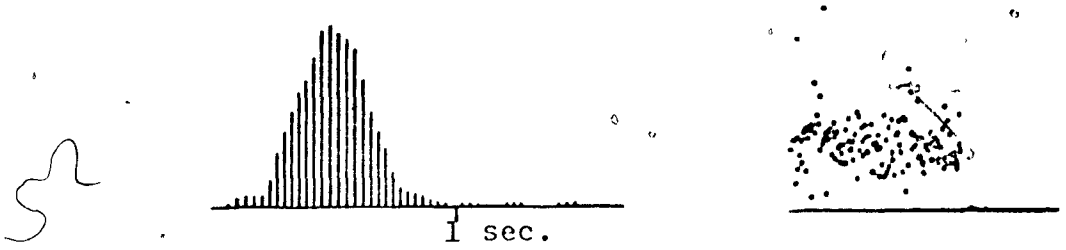
This experiment was conducted on seven subjects. The horizontal travel range of the stripe pattern was reduced to 40 degrees instead of 80; the subjects were asked to follow the stripes voluntarily until they disappeared. They usually made the saccadic refixations to approximately the straight forward gaze position. Thus, the entire range of the following movement was about 20 degrees. Different speeds of the stripes were used as indicated in the results. Results from three subjects are shown in Figs. 4.17, 4.18, and 4.19. In each case the interval histograms contain at least two modes at all speeds. The lower mode occurs at about 0.3 seconds, approximately the same value as the basic mode of previous experiments under involuntary nystagmus condition. This lower mode remains about the same location for all stimulus speeds while the higher mode shifts towards the lower mode as stimulus speed in increased until it is at approximately twice the duration of the lower mode. Thereafter, further increase in stimulus speed does not alter the locations of the two modes.

This is a very interesting phenomenon. The higher mode is apparently caused by the voluntary following which

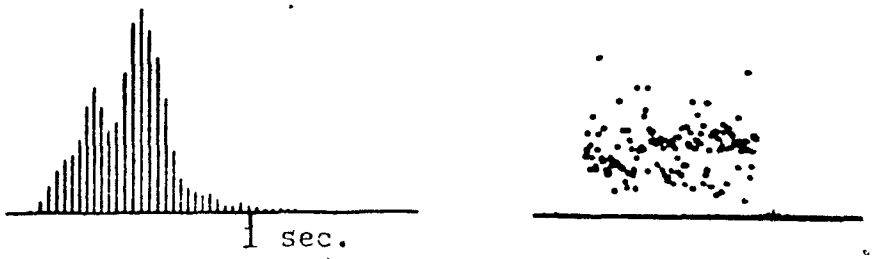
Subject JP
Image speed = 25°/sec

KS-Test

Compare	PROB
1,2	0.35



(1) Low image brightness
Lense aperture = 4



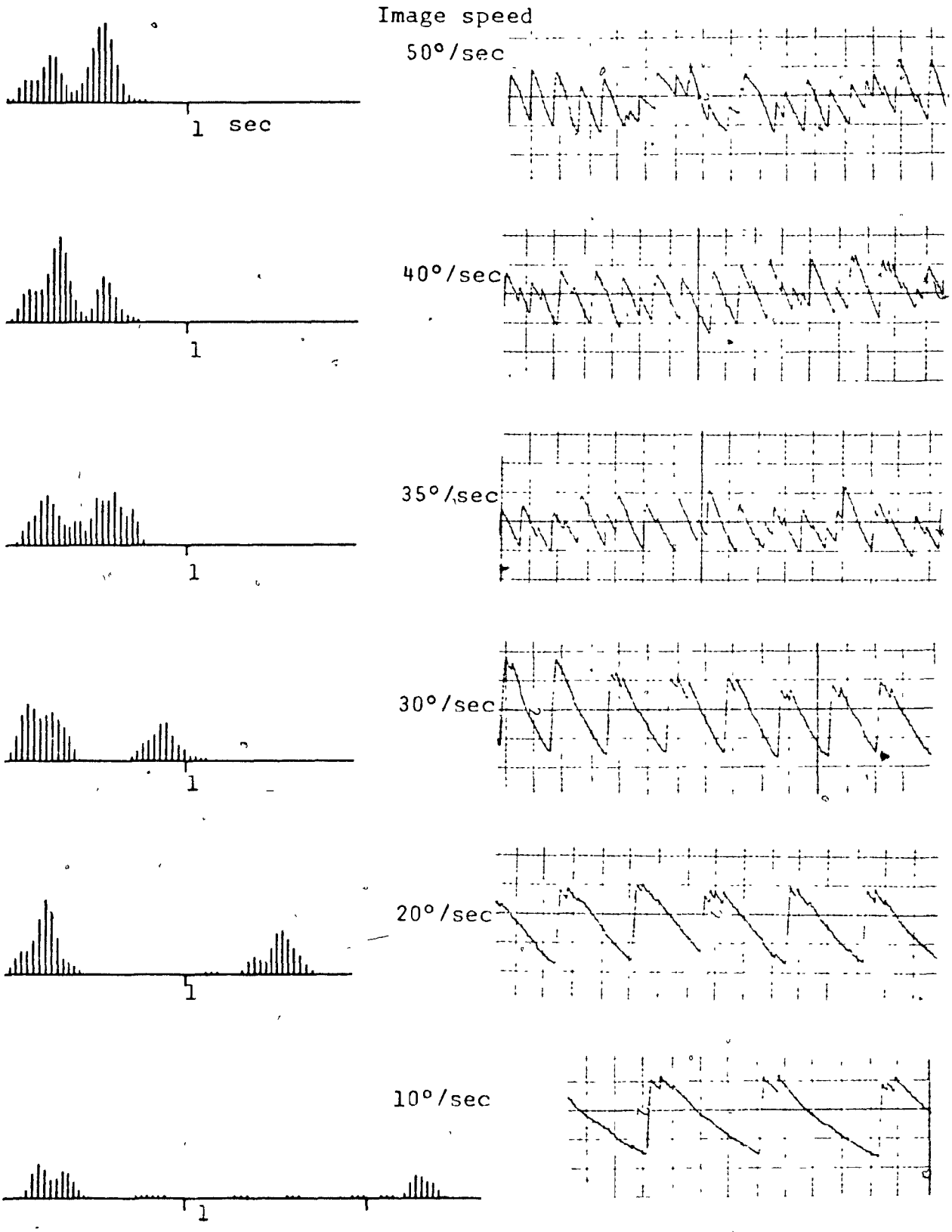
(2) High image brightness
Lense aperture = 1.4

(a) Interval histograms
Each has 134 samples

(b) Sequential display
of interval duration

Fig.4.16 Effect of changing optokinetic stimulus brightness

Subject SR
Each histogram has 58 samples



(a) Interval histograms
Abscissa =interval duration
Ordinate = relative frequency

(b) Waveform tracing
Chart speed= 1 cm/sec

Fig.4.17 Effect of voluntary following of optokinetic stimulus

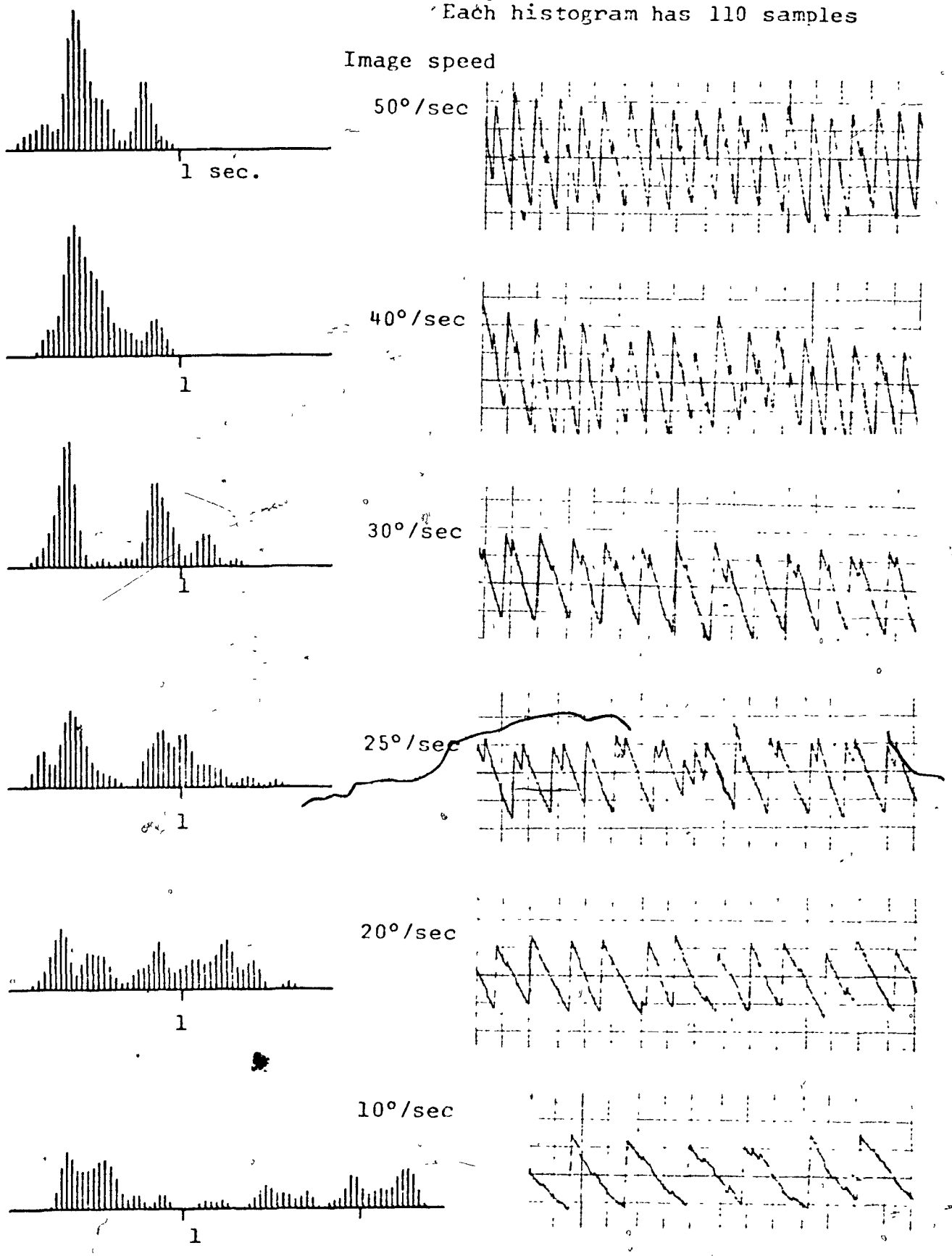
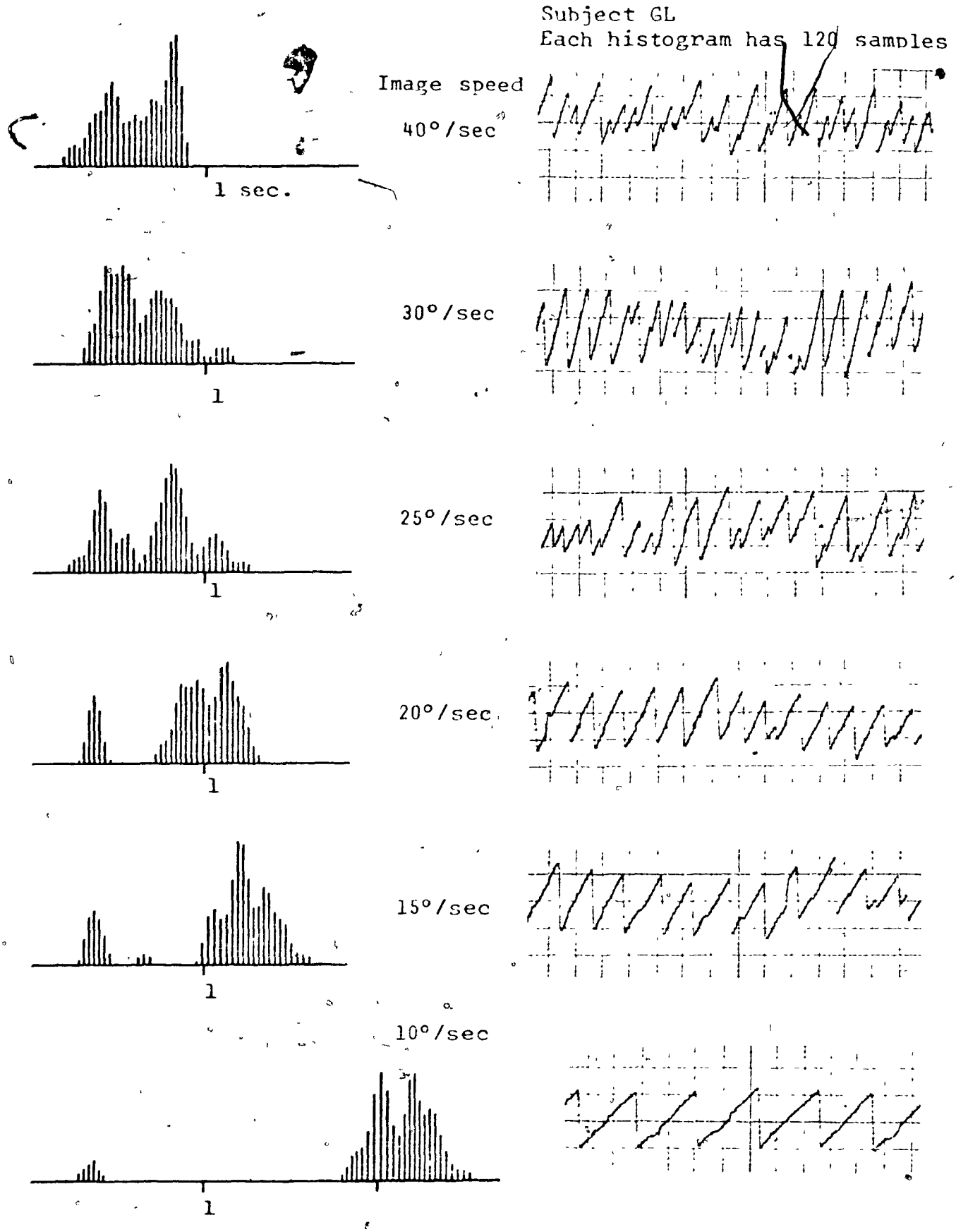


Fig.4.18 Effect of voluntary following of optokinetic stimulus



(a) Interval histograms

(b) Waveform tracing
Chart speed=0.5 cm/sec

Fig. 4.19 Effect of voluntary following of optokinetic stimulus

lengthens the pursuit duration, however, involuntary saccades often set in and these create the lower mode. At higher speeds of stimulus, it seems that the pursuit duration must be lengthened at least twice the basic involuntary saccade intervals. Recalling the stochastic model in section 3.4 in which multi-modal interval histogram of this nature could be created by occasional inhibition of the pseudo-periodic process, it is conceivable that the effect of voluntary following of the optokinetic stimulus is to suppress the natural saccadic components of the optokinetic nystagmus. This is further supported by the fact that during high speed following the second mode, which is located at approximately twice the duration of the basic mode, is very distinct compared with those in multi-modal histograms found in the involuntary optokinetic nystagmus at lower speeds, and also the second mode in some results as shown in Figs. 4.17 and 4.19 is higher than the first mode. The result supports the proposal of suppression of the natural saccadic components of optokinetic nystagmus because at high speed, the natural inter-saccadic intervals are rather symmetrically distributed with a narrow spread as shown in Figs. 4.7 and 4.8, and deletion of the natural saccades should result in distinct multi-modal histograms as demonstrated by the results of the model simulation in Fig. 3.17. The occurrence of the inhibitory impulses during voluntary following, however, would be in a more regular manner.

4.2.5 Summary of Results

Mental arithmetic has a randomising effect on the inter-saccadic intervals during nystagmus.

Multi-modal interval distribution with the higher order modes located at approximately multiple integral values of the basic mode, as found in vestibular nystagmus, also occur in optokinetic nystagmus of low intensity.

There is a characteristic change in the inter-saccadic interval distribution as a result of changing the speed of optokinetic nystagmus. This finding is useful in further studies on nystagmus which will be discussed in section 5.1.

Image density produced no major variation in inter-saccadic intervals when the horizontal spacing between the moving dots was changed within 19 degrees. When this spacing was changed to 25 degrees, a drastic variation occurred; nystagmus became intermittent.

Image pattern and image brightness produced no consistent variation.

Possible explanations for the results of changing image density, pattern and brightness must be postponed to chapter 5 when results from experiments on the retinal contribution to optokinetic nystagmus are available for illustration.

Voluntary following of the optokinetic stimulus has been shown to be accompanied in places by small saccades occurring at intervals similar to those produced in optokinetic nystagmus under the involuntary condition. Over a wide range

of higher stimulus speed a distinct bi-modal inter-saccadic interval distribution with the second mode located at approximately twice the first mode value was found. This led to the proposal that voluntary following response is derived from the basic reflex response.

The stochastic model in section 3.3 can be applied to optokinetic nystagmus as well as vestibular nystagmus.

4.3 RETINAL CONTRIBUTION TO OPTOKINETIC NYSTAGMUS

4.3.1 Introduction

The problem of retinal contribution to optokinetic nystagmus has been introduced in section 4.1.3. In this section, two basic questions will be considered: (1) can central vision produce optokinetic nystagmus in the absence of peripheral vision and vice-versa? (2) are there different types of optokinetic nystagmus resulting from stimulating different parts of the retina?

The finding of the preceeding section that image pattern, image brightness and image density variation within a considerable range did not significantly affect the inter-saccadic interval characteristics also leads directly to the question of retinal contribution. Some suggestions to explain these findings will be given in section 5.3.

Interest in the literature concerning the subject was found since Barany's day. A few examples are Barany (1924), Dodge and Fox (1928), ter Braak (1935), Rademaker and ter Braak (1948), Woelofs (1954), Hood (1967), Dix and Hood (1971) and Young (1971). However, it seems that only Hood performed direct experiments to investigate the problem.

Hood used two conditions of illuminating the interior of a rotating striped drum in which the experimental subject sat: (1) good illumination for foveal vision, (2) ultra-violet

illumination for peripheral vision. Hood reported that nystagmus of entirely different characters, as described in section 4.1.3 were found under these two conditions. The basis of Hood's method appears to be the following. The central part of the retina contains only cone photoreceptors, and since cone receptors have a high threshold of excitation, and are not receptive to ultra-violet illumination, that part of the vision was excluded. However, this central area containing only cones was defined by several authors to subtend a visual angle only of 1 to 2 degrees (Oesterberg, 1935; Polyak, 1941; Yarbas, 1967), and it is questionable whether this has included the foveal vision as there is no general agreement on area definitions of the retina. In this section two methods which do not depend on the precise area definition of the retina but directly stimulate different parts of the retina will be described.

In the first method, different sizes of central vision of the subjects were effectively deleted by EOG signal feedback to the computer generating the optokinetic stimulus. This provided a powerful method in studying the contribution of the peripheral retinal to optokinetic nystagmus.

The second method involved only one moving dot image which provided an optokinetic stimulus to the central vision without stimulating the peripheral retina.

Experiments were performed with D.C. EOG recording and due to the inherent drift of this method, duration of the experiments had to be greatly reduced because experimental

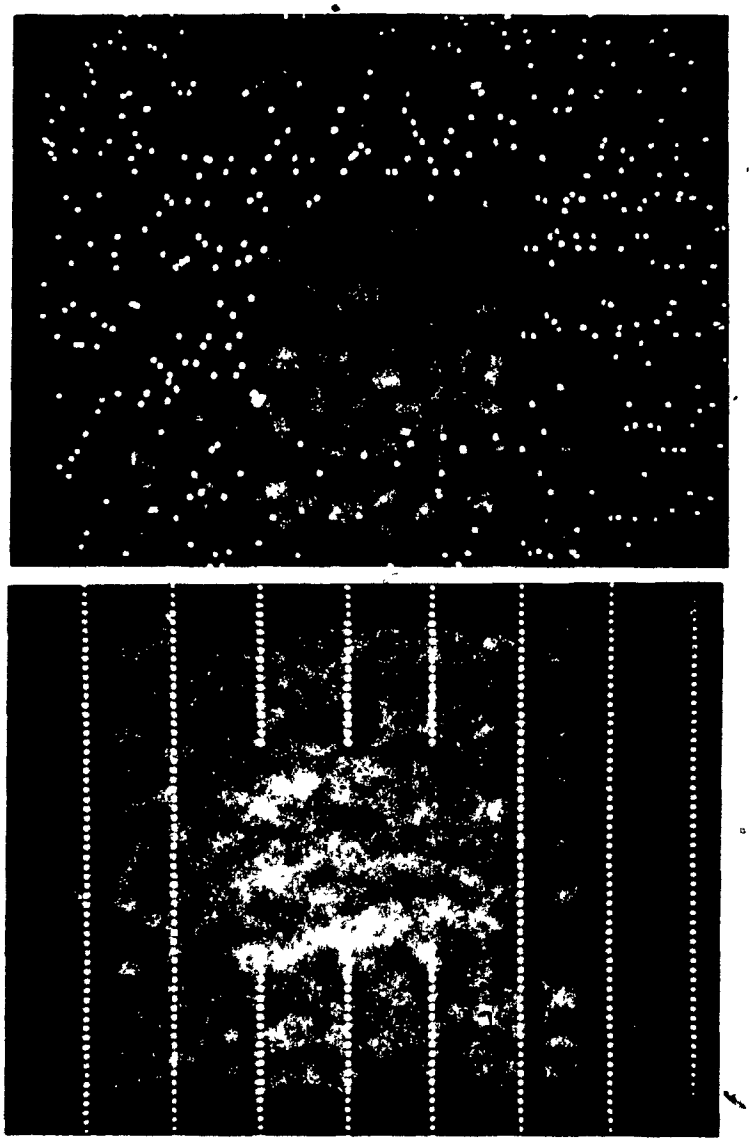


Fig. 4.20 Computer generated optokinetic stimuli with deleted area corresponding to 30 degrees central vision. The position of the deleted area was controlled by EOG feedback so that its center remained concentric with the center of vision.

performance depended critically on the accuracy of the EOG signal feedback. With short record length, it may not be meaningful to perform statistical analysis of inter-saccadic intervals. On the other hand, useful information can be derived by examiningthe general appearance such as the presence or absence of nystagmus, slopes of the slow components, deviations of the eyes, regularity of nystagmus beats; these will be the methods adopted in the entire section 4.3.

The results show that central vision or peripheral vision alone can generate optokinetic nystagmus, and that nystagmus from different parts of the retina are basically of the same type except that nystagmus from the peripheral retina are weaker in intensity, although they can be facilitated by attention.

4.3.2 Experiments on Peripheral Vision

The essential equipment for these experiments was the same as that shown in Fig. 4.5 of section 4.2.2. The central vision of the subject was effectively deleted by not generating the optokinetic stimulus images around the central vision area (see fig. 4.20). The position of the deleted area was made to shift (with a lag of about 30 milliseconds) with movements of the eye by the EOG signal feedback to an analogue input channel of the computer, so that the center of the deleted area remained concentric with the center of vision. A square deleted area

was used whose dimensions could be varied in 0.3 degree steps in both horizontal and vertical directions.

The eye movement signal was measured by skin electrodes (Beckman type 3503) and amplified by a D.C. amplifier (Beckman type 481B) which had a frequency bandwidth of 1 KHz. Low pass filtering (time constant 10 milliseconds) was applied before the EOG signal was fed into the computer. The low pass filter was the main circuit component causing a lag of the generated deleted area after a movement of the eyes and three times the time constant = 30 milliseconds was taken as a rough estimate of the lag.

The accuracy with which the center of the deleted area could be kept coincident with the center of vision during eye movements depended on gain calibrations and linearity of the EOG signal and on the drift of the D.C. amplifier. The gain calibration procedure will be described later. The linearity of the EOG signal was about five percent within 27 degrees of eye movements in either horizontal direction. Drift of the D.C. amplifier was reduced by careful preparation of the electrodes and by allowing at least half an hour for the electrodes to "settle" before an experiment. It was found that within the period of 90 seconds for most experiments, the drift effect was insignificant. In any case, calibration before and after each experiment enabled selection of reliable results.

Calibration was carried out by adjustment of ~~five~~ five potentiometers, two of which controlled the horizontal and

vertical shifts of the deleted area; the other two controlled the gains of the horizontal and vertical EOG feedback signal, while the fifth potentiometer varied the size of the deleted area. Calibration in the horizontal direction was done in the following manner. Three stationary letters 'o', each the size of about two degrees of the visual angle of the subject, were shown together with the optokinetic stimulus pattern. The center 'o' was in the straight forward gaze position of the subject and the other two were at 27 degrees on each horizontal side. The subject was asked to look at the center 'o' and the position and size of the deleted area were adjusted so that the deleted area enclosed the letter 'o' concentrically. Then the subject was asked to look to the letters 'o' on each side in turn, and the gain of the EOG feedback signal was adjusted to bring the deleted area to enclose the letter 'o' The procedure was repeated until each letter 'o' was covered concentrically whenever the subject was asked to look at the letter. After a successful initial calibration, later corrective adjustment during the experiment only required shifting to compensate for amplifier drifts. Calibrations in the vertical direction were done in a similar manner. However, vertical EOG was often interrupted by eye blinking, and since nystagmus was only in the horizontal direction, it was later found that by keeping the deleted area at eye level of the subject and by asking the subject not to look up or down during the experiment, the results did not differ from those with both horizontal and vertical controls.

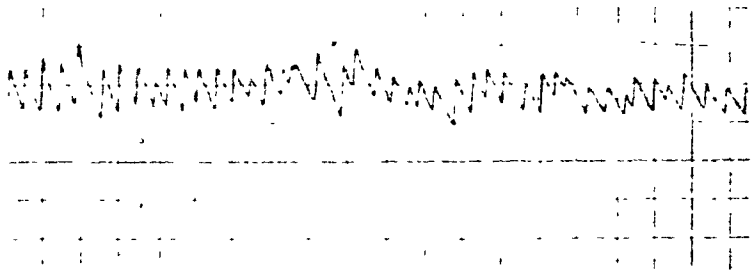
Subsequently, experiments were carried out with only the horizontal EOG signal feedback which were much more convenient to adjust.

After the calibration, the stationary letters were eliminated and the moving stimulus was adjusted at the desired speed. The subjects were asked to follow the same instructions as those in section 4.2, that is, to gaze with attention forward on the screen and to let reflex actions take control of eye movements .

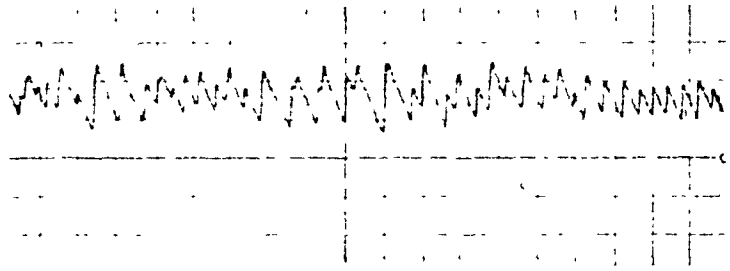
4.3.3 Results from Experiments on Peripheral Vision

Sizes of 0, 5, 10, 20 and 30 degrees of central vision were deleted in random order, each lasting about 15 seconds. Thus an experiment lasted about 80 seconds. Nine normal subjects were tested. A typical response is shown in Fig. 4.21. Nystagmus with full vision of the optokinetic stimulus and that with 5 degrees of central vision deletion show essentially no difference as judged by slopes of the slow component, frequency of nystagmus and deviation of the eyes. However, with a further increase in deleted size of the central vision, nystagmus decreased in slow component speed and in frequency which also became more irregular, eye deviation decreased but still remained in the direction of the saccadic component. Nystagmus intensity for a given size of deleted central vision varied between different

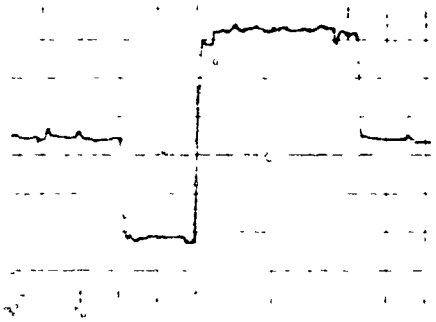
Subject LD
Speed of stimulus
30 deg./sec.
Speed of chart
0.5 cm/sec.



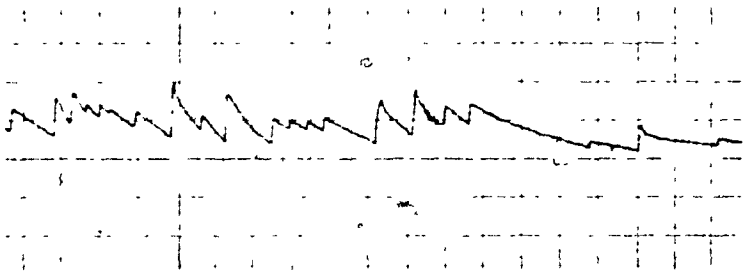
full vision



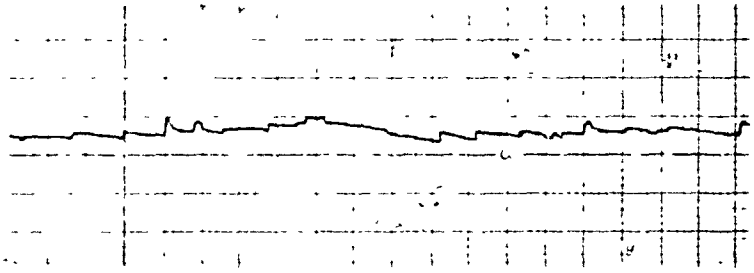
5 degrees central vision deleted



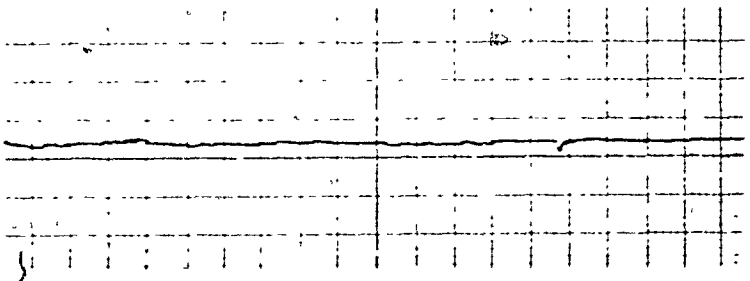
27 degrees calibration
on each side



10 degrees central vision deleted



20 degrees central vision deleted



30 degrees central vision deleted

Fig. 4.21 Optokinetic nystagmus with different sizes of central vision deletion.

subjects, and in the same subject between different tests. Attention difference, to be described later, seemed to be the main cause of the variation. The decline in nystagmus intensity with increasing central vision deletion from 5 degrees onwards was always observed, and when around 20 degrees of central vision was deleted, in six out of nine subjects, nystagmus completely disappeared.

In another experiment, the subjects were first shown the optokinetic stimulus with full vision for 20 seconds. Then a 25 degree central vision deletion was suddenly applied. As a typical result in Fig. 4.22 shows, nystagmus disappeared almost immediately.

The effects of reversal in image direction on eye deviation and initial phase of nystagmus with and without central vision deletion are illustrated in Fig. 4.23. It is seen that in the full vision case, the eyes deviated to the direction of the saccadic component almost immediately after reversal of the image direction, while slow or saccadic components each could occur as initial phase of the reversed nystagmus. The same phenomena were observed when a 10 degree central vision was deleted; the only difference is that in the latter case, nystagmus intensity becomes weaker and more irregular and the deviation in the direction of the saccadic component is smaller.

The above findings disagree with reports from Hood (1962), and Dix and Hood (1971) described in section 4.1.3.

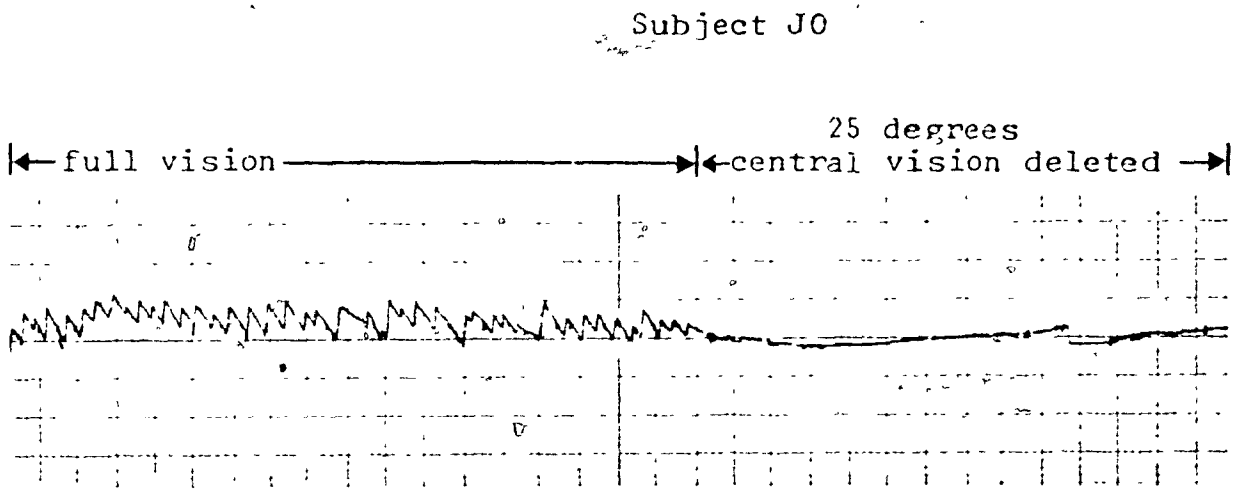


Fig. 4.22 Optokinetic nystagmus with central vision deletion.

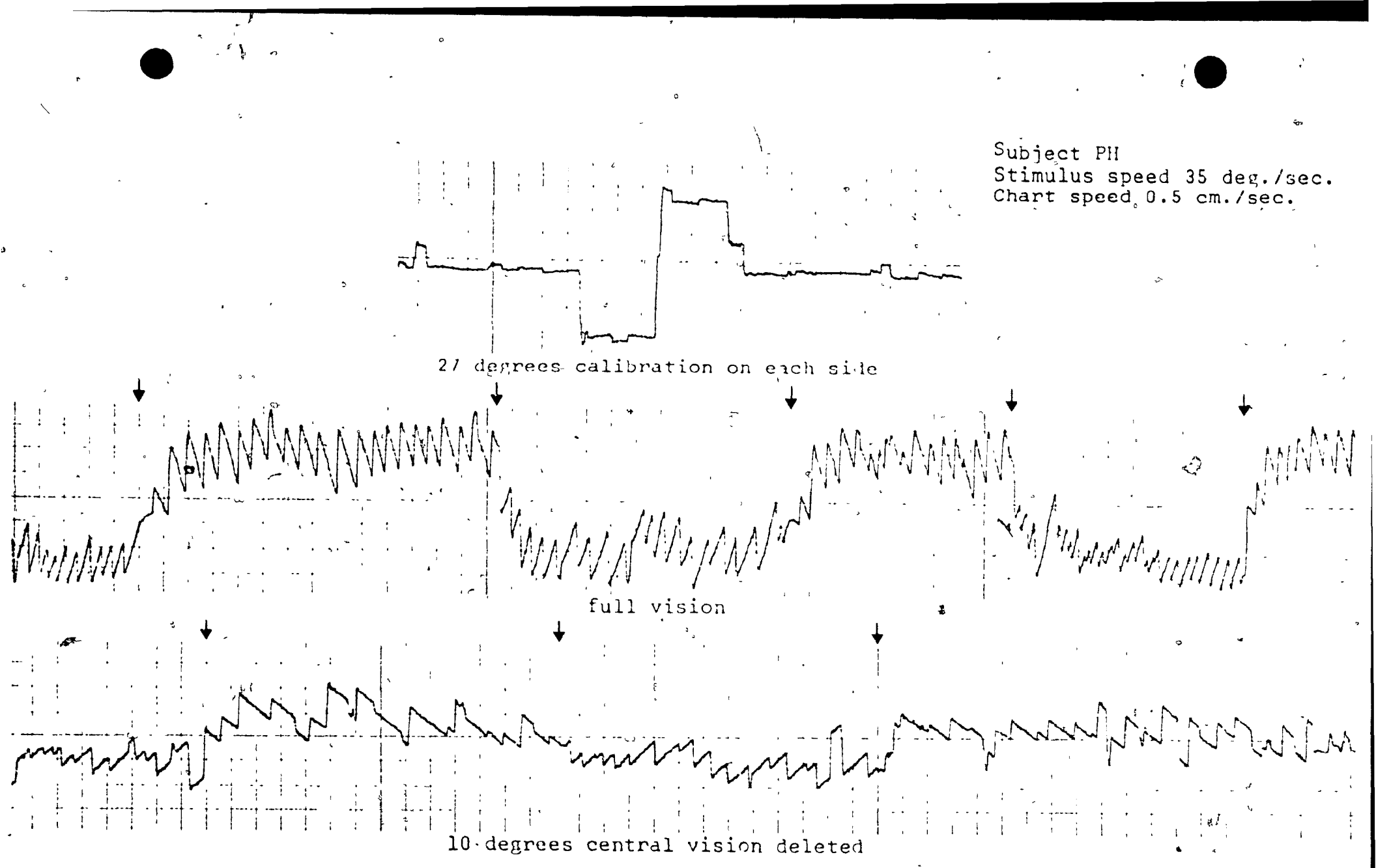


Fig. 4.23 Optokinetic nystagmus showing effects of direction reversal.
Arrows indicate approximate position of stimulus direction reversal.

The Role of Attention. Under normal forward attention, nystagmus ceased in most subjects when more than 20 degrees of central vision was deleted. However, under this condition, if the subject was asked to make a special effort to see the images in the peripheral field, nystagmus appeared as illustrated in Fig. 4.24, and the subject reported seeing the individual moving dots whereas without the special attention, the images were all fused.

Some subjects found it difficult to follow the instruction of paying attention to the peripheral visual field. They were then asked to track the moving images in their peripheral vision. To do this the subject must necessarily direct his attention to the peripheral visual field. Fig. 4.25 shows that the tracking act was accompanied by abundant nystagmus.

These results clearly demonstrate that attention has a facilitating effect on optokinetic nystagmus. It also explains the fact that in patients with central scotoma who had a loss of central vision to various degrees, optokinetic nystagmus could be readily elicited (Dodge and Fox, 1928; Hood, 1967). In such patients, normal attention must naturally be shifted to the peripheral field.

4.3.4 Experiments on Central Vision

All experiments described in section 4.2 actually involved central vision since in these the optokinetic stimuli were presented in full view to the subjects. However, this did

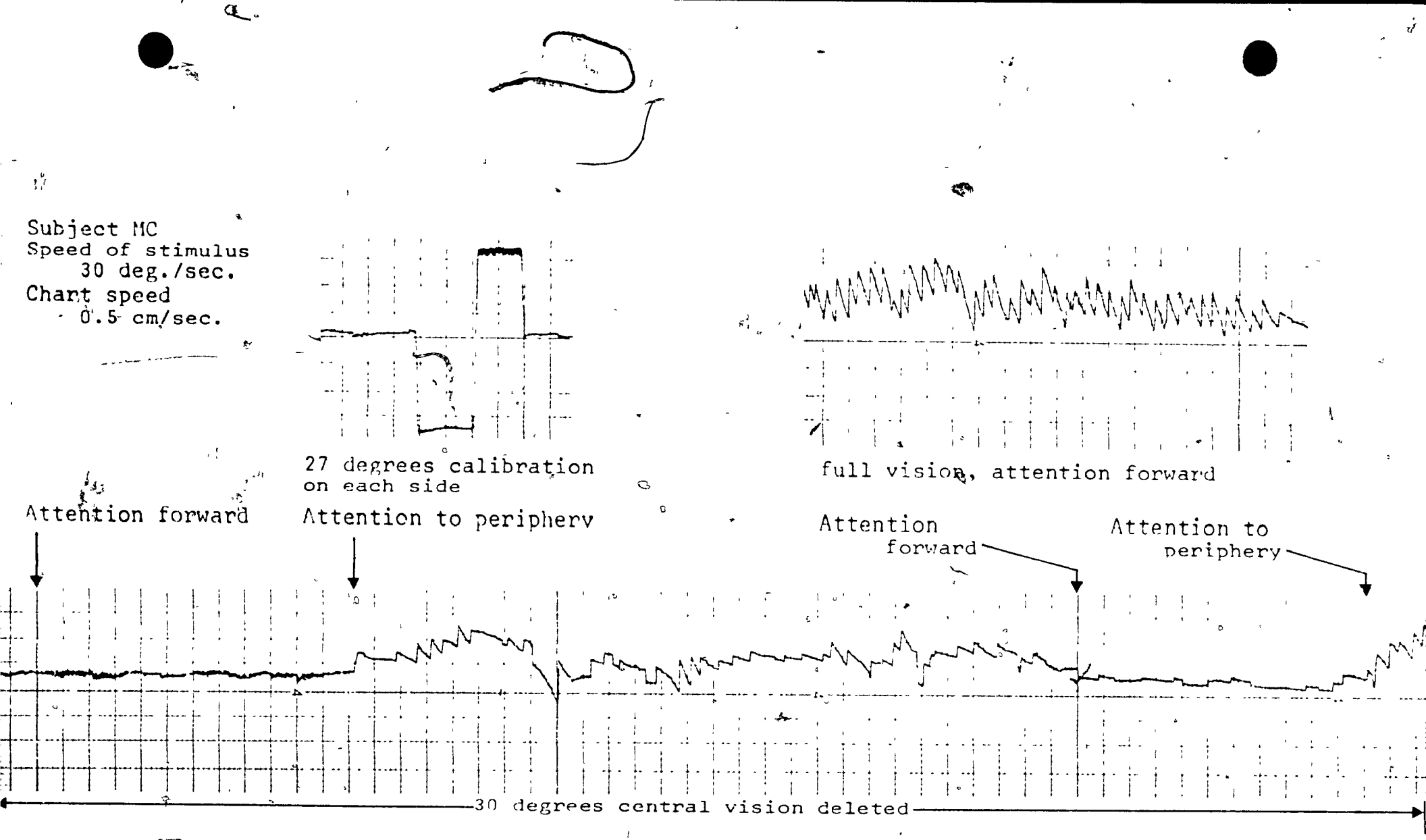


Fig. 4.24 Optokinetic nystagmus resulting from attention to the peripheral visual field.

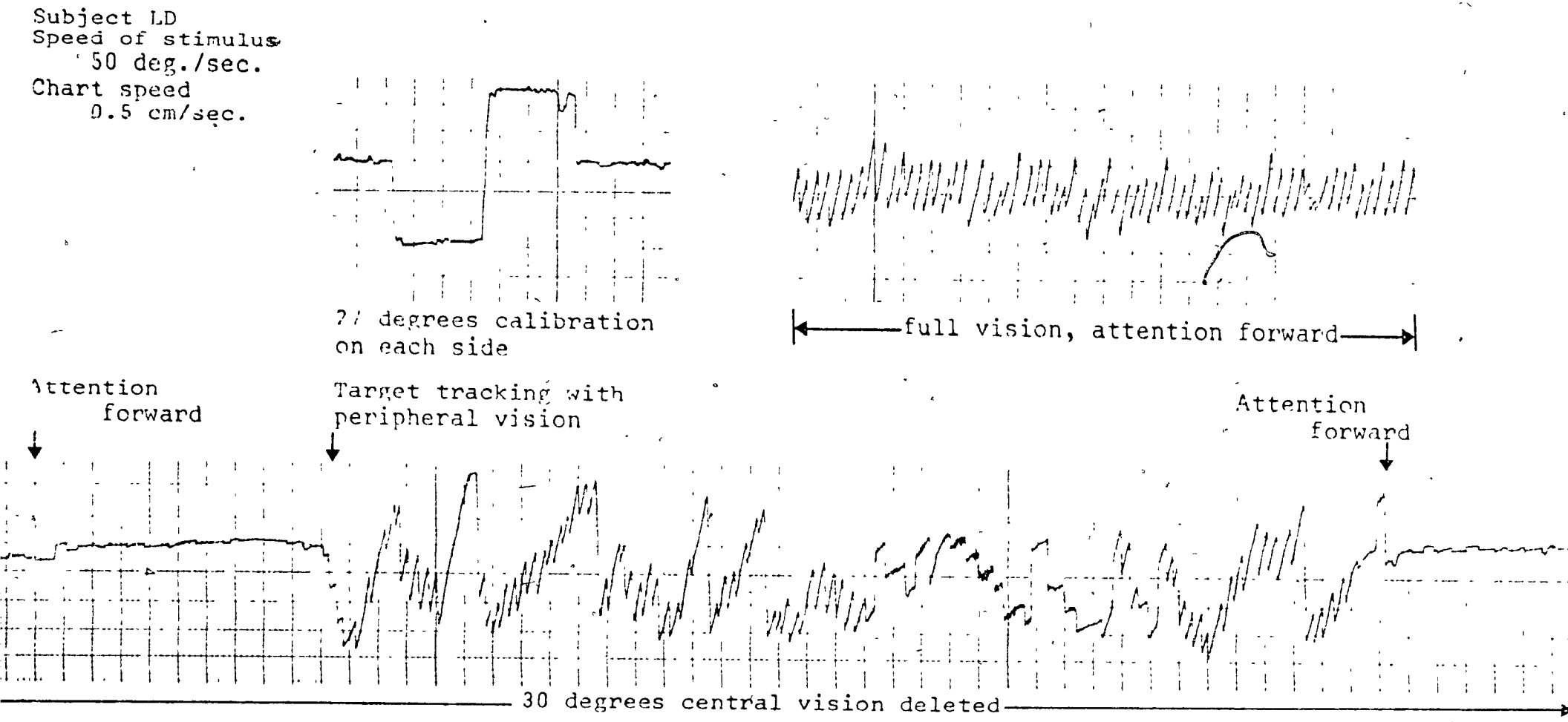


Fig. 4.25 Optokinetic nystagmus resulting from tracking with peripheral vision.

not tell us about the nystagmus response from stimulation of the central vision alone since all peripheral optokinetic stimuli were also present. In section 4.3.2 it was found that contribution to optokinetic nystagmus from the peripheral retina became progressively weaker as the area of central vision deletion was increased more than 5 degrees, and again this did not tell us whether central vision alone, without the contribution from the peripheral stimuli, could produce a nystagmus response. Therefore in this section, experiments will be described in which only one steadily moving dot, of size about 0.5 degrees in diameter, was used as the optokinetic stimulus. Thus all peripheral retinal stimulations were excluded when the moving dot was in the central visual field of the subject. The error signal between the moving target and the forward gaze position of the eyes was measured to enable an estimation of the relative position and velocity of the eyes during the response. It will be shown that nystagmus can be produced by central vision alone and some interesting characteristics were revealed to support the findings of section 4.3.2.

The experimental set-up was essentially the same as that shown in Fig. 4.5 of section 4.2.3. In addition, two extremely faint red lights were placed 40 degrees above and 40 degrees below the point of forward gaze of the subject. The subjects were asked to maintain their gaze on the center of the screen with the aid of the faint red lights placed

symmetrically in the peripheral visual field. The moving dot stimulus traversed through the center of the screen with a range from 35 degrees left to 35 degrees right of the center of the screen. Eye movement response was recorded as described in section 4.3.2. The experiment was conducted without the faint red lights as reference and it was found that the nystagmic eye response did not differ though the subjects found it more difficult to maintain the eyes in the center position.

In order to interpret the results, the meaning of the error signal is explained first with reference to Fig. 4.27. The EOG and the moving dot signals were subtracted on-line to yield the error signal. During the calibration procedure, the gains of the EOG and the moving dot signals were adjusted so that when the eyes were tracking the dot the error signal was zero. Thus, in Fig. 4.27(a), the eyes were fixating on a stationary point in the forward gaze position, and hence the error signal reflects the dot movement. In Fig. 4.27(b), the eyes were tracking the moving dot, and hence the error signal remains for the most part near zero except when the target jumped back to its starting position while the eyes were momentarily lagging behind. The zero error position will be useful later in interpreting the results since during this time, the center of vision stayed locked on the moving dot.

4.3.5 Results from Experiments on Central Vision

The results will be explained with reference to a

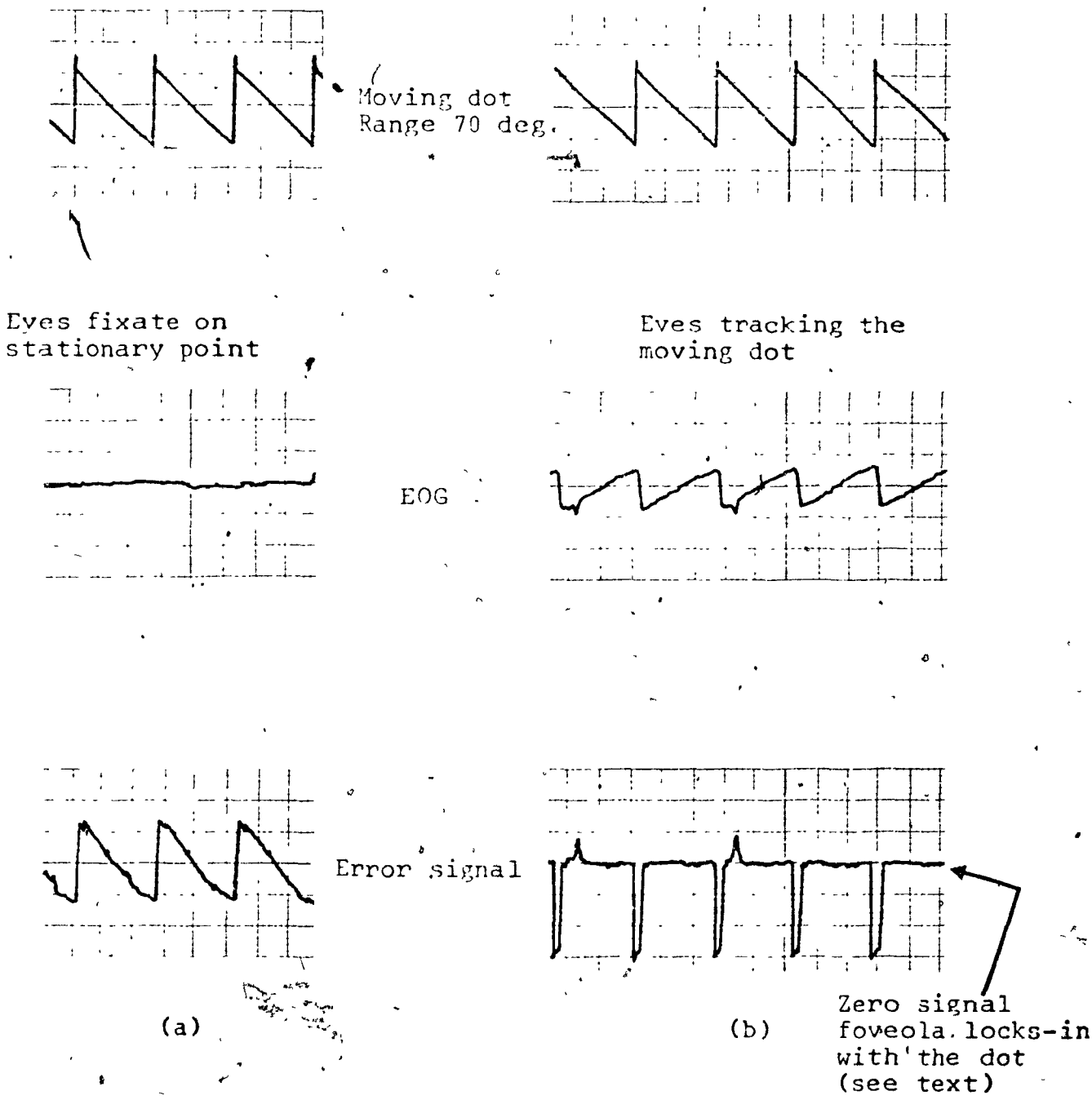


Fig. 4.27
Calibration of error signal between eyes and the dot

typical response shown in Fig. 4.28. The entire range (70 degrees) of the moving dot stimulus was within the visual field of the subject, however, a burst of nystagmus only occurred when the moving dot was within a certain range of central vision. During the burst of nystagmus, up to five beats were observed. The slow component velocity was highest in the middle and lower at the beginning and at the end of the burst. Further, this response could not be voluntarily suppressed provided attention remained on the screen. To examine the response in more detail, the error signal is re-drawn in a somewhat exaggerated manner in Fig. 4.29 for the purpose of explanation.

Nystagmus beat (a) occurred when the moving dot was around 10 degrees on the left side of the center of the retina; the slope of the error signal indicates that the eyes were tracking the dot target but with a slower speed. During nystagmus beats (b) and (c), the zero slopes in the error signals indicate that the eyes were tracking at the same speed as the moving target. The dot target was estimated to be very close to the center of the retina during beat (b), and within 3 degrees on the right of the center during beat (c). Beat (d) again tracked the target with a slower velocity and the target was around 10 degrees on the right side of the center of the retina. These results seem to be in good agreement with results from peripheral vision studies in section 4.3.2, where it was found that nystagmus was essentially the same when up to 5 degrees of central vision was deleted; when a larger area was deleted,

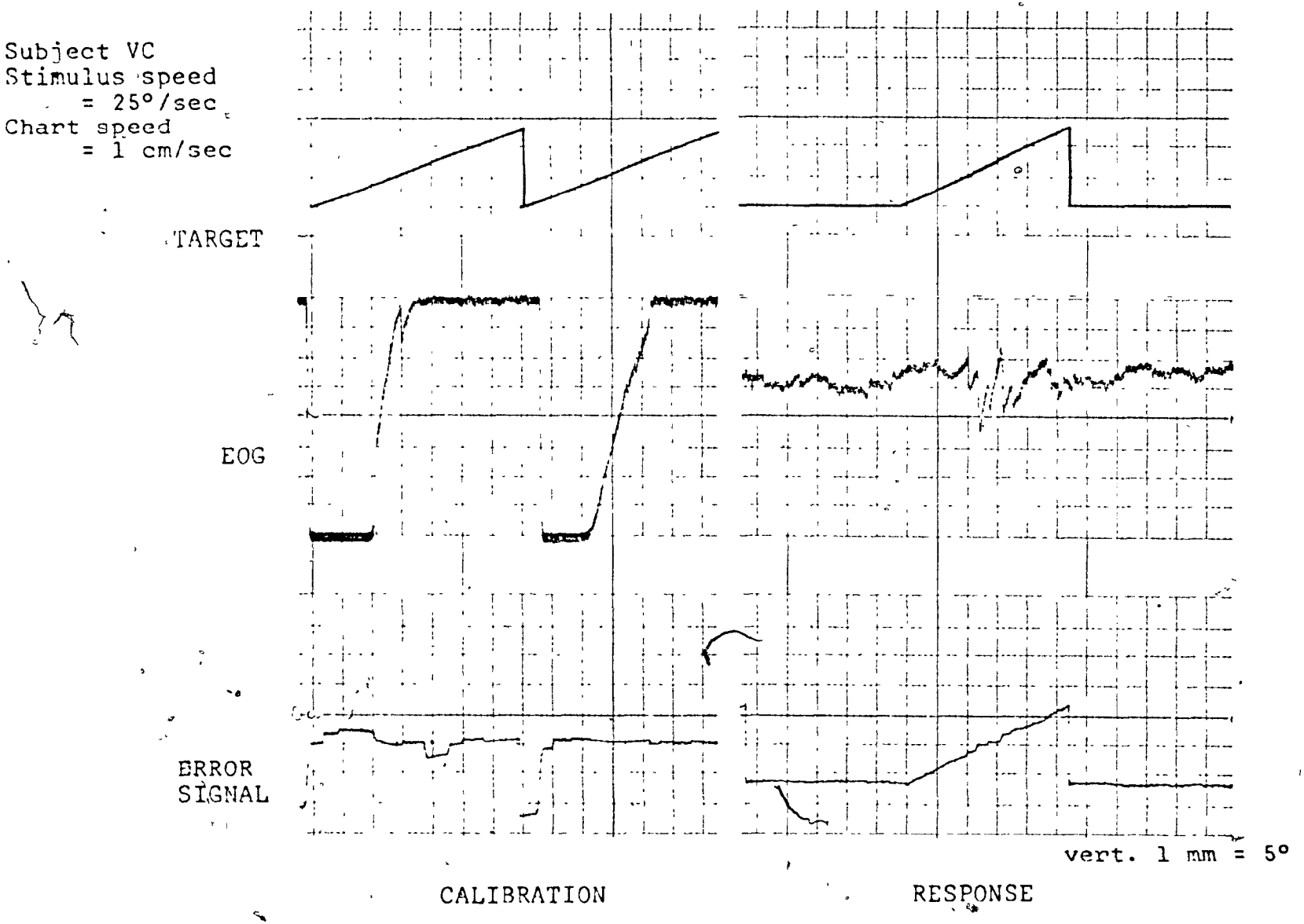


Fig.4.28 Optokinetic nystagmus induced by a single moving dot stimulus

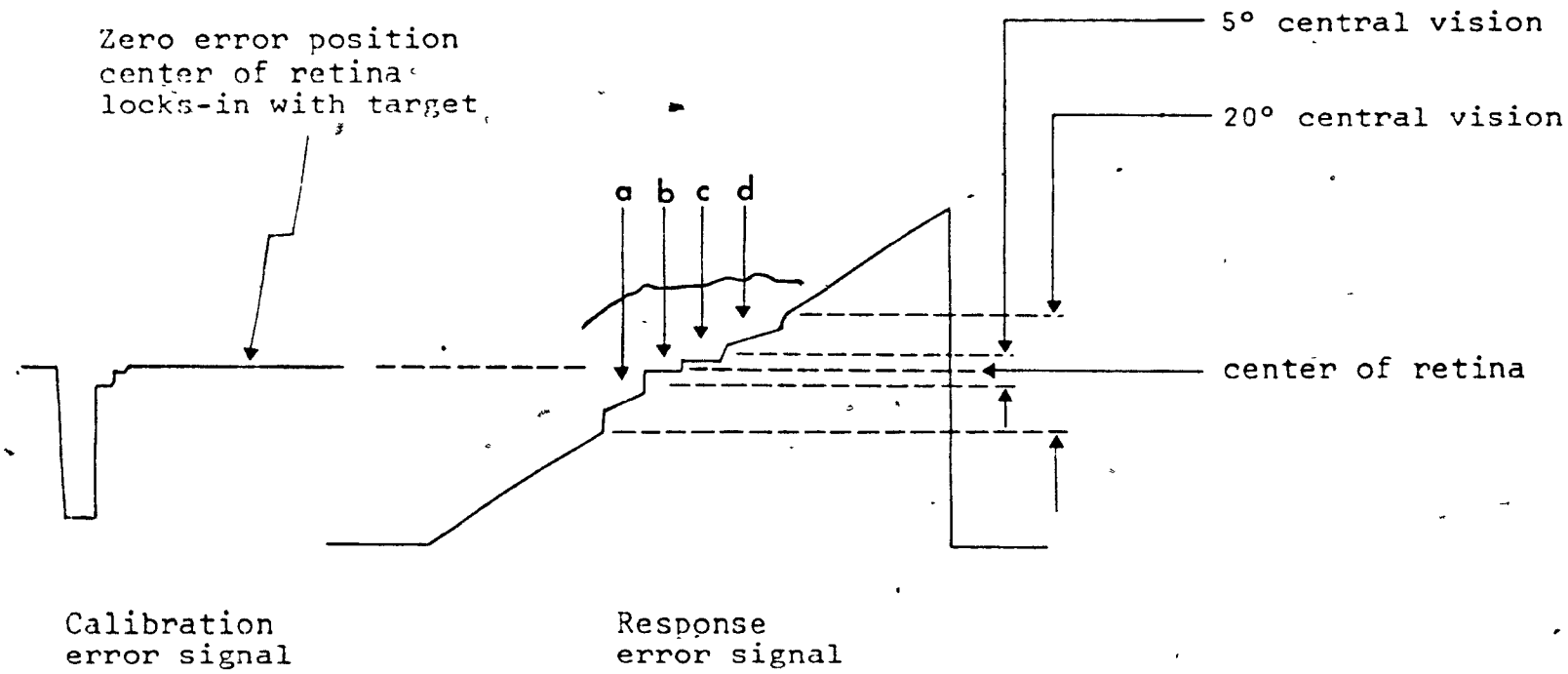


Fig.4.29 Explanation of results in Fig.4.28

nystagmus slow component speed decreased and nystagmus ceased when more than 20 degrees of central vision was deleted.

Fig. 4.30 shows more results from the same experiment. It is seen that as the speed of the moving dot was increased, nystagmus amplitudes also increased. This is also a general finding of section 4.2.

Fig. 4.31 shows that a continuous optokinetic nystagmus was induced by a single moving dot stimulus. The moving dot was programmed to traverse the center of the screen in a 6 degree range in every second; the resulting nystagmus frequency averaged at 2 beats per second with amplitude of about 2 degrees.

These results demonstrate that central vision alone is capable of producing optokinetic nystagmus. No stimulus in the peripheral visual field is necessary to aid the production of the slow component and no succeeding target is necessary to cause a saccadic component. Under normal forward attention, a moving target within an area of about 20 degrees of central vision is capable of eliciting nystagmus.

4.3.6 Discussion

The results from the two different optokinetic stimuli, namely, stimulus with images deleted in the central visual field and the single moving dot stimulus, agree with each other. They seem to suggest two significant areas of

Subject VC
Stimulus range 70 degrees
Chart speed 1 cm/sec.

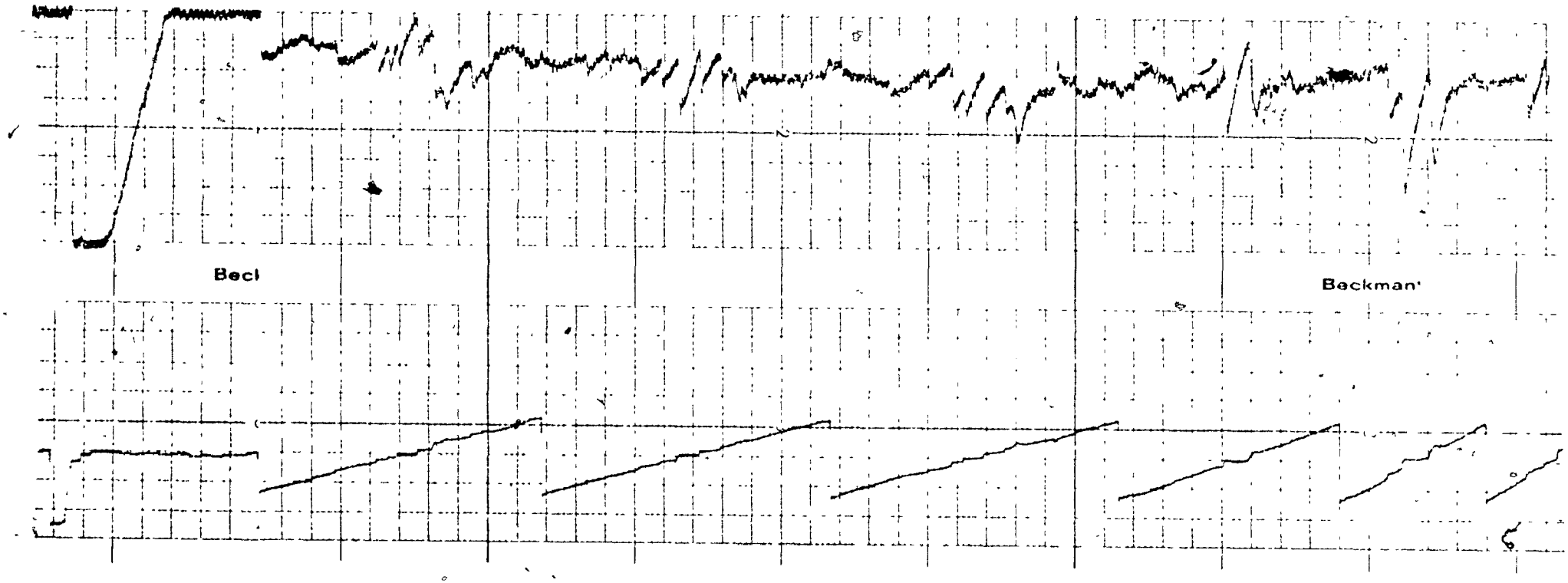


Fig. 4.30 More results of optokinetic nystagmus induced by a single moving dot stimulus

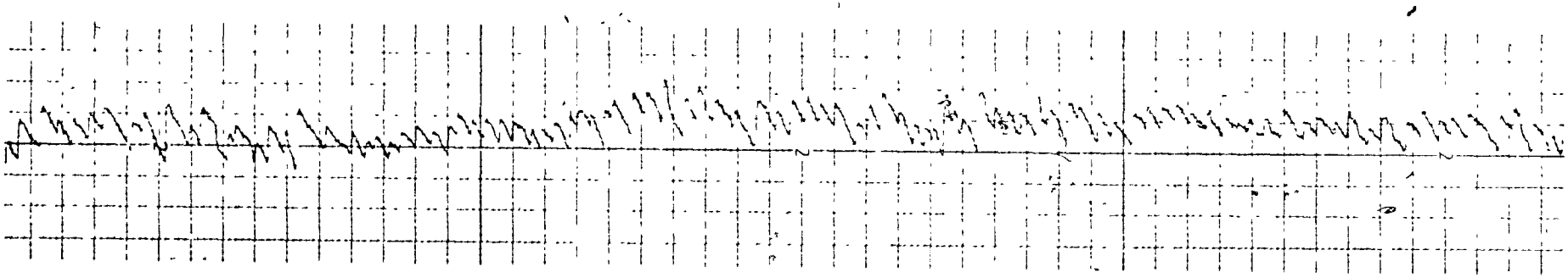


Fig. 4.31 Optokinetic nystagmus resulting from a single moving dot stimulus.
Range of moving dot = 6 degrees
Speed of moving dot = 6 degrees/sec.
Frequency of nystagmus = 2 beats/sec.

approximately 5 degrees and 20 degrees on the central portion of the retina. With normal forward attention, the sensitive area on the retina for optokinetic nystagmus appears to be around 20 degrees, and within 5 degrees of central vision the nystagmus tracking speed could match that of the moving target. (This presumably has a limit. See section 5.4).

It would be interesting at this stage to compare these areas with the subdivisions of the retina in Table 4.1 which is based on data obtained by Polyak (1941). Polyak defined the human fovea to be 5.2 degrees, the yellow spot to be 17 degrees and the peri-fovea to be 19 degrees. The latter two appear to be significantly related to the present finding of the 20 degree area.

The significance of the 5 degree area is further suggested by Wilson and Toyne (1970), who studied the neuronal projections from the retina and the visual cortex to the superior colliculus in monkeys (Macaca mulatta). They reported that there was a dense projection to the superior collioulus from the part of the visual cortex which is devoted to the central 5 degrees of the visual field.

It must be emphasized that this functional correlation of the reported data to my experimental findings was done during the thesis writing stage and no previous consultation to these reports were made before or during experiments.

CHAPTER 5

DISCUSSIONS AND CONCLUSIONS

5.1 THE PATTERN OF VARIATION IN THE RHYTHM OF VESTIBULAR AND OPTOKINETIC NYSTAGMUS

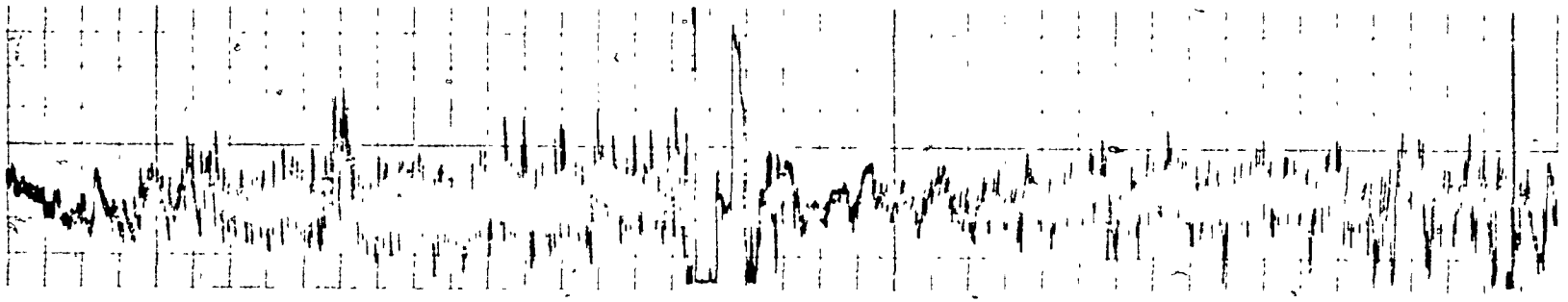
Vestibular and optokinetic nystagmus have been described in the literature as being rhythmic but the nature of rhythmicity was not clearly understood. In this thesis the rhythm of vestibular and optokinetic nystagmus has been analyzed in terms of the intervals between the saccadic components using point process analysis techniques. As a result a characteristic pattern of variation in the rhythm with intensity of nystagmus has been established.

The results so far have shown that multi-modal interval histograms occur in both types of nystagmus. Furthermore, in the case of optokinetic nystagmus, multi-modality occurred at lower intensity levels. This result is consistent with observations made in the vestibular nystagmus section where multi-modality was found more often in spontaneous, positional, alcoholic, and the beginning portion of caloric nystagmus; all these types of nystagmus had comparatively low intensities. Thus, it can be concluded that multi-modality in inter-saccadic interval histograms occurs in low intensity vestibular and optokinetic nystagmus. It remains to be demonstrated that as the intensity of vestibular nystagmus is increased the interval histograms change shape to mono-modal ones in a manner similar to those

in optokinetic nystagmus.

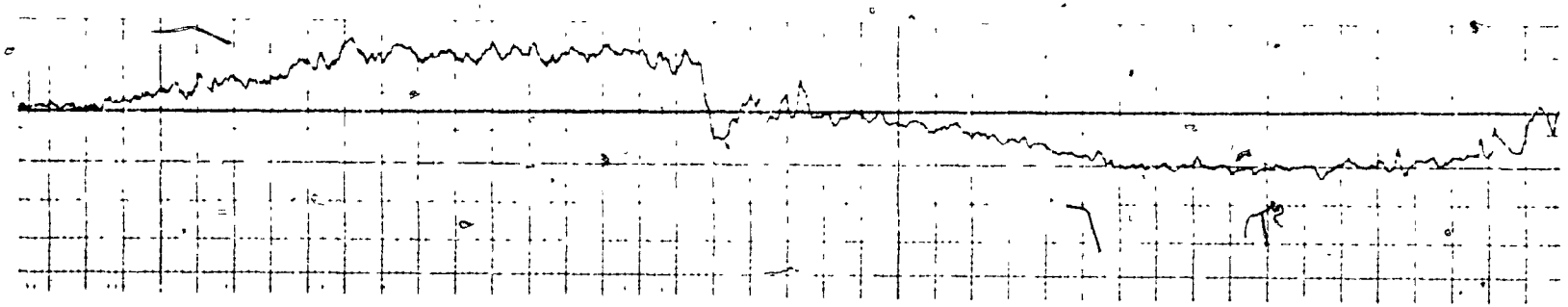
In vestibular nystagmus, it is not possible to induce discrete levels of intensity similar to those in the optokinetic nystagmus experiments. This is because of the elastic return of the cupular receptor after a deflection. On the other hand, caloric nystagmus increases its intensity gradually to a peak and then declines slowly as illustrated by the compressed slow component speed display in Fig.5.1 (see Appendix 4 for description on this slow component speed measuring circuit). The results from caloric nystagmus can thus be segmented into sections of approximately constant intensity, and the corresponding interval histograms plotted for each data segment. This is illustrated in Fig. 5.2 where the change in interval histogram shapes with intensity is to be compared with those in optokinetic nystagmus in Figs.4.7 and 4.8 (page 113). The similarity in the shape change is quite clear. The change in the rhythm for both types of nystagmus can therefore be described as follows.

Generally, as the intensity of nystagmus (or speed of the slow component) is decreased, the occurrence of the saccadic components becomes more irregular. In terms of inter-saccadic interval distributions, the distribution changes from being monomodal and symmetrically distributed with a narrow spread to one with a wider spread. With more reduction in intensity, the spread of the distribution further increases and becomes skewed towards the longer duration. With further reduction in nystagmus intensity, multi-modal distributions appear.



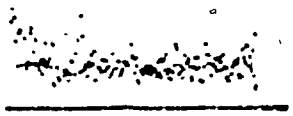
Cold water left ear Cold water right ear

Time compressed graph of caloric nystagmus

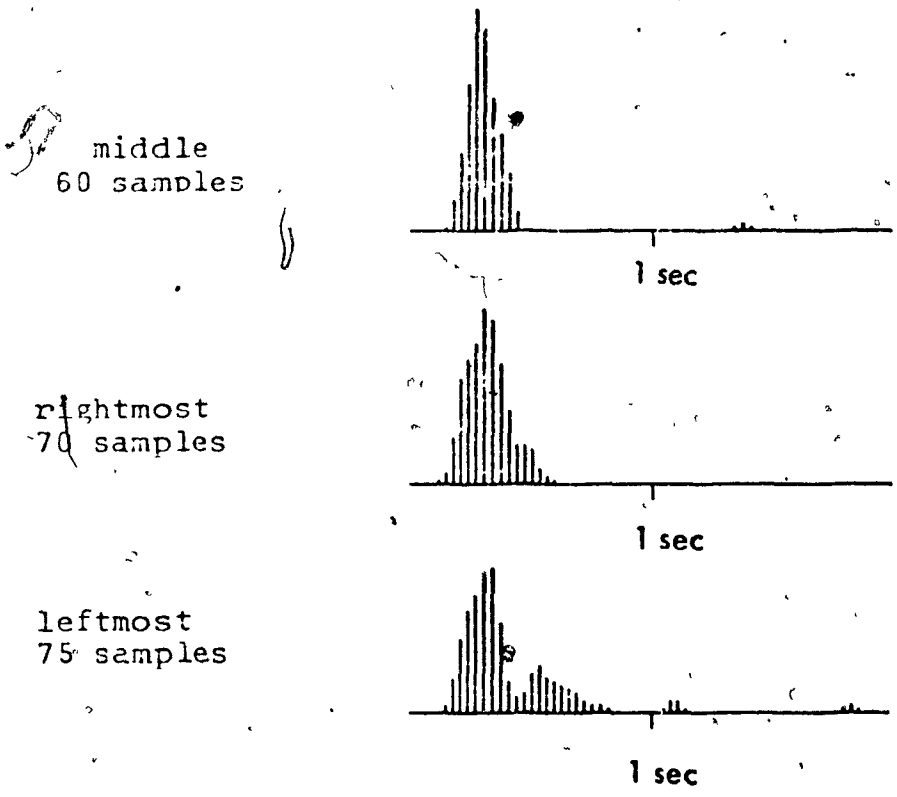


Slow component speed 15 degrees/cm.

Fig. 5.1



Sequential display of interval duration



Interval histograms

Fig. 5.2 Interval histograms of segmented caloric nystagmus data

The finding of this characteristic change in pattern could be applied to further works on nystagmus. Clinically, it would be useful to investigate if there are patients with a certain pathology in the vestibular or visual-oculomotor pathways who do not follow the above pattern change. If definite deviation could be confirmed to exist, the method would become a useful diagnostic tool. Anatomically, the pattern change could be used as an aid in determining which areas are involved in the generation of the nystagmus rhythm. In animal experiments, lesions could be induced into different suspected areas to see if they alter the normal characteristic pattern. Any area which causes a change should be regarded as an integral part of the nystagmus rhythm mechanism. The characteristic pattern could also be used to aid physiological investigations. Maeda et al (1972) has proposed the possibility of mutual inhibitions of the bilateral vestibular nuclei as a mechanism generating the nystagmus rhythm. It would be interesting to see if their proposed model could simulate the above pattern change. In a model, the saccadic components can be replaced by a single pulse in much the same manner as the method used in this thesis.

5.2 A POSSIBLE ROLE OF INHIBITION IN THE RHYTHM OF NYSTAGMUS

The occurrence of the multi-modal inter-saccadic interval distributions in nystagmus reveals a significant aspect of the nystagmus rhythm, which may require a special mechanism for its production. A very simple yet physiologically plausible mechanism to produce occasional impulse intervals at multiple integral values of a basic interval duration would be for an impulse, or a group of impulses, to occur periodically at a basic interval. This occurrence would then be occasionally inhibited, thus producing intervals which double or triple the duration of the basic interval. This mechanism has been found to describe synaptic behavior in some single neuron recordings. The same concept has been used in a model in Section 3.3 to simulate the production of nystagmus rhythm, and it was demonstrated that all observed general characteristics of the nystagmus rhythm could be simulated by the model.

If such a simple concept were the actual overall working principle of the nystagmus mechanism, then it would be useful to investigate where and how this inhibition takes place.

5.3 DISCUSSION ON THE OPTOKINETIC NYSTAGMUS REFLEX MECHANISM

5.3.1 Introduction

It appears that since de Klyn and Rademaker (1928), ter Braak (1935), Rademaker and ter Braak (1948) reported the distinction of a cortical and a subcortical optokinetic nystagmus in animals such as dogs and monkeys, various proposals have been made about different types of optokinetic nystagmus in human. The different types of optokinetic nystagmus proposed were described in Section 4.1.3. In this section, based on the experimertal results of this thesis and on other direct and indirect evidences, it is suggested that the different types of optokinetic nystagmus described in the literature should be thought of not as separate entities but as variants of one basic identity. The variations are due to greater or lesser voluntary influence, or to stimulation of different parts of the retina producing a stronger or weaker nystagmus. The discussion will now be reviewed with respect to the three main factors, described in the literature survey in Section 4.1.3, which might have been used as the basis for the nystagmus classifications.

5.3.2 Mental Set of the Subject

It is doubtful that the response resulting from voluntary following of the optokinetic stimulus (following, look types)

should be regarded as a distinct entity of nystagmus as proposed by Honrubia et al (1968). Judging from the experimental results described in Section 4.2.3 under this condition, it is conceivable that the response from voluntary following of the optokinetic stimulus is produced by suppression of the saccadic components and augmentation of the slow component. The suppression of the saccadic components is suggested by the fact that during the voluntary following phase, involuntary nystagmus with intervals similar to those of nystagmus produced under the involuntary condition occurred frequently, and this may be interpreted as the occasional inability to suppress the basic reflex nystagmus rhythm. Furthermore, bi-modal inter-saccadic interval histograms, with the second mode located at approximately twice the duration of the basic mode, occurred over a wide range of higher stimulus speeds. This may indicate that suppression must be achieved by deleting at least one basic reflex saccade, resulting in a double-length interval. The fact that the second mode is very distinct lends further support to this concept. This has been discussed in Section 4.2.3 with reference to the experimental results from high speed stimuli under the involuntary instruction and with reference to the stochastic model.

Some subjects could voluntarily follow the low speed stimuli without making many small saccades as shown in the results in Fig.4.19, (page 129). However, at high speeds, where intensities of nystagmus produced by the reflex mechanism would normally be high, small saccades inherently set in. This effect is also

observed in the results of Honrubia et al (1968). This brings out an analogy of a voluntary change in the respiration rate. At rest, a person will unconsciously breathe at a certain rate, and this rate can voluntarily be altered by extending or shortening the inhalation or exhalation period without much difficulty. However, after a strenuous physical labour, the basic involuntary breathing rate will pre-dominate and this becomes more difficult to alter voluntarily.

5.3.3 Retinal Contribution and the Role of Attention

As a result of intensive effort by many investigators, the end organ mechanism of the vestibular system, in particular the semicircular canals and the cupular receptors are now quite well understood. A review of this knowledge is given by Outerbridge (1969). In contrast, partly due to the immensely more complex function that the retina has to serve, the retinal mechanism in relation to optokinetic nystagmus has been poorly understood. It is hoped that the findings discussed below may incite further investigation.

The results from the central vision deletion experiments in Section 4.3 showed that with approximately five degrees of central vision deletion, the nystagmus intensity as estimated by slopes of the slow component, eye deviation, and regularities of the nystagmus beats remained essentially unaltered. However, nystagmus intensity gradually declined as the deleted area was increased in size from five degrees, and in most subjects,

nystagmus ceased if more than 20 degrees of central vision was deleted.

There was no indication that a nystagmus of entirely different character was generated at any degree of central vision deletion. There was always a deviation of eye position in the direction of the saccadic component, but the deviation decreased with nystagmus intensity, in particular with the frequency of saccadic components. Both fast (saccadic) and slow initial phases were observed when the direction of optokinetic stimulus was instantly reversed. These findings disagree with those of Hood described in Section 4.1.3.

The response to the single dot optokinetic stimulus agrees closely with results from the central vision deletion experiments. This was discussed in detail in Section 4.3.5.

These results suggest that there is one nystagmus generating mechanism serving the entire retina. The retinal contribution to optokinetic nystagmus decreases with increasing distance from about 2.5 degrees from the center of the retina towards the temperal or nasal sides. The weaker contribution, however, may be facilitated by attention. Thus it is no surprise to see that optokinetic nystagmus could readily be elicited in patients with central scotoma (Dodge and Fox, 1928; Hood, 1967). In these patients, normal attention must quite naturally be shifted to the peripheral visual fields.

The results in Section 4.3.5 also show that a single moving dot within the central visual field was capable of eliciting a continuous optokinetic nystagmus. During the course of appearance

of one single steadily moving dot, up to five very distinct beats of nystagmus were elicited. These demonstrate clearly that no stimulus in the peripheral field is necessary to aid the production of the slow component and no succeeding targets are necessary to cause a saccadic component.

Therefore, it is possible that in the case of a large size optokinetic stimulus, only a small part of the entire stimulus is taken for the tracking reflex and that any part of the optokinetic stimulus may be chosen for tracking through attention facilitation. This may then explain the findings in Section 4.2.3 that optokinetic stimulus pattern, image brightness, and density variation within a considerable range had little effect on the inter-saccadic interval distributions.

The decline in contribution to optokinetic nystagmus from the peripheral retina and the role of attention may also be used to explain the finding of Rademaker and ter Braak (1948), who reported that in decorticated animals, to initiate optokinetic nystagmus, it was necessary that all parts of the visual environment were moving in the same direction. This may indicate that the subcortical pathways depend primarily on the weak contributions from the peripheral retina. Thus in the absence of cortical attention facilitation, more contributions are needed.

It is interesting to note that the prominent psychologist, D. Hebb (1949), connected perception phenomena with the neurophysiological evidence that a neuron will not normally discharge an impulse unless it is excited by two or more pre-

synaptic neurons. Accordingly, a response requires not only excitation from peripheral sensory organ, but also the 'central reinforcement of a sensory process', which Hebb identified with attention.

5.3.4 Neural Pathways and Centers for Optokinetic Nystagmus

There were no experiments in this thesis involving surgical operations and neural recording. Therefore, no direct experimental results are available to support this discussion concerning neural pathways and centers for optokinetic nystagmus. Nevertheless, it may be useful to consider a few indirect evidences.

Regarding the existence of a cortical and a subcortical pathway for optokinetic nystagmus in human, findings such as those of Hoyt and Daroff (1971) that lesions in the frontal eye fields and the occipito-parietal areas resulted in an absence of the saccadic component and defective slow component respectively, suggest that at least two cortical areas are essential for the production of a normal optokinetic nystagmus. Walsh and Hoyt (1969) stated that the production of optokinetic nystagmus served as a proof that the patient was not blind. This, again may indicate that a functioning visual cortex is essential for the production of optokinetic nystagmus in human. It is interesting to ponder on this from an evolutionary point of view.

In fish, the visual and visual-oculomotor functions are

served by the subcortical optic tectum. Through the evolutionary process of increasing encephalisation among higher animals, cats, dogs and other land animals develop the visual cortex, and evidently, visual-oculomotor pathways are partly mediated in the cortex as observed by a change in optokinetic nystagmus after decortication (Rademaker and ter Braak 1948). From a functional point of view, oculomotor reflex without vision seems to serve no survival interest, and in human, a functioning visual cortex seems to be essential for conscious visual perceptions. Therefore, it may be no surprise to find out that the capability of the subcortical pathways to elicit optokinetic nystagmus has been eliminated. However, as stated in Section 4.1.3, optokinetic studies in a decorticated human has not been reported and the problem must remain unresolved.

Concerning the actual centers generating nystagmus, it is clear from the works of Lorente de No (1933, 1938), Robinson (1964, 1965), Fuchs and Luschei(1970), Fuchs (1971), Maeda et al (1972) and many others, that a special neural mechanism is needed to generate nystagmus, so that during each slow component, a steadily increasing impulse train and during each saccadic component, a massive burst of impulses in a 'pulse-step' pattern can be sent to the extra-ocular muscles. Furthermore, a continual alternation of these phases is needed to create the nystagmic eye movements. It is likely that this relatively complicated mechanism can be called into action by command impulses, with their appropriate modulating signals, arriving

from different pathways. For example, cortical, subcortical, central and peripheral retinal connections may eventually all directly or indirectly converge towards this basic mechanism. In fact, evidences described previously from Barany (1907, cited by Lorente de No, 1933), Holmes (1938), Goto et al (1968), Hoyt and Daroff (1971), and the opinion of Yarbus (1967) all suggest that voluntary saccades and pursuit are also closely associated with this mechanism. Moreover, it is likely that the same mechanism may also serve vestibular nystagmus; findings of this thesis provide a strong support for this hypothesis.

According to this concept, the entire 'complex' behaves as a basic versatile mechanism serving a hierarchy of commands, where integration and priorities of control are planned according to some criteria which serve the best efficiency and survival interest of the living creature.

5.3.5 Explanation on More Observed Phenomena in Optokinetic Nystagmus

Based on the findings on the retinal contribution to optokinetic nystagmus in Section 4.3, this section offers some possible explanations to several observed phenomena in optokinetic nystagmus.

In Section 4.2.3, during the image density variation experiments, it was found that no major variation occurred when the horizontal spacing between the moving dots was changed within 19° degrees of visual angle. However, when this spacing was changed

to 25 degrees, a drastic variation occurred; nystagmus became intermittent. In view of the finding that, generally, optokinetic nystagmus stimulus outside the region around 10 degrees from the center of the retina produced no nystagmus with normal straightforward attention, the explanation of the finding in Section 4.2.3 becomes relatively simple. When the eyes fell in between the moving dots after a saccade, no targets were available in the 20-degree sensitive area to immediately sustain the nystagmus and therefore nystagmus became intermittent.

It has generally been reported that the speed of the slow components of optokinetic nystagmus was not constant, although the stimulus speed remained the same (McLay, Madigan and Ormerod, 1957; Jung and Kornhuber, 1964; Komatsuzaki et al, 1969). Jung and Kornhuber stated that the variation in the velocity for ten consecutive slow components may attain 20 percent in normal subjects. Again, the findings of Section 4.3, that nystagmus intensity decreased when the stimulus acted further away from the center of the retina could explain the above phenomenon. Since the amplitudes of the saccadic components are not uniform, which can be observed from Fig.4.7(b) , and assuming that during the tracking phase of nystagmus, only a small part of the entire optokinetic stimulus is used, then it is possible that each saccadic component results in a position where the target being tracked by the eyes is in a different position of the retina. Different tracking speeds thus result. Attention, of course, may also play a role in this phenomenon.

Stark and Nelson (1962), Honrubia et al (1968), Stark (1970), Morisette, Barber and Dayal (1970) all reported that their 'look type optokinetic nystagmus' produced more uniform slow component speeds then those produced by the 'stare type' and for a given stimulus speed abouve 5 degrees per second (Stark and Nelson) or 30 degrees per second (Honrubia et al), the 'look type' had an average slow component speed considerably higher than that of the 'stare type'. Two factors could have contributed to this effect: (1) Under the instruction of voluntary tracking of the optokinetic nystagmus, the subject must necessarily pay attention to the target he is tracking. Attention thus facilitates the tracking speed. (2) Since voluntary tracking is done with the center of the retina (or the foveola), during the tracking phase, the subject would endeavour to place his foveola on the moving targets. This is suggested by observing the records of some voluntary tracking at slow speed as illustrated in Fig.5.3; small saccades in either direction occur often during the tracking phase. It is likely that the majority of the small saccades in the direction of the tracking movement and some saccades in the opposite direction may be the results of efforts to place the foveola on the target. In Section 4.3, it has been shown that tracking within approximately five degrees of central vision could produce eye speeds equal to the target speed (within a certain limit) even under the involuntary tracking condition. Thus, it is not surprising that the above two factors combine to give the response from voluntary following of optokinetic stimulus the special characteristics reported by the said authors.

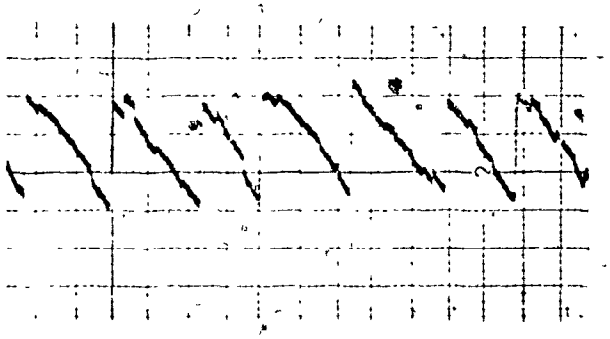


Fig. 5.3

Voluntary following of optokinetic stimulus at 10 degrees/sec.

5.4 THE SUPPORT OF A COMMON CENTRAL MECHANISM FOR VESTIBULAR AND OPTOKINETIC NYSTAGMUS

Since the visual and vestibular systems are closely related to each other in orientation, postural and visual stabilisations, many proposals have been put forward suggesting common centers in the central nervous system serving the two systems. The view that vestibular and optokinetic nystagmus are served by a common central mechanism has been stated by some authors (Rademaker and ter Braak, 1948; Monnier, 1967; Robinson, 1968; and others). Experimental evidence of summation of slow components of vestibular and optokinetic nystagmus was described by Rademaker and ter Braak (1948). They induced vestibular and optokinetic nystagmus simultaneously in rabbits, and reasoned that if the two types of nystagmus were generated from different centers, then when the two nystagmus were induced with different intensities, a complicated form of superimposed nystagmus should result. However, this did not happen but instead a nystagmus with intermediate intensity resulted; the slow component speed was approximately the algebraic sum of those from each individual nystagmus. They supported the view that vestibular and subcortical optokinetic nystagmus were brought about by the same nystagmus center. On the other hand, they were uncertain about whether the subcortical and cortical nystagmus were brought about by the same or by different nystagmus centers.

The similarity in the inter-saccadic interval characteristics in vestibular and optokinetic nystagmus demonstrated in

this thesis provides a strong evidence, on the saccadic component aspect, supporting a common central mechanism generating the two types of nystagmus. To satisfy this view, a seemingly contradictory but important result must be further examined.

Hood (1967) reported that in normal subjects the maximum slow component speed of optokinetic nystagmus that could be induced was about 50 degrees per second, while in patients with central scotoma (loss of central vision), the maximum slow component speed could be induced up to 100 degrees per second. This led Hood, and Dix and Hood (1971) to propose two different optokinetic nystagmus mechanisms serving the central and peripheral vision. However, it may be possible to explain this finding in terms of the common central mechanism concept supported in this thesis.

It is known that the basic vestibulo-ocular reflex is capable of providing compensatory eye movements with velocities up to at least 125 degrees per second (Jones and Milsum, 1965). If optokinetic nystagmus is also produced by this mechanism, then the above finding in patients with scotoma is a logical result. However, the inability for normal subjects to produce optokinetic nystagmus beyond about 50 degrees per second as reported by Hood leads to the following considerations.

In vestibular nystagmus, it is known that the afferent or driving signals are derived from cupular deflection. In the case of optokinetic nystagmus, the nature of the afferent signal is not well understood. However, Barlow, Hill and Levick (1964)

have reported retinal ganglion cells responding selectively to direction and speed of image motion in the rabbit. Oyster and Barlow (1967), and Oyster (1968) postulated that these motion detecting cells could provide the signals necessary to produce optokinetic nystagmus. Recent work by Oyster, Takahashi and Collewijn (1972) has demonstrated a close parallel between the maximal eye velocities reached in open loop condition* and the firing frequency of motion detectors for similar stimulus velocities. This evidence supports motion signals as the afferent for optokinetic nystagmus. At present, little seems to be known about the mechanism of motion detection by the photo receptors in the retina. Nevertheless, some speculations will be presented below that the difference in photo receptor densities on different part of the retina, as shown by Fig. 4.1 , is the main cause of the different tracking capability on different parts of the retina.

It is assumed that the simplest arrangement for motion detection is obtained by a summation of pulses from the photo-receptors** by the ganglion cell as shown in Fig. 5.4 . Suppose the photo-receptors will fire whenever an image moves past and the

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*The eye receiving the optokinetic stimulus is immobilised and optokinetic nystagmus is recorded on the blindfolded eye.

**A similar arrangement has been used by Pavlidis (1964) with the addition of unilateral inhibitory connections between the photo-receptors to obtain unidirectional sensitivity.

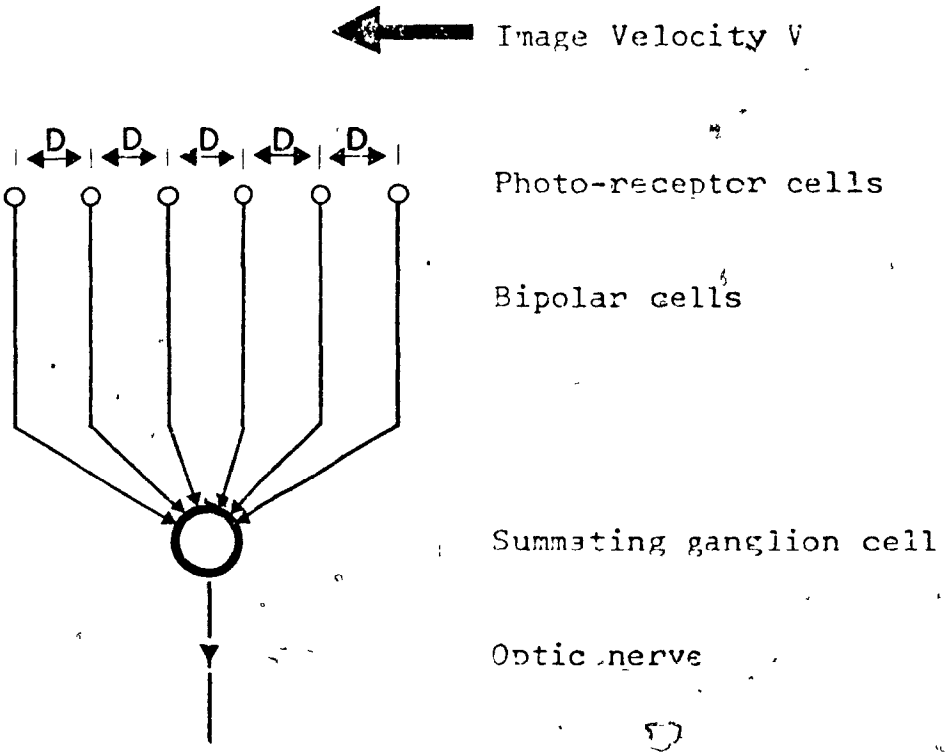

Fig. 5.4 Hypothetical motion detector in the retina

summating cell will fire each time it receives an impulse from any receptor cell. Now if the image has a velocity of V units per second and the photo-receptors are spaced D units apart, the firing rate of the summating cell will be V/D pulses per second. Thus for a fixed receptor spacing, the firing rate of the summating cell will be proportional to the image velocity giving rise to relative motion detection. However, there is an upper velocity of the image at which the impulses from the receptor will arrive too rapidly for the summating cell to transmit because of the refractory property of nerve fibers. This upper velocity fusion limit is dependent on the receptor spacing; the closer the spacing, the lower the velocity fusion limit. From Fig. 4.1. it is shown that the photo-receptors in the foveal region serving direct vision have a much higher density than those in the peripheral regions. It is thus speculated that motion detectors in the foveal region have a lower velocity fusion limit than those in the peripheral retina. Consequently, foveal vision has a lower velocity limit for optokinetic nystagmus. In other words, the low velocity limit is due to failure of the afferent signals, and not due to the inability of the basic generating mechanism.

This hypothesis may also be used to explain the observations that many animals can produce optokinetic nystagmus at much higher speeds than those produced in human. For example, Rademaker and ter Braak (1348) reported that the maximum stimulus speed which could produce nystagmus in dogs and monkeys amounted to 360 degrees

per second. From Polyak's data (1941, p. 201), the receptor density in the foveola (400μ in diameter) of the human retina is estimated to be approximately 3 times denser than those in the corresponding area in the monkey (Rhesus Macaque). Again this may be the cause of a higher speed tracking capability according to the hypothesis above. It is interesting to note that since visual acuity is directly proportional to photo-receptor density and if the hypothesis that tracking capability decreased with increasing receptor density were true, then the price for an increase static visual acuity would be a decrease in visual tracking capability.

Further work in this direction is worth pursuing. If the hypothesis is proved to be true, then it may be possible to develop methods to utilise peripheral vision in viewing targets moving at speeds higher than the tracking capability of central vision.

SUMMARY

(1) Literature pertaining to the anatomical site of origin of the nystagmus rhythm has been reviewed and it is suggested that a new approach should be adopted in its future study. The possibility of multiple areas capable of generating rhythmic activities which are entrained to produce a common rhythm has been considered in view of the contradictory experimental results reported in the literature and the complex function that this mechanism has to serve. The finding of a characteristic pattern of variation in the normal rhythm of nystagmus in this thesis has been suggested to assist further investigation into the validity of this concept.

(2) The rhythm of vestibular and optokinetic nystagmus has been analyzed in terms of the inter-saccadic intervals by means of the point process analysis technique with the following results.

(a) Trends exist in most vestibular nystagmus records to the extent that segmentation of data is often required for analysis. A method of displaying the length of consecutive intervals using dots in a compressed scale has been found to be very informative in revealing trends and other characteristics of the inter-saccadic intervals.

(b) Arousal and mental activity in general have been observed to affect vestibular and optokinetic nystagmus. In particular, mental arithmetic during optokinetic nystagmus has been demonstrated to have a randomising effect on the nystagmus rhythm.

(c) Multi-modal interval distributions with the higher order modes occurring at approximately multiple integral values of the basic mode were found to occur in both vestibular and optokinetic nystagmus. This reveals a significant feature of the mechanism generating the nystagmus rhythm.

(d) A characteristic pattern of variation in the rhythm of vestibular and optokinetic nystagmus has been established. Generally, as the intensity (or slow component speed) of nystagmus is decreased, the occurrence of the saccadic components becomes more irregular. The corresponding inter-saccadic interval distribution changes from being monomodal and symmetrically distributed with a narrow spread to one with a wider spread. With more reduction in intensity, the speed of the distribution further increases and becomes skewed towards the longer duration. With further reduction in nystagmus intensity, multi-modal distributions appear. This characteristic variation may serve as a useful aid in further clinical, anatomical and physiological studies in nystagmus.

(e) These results have demonstrated a striking similarity between the interval statistics of vestibular and optokinetic nystagmus which provides a powerful support for the hypothesis of a common central mechanism generating the two types of nystagmus.

(3) Changing the parameters of optokinetic stimulus has the following effects on inter-saccadic interval statistics.

(a) Image speed caused a characteristic variation described in item 2(d).

(b) Image density produced no major variation when the horizontal spacing between the moving stimuli was changed within 19 degrees of visual angle. When this spacing was changed to 25 degrees, a drastic variation occurred; nystagmus became intermittent.

(c) Image pattern and image brightness produced no consistent variation.

(4) Voluntary following of the optokinetic stimulation has been shown to be often accompanied by small saccades occurring at intervals similar to those produced in optokinetic nystagmus under the involuntary condition. Over a wide range of higher stimulus speeds, very distinct bi-modal inter-saccadic interval distribution with the second mode located at approximately twice the first mode value was found. It is proposed that the response from voluntary following is produced by the suppression of the saccadic components and augmentation of the slow components of optokinetic nystagmus produced by the basic reflex mechanism.

(5) A simple stochastic model has been described which could simulate all the observed inter-saccadic interval characteristics of vestibular and optokinetic nystagmus. In particular, simulated results of spontaneous nystagmus agree closely with clinical results in six different statistical measures. This model suggests a possible role of inhibition in the generation of nystagmus rhythm.

(6) Retinal contribution to optokinetic nystagmus has been studied by two different methods with the results supporting the findings of each other. These findings are:

(a) Central vision can produce optokinetic nystagmus in the absence of stimulus in the peripheral fields and vice versa. A single moving dot can elicit a continuous optokinetic nystagmus.

(b) A deletion of central vision up to 5 degrees produced no noticeable variation in optokinetic nystagmus.

(c) From 5 degrees on, increasing the size of central vision deletion resulted in a progressively weaker nystagmus, and in most normal subjects, nystagmus ceased when more than 20 degrees central vision was deleted.

(d) These functional findings on the retina were later correlated to the anatomical data of Polyak (1941) and of Wilson and Toyne (1970). Polyak described the fovea on the human retina to be 5.2 degrees, the yellow spot to be 17 degrees, and the peri-fovea to be 19 degrees. Wilson and Toyne reported a dense projection to the superior colliculus from the part of the striate cortex which is devoted to the central 5 degrees of the visual field.

(e) Visual attention has been demonstrated to have a strong facilitatory role in optokinetic nystagmus. In particular, it facilitates the responses to stimulation in the peripheral retina.

(f) These findings on the retinal contributions to optokinetic nystagmus have been used to explain the results in items 3(b) and (c) above and several commonly reported phenomena in optokinetic nystagmus.

(7) Based on the present findings, it has been suggested that the different types of optokinetic nystagmus proposed in the literature should be regarded not as different entities of nystagmus but as variants of one entity, the variation being due to greater or lesser voluntary influence, or to stimulation of different parts of the retina producing a stronger or weaker nystagmus.

(8) An explanation has been offered to the reported findings that patients with central scotoma, and animals such as dogs and monkeys could produce optokinetic nystagmus up to a much higher stimulus speed when compared with normal human; a simple model of the retinal receptor connections has been described.

(9) In Appendix 1, the nystagmus waveform has been idealised and mathematically formulated, and a method has been introduced to obtain a simple set of criteria which provides a rational basis for specifying bandwidths for electronic recording.

APPENDIX 1

A Theoretical and Digital Computer Spectral Analysis of the Nystagmus Signal

Introduction

Electronic recording of ocular nystagmus has become a useful tool for routine clinical vestibular examination and laboratory research. A knowledge of the frequency content of the nystagmus waveform is desirable in order to specify the bandwidth of the recording system, since an amplifier with too narrow a bandwidth will distort the required signal, whereas too wide a bandwidth will amplify unwanted signals such as electronic noise or electromyographic activity from facial or extra-ocular muscles. In this paper theoretical analysis of an idealized nystagmus waveform leads to a simple set of criteria which provide a rational basis for specifying the required bandwidth. The results of spectral analysis of typical clinical records are presented to illustrate the use of these criteria.

Theoretical Considerations

Assume the nystagmus to be a repetitive assymetric triangular wave with slow and fast phases as shown in Fig. 1. In the interval $0 \leq t \leq T$ the nystagmus waveform may be described by the function

$$f(t) = t, \qquad 0 \leq t \leq T_1 \tag{1}$$

$$= r(T-t), \qquad T_1 \leq t \leq T \tag{2}$$

where T is the period, or time taken for the complete nystagmus beat, and r is the ratio of the fast-phase speed to slow-phase speed.

The harmonic content of the repetitive waveform may be found by expanding f(t) in the Fourier Series (Lee, 1964). In other words, the function f(t) is broken down into a series of sinusoidal components. The nth Harmonic is given by

$$F(n) = \frac{1}{T}\int_0^T f(t)\, e^{-jn\omega t}\, dt \tag{3}$$

where $\omega = \frac{2\pi}{T}$, $j = \sqrt{-1}$

In the present case, after solving equation (3), the complex spectrum is

$$F(n) = \frac{T(1+r)}{(2\pi n)^2}\left[\left(\cos 2\pi n\left(\frac{r}{1+r}\right) - 1\right) + j \sin 2\pi n\left(\frac{r}{1+r}\right)\right] \tag{4}$$

To simplify writing later equations, let $\frac{r}{1+r} = a$

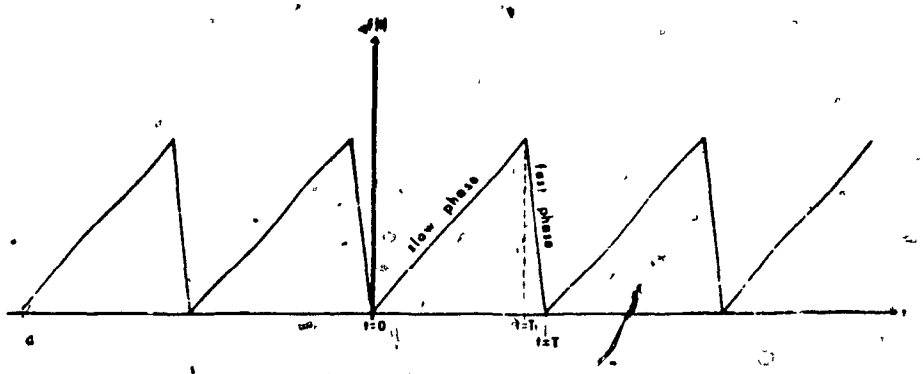

Fig. 1 An idealised nystagmus wave.

From equation (4) the amplitude of the nth harmonic is found to be

$$|F(n)| = \frac{T}{(2\pi n)^2(1-a)}\sqrt{(\cos 2\pi na - 1)^2 + (\sin 2\pi na)^2} \qquad (5)$$

A graph of amplitude $|F(n)|$ versus the harmonic number, n, (or equivalently, frequency) is the relative harmonic amplitude spectrum of f(t), and is often used to characterize the time function f(t) in the frequency domain.

Again from equation (4), the phase of the nth harmonic is

$$\angle F(n) = \tan^{-1}\frac{\sin 2\pi na}{\cos 2\pi na - 1} \qquad (6)$$

A graph of phase angle $\angle F(n)$ is the harmonic phase spectrum of f(t).

Given the relative harmonic amplitude and phase spectra, one can, if desired, reconstruct graphically the function f(t) from a series of sinusoidal waves. The exact re-synthesis may be expressed mathematically as the summation of an infinite number of harmonic components, i.e.

$$f(t) = \sum_{n=-\infty}^{\infty} F(n)\cdot e^{jn\omega t} \qquad (7)$$

However, in practice, only a finite number of harmonic components are chosen to resynthesize the original waveform. In other words, the infinite series in equation (7) will be truncated. The degree of distortion then depends on the number of harmonic terms included.

To set a limit on the number of harmonics necessary in order to resynthesize the wave without significant harmonic distortion, the following consideration is proposed. It is customary to speak of the squared value of a signal or waveform as its "power", in the same sense that electrical power is proportional to the square of the voltage or current. The total power of the idealized nystagmus wave consists of A.C. power (or harmonic power) and D.C. power, thus

Total harmonic power = Total power - D.C. power (8)

Now it is reasonable to assume that if (say) 98% of the total harmonic power is included after truncation of the series, fidelity of the wave will not be significantly distorted.

With equations (1) and (2) and by integration in the time domain

$$\text{Total power} = \frac{1}{T}\int_0^T [f(t)]^2\, dt \qquad (9)$$

$$= T^2\left[\frac{a^3}{3} + \left(\frac{a}{1-a}\right)^2\left(\frac{1}{3} - \frac{a^3}{3} + a^2 - a\right)\right] \text{ units}$$

$$\text{D.C. power} = \left[\frac{1}{T}\int_0^T f(t)\, dt\right]^2 \qquad (10)$$

$$= T^2\left[\frac{a^2}{2} + \frac{a}{1-a}\left(\frac{1}{2} + \frac{a^2}{2} - a\right)\right]^2 \text{ units}$$

Thus, with equations (8), (9) and (10), total harmonic power of the wave can be calculated. The cumulative harmonic power P(m) furnished by an arbitrary successive number of harmonic components can be obtained from the frequency domain equation in (5) :

$$P(m) = 2\sum_{n=1}^{m}|F(n)|^2 \qquad (11)$$

$$= 2T^2\sum_{n=1}^{m}\left[\frac{1}{(2\pi n)^2(1-a)}\right]^2\left[(\cos 2\pi na - 1)^2 + (\sin 2\pi na)^2\right]$$

P(m) means the cumulative harmonic power delivered by including the

first m harmonic components.

Knowing the total harmonic power (delivered by the infinite series) and the partial cumulative harmonic power (delivered by the truncated series), the percentage of the total harmonic power content furnished by a finite number of harmonic components can be calculated. The results for several values of "r" are shown in Table I. From Table I, it is seen that the larger the value of "r" the higher the harmonic component we have to include to achieve 98% of the total harmonic power. A high fast-phase speed and a low slow-phase speed combination will give a high "r" value.

To illustrate the use of this table, pick a possible high fast-phase speed of 400°/sec. and a low slow-phase speed of 4°/sec. so that r = 100. Now if the nystagmus rate is five beats per second, it is necessary to include the 17th harmonic which is 85Hz. in order to include 98% of the total power. However in clinical records the "r" value will rarely be as high as this (see discussion). From a typical clinical recording shown in Fig. 2a, the "r" value was measured to be nine and the nystagmus estimated to be at most four beats per second. From Table I, to include 98% of the total harmonic power, it is necessary to include the 5th harmonic of 4Hz. which is 20Hz. If one is interested in preserving the fidelity of an occasional fast beat in the record, the reciprocal of the shortest nystagmus beat period time should be used as the fundamental frequency.

Digital Computer Spectral Analysis of Clinical Records

Horizontal nystagmic eye movements evoked by caloric irrigation in man were recorded using bitemporally-placed miniature Ag-AgCl skin electrodes (Beckman, type 3503) having an electrode area of about 8mm^2 each. Skin potentials were amplified by an AC coupled (3 sec. time constant) differential amplifier having a differential input impedence of about 50MΩ and high frequency bandwidth of 100Hz. The high input impedence of the amplifier was such as to ensure that the electrodes did not decrease the frequency bandwidth of the measurement (Geddes and Baker, 1966; Geddes, Baker and McGoodwin, 1967). Following amplification, signals were recorded on an FM magnetic tape recorder having a bandwidth of 0-625Hz.

A horizontal eye movement recording resulting from left cold (37°C.) caloric irrigation is shown in Fig. 2(a). The magnetic record of this tracing was played back and a segment of the record, as indicated by the arrows in Fig. 2(a), was digitised at 200 samples per second using a LINC-8 computer. A total length of 10.24 seconds (2048) samples was taken. The digitized waveform, as displayed on a digital plotter, is shown in Fig. 2(b).

The digitized ENG data were fed into an IBM 360/75 computer. First they were multiplied by a smoothing function (or data window) consisting of two half cosine bells each one tenth the length of the data (Bingham, Godfrey and Tukey, 1967), following which a Fast Fourier Transform program (Bingham et al, 1967) was used to transform the data. The accuracy of this transform program was tested by transforming a ramp function of 2048 samples, and found

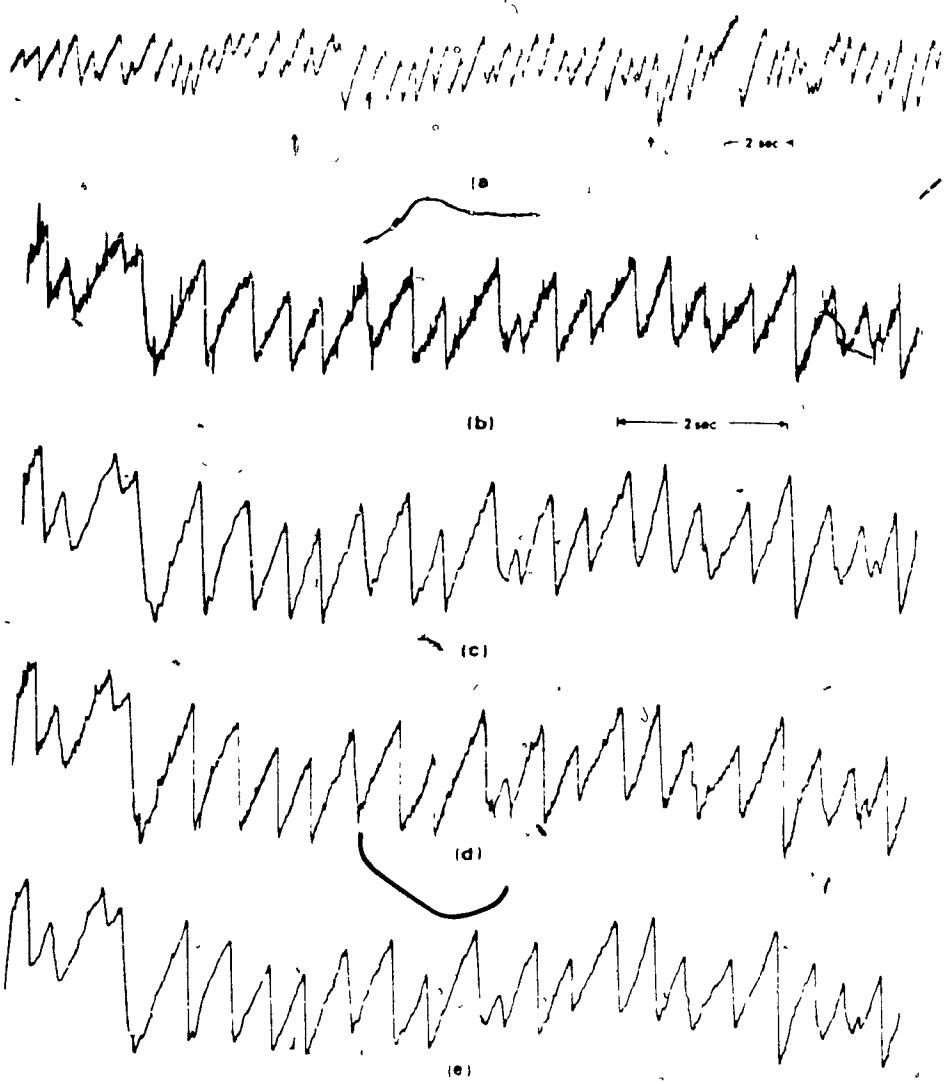

Fig. 2 (a) Portion of a clinical record of caloric nystagmus.

(b) Enlarged plot of a segment of record (a) (between arrows) which was used for computer analysis. The more pronounced high frequency noise in this record results from the greater bandwidth of the digital data reduction system.

(c) Resynthesized waveform after elimination of frequency components higher than 20Hz.

(d) Resynthesized waveform after an equivalent first order lag filter with cut-off frequency at 20Hz.

(e) Resynthesized waveform after an equivalent two sections of the lag filter in cascade.

TABLE I Some results of cumulative harmonic power as a percentage of total harmonic power for different values of r

Cumulative Harmonic Power P(m) in percentage of tot	r=9	r=12	r=16	r=24	r=10
P(1)	72.6157	70.3250	67.9903	65.6178	[illegible]
P(2)	89.0360	86.8159	84.3910	81.7646	[illegible]
P(3)	95.1807	93.3972	91.2547	88.7504	[illegible]
P(4)	97.8575	96.5636	94.7992	92.5403	[illegible]
P(5)	99.0842	98.2092	96.8270	94.8494	[illegible]
P(6)	99.6149	99.0332	98.0503	96.3598	[illegible]
P(7)	99.8222	99.5401	98.8069	97.3927	[illegible]
P(8)	99.8863	99.7674	99.2778	98.1197	[illegible]
P(9)	99.8974	99.8703	99.5683	98.6410	[illegible]
P(10)	99.8974	99.9096	99.7435	99.0188	[illegible]
P(11)	99.9024	99.9201	99.8450	99.2941	[illegible]
P(12)	99.9150	99.9210	99.9005	99.4947	96.8237
P(13)	99.9325	99.9216	99.9280	99.6404	[illegible]
P(14)	99.9504	99.9256	99.9397	99.7453	[illegible]
P(15)	99.9654	99.9334	99.9434	99.8200	97.7232
P(16)	99.9759	99.9437	99.9438	99.8722	[illegible]
P(17)	99.9818	99.9548	99.9439	99.9078	[illegible]
P(18)	99.9843	99.9603	99.9451	99.9314	[illegible]
P(19)	99.9849	99.9739	99.9476	99.9435	[illegible]
P(20)	99.9849	99.9804	99.9519	99.9555	[illegible]

to detect the first 100 harmonics with less than 1% error.

The resulting relative harmonic amplitude spectrum of the ENG waveform is shown in Fig. 3, from which it is seen that the small amplitude components become relatively constant after about 15Hz. They presumably arise as a combination of low-amplitude, high-frequency components in the eye tremor, muscle and skin artifacts, electronic noise, and aliasing of the spectrum. The rather marked 60Hz. component is caused by pickup from the power supply. From this spectrum, it would appear the significant frequency components for this ENG were below 20Hz. In order to check this assumption, the amplitude of the spectrum components above 20Hz. were all set to zero, and the ENG wave was resynthesized by performing an inverse transform. The result is shown in Fig. 2(c). The erratic noise signals have largely disappeared while the basic waveform is retained. Spectra of records from 10 different patients all showed significant components to be within 20Hz.

Waveform re-synthesis from a truncated Fourier series, as just described, represents an ideal filtering operation by digital computers. In the clinical environment, filtering is usually done by analog filters which are far from ideal, producing gradual phase shifts as well as attenuation in signal amplitude adjacent to the cut-off frequency. Fig. 2(d) is the result obtained by multiplying the non-truncated spectrum with a function $20/(20+jm)$ where m is the order of the harmonic, before re-synthesizing the ENG wave. This is equivalent to filtering the ENG signal with a first order lag filter with a bandwidth of 20Hz. (time constant 1/40 sec.).

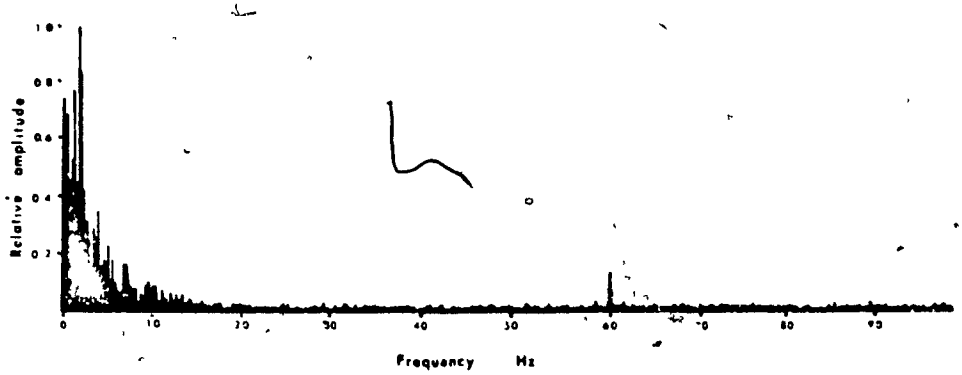

Fig. 3 Frequency spectrum of the clinical ENG.

Fig. 2(e) is the result from using two such filter sections in cascade. Super-imposing the tracings on top of one another shows negligible phase distortion errors. Thus, in the ordinary clinical environment, a second order low pass filter with a cut-off frequency at 20Hz. should result in satisfactory recording of nystagmus.

DISCUSSION

In recording signals using skin electrodes the investigator has at his disposal two principal methods to eliminate unwanted artifacts. Elimination of artifacts having frequency components within the bandwidth of the desired signal must depend largely upon careful skin preparation and electrode placement. On the other hand the effects of artifacts having frequencies outside the bandwidth of the desired signal may be minimized by proper adjustment of the instrumentation bandwidth. To do this effectively, however, one requires precise knowledge of the actual bandwidth of the signal of interest.

Theoretical consideration of the nystagmus waveform shows that the width of its harmonic spectrum for a given percentage of the total harmonic power content depends on (1) the ratio of fast-phase and slow-phase speeds, and (2) the basic period of the nystagmus beat. Calculations such as those in Table I can provide a guide to selection of the appropriate instrumentation bandwidth in individual cases. If nystagmus amplitude remains approximately constant, a high value of "a" will normally be associated with a long period T_1 (Fig. 1)

and vice versa. This relationship is likely to prevent a large variation in bandwidth requirements in most cases.

It should be noted that this analysis applies specifically to studies of the nystagmus waveform, in which slow-phase and fast-phase speed are the variables of interest. Fidelity of reproduction of the transition periods between slow and fast phases has not been considered. In recording eye movements having a stepwise, or staircase type of waveform, or when slow-phase to fast-phase transitions are of interest, the necessary bandwidth may be considerably higher than that indicated here (Robinson, 1964; Zuber et al, 1968; Kris, 1960; Shackel, 1967).

REFERENCES

1. Bingham, C., Godfrey, M.D. and Tukey, J.W., 1967: Modern techniques of power spectrum estimation. IEEE Trans. on Audio and Electroacoustics. Vol. AU-15, No. 2, 56.

2. Geddes, L.A. and Baker, L.E., 1966: The relationship between input impedance and electrode area in recording the ECG. Med. Biol. Engng. 4, 439.

3. Geddes, L.A., Baker, L.E. and McGoodwin, M., 1967: The relationship between electrode area and amplifier input impedance in recording muscle action potentials. Med. Biol. Engng. 5, 561.

4. Kris, E.C., 1960: in Medical Physics, Vol. 3, O. Glasser, Ed., Year Book Publishers, Chicago.

5. Lee, Y.W., 1964: Statistical Theory of Communication, J. Wiley and Son.

6. Robinson, D.A., 1964: The mecharics of human saccadic eye movement. J. Physiol., 174, 245.

7. Shackel, B., 1967: Eye movement recording by electro-oculography. A manual of psychophysiological methods, P.H. Venables, ed. North-Holland Publishing Company, Amsterdam.

8. Tibbling, L., 1969: The rotatory nystagmus response in children. Acta Otolaryngol., 68,459.

9. Zuber, B.L., Sammlow, J.L. and Stark, L., 1968: Frequency characteristics of saccadic eye movement. Biophys. J., 8, 1288.

Appendix 2

The Poisson Process

The essential features of a Poisson process are that

(a) the probability of occurrence of events does not vary with time so that there is no trend;

(b) the chance of two or more events occurring simultaneously is negligible;

(c) the chance of an event occurrence at any time is quite independent of what happens up to that time.

The number of event, n, occurring in an arbitrary interval of length, k, is distributed according to the Poisson probability law.

$$P_n(t) = \frac{(\mu t)^n}{n!} e^{-\mu t}$$

The time interval, T, between successive events is distributed according to the exponential distribution law.

$$f(T) = \mu e^{-\mu T}$$

The time interval, τ, between every rth event is distributed according to the gamma distribution law.

$$f(\tau) = \frac{\mu(\mu\tau)^{r-1}}{(r-1)!} e^{-\mu\tau}$$

Appendix 3

Testing of Poisson Hypothesis

The computer program SASE 4 (SASE stands for statistical analysis of series of events) was written for the IBM 360 computers by Lewis, Katcher and Weis (1969) and is based on a monograph by Cox and Lewis (1966).

Two sets of inter-saccadic interval data were tested for the Poisson hypothesis. Both sets of data were derived from spontaneous nystagmus records. Set A (used in the graphical displays Fig.3.5 through Fig.3.8.(a)) was obtained from a patient suspected of a labyrinthine lesion. Set B (the interval histogram of which is shown in Fig.3.8.(b)) was obtained from a subject found to have spontaneous nystagmus thought to be due to vestibular neuronitis secondary to influenza. In addition to testing the two whole sets of data, each was halved so that four more data sets, each having half the original number of intervals, were analyzed. The purpose was to see the difference between results of the two half data sets. The results of the test are summarised in Table A.3.1. The critical values corresponding to 0.05 and 0.01 significance levels for the test statistics are shown in Table A.3.2.

The U statistics is for testing the null hypothesis that there is no trend in the interval data. Moran, DN, WN2 are different statistics all testing the null hypothesis that the intervals are generated by a Poisson process.

Set A as a whole has just passed the 5% significance level indicating that there is a trend detected by the program.

No significant trend is indicated in other interval sequences. The results of Moran, DN, WN2 statistics all strongly reject the Poisson hypothesis. There seems to be considerable difference between the corresponding statistics of the two half data sets.

TABLE A.3.1

Summary of results from SASE 4

Program Subroutine	Statistics	SET A Whole 512 samples	SET A First half 256 samples	SET A Second half 256 samples	SET B Whole 398 samples	SET B First half 199 samples	SET B Second half 199 samples
TREND	U	2.07	0.85	0.08	0.57	0.71	0.13
	mean msec.	547	496	596	807	780	865
	variance	6528	4230	8497	10932	9197	12514
	standard deviation	80	65	92	104	95	111
	coeff. of variation	0.56	0.49	0.58	0.50	0.49	0.51
INTER	3rd central moment	0.98×10^{6}	0.39×10^{6}	0.14×10^{7}	0.33×10^{7}	0.27×10^{7}	0.39×10^{7}
	coeff. of skewness	1.86	1.43	1.80	2.94	3.09	2.83
	4th central moment	0.32×10^{9}	0.87×10^{8}	0.49×10^{9}	0.19×10^{10}	0.16×10^{10}	0.22×10^{10}
	coeff. of kurtosis	7.60	4.90	6.88	16.53	19.81	14.44
EXPO	Moran	129.0	55.0	71.2	56.6	29.1	29.7
DURB	DN	9.81	7.75	6.51	8.33	5.72	6.09
	WN2	151	92	67	127	65	63

TABLE A.3.2

Critical values of test statistics

Statistics	Significance Levels 5%	1%
U	1.96	3.08
Moran	1.96	3.08
DN	1.36	1.63
WN2	2.49	3.86

APPENDIX 4

Instrumentations and computations

Instrumentation Aspect. The author has designed the following instruments used in the work of this thesis:

(1) Two channels of EOG amplifiers

(2) A circuit for measuring the slow component speed of nystagmus*

(3) Photo-electric curve reader compatible with the PDP-8/s computer

(4) An interfacing system for automatic magnetic tape recording of clinical ENG data.

(2) and (3) were designed in collaboration with J. S. Outerbridge. The instruments were built mostly by C. Granja, H. Graaf and V. Ferch.

*A very simple electronic circuit has been designed, which can continuously measure the slow component speed of nystagmus and also indicate the nystagmus direction. An example of the circuit performance is shown in Fig. 5.1.

Computation. Three digital computers have been used. The Digital Equipment Corporation LINC-8 in the Royal Victoria Hospital, the IBM 360/67 and the IBM 360/75 in the McGill University Computing. Communication between the computers of the two locations were via telephone lines.

Except the SASE 4 (Appendix 3) and the Fast Fourier Transform programs (Appendix 1), all other computer programs were written by the author.

BIBLIOGRAPHY

Barany, R. (1907)
Die Untersuchung der reflektorischen vestibularen und optishen Augenbewegungen und ihre Bedeutung fur die topishe Diagnostik der Augenmuskellahmungen.
Munch. Med. Wsehr. 54, 1072 - 1075, 1132-1135.

Barany, R. (1907) cited by Lorente de No, 1933.
Physiologie und pathologie des Bogengang-Apparates beim menschen.
Vienna, Franz Deuticke.

Barany, R. (1921)
Zur Klinik und Theorie des Eisenbahnnystagmus.
Arch. Augenheilk 88, 139

Barlow, H.B., Hill, R.M., Levick, W.R. (1964)
Retinal ganglion cells responding selectively to direction and speed of image motion in the rabbit.
J. Physiol. (London) 173:377.

Bishop, P.O., Levick, W.R., and Williams, W.O. (1964)
Statistical Analysis of the Dark Discharge of Lateral Geniculate Neurones,
J. Physiol. (London) 170:588.

Blegvod, B. (1962)
Caloric vestibular reactions in unconscious patients.
Arch. Otolary 75:506

Borries, G. (1921)
Fixation und Nystagmus
Kopenhagen - Th. Linas Eftf. 1-112.

Boyd, I.A., Martin, A.R. (1956)
The end-plate potential in mammalian muscle
J. Physiol. (London) 132:74

ter Braak, J.W.G. (1935)
Optokinetische Nystagmus.
Diss. Nijdschr. Geneek. 79,1.

Brodal, A., Pompeiano, O., Walberg, F. (1962)
The vestibular nuclei and their connections; anatomy and functional correlations
Oliver and Boyd

Brucher, J.M. (1966)
The frontal eye fields of the monkey
Int. J. Neurol., 5:262

Carmichael, E.A., Dix, M.R., Hallpike, C.S. (1954)
Lesions of the cerebral hemispheres and their effects upon optokinetic and caloric nystagmus.
Brain, 77:345

Carpenter, M.B., Strominger, N.L. (1965)
The medial longitudinal fasciculus and disturbances of conjugate horizontal eye movements in the monkey.
J. Comp. Neurol. 125:41

Coates, A.C. (1968)
Central and peripheral optokinetic asymmetry.
Ann. Otol. 77:938

Coates, A.C. (1971)
Galvanic body sway in normals and patients with 8th nerve lesions.
Barany Society Meeting, Toronto, Canada.

Cohen, B., Goto, S., Shanzer, S., Weiss, A.H. (1965)
Eye movements induced by electric stimulation of the cerebellum in the alert cat.
Exptl. Neurol. 13:145

Collewijn, H. (1970)
Dysmetria of fast phase of optokinetic nystagmus in cerebellectomised rabbits.
Exptl. Neurol. 28.144

Collins, W.E. (1962)
Manipulation of arousal and its effects on human vestibular nystagmus induced by caloric irrigation and angular accelerations.
Federal Aviation Agency CARI report 62-17

Connelly, A.L. (1970)
Pseudorandom number generator
Decuscope 9(1)

Cords, R. (1926)
Zur Theorie des optomotorischen nystagmus. Eine Widerlegung Ohms
Klin. Mbl. Augenheilk. 77:781

Cox, D.R. (1962)
"Renewal Theory"
Methuen: London

Cox, D.R., and Lewis, P.A.W. (1966)
"The Statistical Analysis of Series of Events"
Methuen: London

Crampton, G.H. (1964)
Habituation of ocular nystagmus of vestibular origin.
Chap 16 "The Oculomotor System", ed. M.B. Bender
Hoeber, New York

Crosby, E.C., Henderson, J.W. (1948)
The mammalian midbrain and isthmus regions
J. Comp. Neurol. 88:53

Crosby, E.C., Voss, R.E., Henderson, J.W. (1952)
The mammaliam midbrain and isthmus regions
J. Comp. Neurol. 94:357

Deecke, L., Schwarz, D., Fredrickson, J. (1971)
Vestibular Thalamus in the Rhesus Monkey
Barany Society Meeting, Toronto, Ontario.

Dichgans, J. (1972)
Eye movement related unit activity in the vestibular nerve
Spring meeting of the association for research in vision and opthalmology. Sarasota, Fla., USA

Dix, M.R., Hood, J.D. (1971)
Further observations upon the neurological mechanism of optokinetic nystagmus.
Acta Otolaryng. 71:217

Dodge, R., Fox, J.C (1928)
Optic Nystagmus
Arch. neurol & Psychiat. 20:812

Dohlman, G. (1938)
On the mechanism of transformation into nystagmus of stimulation of the semicircular canals
Acta Otolaryng. 26:425

Duensing, F., Schaefer, K.P. (1957)
Die Neuronenaktivitat in der Formatio reticularis des Rhombencephalons beim vestibularen Nystagmus.
Arch. f. Psychiat. 196:265

Duensing, F., Schaefer, K.P. (1958)
Die Activitat einzelner Neurone im Bereich des Vestibularis kerne bei Horizontal beschleinigungen unter besonderer Berucksichtigung des Vestibularen Nystagmus
Arch f. Psychiat. 198:225

van Egmond, A.A., Groen, J.J. Jongkees, L.B.W. (1949)
The mechanics of the semicircular canals
J. Physiol. 110:1

Ewald, J.R. (1892) cited by McCabe, 1965
Physiologische Untersuchungen uber das Endorgan des Nervus Octavus
J.F. Bergmann, Weisbaden

Fuchs, A.F., Luschei, E.S. (1970)
Firing patterns of abducens neurons of alert monkeys in relationship to eye movement.
J. Neurophysiol. 33:382

Fuchs, A.F. (1971)
The saccadic system
In "the control of eye movements", ed. Bach-y-Rita et al
Academic Press, New York

Gernandt, B.E. (1964)
Vestibular connections in the Brainstem
Chap 9, "The Oculomotor System," ed. M.B. Bender
Hoeber, New York

Gerstein, G.L., Perkel, D.H. (1969)
Simultaneously Recorded Trains of Action Potentials: Analysis and Functional Interpretation
Science 124:828

Goto, K., Tokumasu, K., Cohen, B.
Return eye movements, saccadic movements, and the quick phase of nystagmus
Acta Otolaryng. 65:426

Griffith, J.S., Horn, G. (1966)
An analysis of spontaneous impulse activity of units in the striate cortex of unrestrained cats.
J. Physiol. (London) 186:516

Guyton, A.C. (1966)
"A Textbook of Medical Physiology"
Saunders, Philadelphia

Hagiwara, S. (1954)
Analysis of interval fluctuation of the sensory nerve impulse.
Japan. J. Physiol. 4:234

Harmon, L.D. (1964)
Neuromimes: action of a reciprocally inhibited pair.
Science 146:1323

Harmon, L.D., Lewis, E.R. (1966)
Neural modeling
Physiol. Rev. 46:513

Hebb, D.
"The Organization of Behavior"
Wiley, New York

Henry Ford Hospital Symposium, (1958)
"Reticular Formation of the Brain"
Little, Brown & Co., Boston

Herz, A., Greutzfeldt, O., Fuster, J. (1964)
Statistische Eigenschaften der Neuronenaktivitat im ascendierenden visuellen system
Kybernetik 2:61

Holmes, G. (1938)
The cerebral integration of the ocular movements
Brit. Med. J. July 16 : 107

Hood, J.D. (1967)
Observations upon the neurological mechanism of optokinetic nystagmus with special reference to the contribution of peripheral vision.
Acta Otolaryng. 63:208

ten Hoopen, M., Reuver, H.A. (1965)
Selective interaction of two recurrent processes.
Journal of Applied Probability Vol.2, No. 2, p. 286-292.

ter Hoopen, M., Reuver, H.A. (1965b)
An n-fold Coincidence Problem in Physiology
J. Theoret. Biol. Vol. 9, pp. 117-123

ten Hoopen, M., Reuver, H.A. (1966)
The Superposition of Random Sequence of Events
Biometrika Vol. 53, 3 and 4, p. 383

ten Hoopen, M. (1966)
Impulse sequences of thalamic neurons- an attempted theoretical interpretation
Brain Rev. 3:123

ten Hoopen, M. (1967)
Pooling of Impulse Sequences, with Emphasis on Application to Neuronal Spike Data
Kybernetik, 4. Band. 1. Heft, Aug. 1967.

Honrubia, V., Downey, W.L., Mitchell, D.P., Ward, P.H. (1968)
Experimental Studies on Optokinetic Nystagmus in Normal Humans
Acta Otolaryng. 65 : 441

House, E.L., Pansky, B. (1967)
"A Functional Approach to Neuroanatomy" 2nd edition
McGraw Hill

Hoyt, W.F., Daroff, R.B. (1971)
Supranuclear disorders of ocular systems in man
In "the control of eye movements", ed Bach-y-Rita et al
Academic Press, New York

Jones, G.M., Barry, W., Kowalsky, N. (1964)
Dynamics of the semicircular canals compared in yaw, pitch and roll.
Aerospace Med. 35 p. 984

Jones, G.M., Wilsun, J.H. (1965)
Spatial and dynamic aspects of visual fixation
IEEE Trans. Biomed. Eng. BME-12:54

Jung, R., Kornhuber, H.H. (1964)
Results of electronystagmography in man
Chap. 19 "the oculomotor system", ed. M.B. Bender
Hoeber, New York

Kendall, M.G., Stuart, A. (1967)
"The Advanced Theory of Statistics"
C. Griffin and Co., London

Kestenbaum, A. (1948)
"Clinical Methods of Neuro-opthalmological examination"
W. Heinemann, London

Kestenbaum, A. (1957)
Nystagmus: Review of the Literature in 1946-1954
Adv. Ophthal. 7 221-286

de Klyn, A., Rademaker, G.G.J. (1928)
Nederl. Tijdschr. v. geneish. Vol. 2. p. 5529

de Klyn, A. (1948) cited by Kestenbaum (1957)
Acta Otolaryng. Suppl 78:8

Komatsuzaki, A., Harris, H.E., Alpert, J., Cohen, B. (1969)
Horizontal nystagmus of rhesus monkeys
Acta Otolaryng. 67:535

Kornhuber, H.H., Fonseca, J.S. da (1964)
Optovestibular integration in the cat's cortex
Chap. 10 "The Oculomotor System" ed. M.B. Bender
Hoeber, New York

Kornhuber, H.H. (1971)
Cerebellar control of eye movement
Barany Society Meeting, Toronto, Canada

Krieger, H.P., Bender, M.B. (1957)
Eye movements and the primate cerebrum
Progr. Neurol. Psychiat. 12:180

Lachmann, J., Bergmann, F. (1961)
Mutual influence of nystagmogenic centers during labyrinthine or central nystagmus
Acta Otolaryng. 53:295

Iadpli, R., Brodal, A. (1968)
Experimental studies of commissural and reticular formation projections from tje vestibular nuclei in the cat
Brain Rev. 8:65

Lewis, P.A.W. (1964)
A Branching Poisson Process Model for the Analysis of Computer Failure Patterns
Journal of the Royal Statistical Society, Series B 26 398-456

Lewis, P.A.W., Katcher, A.W., Weis, A.H. (1969)
SASP 4 - an improved program
IBM Research RC2365

Lowenstein, D. (1966)
The functional significance of the ultra structure of the vestibular end organ
Second Sym. on the role of the vestibular organs in space exploration NASA SP-115

Lorente de No, R. (1933)
Vestibulo-Ocular Reflex Arc
Arch. Neurol and Psychiat., 30:245

Lorente de No, R. (1933b)
Reflex reversal and interaction of allied vestibular nystagmus reflexes.
Am. J. Physiol. 105:122

Lorente de No, R. (1935)
Observations on Nystagmus
Acta Otol-laryng. 21:416

Lorente de No, R. (1938)
Analysis of the activity of the chains of internuncial neurons
J. Neurophysiol. 1:207

Maeda, M., Shimazu, H., Shimoda, Y. (1972)
Nature of synaptic events in cat abducens motorneuronsat slow and quick phase of vestibular nystagmus.
J. Neurophysiol. 35:279

Manni, E., and Giretti, M.L. (1970)
Central eye nystagmus in pontomesencephalic preparation
Exp. Neurol. 26:302

Mackensen, G., Schumacher, J. (1960)
Die Geschwindigkeit der raschen Phase des optokinetischen Nystagmus
Graefes Arch. Ophthol. 162:400

McLay, K., Madigan, W.F., Ormerod, F.C. (1957)
Anomalies in the recorded movements of the eye during optokinetic rotatory and caloric stimulation in normal subjects
Annals of ORL, 66:473

McCabe, B.F. (1965)
The quick component of nystagmus
Laryngoscope, 75:1619

McIntyre, A.K. (1939)
The quick component of nystagmus
J. Physiol. 97:8

Money, K.E., Johnson, W.H., Corlett, B.M. A. (1965)
Role of semicircular canals in positional alcoholic nystagmus
Am. J. Physiol. 208:1065.

Monnier, M. (1967)
Central mechanisms of vestibular and optokinetic nystagmus
A.V.S. de Reuck ed CIBA symp. J.&A. Churchill Ltd., London

Moore, G.P., Perkel, D.H., Segundo, J.P. (1966)
Statistical analysis and functional interpretation of neuronal spike data.
Ann. Rev. Physiol. 28:493

Morisette, Y., Barber, H., Dayal, V. (1970)
Studies on optokinetic nystagmus
Otolaryngological meeting, Hotel Bonaventure, Montreal, Canada.

Nathanson, M., Bergman, P.S. (1958)
Newer methods of evaluation of patients with altered states of consciousness
Med. Clinic of North America, May 1958

Nelson, G.P., Stark, L. (1962)
Optokinetic nystagmus in man
QPR No. 66 Res. Lab. of Electronics, M.I.T. p. 366

Oesterberg, G. (1935)
Topography of layer of rods and cones in the human retina
Acta Ophtnal. Kbh. Suppl. 6:1

Ohm, J. (1922)
Das Verhaltnis von Auge und ohr zu den Augenbewegungen
Graafes Arch. Ophthal. 107, p. 298

Outerbridge, J.S. (1969)
Experimental and theoretical investigation of vestibular-driven head and eye movement.
Ph.D. Thesis, McGill University, Montreal

Oyster, C.W., Barlow, H.B. (1967)
Directional-selective units in rabbit retina: distribution of preferred direction.
Science, 155:841

Cyster, C.W. (1968)
The analysis of image motion by the rabbit retina
J. Physiol. (London) 199:613

Cyster, C.W., Takahashi, E., Collewijn, H. (1972)
Direction-selective retinal ganglion cells and control of optokinetic nystagmus in the rabbit
Vision Rev. 12:183

Pasik, P., Pasik, T. (1964)
Oculomotor function in monkeys with lesions of the cerebrum and the superior colliculi.
Chap. 3 "The Oculomotor System", ed. M.B. Bender
Hoeber, New York

Perkel, D.H., Gerstein, G.L., Moore, P.G. (1967)
Neuronal Spike trains and stochastic point processes
Memorandum RM-4816-PR The Rand Corporation

Poggio, G.F., Viernstein, L.J. (1964)
Time series analysis of impulse sequences of thalamic sensory neurons.
J. Neurophysiol. 27:517

Pavlivis, T. (1964)
Analysis and synthesis of pulse frequency modulation feedback system
Ph.D. Thesis, Univ. of California. Berkely

Polyak, S.)1941)
"The Retina"
University of Chicago Press, Chicago, Ill.

Purkinje, J.E. (1825)
Beobachtungen und Versuche zur Physiologie der Sinne
2, 50-74 Berlin: G. Reimer

Rademaker, G.G.J., ter Braak, J.W.G. (1948)
On the central mechanism of some optical reactions
Brain 71, 48

Roberge, F.A., Nadeau, R.A. (1966)
Simulation of sinus node activity by an electronic relaxation oscillator.
Canadian J. Physiol. 44:301

Roberge, F.A., Nadeau, R.A. (1967)
The mechanism of synchronization between pacemakers.
Canadian Fed. of Biol. Soc. 10:143

Robinson, D.A. (1964)
The mechanics of human saccadic eye movements.
J. Physiol. (London) 174:245

Robinson, D.A. (1965)
The mechanics of human smooth pursuit eye movement
J. Physiol. (London) 180:569

Robinson, D.A. (1968)
The oculomotor control system: A review
IEEE Proc. 56:1032

Rodieck, R.W., Kiang N. Y-S., and Gerstein, G.L. (1962)
Some quantitative methods for the study of spontaneous activity of single neurons.
Biophysical Journal Vol. 2, p. 351

Roelofs, C.O. (1954)
Optokinetic Nystagmus
Docum. ophthal., Den Haag 7, 579

Savers, B. McA. (1970)
Inferring significance from biological signals, chapter 4
"Biomedical Engineering Systems", ed. Clynes and Milsum
McGraw-Hill

Schwarz, D. Fredrickson, J., Deecke, L. (1971)
Organization of the vestibular cortex in the rhesus monkey
Barany Society Meeting, Toronto

Spiegel, E.A. (1926) cited by Spiegel and Price, 1939
Arch. f.d. ges. Physiol. 215: p. 106

Spiegel, E.A., Price, J.B. (1939)
Origin of the quick component of labyrinthine nystagmus.
Arch. Otolaryng. Chicago 30: p. 576

Siegel, S. (1956)
"Nonparametric Statistics for Behavioral Sciences"
McGraw-Hill, New York

Spiegel, E. A. (1929), cited by Spiegel and Price, 1939
Z. Hals - Nas. - Ohrenheilk, 25:200

Smith, K. (1939)
The neural centers concerned in optic nystagmus
Am. J. Physiol. 126, 631

Smith, J.L., Cogan, D.G. (1960)
Optokinetic nystagmus in cerebral disease. A report of 14 autopsied cases.
Neurology 10:127

Smith, J.L. (1963)
"Optokinetic Nystagmus, its Uses in Topical Neuro-ophthalmological Diagnosis"
Charles C. Thomas

Stark, L. (1971)
The control system for versional eye movements
In "The Control of Eye Movements" ed Bach-y-Rita et al
Academic Press, New York

Szentagothai, J. (1950)
The elementary vestibulo-ocular reflex arc.
J. Neurophysiol. 13:395

Szentagothai, J. (1964)
Pathways and synaptic articulation patterns connecting vestibular receptors and oculomotor nuclei.
Chap. 8 "The Oculomotor System" ed. M.B. Bender
Hoeber, New York.

Vetzeboer, C.F.J. (1952)
Bilateral cortical hemianopsia and optokinetic nystagmus
Ophthalmologica 123, 187

Viernstein, L.J. and Grossman, R.J. (1961)
Neural discharge patterns in the transmission of sensory information.
Information Theory 4th London Symposium

Walsh, F.B., Hoyt, W.F. (1969)
"Clinical Neuro-ophthalmology" vol. one, 3rd edition.
Williams and Wilkins Co., Baltimore

Weiss, A., Tole, J. (1971)
Effects of galvanic vestibular stimulation on rotation testing
Barany Society Meeting, Toronto, Canada

Wilcock, M.E., Kirsner, R.L.G.
A digital data for biological data
Med. & biol. Eng. 7:653

Wilson, V.F., Toyne, M. (1970)
Retino-tectal and cortico-tectal projections in Macaca mulatta
Brain Res. 24.395

Wyszecki, G., Stiles, W.S. (1967)
"Colour Science"
John Wiley

Yarbus, A.I. (1967)
"Eye Movements and Vision"
Plenum Press, New York

Young, L.R., Stark, L. (1963)
A discrete model for eye tracking movements
IEEE Trans. Mil. Electr. MIL-7:113

Young, L.R. (1971)
Pursuit eye tracking movements
In "The Control of Eye Movements", ed. Bach-y-Rita et al
Academic Press, New York