A Signal Analysis Investigation

of

Brainstem Auditory Evoked Potentials

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ABSTRACT

The aim of the present study was to develop a fully objective method for assessing auditory threshold for the group of auditory brainstem potentials. A detailed signal analysis investigation was made and a number of methods for the objective determination of threshold evaluated.

A cross-correlation method was assessed first in a simulation study and subsequently in a group of normal hearing subjects. Cross-correlation coefficients were calculated between individual post-stimulus records and the coherent grand-average of the ensemble. The presence of a response embedded within the background E.E.G. produced a positive shift in the frequency distribution of ensemble correlations and this shift was reflected in the mean correlation value. While this statistic showed a systematic inverse relationship with stimulus intensity, intersubject variability was large and threshold using the method was, on average, 30 dB above that obtained with conventional visual scoring.

The limitations in the sensitivity of the correlation procedure prompted a more detailed signal analysis investigation. Amplitudes and phases of significant Fourier harmonics of individual responses were examined. For a wide range of stimulus intensities consistent aggregations were observed in the phases of individual harmonics of post-stimulus records. One measure of phase constraint, standard deviation, was found to be extremely sensitive and in a study of normal hearing subjects a high level of agreement was obtained between threshold determined using this objective method and visual scoring. Because of the sensitivity of the phase aggregation method it was decided to investigate whether the time domain patterning observed in the evoked brainstem response could best be accounted for in terms of either a superposition model or a synchronisation model. The findings of this study indicated that the behaviour of scalp recorded far field potentials were consistent with the superposition model. In a clinical trial of the method in a group of hearing impaired children and adults, a highly significant correlation, exceeding 0.9, was obtained between the objective method and visual scoring.

The results of these studies indicate that a reliable and fully objective estimation of auditory threshold can be provided by attending to the aggregations that occur in the phases of individual Fourier harmonics of the Brainstem Evoked Potentials in response to a sound stimulus.

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CONTENTS

CHAPTER 1

INTRODUCTION

CLINICAL BACKGROUND

The prevalence of deafness in pre-school children has been generally established to be between 0.5 and 1/1,000 (Budden et al., 1974). It is now widely accepted that deafness in infancy and early childhood can have major effects on language acquisition and on cognitive, emotional and social development. The importance of early rehabilitation, parent counselling and educational programmes for the pre-school child has been stressed (Wong and Shah, 1979). Delaying therapy until a child is 3 or more years' old often results in severe limitation of speech development, language acquisition and learning (Glorig and Curtis, 1976; Zink, 1976). Implicit within any programme of rehabilitation of the deaf infant is the early diagnosis of hearing loss. In the light of these facts it is obvious that the diagnosis of hearing impairment should be made as near birth as possible. At present the timing of diagnosis depends on each of the following:

(i) Parental suspicion that the child's communication or speech is not developing normally.

(ii) Conformation of these suspicions by general practitioner and consideration being given to the possibility of hearing impairment to account for such delays.

(iii) Identification of hearing loss in the Audiology Clinic.

Each of these processes can contribute variable delays in individual cases. In a recent survey of deaf children only 10% of parents suspected hearing impairment in their children before the age of one year, and even by the age of 3 years only 50% of parents had suspected hearing impairment in their children (Seid et al., 1979). Second the difficulties of early diagnosis in pre-school age and pre-lingual children often add additional delays (Seid et al., 1979; McClelland, Lyness and McCrea, 1979; Wong and Shah, 1979). In a recent survey of 8 year old children throughout the European Community the average age at diagnosis was 3 years' of age (Martin, 1979).

For these reasons recommendations have been made for the early screening of children at risk of hearing impairment within the perinatal period. In addition to the formation of a high risk register various methods of screening have been suggested (Feinmesser and Tell, 1976; Recommendations of the Nova Scotia Conference on the early diagnosis of hearing loss, 1976). The difficulties and limitations of conventional audiometry and behavioural tests of hearing has prompted the search for more objective methods of assessing auditory function in infants and young children.

DEVELOPMENT OF EVOKED POTENTIAL AUDIOMETRY

Two main kinds of brain electrical activity can be recorded from the surface of the human scalp, the spontaneous rhythms of the electroencephalogram (E.E.G.) and potentials related to definable events (E.P.). The best known type of event-related potential is the sensory response evoked by an exteranl stimulus. E.E.G. recording may be obtained in a relatively direct manner by amplifying and displaying the activity picked up by electrodes placed on the scalp, but most E.P. activity can be displayed only after application of special averaging methods to the E.E.G. This is because the E.P. activity is generally embedded in E.E.G. activity of greater amplitude than the E.P. (Shagass, 1976).

The first observations of brain electrical activity were made on the exposed brains of rabbits and monkeys by Caton, in 1875. It was not until 1929 however, that the electrical activity of the human brain was recorded non-invasively using electrodes placed on the skull (Berger, 1929). The neural origins of this activity were confirmed in 1934 by Adrian and Matthews. The earliest form of electric response audiometry in humans, excluding electrodermal reactions, was based on alterations in the pattern of the on-going electroencephalogram. The alterations included "blocking" of the alpha rhythm, alterations associated with changes in the depth of sleep, or the appearance of the "K-complex". The K-complex is a non-specific response to almost any sudden sensory stimulus given during a particular stage of sleep. Some of these reactions are very clear when they do occur, but they do not always occur.

The first identification of auditory evoked potentials in the human extracranial electroencephalogram in the waking state was by P.A. Davis in 1939. In some subjects responses were detected to auditory stimuli. Bi-polar recordings from electrodes placed at the vertex and a reference electrode at or near the ear gave the largest responses and this led to the designation of these evoked potentials as "vertex potentials". The responses were small, however, and the signal-to-noise ratio was usually so unfavourable that they were practically neglected until after the introduction of the method of signal averaging (Dawson, 1954).

Geisler, Frishkopf and Rosenblith (1958) were the first to apply averaging to auditory evoked potentials. Using electrodes applied to the surface of the scalp responses were observed with latencies of 8 to 30 ms and they were considered to be neurogenic in origin. It was later shown by Bickford and his associates (1964) that their source was in fact myogenic. These potentials are now referred to as the Post-Auricular Response.

Williams and Graham (1963) reported a response to auditory stimuli with a duration of 250 ms. These "slow" auditory evoked potentials have been shown to originate from within the cortex, and confirmed the responses originally described by Davis in 1939.

Yoshie, Ohashi, and Suzuki (1967) recorded early potentials during the first 10 ms post-stimulus from an electrode placed in the external auditory meatus. Portman, Le Bert and Aran (1967) obtained VIII nerve action potentials from a needle electrode which pierced the tympanic membrane and with the tip placed on the bony promontary.

Using the earlobe as an electrode position Sohmer and Feinmesser (1967) recorded the first brainstem potentials. The VIII nerve action potentials recorded were much smaller (0.1 to 0.5 µV) than those obtained using the promontary electrode position (10 to 30 µV). However, they did obtain a multiwave complex, each component of this attributed to different levels of the ascending auditory pathways. Jewett, Romano and Williston (1970) confirmed the sources of the brainstem auditory evoked potentials and it was shown by Jewitt and Williston (1971) that they could be recorded from a wide area of the scalp. These potentials and the others which have been described by various investigators were classified by Davis (1976) using a system based primarily on latency (Table 1)

Class	Probable Source	Response	Latency (ms)
First	Organ of Corti	(Cochlear microphenic) (Summation potential)	0
	Auditory nerve	Action potential (VIII)	1-4
Fast	Auditory nerve Brainstem	I II-VI	2-12
Middle	Neurogenic (cortex) Myogenic	 PAM	12-50
Slow	Cortex II (waking) Cortex III (asleep)		50-300 200-800
Late	Cortex IV	CNV	250-600 (DC shift)

TABLE 1: Classification of auditory evoked potentials (Modified from Davis, 1976).

The brainstem auditory evoked potentials appear to be volume conducted to the surface of the scalp the electrodes recording them as far-field sources. On the basis of cat recordings (Jewitt, 1970; Lev and Sohmer, 1972; Buchwald and Huang, 1975), primary generators of the first five brainstem evoked potentials (wave complexes) have been suggested as shown in Table 2.

Brainstem Wave Complex	Primary Generator
I	Acoustic VIII nerve
II	Cochlear nucleus
III	Neurons of the superior olivary complex activated by projections crossing the mid-line.
IV	Neurons of the ventral nucleus of the lateral lemniscus and pre-olivary region activated equally by crossed and uncrossed projections
V	Neurons of the inferior colliculus activated primarily be crossed projections

TABLE 2: Suggested Primary Generators of the First Five Auditory Evoked Brainstem Wave Complexes, (Modified from Buchwald and Huang, 1975).

Since then there has been much discussion as to the sources or generators of these waves. Evidence that there is at least a spatial ascending arrangement of generators which parallels the temporal arrangement of the waveforms has been provided by a number of observations. Firstly, in normal adults the interval between waves I and V is approximately 4 ms and has been considered to be a function of brainstem conduction time (Starr and Achor, 1975). This is the time interval between the response entering the brainstem and reaching the level of the inferior colliculus. In premature infants the I-V interval is long and shortens gradually as the child gets older (Hecox and Galambos, 1974; Schulman-Galambos and Galambos, 1975; Beagley and Sheldrake, 1978; Rowe, 1978; McClelland and Houston, 1980). The reduction in I-V interval with maturity parallels myelination and increased synaptic efficiency in the brainstem (Hecox, 1975). This observed shortening of the I-V interval correlating with known changes in brainstem conduction, is evidence to support a spatial arrangement of response generators. A second piece of evidence to support this concept is provided by the latency differences between males and females (McClelland, Houston, 1980). These authors correlated observed latency differences between males and females with predicted differences in neuronal length, based on head diameter measurements. They postulated that the larger head diameter of the male as compared with the female refelcted a longer neuronal pathway in the male and hence a larger I-V interval. Again, the correlation which exists between predicted neuronal length and I-V interval is evidence for a spatial arrangement of generators.

Most of the early evidence for this arrangement of generators, as first postulated by Jewett (1970) in his ascending nuclear concept, came from work involving either sterotactically controlled recording or the production of surgical lesions at various levels in the brainstems of experimental animals (Lev and Sohmer, 1972; Buchwald and Huang, 1975; Starr and Achor, 1975). More recently, similar studies have thrown doubt on the validity of assigning waves to specific generator sites. Using the cat as an experimental model, Starr and Achor (1978) demonstrated that some of the waves reflected activity originating in at least six brainstem sites. They also showed that discreet lesions produced in inferior colliculus, lateral lemniscus and dorsal cochlear nucleus produced no change in the recorded brainstem potentials in the cat, suggesting that these sites did not contribute to the response.

All of these studies involving the production of surgical lesions are open to the criticism that it is imposssible to control accurately the size, site or effectiveness of the lesion. Comparisons of the effects produced by similar lesions are, therefore, often difficult. Starr and Achor also correlated changes in the human brainstem potentials with the anatomical distribution of the pathological processes in patients who subsequently died. They pointed out that human brainstem lesions had to be relatively large before they are diagnosed and so have widespread effects on brainstem functions due to pressure or vascular changes. For this reason, attempts at identifying specific generator sites by correlating changes in potentials with pathology have been conflicting. Starr and Achor pointed out, however, that there was good evidence to suggest that wave I does originate outside the brainstem. Mair, Elverland and Laukli (1979) cast further doubt on the ascending nuclear level concept. In a discussion of the effects on the brainstem potentials of changing the rate of stimulation, they reached the conclusion that the different brainstem potentials do not have spatially restricted generators. They further suggested that the electrical changes at the cochlear nerve and nucleus contribute to the later responses and that the individual waves represented polysynaptic activity from more than one level of the auditory pathway.

McClelland, McAllister and Armstrong (1980) suggested that the main features of the Brainstem Auditory Evoked potentials are produced by the highly synchronised and unidirectional axons of the auditory pathway rather than the diffusely orientated synaptic events at nuclei. They outlined a dipole model to explain the origins of the potentials postulating that the potentials represent the discharge of many neurones occurring in synchrony. This provides an advancing wave of depolarisation which can be considered as the movement of a simple dipole recordable by scalp electrodes.

Although controversy exists as to the precise origins of these early potentials, the balance of evidence suggests that waves I, III and V at least, are time markers which represent activity at ascending levels in the auditory pathway (Galambos, 1980).

In order that the auditory brainstem potentials may be of use in audiological evaluation at least two requirements should be met. First parameters of the response should show a clear preferably linear relationship with stimulus intensity. Second both intrasubject and intersubject variabilities should be small. The first of these requirements have been well met by response latency and amplitude or power (Picton et al., 1974). Intrasubject variability of response latency is much less than amplitude variability due largely to the effects of background E.E.G. and E.M.G. nosie (Thornton, 1975). Intersubject variability of response latency can be reduced to clinically acceptable levels by controlling for the effects of age and gender (Hecox and Galambos, 1974; McClelland and McCrea, 1978; McClelland and Houston, 1980). Latency measures are of value in diagnosis of retrocochlear pathology and in conductive hearing loss (Salters and Brackmann, 1977; Starr and Hamilton, 1976). However, because of the variable relationship between response latency and stimulus intensity in neurosensory deafness, latency measures in the audiological assessment of this important clinical group is greatly reduced. The great majority of young children with moderate and severe hearing impairment in western society have neurosensory deafness (Martin, 1979).

For this reason interest has remained with at least one aspect of response amplitude or power - namely threhold. The problems of intrajudge and interjudge reliability in threhold estimation has been demonstrated from studies of the late cortical evoked potentials

(Rose et al., 1971). Because of the low signal to noise ratio and the extreme variability of noise behaviour the problem of accurate threshold estimation exists for the early brainstem evoked potentials. The difficulties encountered with conventional visual inspection of records particularly in the region of threshold has prompted the search for a fully objective method of E.R.A. where the presence or absence of an evoked potential is decided without the subjective intervention of a tester (Schimmel et al., 1974). Several methods of been studied for the late cortical evoked potential. One of the earliest was based on signal power in the averaged post-stimulus records. This achieved only limited success and a more recent investigation has shown serious shortcomings in the use of signal power as an indication (Ross, 1979). A method based on pattern recognition and derived from studies of the phase sepctrum of lower harmonics of the post-stimulus E.E.G. has been shown to be both practicable and valid (Beagley, Sayers and Ross, 1979).

AIMS OF THE PRESENT STUDY

The aim of the present study was to develop a fully objective method for the detection and analysis of the far-field brainstem auditory evoked potentials. If successful an objective method should be of assistance to the audiologist in the hearing assessment of young children. Further, it is proposed that such an ojbective method would considerably enhance the development of hearing screening for neonates at risk of deafness.

Chapter 2

Methods

NORMAL HEARING GROUP

Fourteen male and twenty female subjects, ranging from 9 to 34 years of age, were studied. All had normal hearing, and none had previous history of ear disease, or neurological disorder.

Hearing was tested using the Hughson and Westlake method in an acoustic booth. A Peters AP5 audiometer was used and the hearing of all subjects was 10 dB (I.S.O.) or better, over the audiometric frequencies of 500 Hz. to 4,000 Hz.

The subjects' thresholds to 80 μs clicks were determined using an Amplaid Mark III audiometer, with respect to a biological callibration of threshold using a jury of normal hearing subjects (0 dBnHL). They were tested in a sound-proofed room. The click threshold was defined as the lowest intensity level at which responses were obtained in at least two out of four ascending trials.

HEARING IMPAIRED GROUP

A total of 37 hearing impaired patients were tested. Sixteen were males and 20 females and their ages ranged from 2 months to 42 years. Only four were less than one year at time of E.R.A. testing, 16 were between one and 3 years' of age and 8 were older than 9 years. Mild sedation was used in 26 patients to reduce unwanted muscle artifact.

	No Sedation	Diazepam (Valium) .25mg/kg	Trimeprazine (Vallergan) 2mg/kg
Children under 6	6	0	22
6 and over	5	4	1
Total	11	4	23

EVOKED POTENTIAL GENERATION AND DATA ACQUISITON

An Amplaid Mark III audiometer provided 20 us clicks through one side of TDH 39 headphones (Figure 2.1). The headphone response to this click input is shown in Figure 2.2. The frequency response was essentially flat, from 200 Hz. to 5,000 Hz. with a small peak at 3,500 Hz. (Figure 2.3).

After cleaning the scalp with industrial spirit three silver/silver chloride disc electrodes were attached to the subject's scalp. One electrode was placed at FPz (pre-frontal), one was placed on the mastoid of the ear being tested, and an earth electrode was placed on

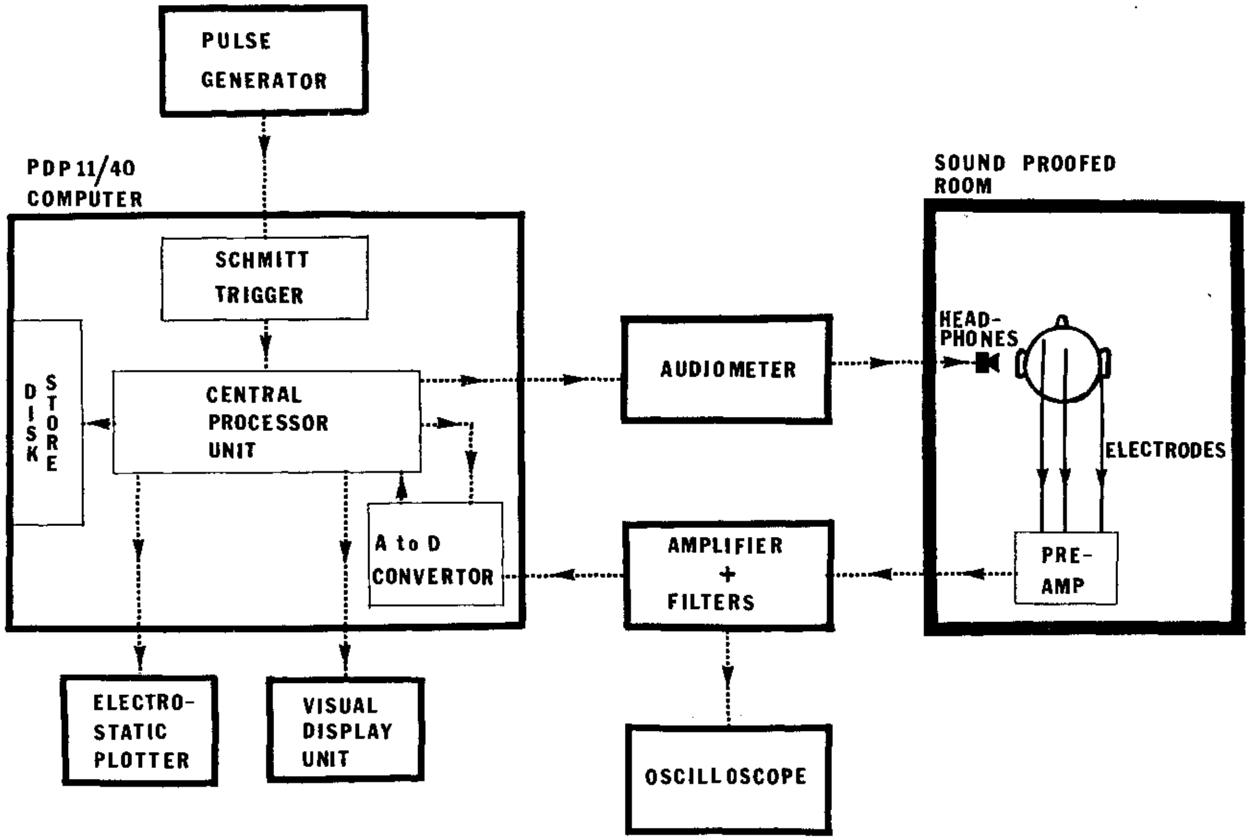
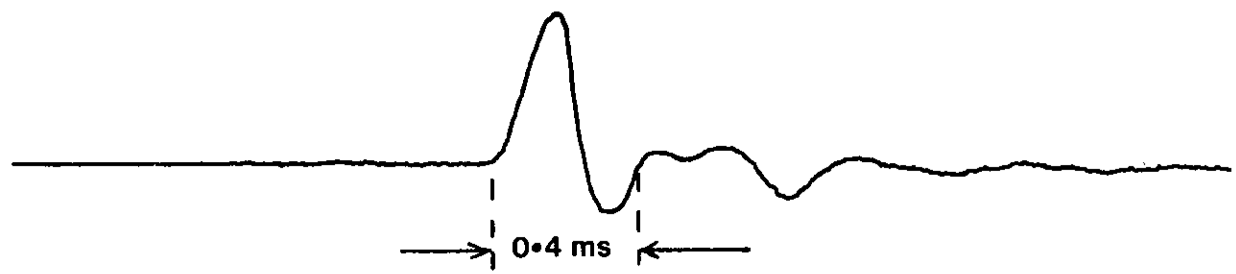


FIGURE 2.1: Block diagram of recording system.



HEADPHONE RESPONSE TO 80μs CLICK

FIGURE 2.2

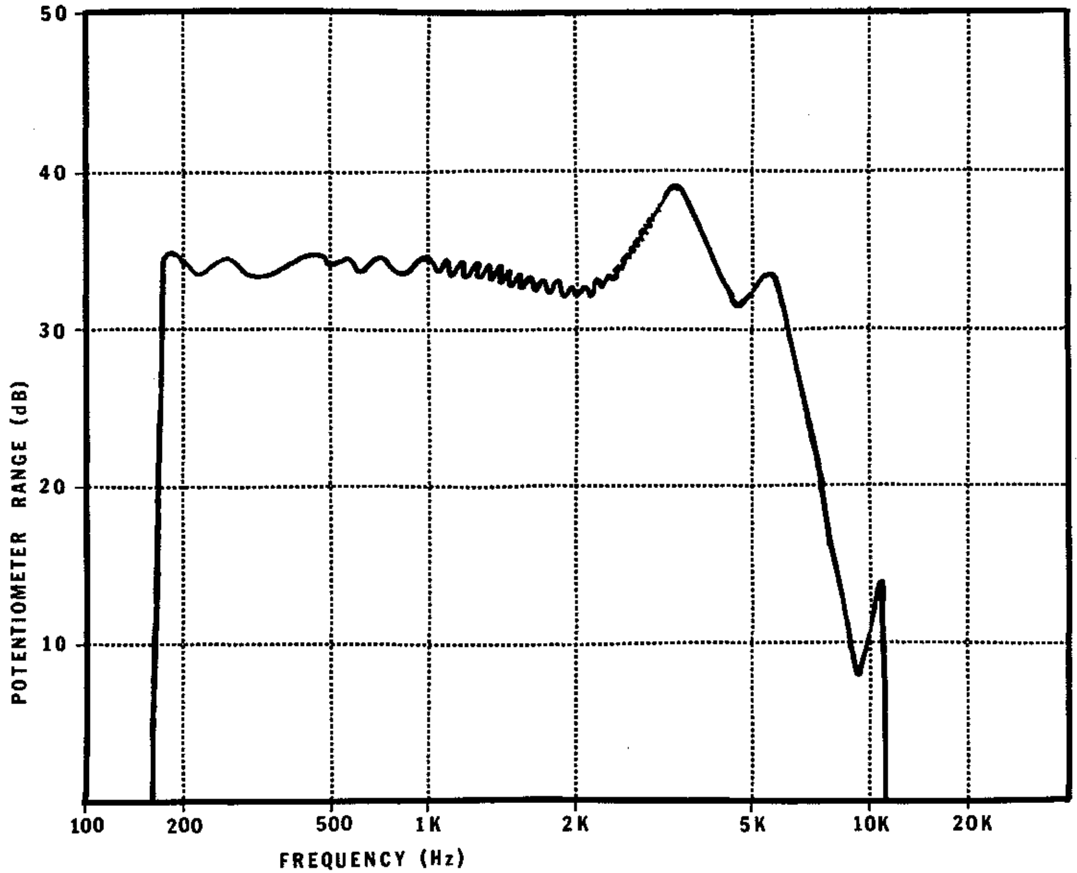


FIGURE 2.3: Frequency response of TDH 39 headphones to 70 dBnHL µs pulse.

the forehead. Electrode gel was inserted into each electrode cup using a stainless steel hypodermic needle. This blunt needle was also used to abraid the skin, so lowering its impedance to < 2 kohms.

A pulse generator (Farnell FG1) presented pulses via a Schmitt trigger to the central processing unit of a PDP 11/40 computer which triggered the A to D convertor, and 10 ms later triggered the audiometer. This enabled 10 ms of pre-stimulus and post-stimulus E.E.G. to be collected with a smapling rate of 12.8 kHz. The triggering rate varied randomly from 7 to 20 pulses per second with an average of 10 pulses per second.

Subjects lay on a couch in a sound-proofed room. A period of relaxation helped reduce muscle artifact. Clicks were presented through the headphones at 70 dB (nHL). Bipolar recordings (pre-frontal to Ipsilateral mastoid) were amplified (X 50,000), filtered (with a band-width of 80 Hz to 3,200 Hz), and fed to the analogue to digital convertor of the computer. A total of either 1,024 or 2,048 sweeps were collected and the grand-average was displayed. On-line decisions were made as to the presence or absence of a response. If a response was detected the stimulus intensity was reduced by 10 dB and another averaged response obtained. This was repeated until sub-threshold conditions were reached, that is no response was observed. All responses were stored on disc for more detailed analysis off-line. One ear only was tested in each subject.

An off-line evaluation of thresholds was made jointly by two experienced observers (H.G.H. and R.J.McC.) and three criteria were chosen to establish the presence of a response:

(i) The A.C. power of the post-stimulus E.E.G. was larger than the pre-stimulus trace.

(ii) The two sub-averages should show significant overlap of the main features of the post-stimulus E.E.G. but no such constraints should be apparent in the pre-stimulus period.

(iii) A pattern of increasing latency and decreasing amplitude of the main features with reductions in stimulus intensity should be observed in the ensemble of grand-averages.

GUINEA PIG RECORDINGS

Responses were studied in 5 guinea-pigs (Cavia porcellus). These were mixed strain adults of average weight 519g (range 350g-720g). Before testing each animal was sedated using Pentobarbitone (Sagital)

0.4ml/kg given by intraperitoneal injection. Bipolar recordings were obtained from electrodes placed on the vertex and cervical regions. Each guinea-pig was placed in the prone position and draped to maintain body heat. Room temperature was maintained at 37-38^{o}C. Click stimuli were delivered to a TDH 39 headphone placed 150mm in front of the guinea-pig, resulting in binaural stimulation. The frequency spectra of the free-field stimulus has been plotted in Figure 2.4. The method of data acquisition was identical to that described below for human subjects. Two ensembles, each of 16 sweeps, were collected at each stimulus level. Responses were recorded for the range of intensities 90 dBnHL to 0 dBnHL in 10 dB increments.

BACKGROUND TO SIGNAL ANALYSIS PROCEDURES

Recordings of the E.E.G. in the interval of interest (10 ms) following the presentation of an auditory stimulus can be considered to consist of two components:

(i) Stimulus-evoked activity of the brain (signal),

(ii) Other activity of brain or muscle origin unrelated to stimulus (noise).

Due to the small signal to noise ratio it is generally not possible to see individual responses in the post-stimulus E.E.G. and for this reason methods have been developed to separate the stimulus-evoked activity from the background noise. Averaging is such a procedure and to date the majority of information derived from studies of the brainstem auditory evoked response has been based on observations made on the average of many individual responses. However, inferences about the properties of the underlying individual responses derived from the average is only justified if certain conditions approximately hold:

(i) The signal and noise linearly sum together to produce the recorded waveform.

(ii) The evoked signal waveshape is the same for each repetition of the stimulus.

(iii) The noise contributions can be considered to constitute the statistically independent samples of a random process, uncorrelated with the response.

The averaging procedure consists of adding together the set of recorded responses associated with each stimulus presentation. If the common signal waveform is synchronised with the stimulus while the noise waveforms are asynchronous, the signal will sum in direct proportion to the number of stimuli while the net noise waveform

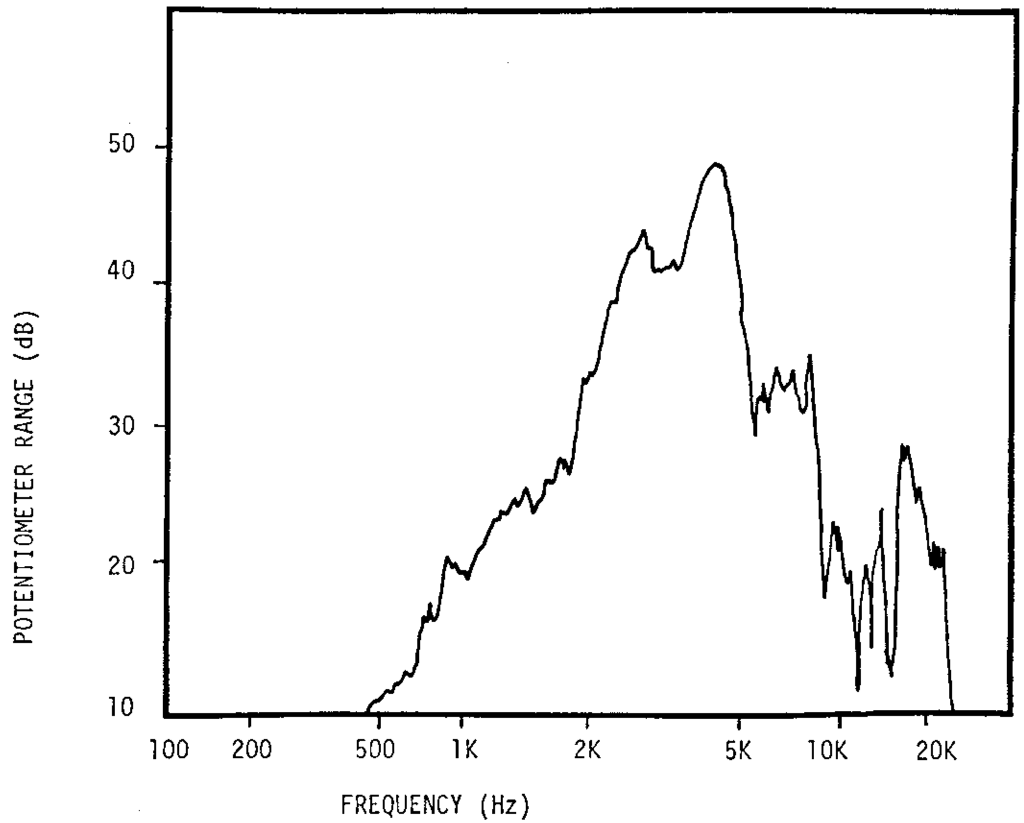


FIGURE 2.4: Free-field frequency characteristics of TDH 39 headphone at 150 mm.

will increase less rapidly due to cancellation effects. The average is formed by dividing the sum of total response waveforms by the number of stimuli presented. Stated more formally let each recorded waveform be denoted by:

$$x_i(t) = S(t) + n_i(t) \qquad ;i = 1,2, \ldots N;\ o<t<T$$

Where N is the number of stimuli, $x_i(t)$ the response to the ith-stimulus, S(t) signal, $n_i(t)$ the noise during the interval associated with the ith-stimulus, T the duration of the time epoch over which each waveform is recorded. The average evoked response is denoted by X (t), where

$$X(t) = \frac{1}{N} \sum_{i=1}^{N} x_i(t) = S(t) + \frac{1}{N} \sum_{i=1}^{N} n_i(t) \qquad \text{-------(1)}$$

Equation (1), a complete description of the averaging procedure , indicates that the quality of the estimator X(t) depends upon the relative magnitude of S(t) and the average of the noise waveforms. Assuming independence of noise smaples the expected value of $n_i(t)$ will be zero. Thus the expected value of X(t) is:

$$E\left[X(t)\right] = E\left[\frac{1}{N} \sum_{i=1}^{N} x_i(t)\right]$$

$$= S(t) + \frac{1}{N} \sum_{i=1}^{N} E\left[n_i(t)\right]$$

$$= S(t) + 0$$

$$E\left[X(t)\right] = S(t) \qquad \text{----------(2)}$$

Equation (2) indicates that the averaging procedure is an unbiased estimator of the evoked signal. However, it does not state how effectively the noise is attenuated for a given number of stimulus repetitions. Calculation of the standard deviation of the average provides an estimate of the expected magnitude of the noise residual.

$$(SE)^2 = E\left[X(t) - S(t)^2\right]^2$$

$$= E\left[\frac{1}{N} \sum_{i=1}^{N} n_i(t)^2\right]^2 = \frac{1}{N^2} \sum_{i=1}^{N} \sum_{j=1}^{N} E\left[n_i(t) n_j(t)\right]$$

$$= \frac{1}{N^2} \sum_{i=1}^{N} E\ n_i^2(t)$$

$$= \frac{1}{N^2} N.Var. \text{ (where Var. = Variance of Noise)}$$

$$\text{Thus } SE = (Var / N)^{\frac{1}{2}} \qquad \text{-----------------(3)}$$

The essential assumptions in the foregoing are that the evoked signal waveforms are identical for all stimuli and that the noise waveforms are uncorrelated stationary random variables. If the noise is not uncorrelated then equation (3), the standard error, may not be valid. If the signals are not identical then neither equation (1), the expected sample average, nor equation (3) are valid.

An important alternative to methods based on the more traditional time domain measures are methods based on the frequency spectrum. A continuous variable can be represented by a more or less repetitive waveform. According to Fourier (Stuart, 1961) a repetitive waveform can be synthesised by adding together a set of cosinusoidal waveforms of different frequencies, namely the fundamental repetition frequency and its harmonics, whose amplitudes and relative phases are uniquely determined by the original waveform. Stated mathematically a function of time f(t) of repetition frequency f_o is described by:

$$f(t) = \frac{a_o}{2} + a_1\cos(2\pi(f_o)t + \phi_1) + a_2\cos(2\pi(2f_o)t + \phi_2) + a_n\cos(2\pi(nf_o)t + \phi_n) + \ldots$$

where $\frac{a_o}{2}$ is a zero frequency term (that is a constant),

a_n is the coefficient determing the size of the nth harmonic frequency component, and ϕ_n is its phase angle at t = 0.

Throughout the present investigation of human brainstem potentials 10 ms epochs of data were selected for study. Before F.F.T. a Hanning window was applied to the first and last 13 points (10%) of the 128 point average. In the case of the Guinea-Pig Study and because of the much shorter duration of the response, 5 ms epochs were selected.

CHAPTER 3

EVALUATION OF THE CROSS-CORRELATION METHOD FOR THE OBJECTIVE DETECTION OF AUDITORY THRESHOLD FOR AUDITORY BRAINSTEM POTENTIALS

INTRODUCTION

Template matching techniques assume a similar pattern to be present in the reference waveform to that in the signal being studied. The cross-correlation co-efficient, r, may be used to quantify the degree of similarity between these two waveforms provided this dependence is linear in nature. Figure 3.1 illustrates the application of the method. Here the correlation co-efficient between two high level coherent averages have been calculated for each of 4 normal hearing subjects. The plots show two superimposed grand-averages each consisting of 512 sweeps for each subject. A high degree of overlap in the waveform characteristics for the post-stimulus E.E.G. can be seen. This was reflected in the high correlations obtained between the two waveforms. If X_i are the sample values of the template, and Y_i the samples from the waveform to be compared, then the cross-correlation co-efficient is given by:

$$r = \sum_{i=1}^{N} \frac{(X_i-\bar{X})\ (Y_i-\bar{Y})}{S_x S_y}$$

where $\bar{X}$ and $\bar{Y}$ are within sample means of X and Y respectively, and S_x and S_y are their respective standard deviations. Theoretically r can take any value from -1 to +1, the higher the value of r, the greater the similarity between x and y. The choice of a suitable template is critical and generally some prior knowledge of the pattern to be detected must first be available. In selecting a template consideration needed to be given to all known sources of variability. At the outset of this study several choices of reference waveform were available. For example, a template may have been modelled on a typical coherent grand-average. However, the well-recognised high intersubject variability in response pattern was reason against such a choice. An alternative was to use the coherent grand-average obtained with a high intensity stimulus as a template to investigate responses at lower levels. However marked differences in the pattern of the coherent grand-average have been observed at different stimulus intensities (Figure 3.13) and this was also reflected in the frequency spectra (Figure 3.18). For these reasons the coherent grand-average obtained at the stimulus level being investigated was selected as the most appropriate template to study individual responses. The correlation co-efficients between individual ensemble members and the coherent average were calculated and the mean for the ensemble ($\bar{r}$) established.

THRESHOLD CRITERIA

A major issue in the use of the correlation technqiue was to decide what level of positive value of $\bar{r}$ indicated that a response was

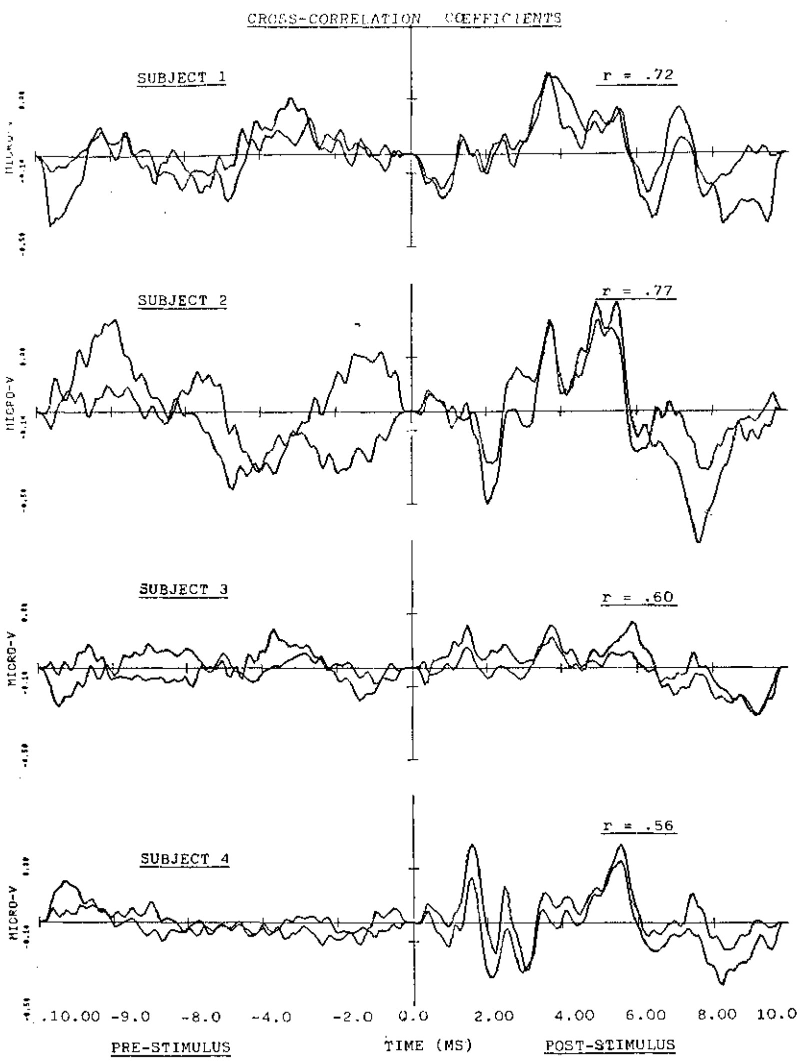


FIGURE 3.1: In 4 normal hearing subjects 2 high level coherent grand-averages each consisting of 512 individual sweeps have been plotted. The cross-correlation coefficients for the 10 m.sec. intervals post-stimulus have been included.

present and how much confidence to attach to the result. For this reason it was decided to study first the behaviour of unstimulated E.E.G. to determine the statistical behaviour of r for "no response" conditions. If on average X and Y have no linear relationship with one another, as one would expect for unstimulated E.E.G., the expected value of r, $\bar{r}$, should be zero.

Assuming that sub-threshold post-stimulus conditions closely approximated to unstimulated conditions it was possible to arrive at a statistical definition of threshold by examining the behaviour of unstimulated E.E.G. To this end the pre-stimulus records from 4 normal hearing subjects were evaluated. From each subject 2,048 individual sweeps, each of 10 m.sec. duration, were collected and the correlations between each pre-stimulus grand-average and the individual sweeps calculated. The frequency distributions of the correlation coefficients have been plotted in Figure 3.2 and the pooled correlation distribution from all 4 subjects plotted in Figure 3.3. As expected the average correlation for each subject approximated to zero (-.014, -.031, -.062, -.020). However, individual correlations ranged from -.89 to +.86 and associated with this the standard deviation was quite large for the total population of 8,192 observations, .367. The standard deviation for each subject was also large (.389, .272, .339, .444). The histogram of frequency distribution gave an estimate of the probability density function of r and was approximately normally distributed. As the aim was to differentiate between "no response" and "response" conditions only the positive tail of the distribution needed to be considered and the confidence intervals established for the one tailed situation. Assuming the probability density function was Guassian then the confidence interval for r was defined in the following way;

$$r_c = \bar{r} + t \times S.E.$$

where t was taken from a table of normal variables

S.E. (Standard Error) = $S.D./\sqrt{N}$

and N was the size of the ensemble.

In the above ensemble of 8,192 sweeps the 1% probability level of r for the one tailed situation was;

$$\bar{r} + 2.326 \times S.D./\sqrt{N} = -.032 + 2.326 \times .367/\sqrt{8192}$$
$$= -.023$$

In this situation the 1% confidence level for r was close to zero. However, it was impractical to consider using ensembles consisting of 8,192 sweeps, or even 2,048 sweeps, because of the

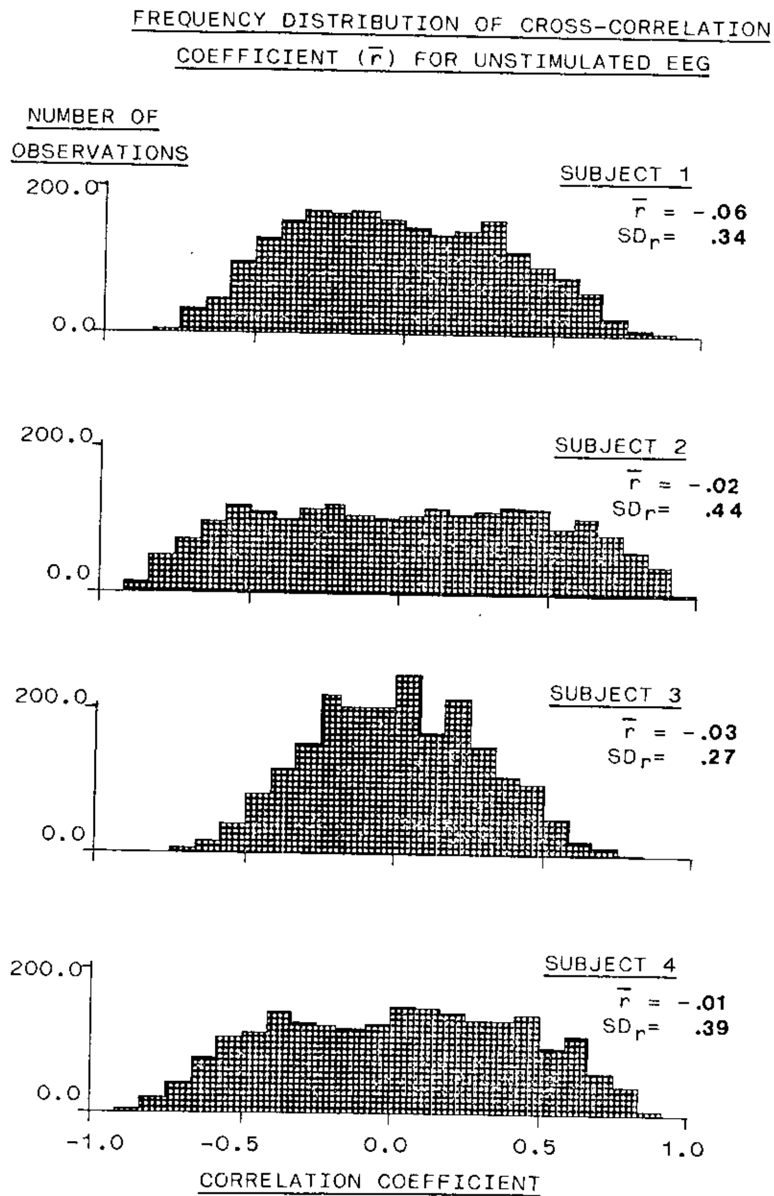


FIGURE 3.2: Frequency distributions of individual cross-correlation coefficients for the pre-stimulus (unstimulated) intervals in 4 normal hearing subjects.

FREQUENCY DISTRIBUTION OF

CROSS-CORRELATION COEFFICIENT (r) FOR POOLED DATA

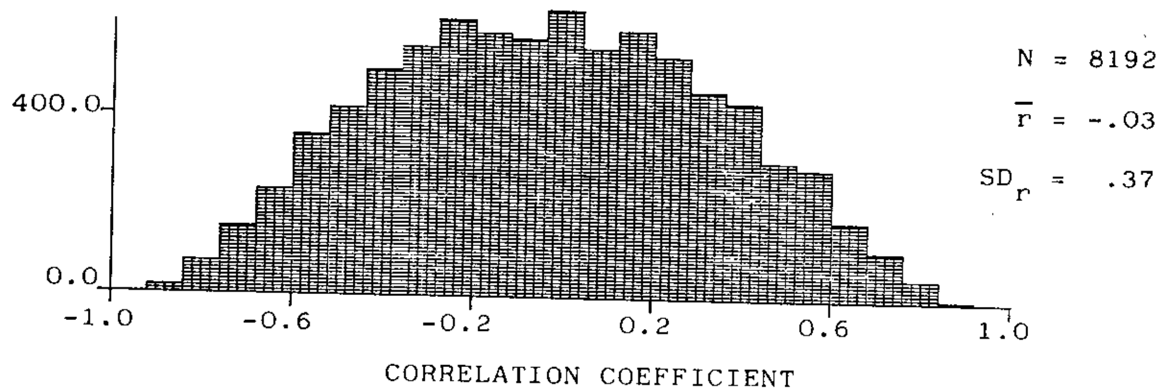


FIGURE 3.3:

volume of data and the time taken to calculate correlations for such large ensembles. Ensembles in the range of 16-64 sweeps were considered to be a compromise between efficiency and the requirements of sampling statistics. The effects of ensemble size upon the confidence intervals of r associated with any specific probability level had therefore to be evaluated. Further it had been assumed that the underlying probability density function of r was normally distributed. Using the Kolomogorov Smirnov Test the frequency distribution of r observed for the 8,192 observations was found to be significantly different from Gaussian ($D = .031$, $p < .01$). So further caution needed to be attached to precise values of the confidence interval.

CONFIDENCE INTERVALS ASSOCIATED WITH 1% PROBABILITY LEVEL

NO. OF OBSERVATIONS	THEORETICAL CONFIDENCE INTERVAL	OBSERVED CONFIDENCE INTERVAL
8	.38	.41
16	.24	.32
32	.16	.26
64	.11	.19

TABLE 1

Average correlations, $\bar{r}$, were calculated for ensembles of different sizes, ranging from 1 to 64, using the pre-stimulus E.E.G. from the same 4 subjects. A total of 330 observations were made and for each ensemble average correlations were calculated for 1, 2, 4, 8, 16, 32 and 64 sweeps. The frequency distributions of $\bar{r}$ were then plotted (Figure 3.4). The distribution of $\bar{r}$ for single sweeps was very similar to that for the entire population (Figure 3.3). The mean obtained for the 330 observations of single sweeps was .013 and the standard deviation .395. Both these results were very close to the first 2 moments of the larger population ($\bar{r}$ = -0.32, S.D. = .367). As can be seen the main effects of increasing ensemble size on the frequency distributions of $\bar{r}$ was a decrease in the spread of values and this was reflected in the second moment of the distribution. A second effect was that the distribution became more normally distributed and reflected in the value of "D" in the Kolomogorov Smirnov Test (for single sweep D = .032, for 64 sweeps D = .023). This latter feature might have been predicted from the Central Limit

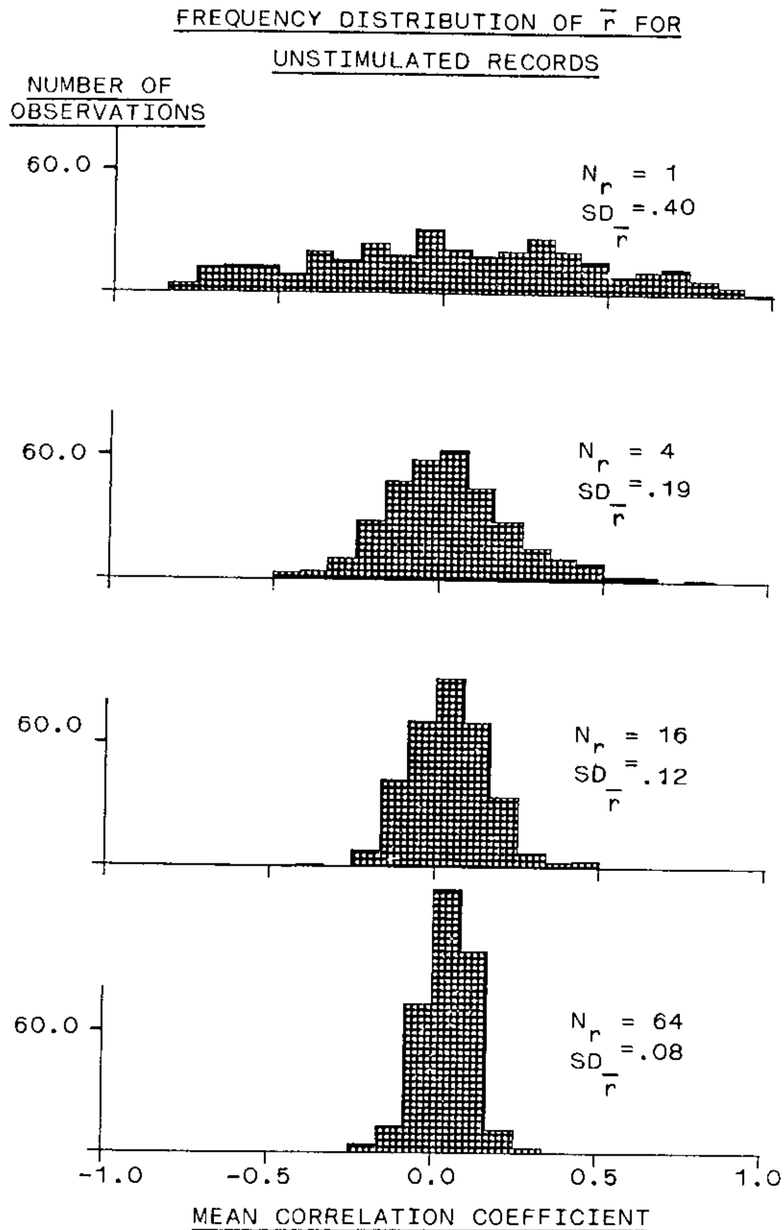


FIGURE 3.4: Frequency distribution of ensemble mean cross-correlation coefficient, $\bar{r}$, for unstimulated records showing the effects of ensemble size on the frequency distribution

Theorem. The average value remained essentially unchanged throughout at 0.0. The 1% level from these observed distributions have been compared in Table 1 with those predicted from the estimated probability density function of Figure 3.3. The 1% confidence interval, $\bar{r}_c$, depended critically on sample size, smallest $\bar{r}_c$ values being associated with the largest sample size used to generate $\bar{r}$. In addition these observed levels of S.D. and confidence tended in all cases to be slightly larger than the theoretical estimates, the discrepancy between observed and theoretical being greatest for the largest sample size. The discrepancies between observed and theoretical values were probably attributable to inaccuracies in the theoretical estimates due to the non-Guassian nature of the underlying frequency distribution which in turn may in part have resulted from non-stationarities in the underlying signal. For this reason the <u>observed</u> confidence intervals have been used as threshold estimates in subsequent experiments.

With these observations in mind the cross-correlations for the 2 high level averages of Figure 3.1 were re-examined comparing pre-stimulus and post-stimulus correlations (Figure 3.5). The following values of r were obtained;

	SUBJECTS			
	1	2	3	4
Pre-stimulus	.61	.12	.45	-.06
Post-stimulus	.72	.77	.60	.56

While higher values were consistently obtained for corresponding post-stimulus intervals a wide range of pre-stimulus values were observed. Such highly variable behaviour would be expected from the observed dependency of $\bar{r}$ on ensemble size. In the above example the ensemble size used to generate $\bar{r}$ was one. The cross-correlation functions of pre-stimulus and post-stimulus intervals have been plotted in Figure 3.6, and again the highly variable behaviour of the pre-stimulus functions can be seen.

<u>SIMULATION STUDY</u>

With knowledge of the statistical behaviour of the correlation coefficient for the unstimulated condition, it was now possible to examine formally the sensitivity of the method for detecting evoked potentials. It has generally been assumed that the volume conducted far field potentials of the auditory brainstem response are added to the on-going background E.E.G. activity. The assumptions underlying such a superposition hypothesis have been evaluated in a later study.

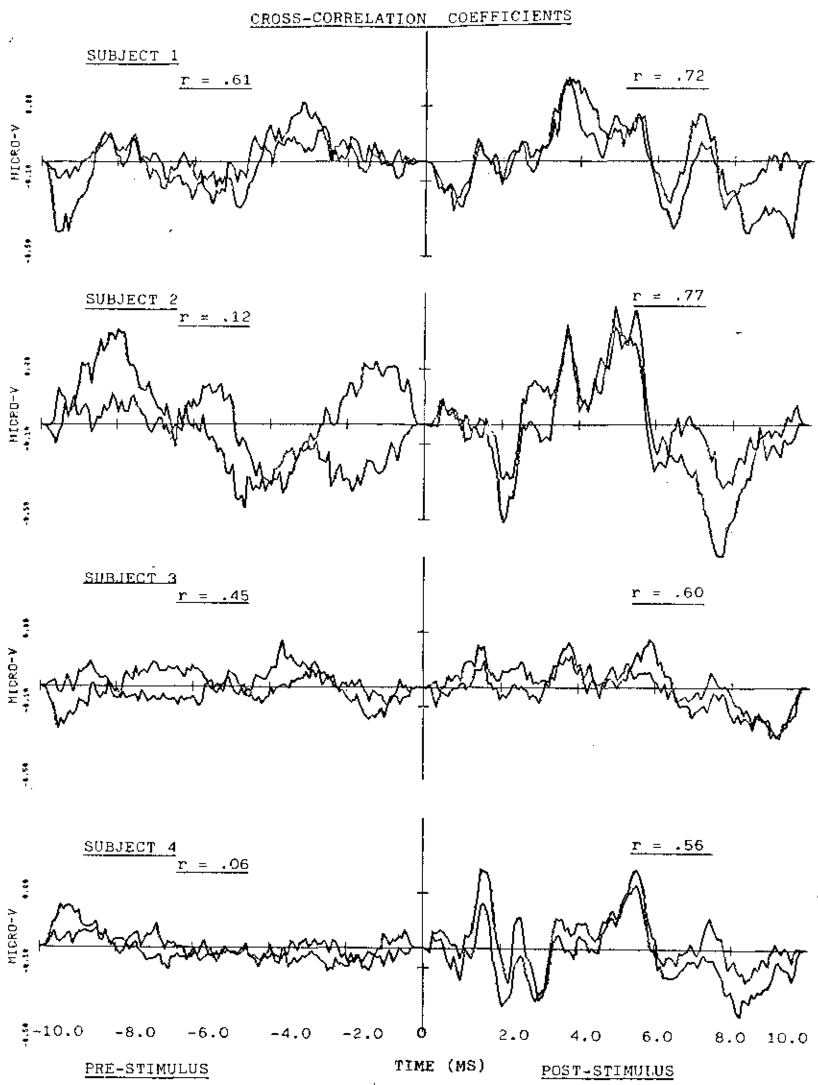


FIGURE 3.5: Cross-correlation coefficient for 2 grand-averages each consisting of 512 sweeps. The correlation coefficients have been calculated for pre-stimulus and post-stimulus intervals.

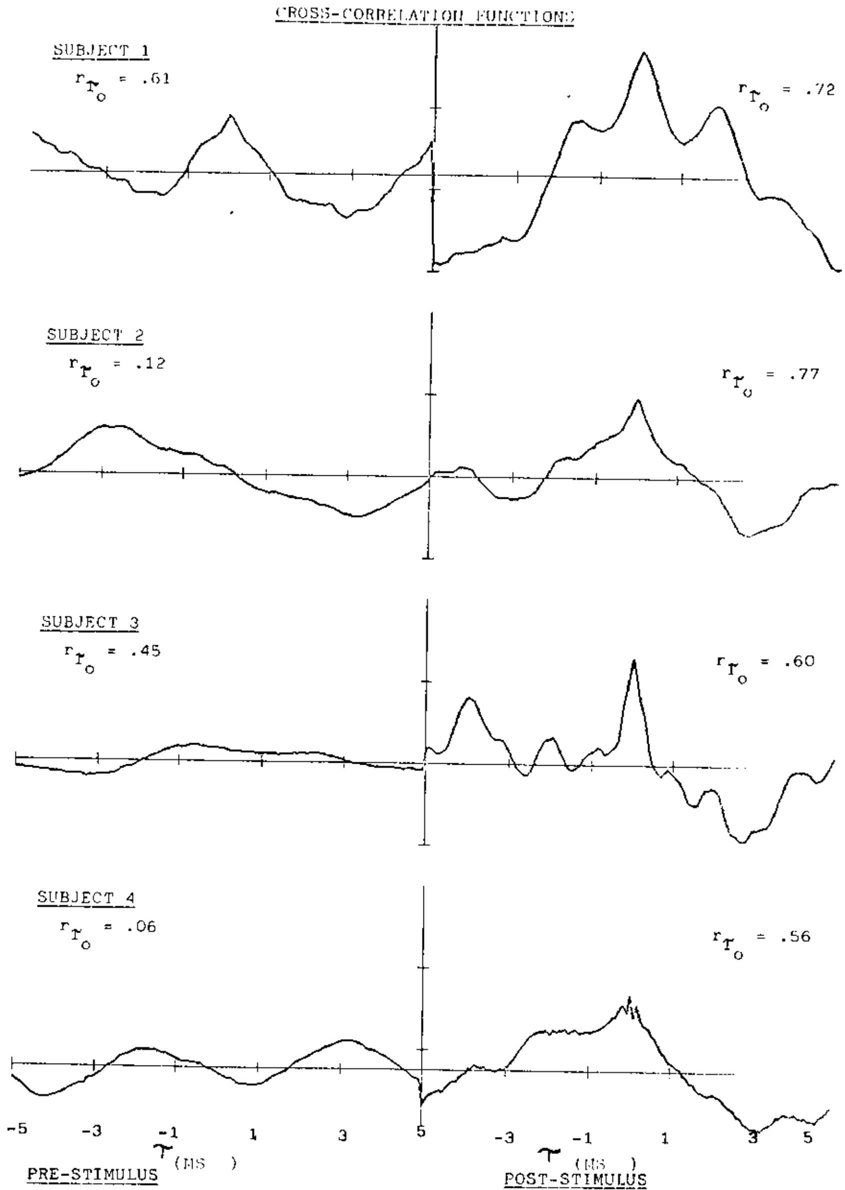


FIGURE 3.6: Cross-correlation functions for pre-stimulus and post-stimulus intervals for the records of Figure 3.5.

For the present the correctness of such a model has been assumed so that the general sensitivity of the template matching method may be evaluated using the cross-correlation coefficient. The method was first examined in 4 normal hearing subjects in the following manner. Coherent grand-averages from 1,024 post-stimulus records were used as the response template (Figure 3.7). The template was then added to each pre-stimulus record, so generating an ensemble of simulated responses. In all cases simulated response ensembles of 256 individual sweeps were studied.

Correlations between unsimulated ensembles with the pre-stimulus grand-average have been compared with the correlations obtained between the post-stimulus grand-average template and the simulated responses. The presence of a response altered the frequency distribution of individual cross-correlations and was assessed using the ranked correlations of 256 sweeps (Figure 3.8). The presence of a response caused a positive shift in the correlation distribution. The "S" shape distribution of ranked correlation values indicated that the most frequently occurring values were grouped around the centre of gravity of the distribution. This suggested that the median or mean value might be useful parameters of the distribution. To test this, 8 independent observations of $\bar{r}$ for 256 sweeps were calculated for each subject. The changes in the level of $\bar{r}$ have been plotted in Figure 3.9b. In only one subject did the mean correlation from the simulated response, on average, exceed the 1% confidence interval ($\bar{r}_c$ = .05). Therefore while the presence of a response altered the frequency distribution cross-correlations, the magnitude of the change was small.

The next step was to find ways of improving the differentiation between "response" and "no response" conditions. This centred on methods of improving the signal to noise ratio before calculating the correlation coefficient. In this simulation study one simple way of increasing signal size was to scale up the simulated response. This produced successive positive shifts in the cross-correlation distribution proportional to the amount of scaling (Figure 3.9a, b). An alternative to increasing the size of the response was a reduction in the background E.E.G. activity level. In the in vivo situation this could be obtained by averaging. Assuming that the E.E.G. was stationary and uncorrelated to the response then reduction in the noise would be expected in proprotion to $\sqrt{N}$, where N was the number of sweeps. In a second experiment the simulation study was repeated

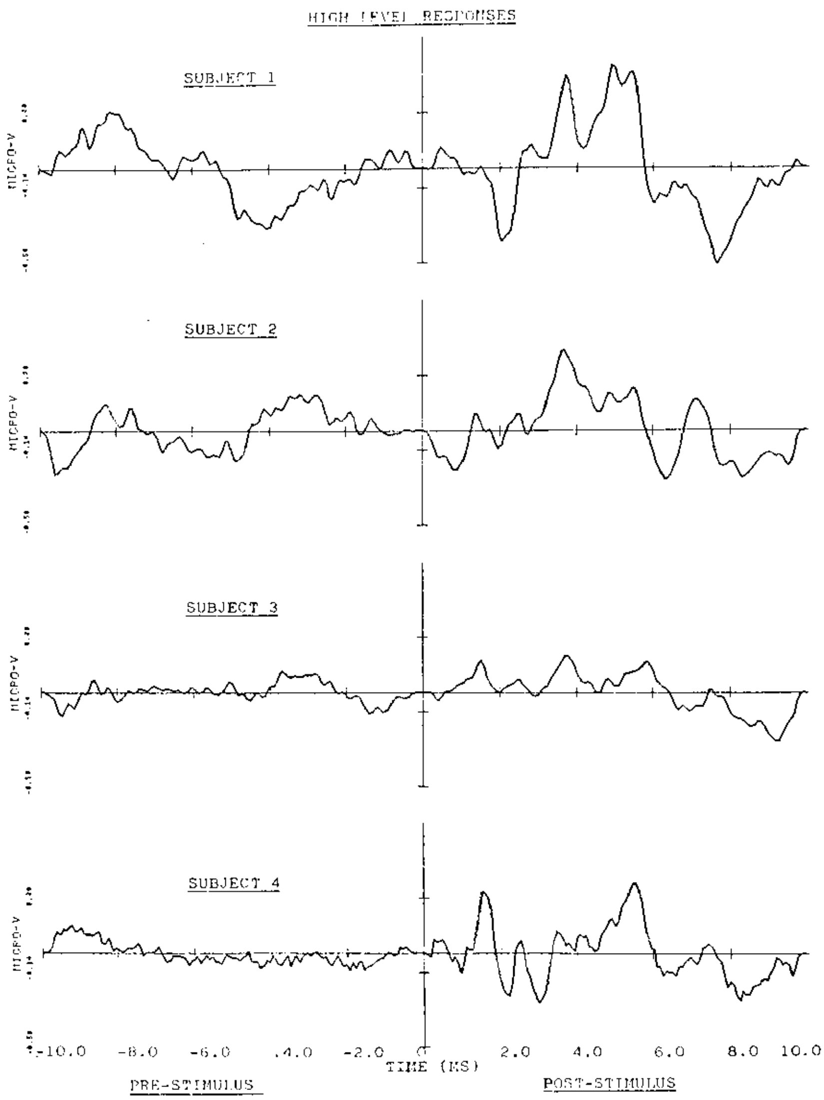


FIGURE 3.7: Coherent grand-averages of responses to 70 dBnHL clicks in 4 normal hearing subjects. Averages based on 1,024 individual sweeps.

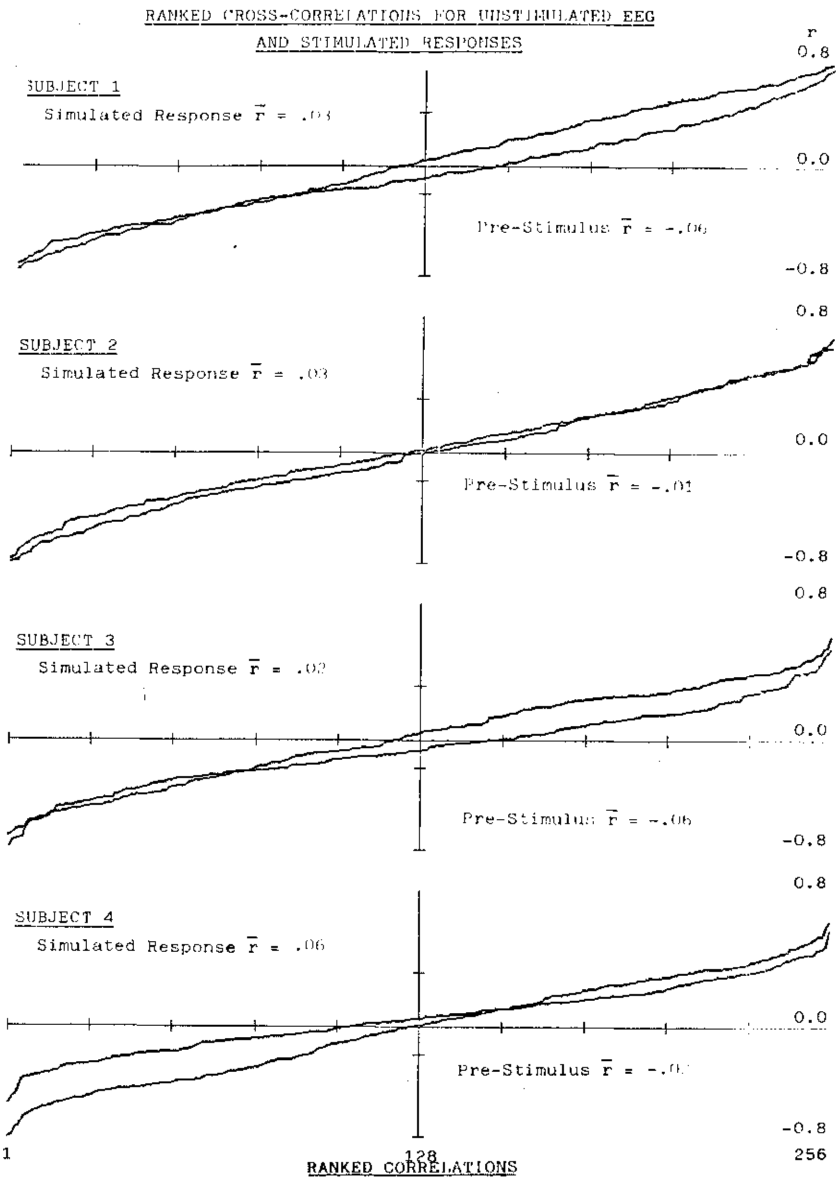


FIGURE 3.8: Simulation study in 4 normal hearing subjects. Correlation coefficients were calculated between the coherent grand-average and individual sweeps and rank ordered. In the pre-stimulus condition the grand-average was obtained for the pre-stimulus period. For the simulated response the correlation was calculated between pre-stimulus ensembles in which the post-stimulus grand-average had been embedded and the post-stimulus coherent grand-average.

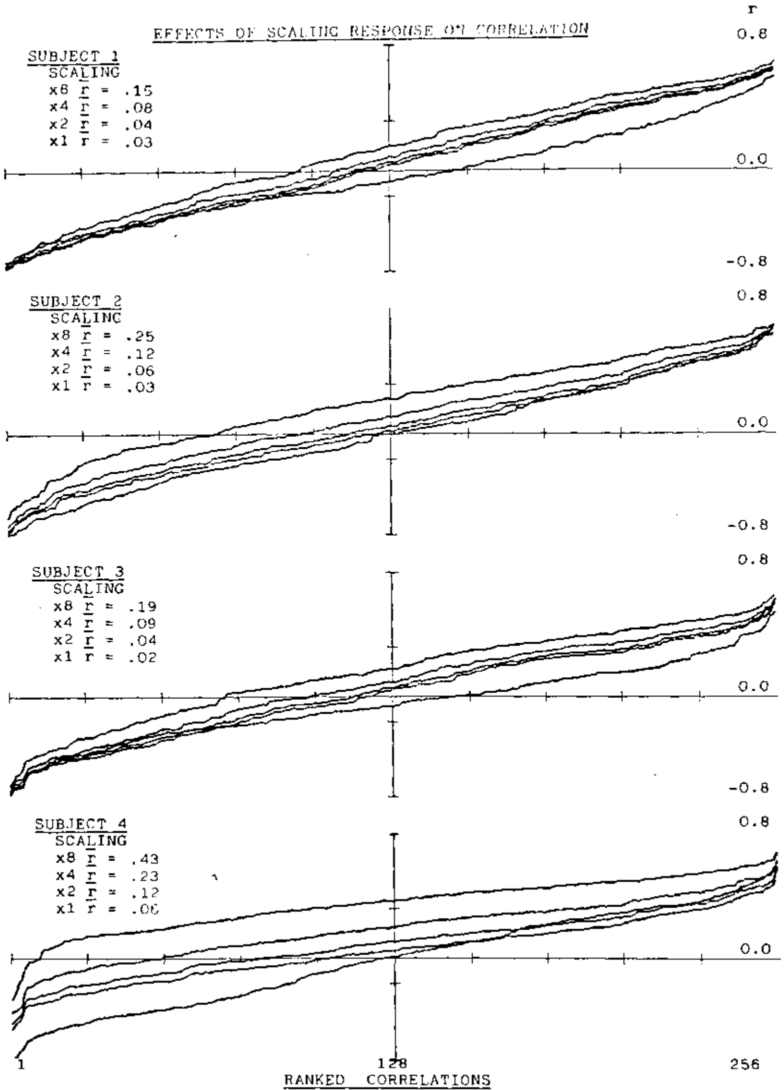


FIGURE 3.9a: Simulation study showing the effects of scaling size of the simulated response on the cross-correlation coefficient distribution. Successive increases in scaling produced small positive shifts in the correlation distributions.

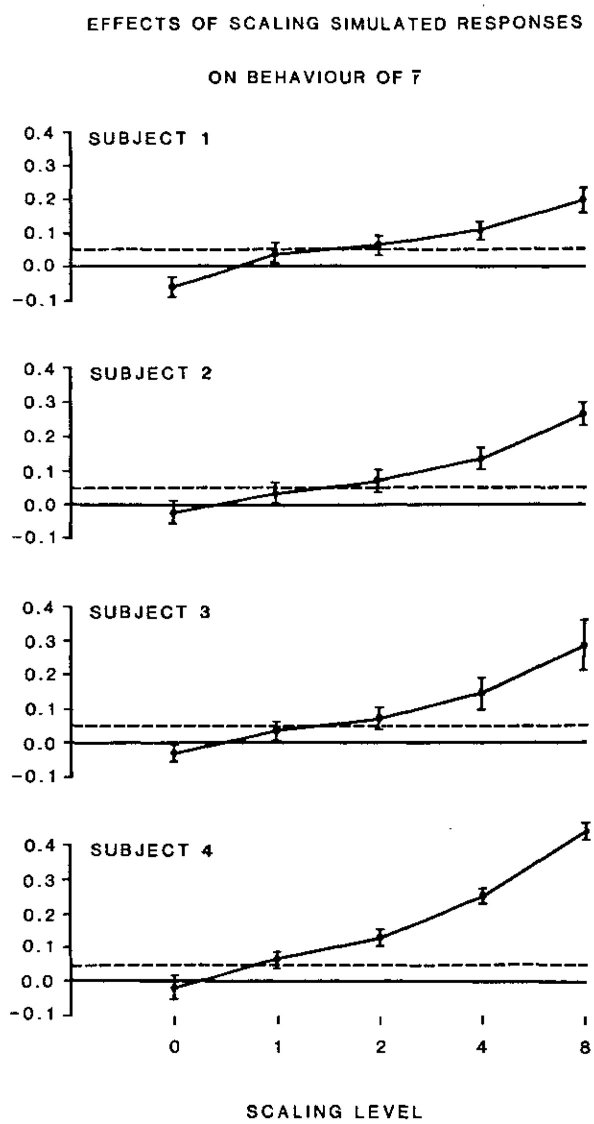


FIGURE 3.9b: Simulation study showing effects of different scaling levels on $\bar{r}$. Standard Error included.

under conditions where the noise had been successively reduced by forming sub-averages consisting of 4, 16 and 64 sweeps. Individual correlations for 256 sweep ensembles were ranked and plotted (Figure 3.10a) and the results compared with the original simulation study (Figure 3.10b). Sub-averages of 4, 16 and 64 have been compared with scalings of 2, 4 and 8 respectively. The findings suggested that the improvements in correlation obtained by scaling a simulated response could be produced equally successfully by the averaging method of noise reduction.

In a final experiment an in vivo study was carried out using post-stimulus ensembles of 256 sweeps, rank ordering the correlations and comparing the average correlation values so obtained for ensembles of 4, 16 and 64 sweeps (Figure 3.11a, b). The same general trend was clearly evident. When the coherent grand average template was correlated with individual sub-averages consisting of successively larger ensembles, the correlation distribution showed progressive positive shifts and again this was reflected in the mean correlation values from 256 observations. In practice for these 4 subjects there did appear to be small improvements in the real situation compared with the simulation for 3 of the subjects.

From the foregoing studies the following conclusions were reached:

(1) A strong positive correlation was found to exist between individual coherent grand-averages under similar conditions of stimulation in the same subject.

(2) The confidence attached to individual correlation values depended on the behaviour of the spontaneous E.E.G.

(3) The correlation distribution for unstimulated E.E.G. was not normally distributed, although it did approximate to Gaussian. The histogram of frequency distribution for averaged correlations became progressively more normally distributed when $\bar{r}$ had been generated by successively larger ensembles. The ensemble size underlying $\bar{r}$ was also a major determinant of the standard deviation and the confidence interval of $\bar{r}$. In the present study the 1% probability level has been chosen as "threshold".

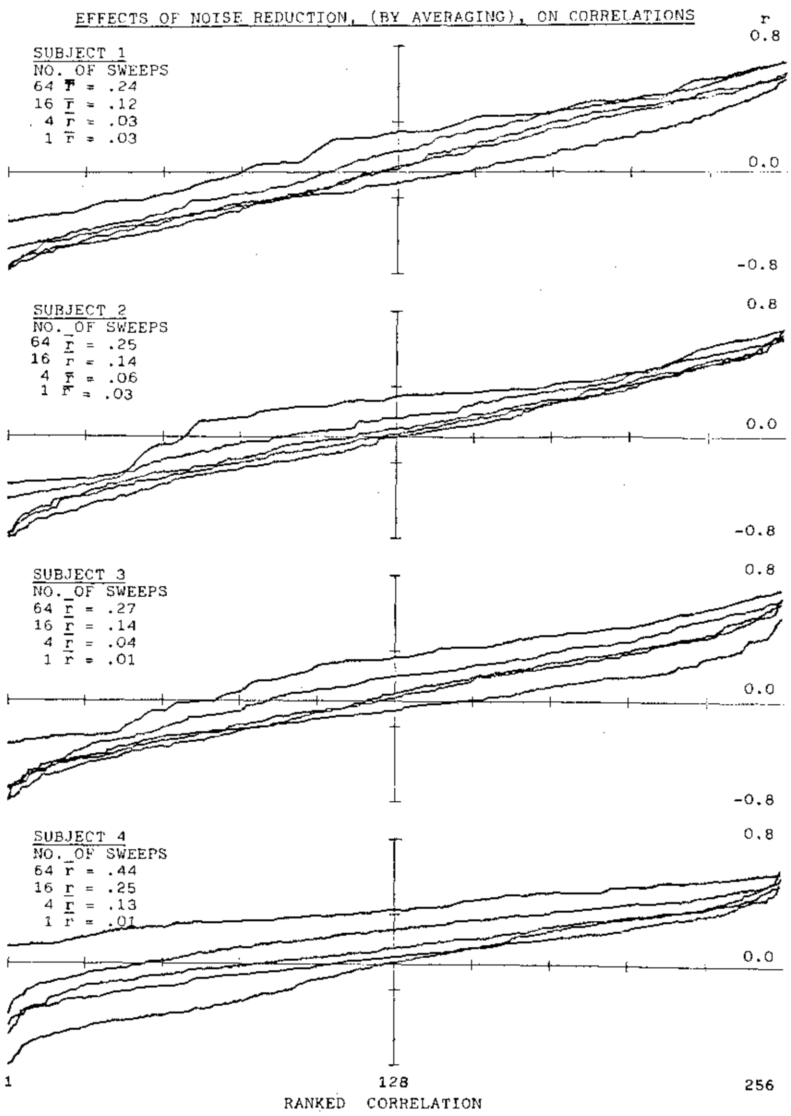


FIGURE 3.10a: Simulation study showing the effects of noise reduction by averaging on the distribution of the cross-correlation coefficient.

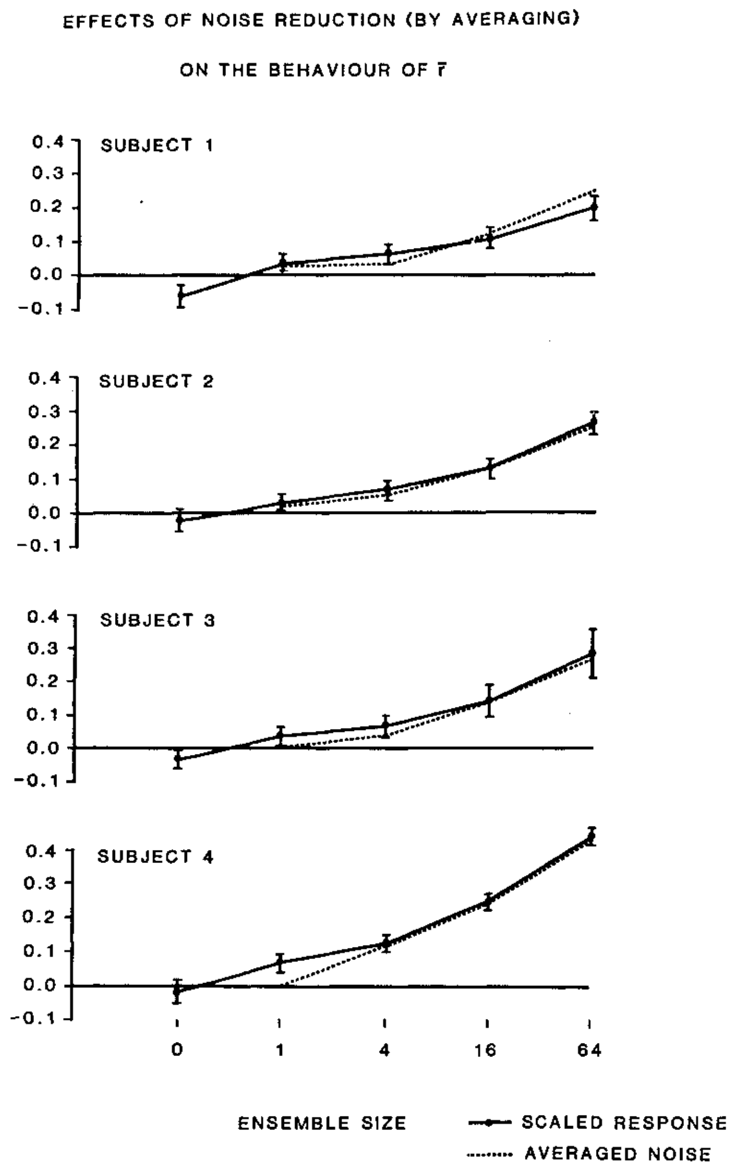


FIGURE 3.10b: Simulation study comparing $\bar{r}$ for ensembles of scaled responses and ensembles in which the noise has been reduced by averaging.

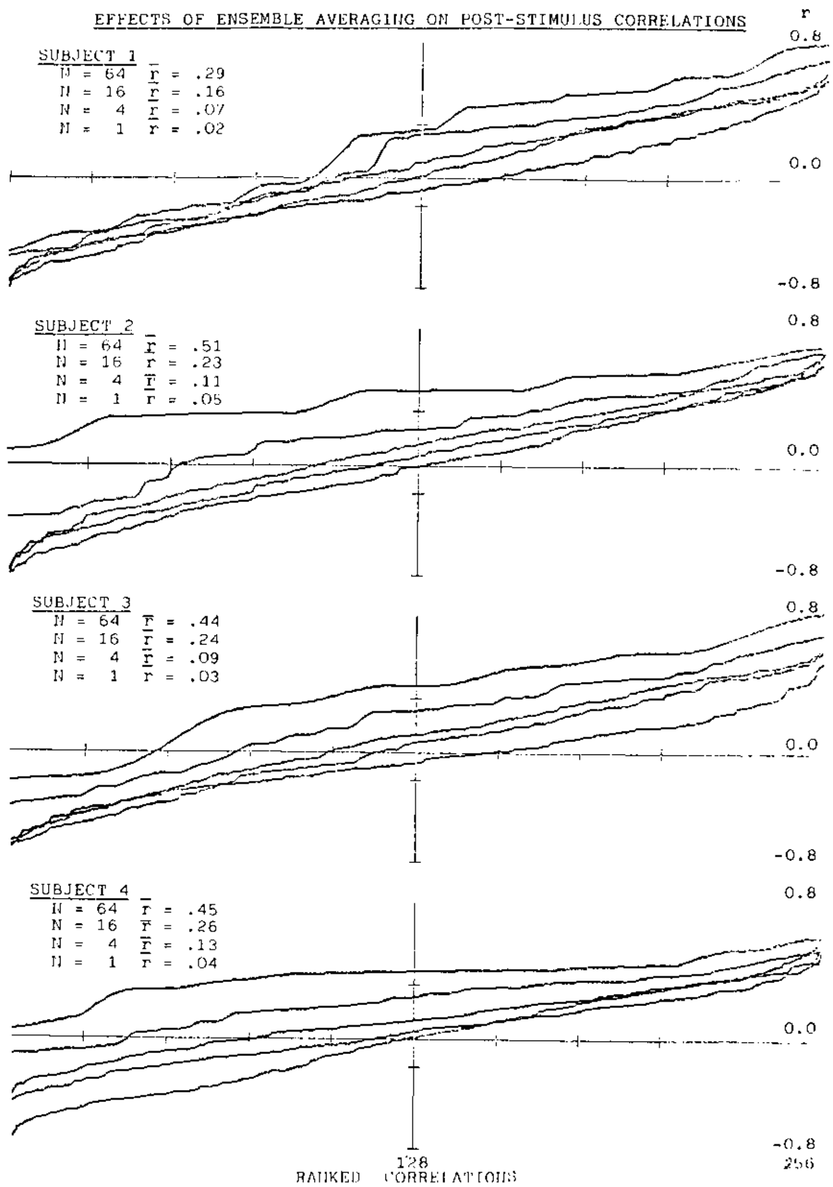


FIGURE 3.11a: In vivo study showing the effects of noise reduction by averaging on the post-stimulus ensemble corss-correlation coefficients.

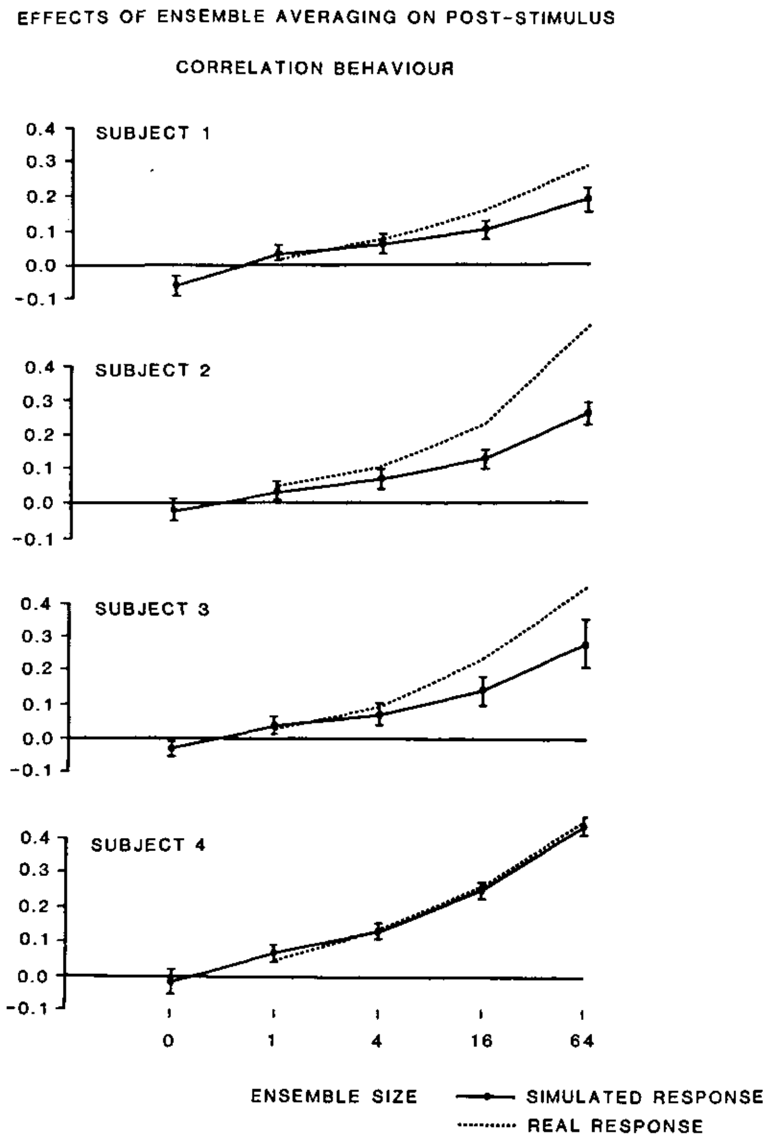


FIGURE 3.11b: Comparison of $\bar{r}$ for simulated and real responses.

The associated $\bar{r}_c$ values for 16 and 32 sweep ensembles were as follows:

$$N = 16 \quad \bar{r}_c = 0.33$$

$$N = 32 \quad \bar{r}_c = 0.27$$

(4) The presence of a response embedded within the background E.E.G. noise produced a positive shift in the correlation distribution. The size of the shift depended on the signal to noise ratio.

(5) The E.E.G. noise can be reduced by forming sub-averages. The observed improvement in correlations agreed well with theoretical estimates, and approximately proportional to $\sqrt{N}$.

(6) Using the coherent grand-average as the reference template in the in vivo situation, the template matching method was effective in detecting the presence of a response embedded within the spontaneous E.E.G. The size of the cross-correlation for this condition was increased as predicted by grouping individual ensemble members into small sub-averages and treating each of these sub-averages as a new ensemble. The improvement observed was in keeping with the theoretical prediction (See 5).

A STUDY OF NORMAL HEARING SUBJECTS

The practical implementation of this correlation procedure entailed collecting many individual responses. The limitations of space and speed were major constraints on the number of sweeps that could reasonably be collected. In most clinical situations coherent averages are formed from between 1,000 and 2,000 individual responses. In the present implementation of the correlation technique a compromise needed to be reached between grouping individual responses into small numbers of sub-averages on the one hand and optimising the correlation sampling statistics by maximising the ensemble size on the other. Both the noise reduction achieved by forming sub-averages and the improvement in the sampling statistics by increasing ensemble size were directly proportional to $\sqrt{N}$. In the clinical study which follows either 1,024 or 2,048 individual responses were obtained at each stimulus level and these were grouped into sub-averages. Each sub-average consisted of 64 individual responses and the resulting ensembles numbered either 16 or 32 respectively.

In order to assess the sensitivity of the correlation method 34 normal hearing subjects were studied. Auditory brainstem potentials were collected at stimulus intensities ranging from 70 dBnHl to threshold. In order that the objective method may be of clinical use the following criteria needed to be met:

(1) There should be a high level of agreement between objective method and conventional visual analysis of the responses.

(2) Threshold using the objective method should be near subjective threshold in order to provide a wide dynamic range for use in hearing impaired subjects.

(3) Intersubject variability of threshold for the objective method should be small so allowing a reliable normal threshold level to be established as a reference for the study of hearing impaired subjects.

From the single sweep study the criterion level for the 1% probability based on 330 observations was .33 for 16 sweep ensembles. The pre-stimulus epochs from normal hearing subjects provided an opportunity to test the reliability of this confidence level. From the 34 subjects a total of 310 ensembles were obtained. These were 16 member ensembles and comparison was made between the frequency distribution obtained from this population with that obtained from the single sweep study (Figure 3.12). The frequency distributions were virtually identical and there were no significant differences in the first or second moments (means; .00, .01 S.D.'s; .12, .12). The confidence interval associated with the probabilities of 5% and 1% were as follows:

Probability Level	Confidence Interval for Single Sweep Study	Confidence Interval for Normal Hearing Subjects
5%	.20	.22
1%	.33	.31

As these values were in close agreement the original criteria of threshold were used in the subsequent assessment of the sensitivity of the template matching procedure. Correlation coefficients were calculated for post-stimulus ensembles obtained at stimulus intensities ranging from 70 dBnHL to 0 dBnHL in 10 dB decrements.

FREQUENCY DISTRIBUTION OF $\bar{r}$ FOR 16 SWEEP ENSEMBLES
IN 40 NORMAL HEARING SUBJECTS (N=310)

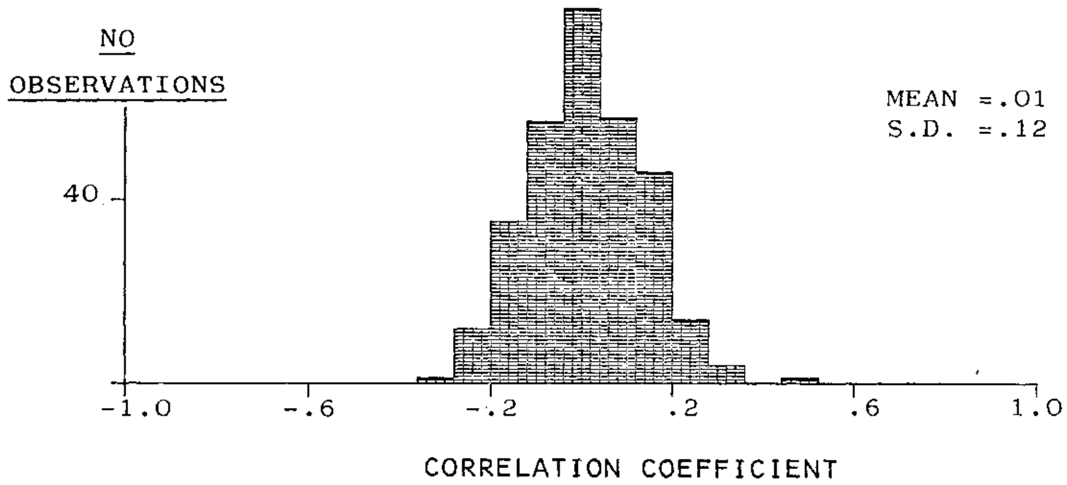


FIGURE 3.12

Figure 3.13 shows examples of the coherent grand-averages and associated ensemble $\bar{r}$ in 2 normal hearing subjects. The total group averages of $\bar{r}$ at each stimulus intensity were calculated and plotted (Figure 3.14). A systematic inverse relationship was found between $\bar{r}$ and stimulus intensity. Even at 10 dB the group average of $\bar{r}$ was significantly greater than $\bar{r}$ for unstimulated records ($p < .01$). However, in the clinical situation one is not interested in differentiating between populations but deciding whether an individual response is likely to be supra-threshold or sub-threshold and what confidence can be attached to the conclusion. Figure 3.15 shows the underlying frequency distributions of the statistic $\bar{r}$ for the same intensity levels. A systematic shift was observed in the frequency distribution histograms, with the populations of $\bar{r}$ shifting from positive values towards 0 as stimulus intensity was decreased. High level responses in almost all cases produced $\bar{r}$ values exceeding the criterion level of threshold, 0.33. The majority of $\bar{r}$ for 50 dB also exceeded the threshold criteria. At 30 dB however, 50% of the responses failed to reach threshold level and at 10 dB, 95% failed to reach criterion level.

The relative sensitivity of this template method was then compared with the conventional visual determination of threshold (Figure 3.16). Using the 1% probability level with the correlation method the average stimulus level of threshold for the 34 subjects was 39 dB compared with 11 dB for the visual method. In addition, with the correlation method a very wide scatter of the intensity level for threshold was found. This was reflected in a high, 20 dB, standard deviation compared with 7 dB with the visual method. The high mean threshold greatly reduced the dynamic range of the procedure while the large spread greatly impeded the formation of a "normal" threshold level.

When the 5% probability level was used the average threshold value was reduced to 24 dB and paralleling this there was reduction in the scatter of threshold intensities (standard deviation = 12 dB). Nevertheless, the scatter was still unacceptably high, while the probability of obtaining a false positive result was correspondingly increased.

OPTIMISING THE CORRELATION PROCEDURE BY FILTERING

A detailed analysis of the relationship between harmonic behaviour and the time domain correlation coefficient has been made in the next chapter. In the present section an assessment of the importance

ENSEMBLE CORRELATIONS FOR DIFFERENT STIMULUS INTENSITIES
(PASS BAND 1-32 HARMONICS)

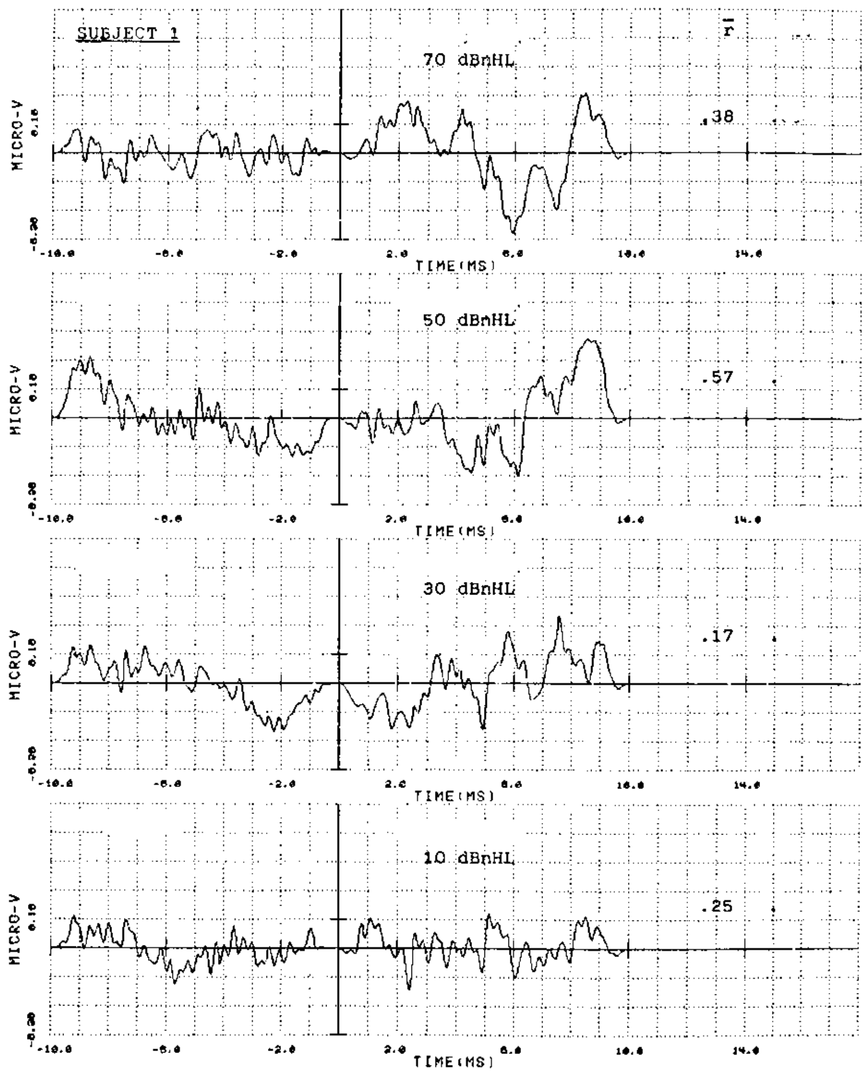


FIGURE 3.13a: In this and the subsequent Figure the mean ensemble cross-correlation coefficients at 4 discreet stimulus intensities have been compared. The total number of sweeps at each stimulus level was 1,024. These were grouped into small 64 sweep sub-averages, forming a new 16 member ensemble.

ENSEMBLE CORRELATIONS FOR DIFFERENT STIMULUS INTENSITIES
(PASS BAND 1-32 HARMONICS)

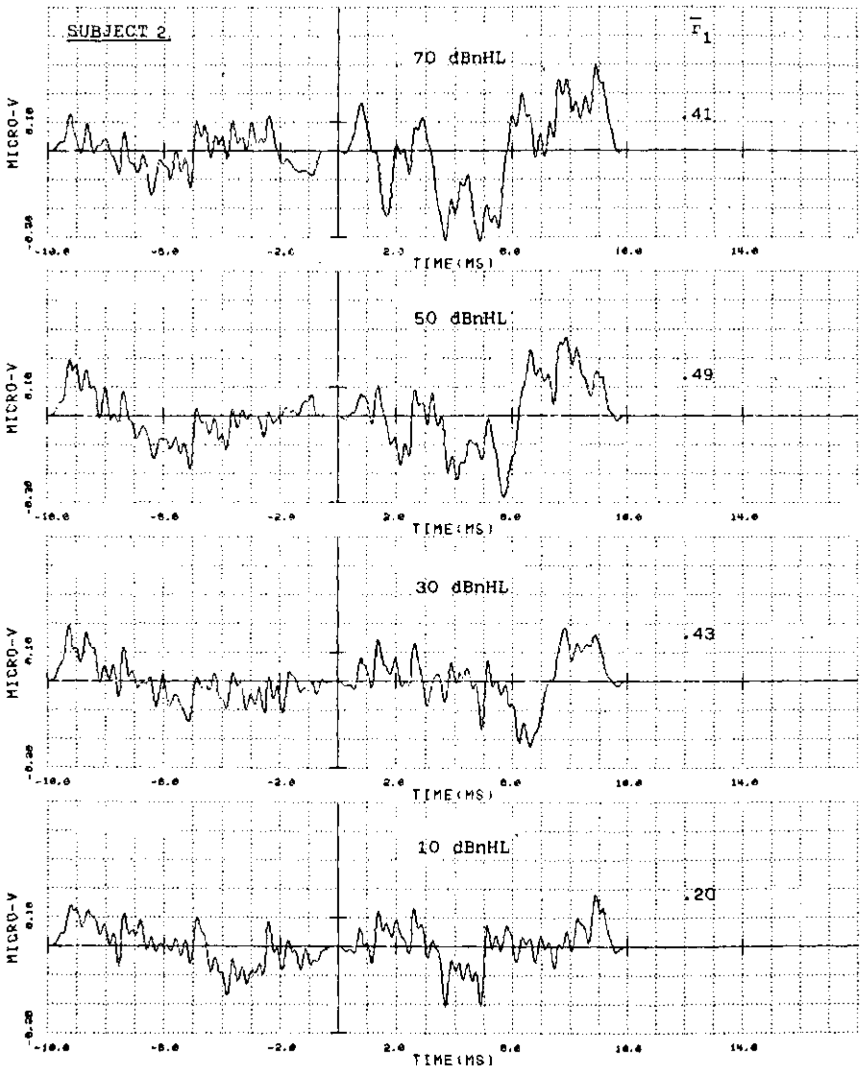


FIGURE 3.13b

RELATIONSHIP BETWEEN CORRELATION AND STIMULUS INTENSITY

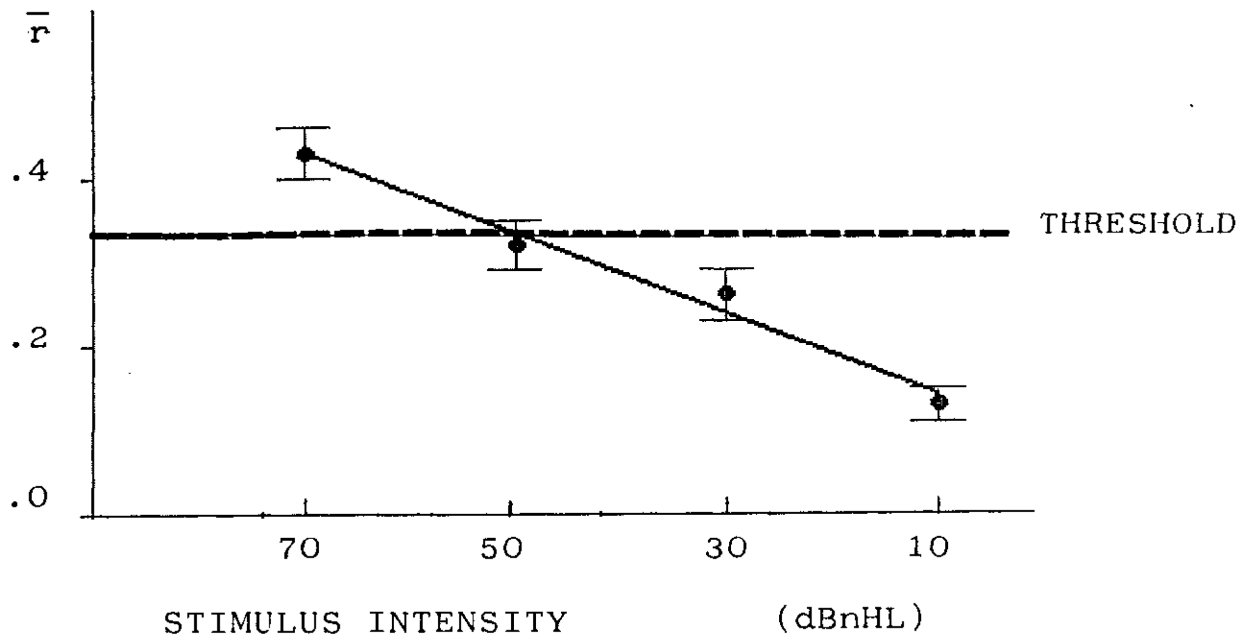


FIGURE 3.14: Mean and standard error of $\bar{r}$ obtained from a group of normal hearing subjects at 4 stimulus intensities.

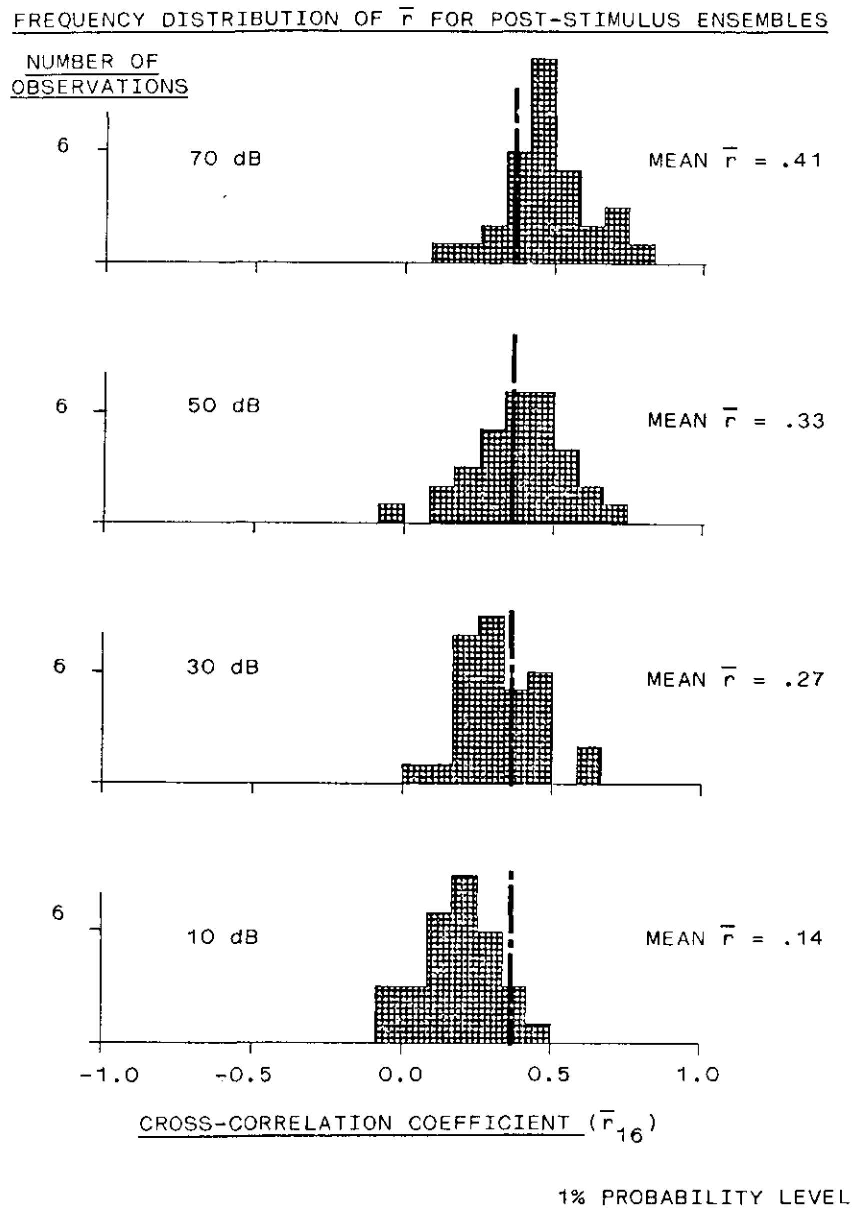


FIGURE 3.15: Histograms of frequency distribution of the mean cross-correlation coefficients obtained from a group of normal hearing subjects. The 1% confidence interval has been included.

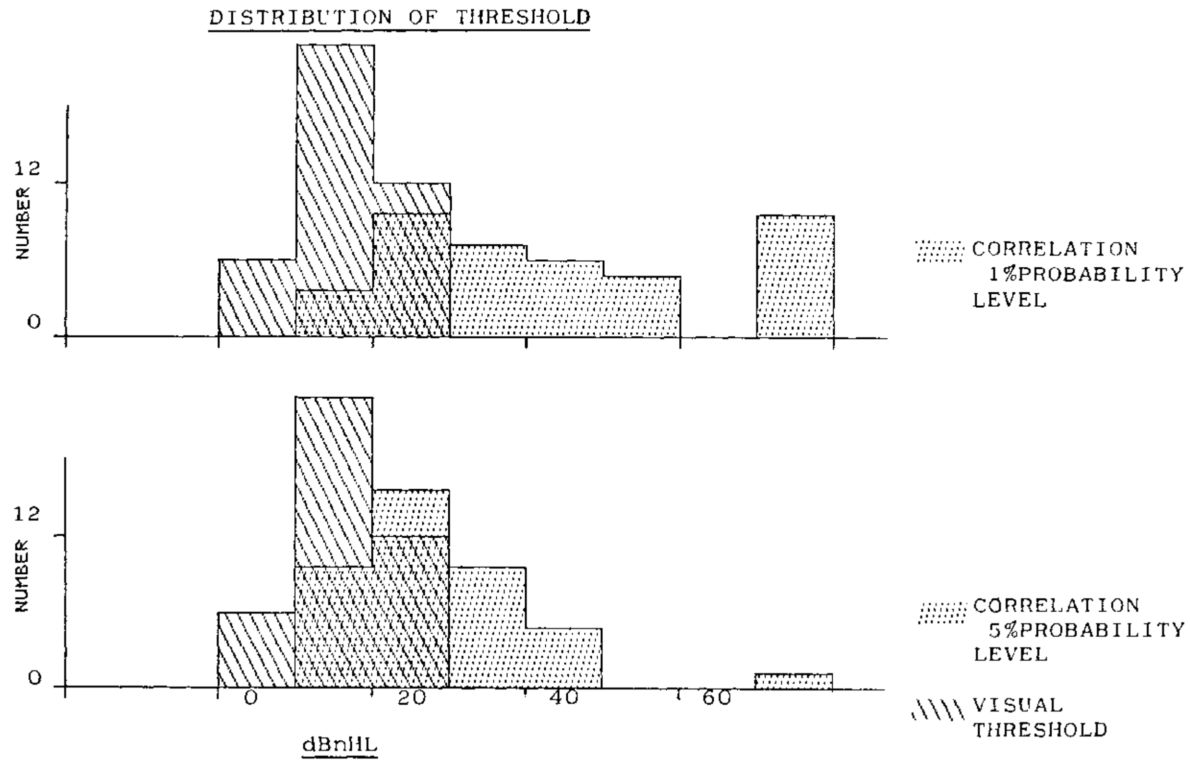


FIGURE 3.16: Distribution of threshold for the objective cross-correlation method and for conventional visual analysis. The upper plot shows the distribution of threshold employing the 1% probability criterion. Below the less strict 5% criterion level has been employed showing a clear lowering in the intensity distribution of threshold for the corss-correlation method.

of attending to the harmonic features of the evoked potentials has been made by studying the effects of filtering both the coherent average and individual ensemble members. The contribution of individual Fourier harmonics to the coefficient is totally determined by the amplitudes of individual harmonics and their relative phases in the template and within the ensemble. By examining the amplitude spectrum of the coherent grand-average some assessment can be made of the relative contribution to the time domain pattern of individual harmonics. The means of the amplitude spectra of high level responses obtained from normal hearing subjects were calculated and plotted together with their standard deviations (Figure 3.17). Low frequency components in the signal dominated the amplitude spectra. Harmonics higher than the 12th were less than 10% of the amplitude values of the first 3 harmonics. It was unlikely therefore that such higher harmonics contributed significantly either to the time domain pattern or to the correlation coefficient. There was a large intersubject variability in the amplitude values of individual harmonics and standard deviations (S.D.) were greatest for the first few harmonics. Comparison was also made between the high level post-stimulus amplitude spectra and the amplitude spectra obtained from the pre-stimulus grand-averages. Differences between pre-stimulus and post-stimulus amplitudes approached zero around the 12th harmonic, further reasons for assuming that harmonics above this were unlikely to contriubte significantly. The large intersubject variability in pre-stimulus amplitude levels were again greatest for the first few harmonics.

From visual inspection of many records it was apparent that the changes in pattern of the coherent grand-average at lower stimulus intensities involved not only an amplitude change and bulk latency shift of the signal, but also a loss of the higher frequency content. The mean amplitude spectra for 111 responses in the region of threshold were also calculated (Figure 3.18). Individual harmonics corresponding to those of the high level responses were of much smaller amplitude and the differences between pre-stimulus and post-stimulus amplitudes were also much less, approaching zero in the region of the 10th harmonic.

For these forgoing reasons it was decided to repeat the cross-correlation analysis for normal hearing subjects using a narrower frequency band, specifically the frequency band including the 3rd to 10th harmonics. Individual responses were digitally filtered before calculating the cross-correlation coefficient. The effects of filtering on the $\bar{r}$ have been illustrated in Figure 3.19 for the same 2 subjects shown in Figure 3.13. Definite improvements were observed.

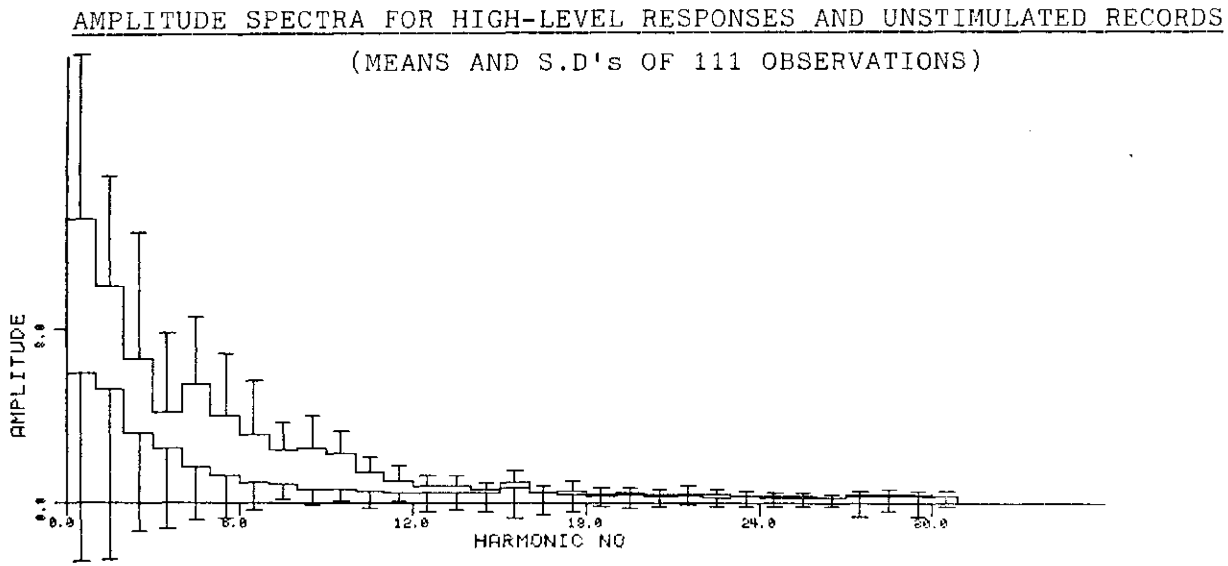


FIGURE 3.17: Amplitdue spectra for high level coherent grand averages from 34 normal hearing subjects. The larger distributions were obtained from the post-stimulus grand-averages and the lower from the pre-stimulus grand-averages.

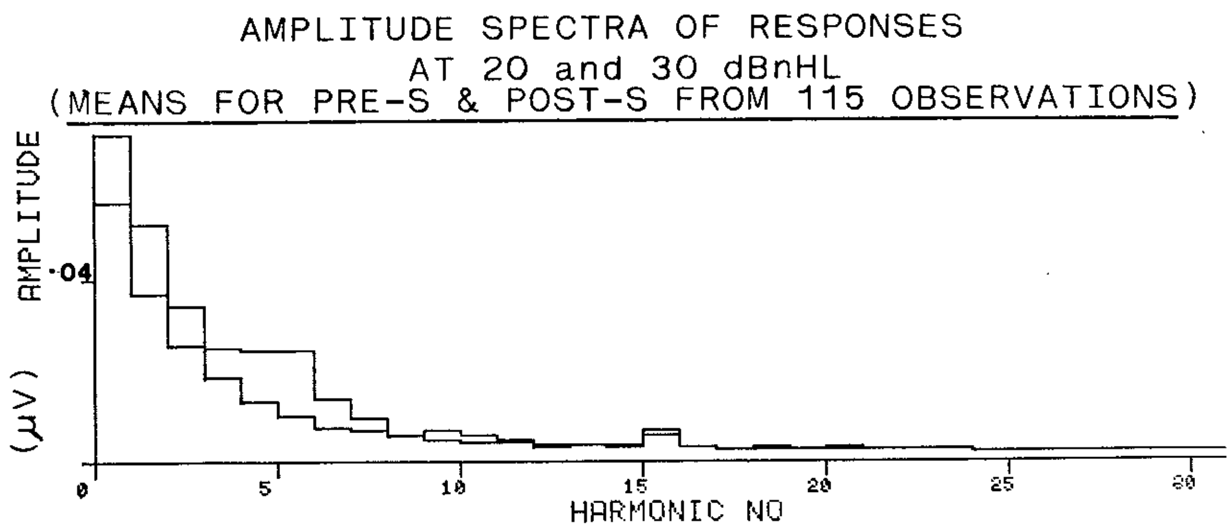


FIGURE 3.18: Amplitude spectra of responses obtained with 20 and 30 dBnHL stimuli. For each harmonic the larger value was obtained from post-stimulus coherent averages, the smaller from pre-stimulus averages.

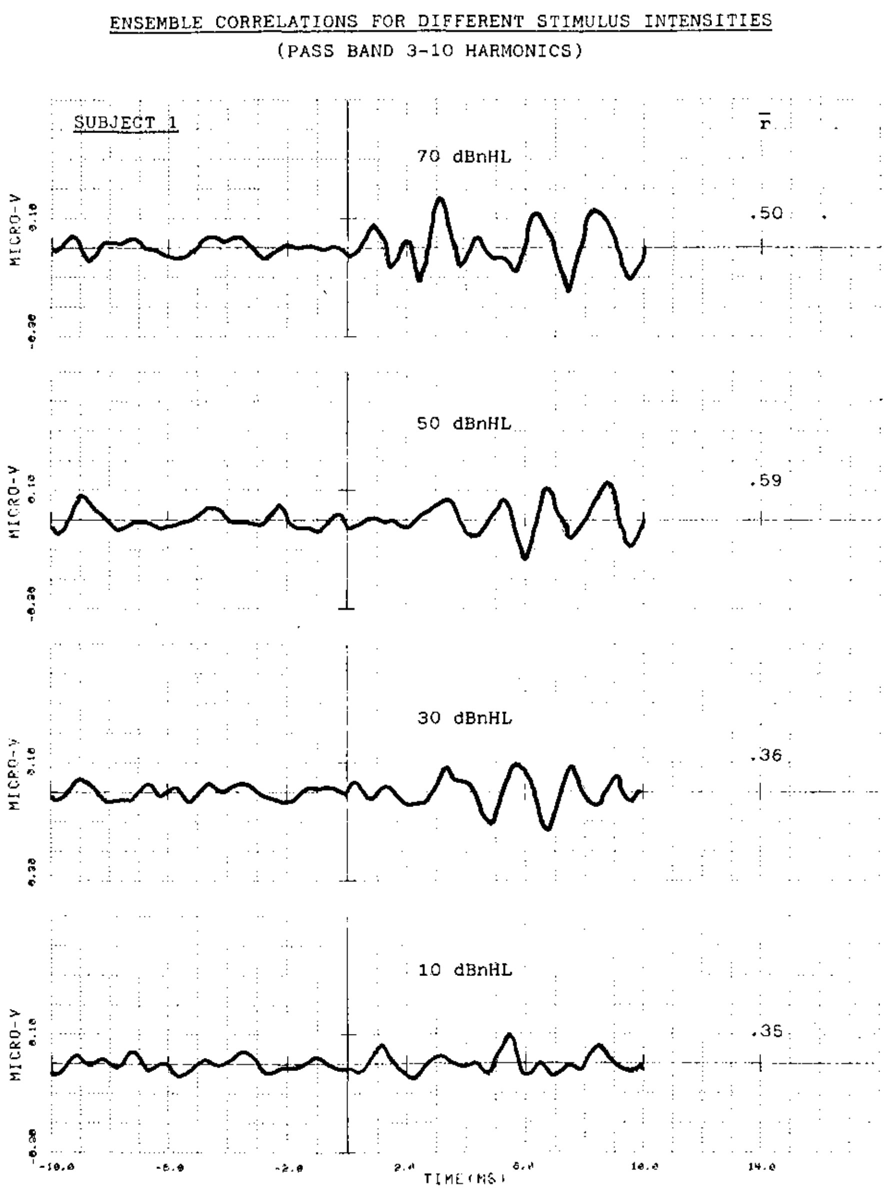


FIGURE 3.19a: In this and the subsequent figure the effects of filtering of the response (300-1,000 Hz) on the ensemble mean cross-correlation coefficient has been illustrated. Note the improvement in the $\bar{r}$ compared with corresponding broad band responses of Figure 13a and b.

ENSEMBLE CORRELATIONS FOR DIFFERENT STIMULUS INTENSITIES
(PASS BAND 3-10 HARMONICS)

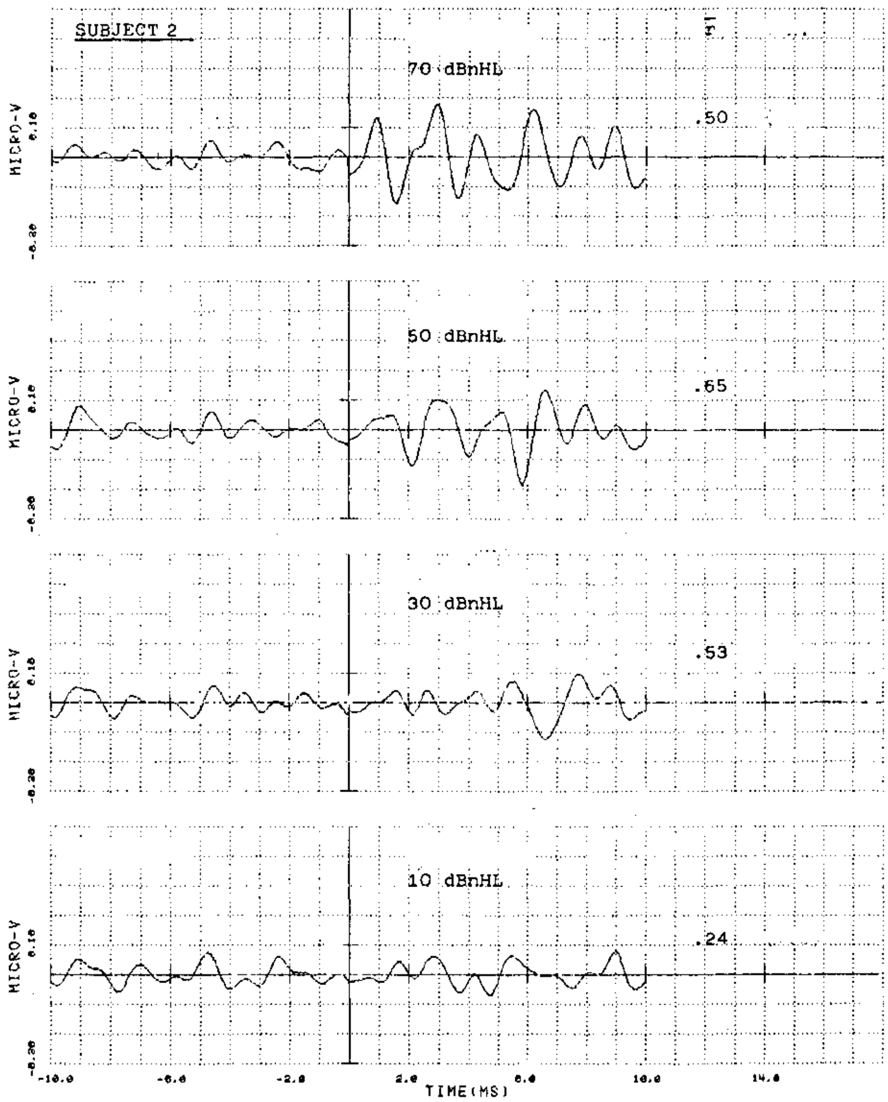


FIGURE 3.19b

The pooled results from 25 subjects for narrow band and broad band responses were compared (Figure 3.20). A positive shift in the average correlation value was obtained at all stimulus intensities for the group. For the wide band responses only high intensity stimului produced correlation values which exceeded, on average, the threshold criteria (1% probability level). Digitally filtered responses, on average, exceeded the 1% probability at 70, 50 and 30 dB. The intensity distribution of the thresholds obtained for these 25 subjects was compared in Figure 3.21. Threshold for the filtered response was on average at 35 dB compared with 39 dB for the unfiltered situation. There was however little difference in the overall spread of results.

While filtering the responses (300 Hz-1,000 Hz) conferred a small improvement in threshold estimation using the correlation procedure, it was perhaps not surprising that such a fixed choice of bandwidth had a variable effect. Significant increases in $\bar{r}$ were observed for some subjects, but little change was observed in others. It seemed likely that some harmonics may possibly be important in all subjects, but the relative contributions of other harmonics to the overall correlation value varied from subject to subject and also from intensity level to intensity level. The problem then became one of selecting correct harmonics. More attention therefore, needed to be paid to the behaviour of individual harmonics themselves, selecting "significant" harmonics only into the pattern recognition technique.

EFFECTS OF FILTERING ON
CORRELATION/INTENSITY RELATIONSHIP

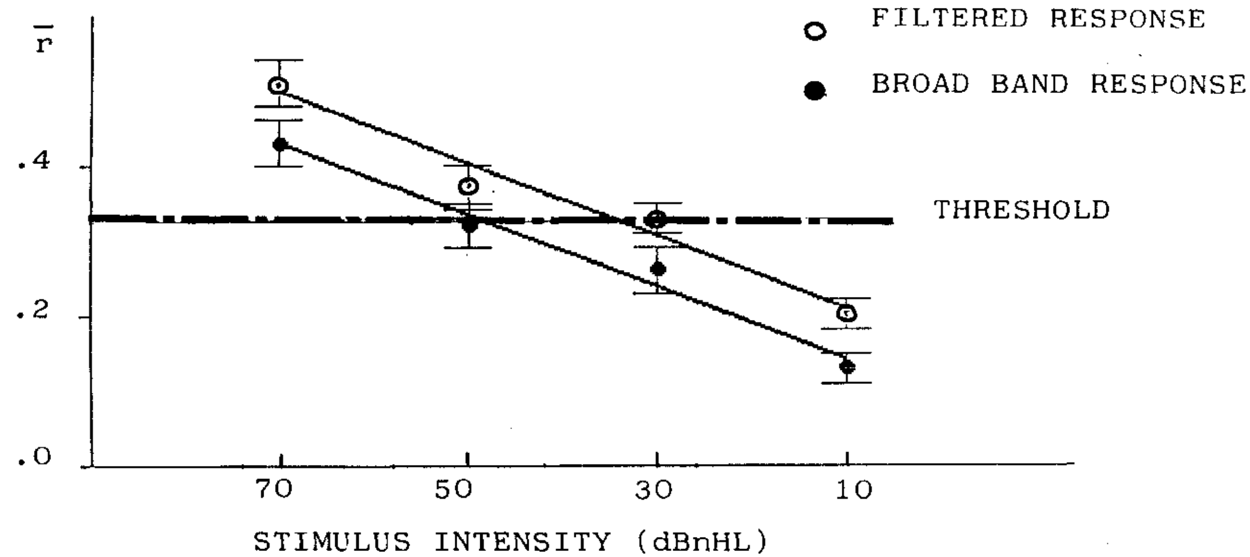


FIGURE 3.20: Comparison of the behaviour of $\bar{r}$ for filtered and unfiltered responses. The band-width of the digitally filtered responses was 300-1,000 Hz.

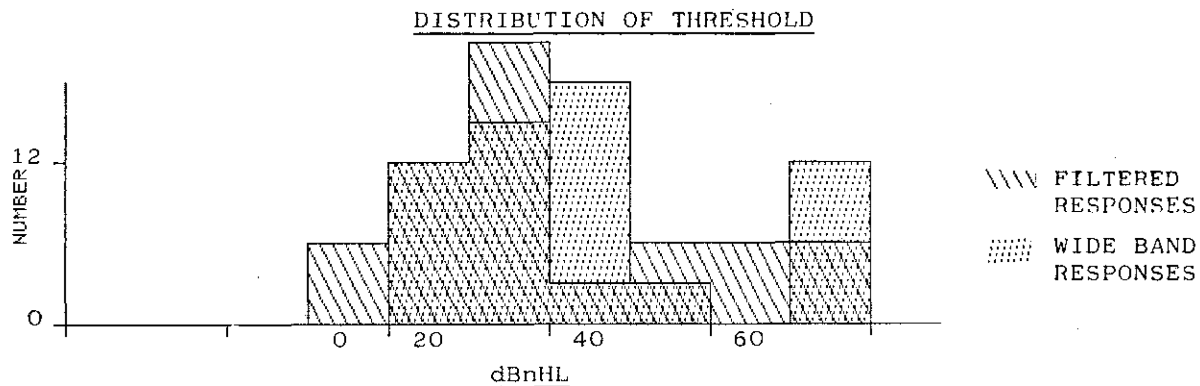


FIGURE 3.21: The distribution of threshold for the correlation method comparing filtered and wide-band responses. Note a small but definite lowering in threshold for filtered ensembles.

CHAPTER 4

A SIGNAL ANALYSIS INVESTIGATION OF BRAINSTEM AUDITORY EVOKED POTENTIALS IN THE GUINEA-PIG (CAVIA PORCELLUS)

INTRODUCTION

The results of the previous section indicated severe limitations in the sensitivity of a simple correlation technique for detecting auditory brainstem potentials in normal hearing subjects. This prompted a more detailed signal analysis investigation of the response and the associated characteristics of the background noise. It was considered that a detailed analysis might provide greater insight into the nature of the mechanism generating the observed time domain pattern and as a result establish a more sensitive detection method.

One major difficulty with human auditory brainstem potentials was the very small signal to noise ratio. In order to simplify the study of the brainstem potentials it was decided to begin with a series of investigations in the guinea-pig, Cavia porcellus, in which the signal to noise ratio was many times greater. The methods of stimulation and recording in the guinea pig have been described in Chapter 2. Responses were obtained from 5 guinea-pigs at intensities ranging from 90dBnHL to sub-threshold in 10dB increments. Two ensembles each consisting of 16 sweeps were obtained at each intensity level and a total of 88 ensembles were collected. The time domain pattern of the guinea-pigs' responses under different stimulus conditions was very similar to the human potentials (Figure 4.1-4.5) and was accepted as justification for using this much simpler animal model for initial investigation. Further justification for accepting the model emerged from a comparative study of the template matching method in the guinea-pig and human.

Using the method employed in the human study, the ensemble mean cross-correlations, $\bar{r}$, at each stimulus level was calculated and the pooled $\bar{r}$ plotted (Figure 4.6). The observed relationship between the ensemble mean correlation coefficient and stimulus intensity was almost linear and for sub-threshold conditions the average correlation was approximately zero. The relationship between mean correlation coefficient and stimulus intensity was similar to that observed in the human although, as expected, the magnitudes of the correlations obtained for all supra-threshold conditions were much greater. As in the human study the criteria for assigning a given correlation as a "response" depended on establishing the confidence interval of the correlation statistic $\bar{r}$ for unstimulated conditions. A histogram of frequency distribution of $\bar{r}$ was constructed from 63 ensembles of unstimulated records (Figure 4.7). This was compared with the frequency distribution of $\bar{r}$ for human data for the same ensemble size (16). There were no significant differences in either the means

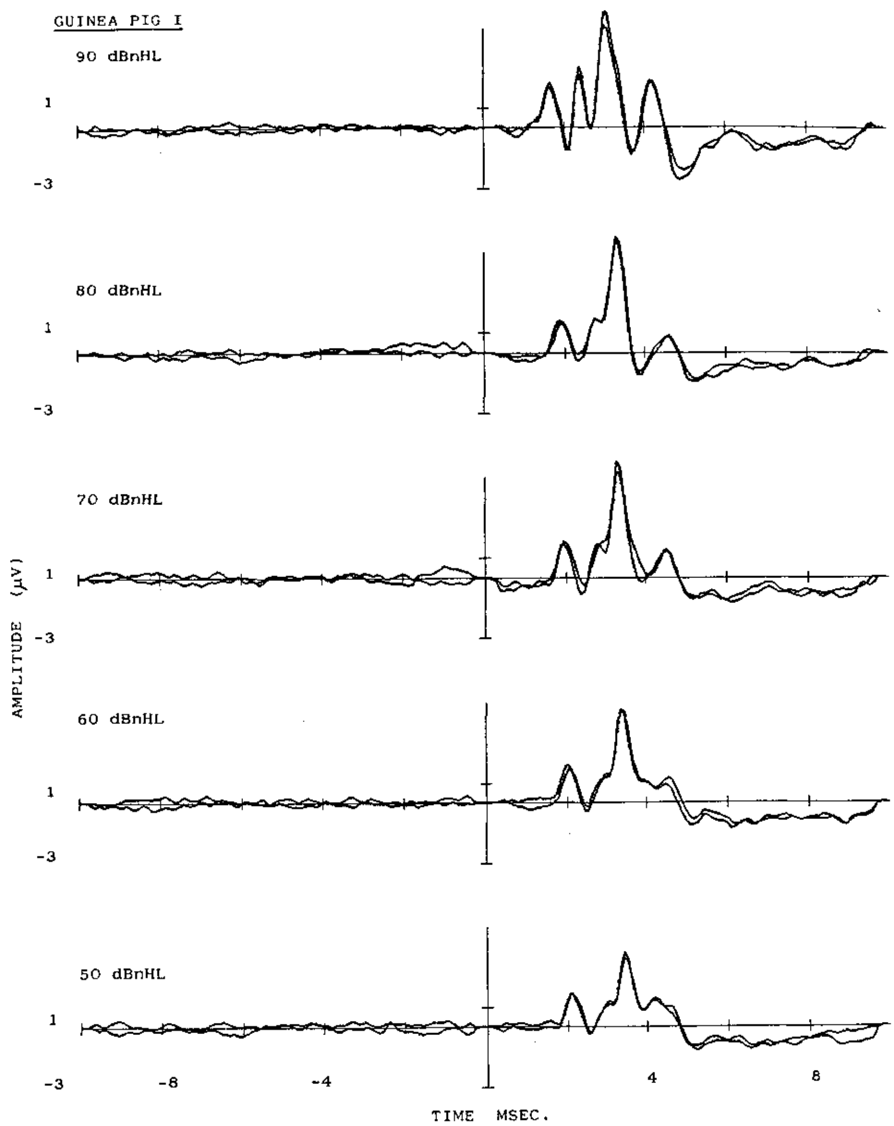


FIGURE 4.1a: In this and the next 9 figures coherent grand-averages obtained from 5 guinea-pigs for a range of stimulus intensities have been plotted. The two averages at each level were formed from 16 sweep ensembles.

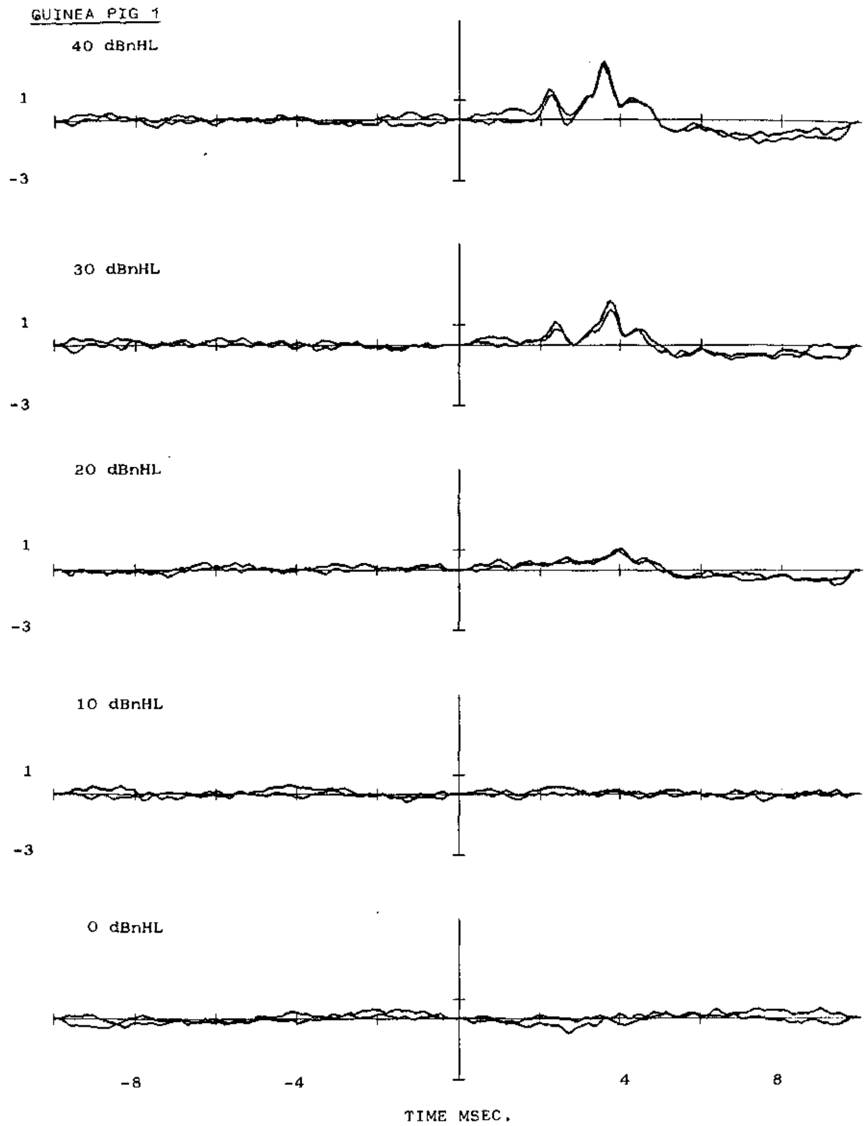
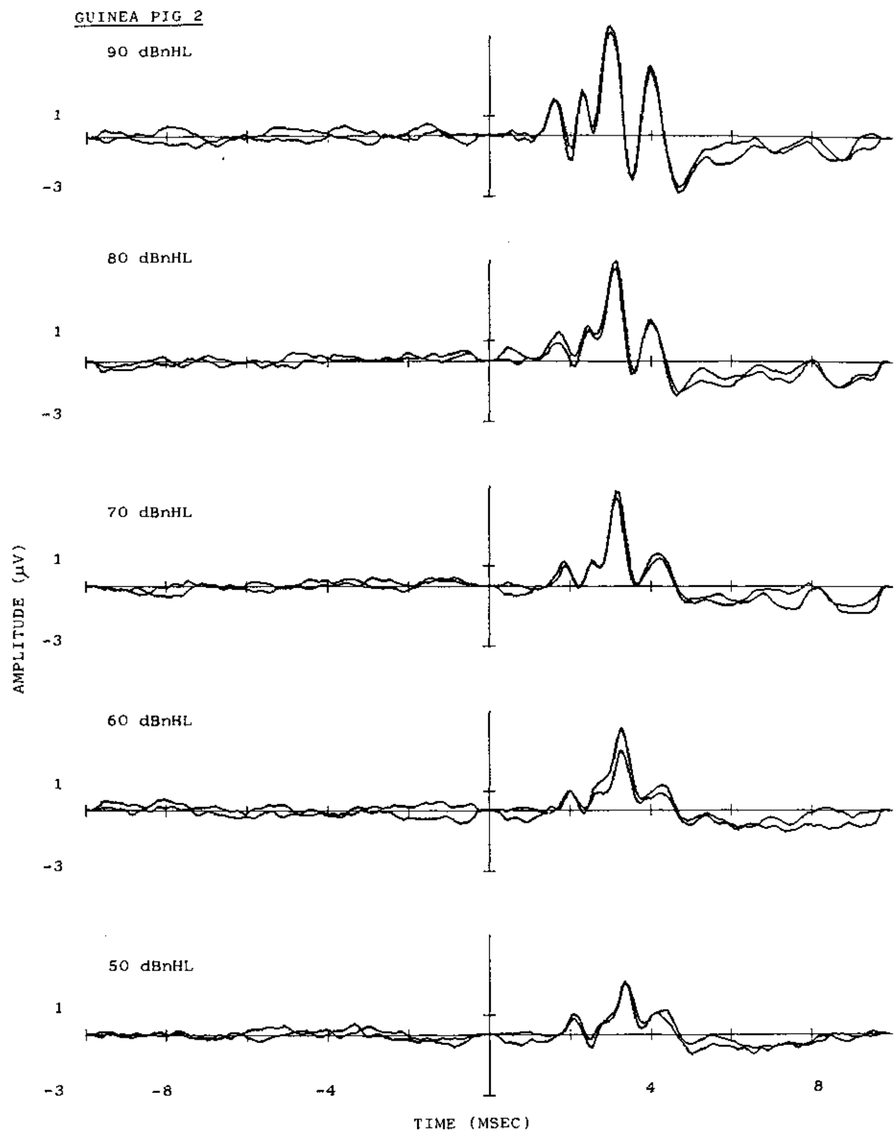

GUINEA PIG 1
40 dBnHL
1
-3
30 dBnHL
1
-3
20 dBnHL
1
-3
10 dBnHL
1
-3
0 dBnHL
-8
-4
4
8
TIME MSEC.

FIGURE 4.1b



GUINEA PIG 2
90 dBnHL
80 dBnHL
70 dBnHL
60 dBnHL
50 dBnHL
1
-3
AMPLITUDE (µV)
-8
-4
4
8
TIME (MSEC)

FIGURE 4.2a

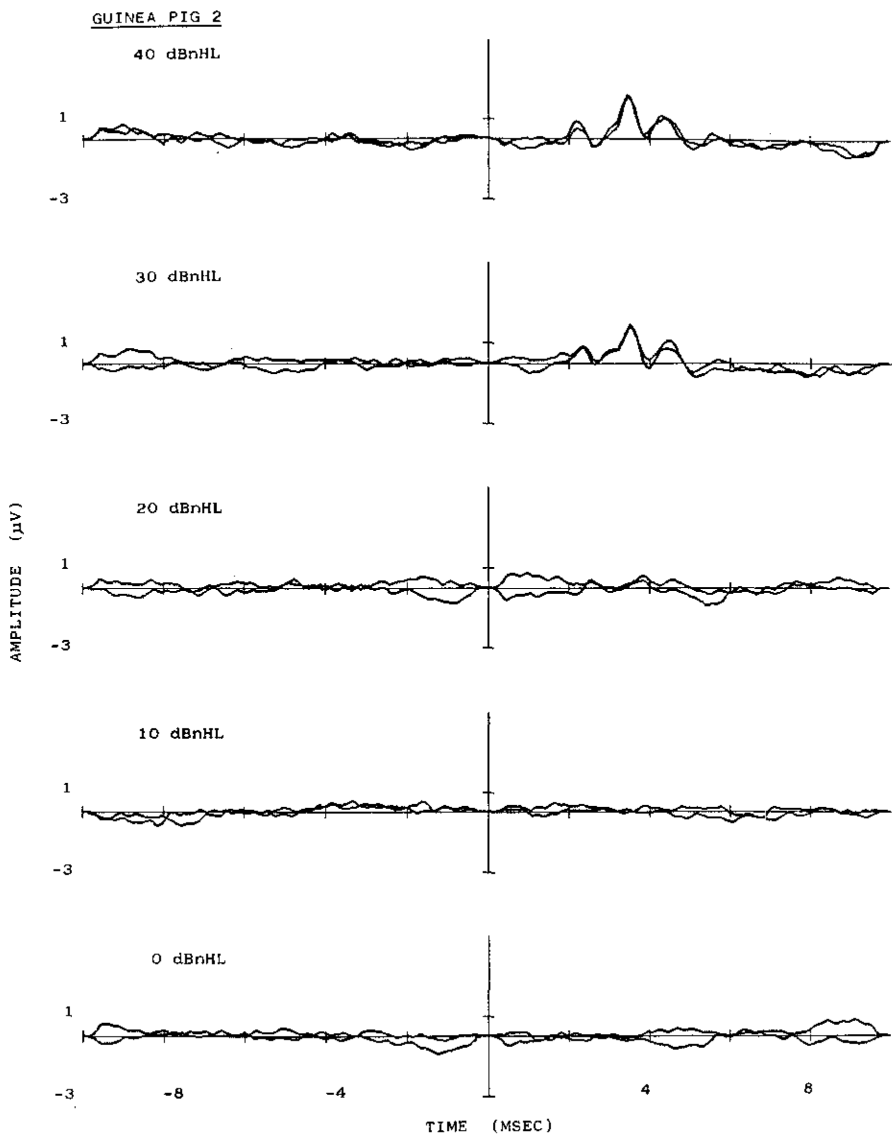

GUINEA PIG 2
40 dBnHL
30 dBnHL
20 dBnHL
10 dBnHL
0 dBnHL
AMPLITUDE (µV)
1
-3
-8
-4
4
8
TIME (MSEC)

FIGURE 4.2b

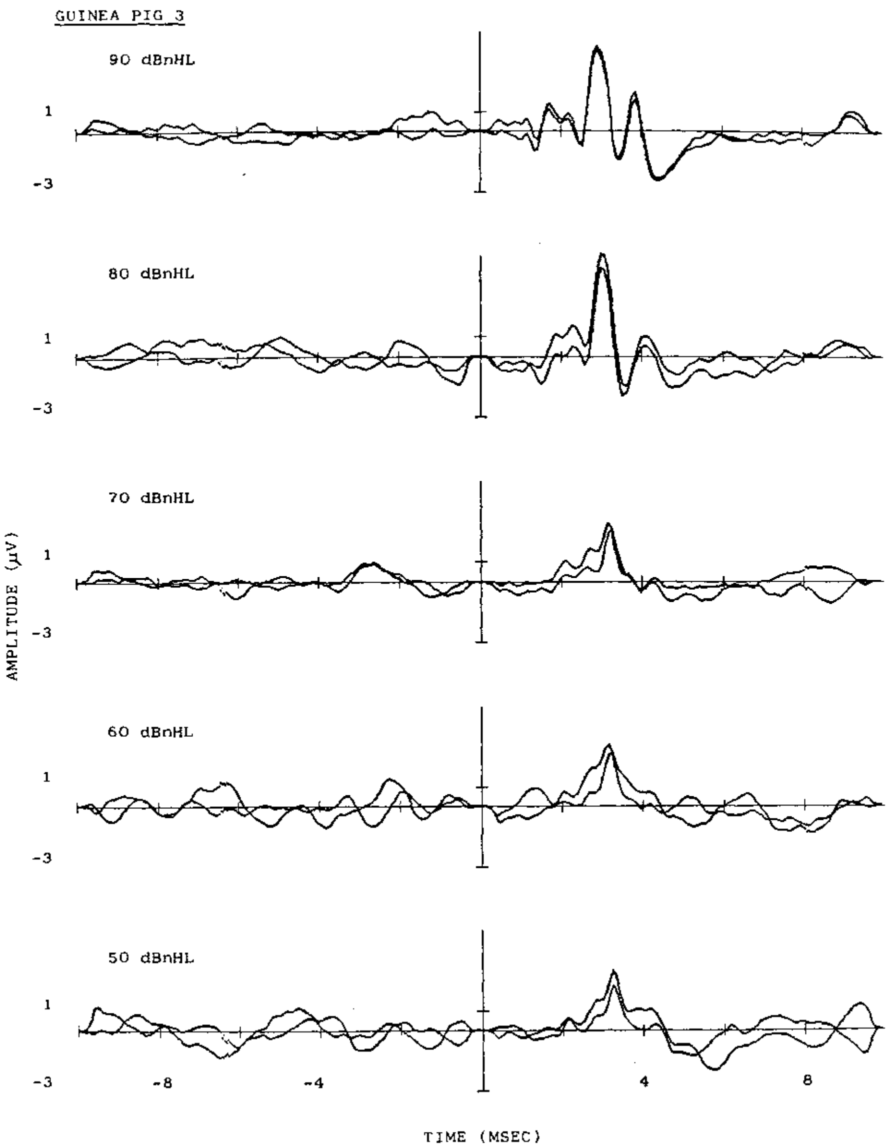

GUINEA PIG 3
90 dBnHL
80 dBnHL
70 dBnHL
60 dBnHL
50 dBnHL
1
-3
AMPLITUDE (µV)
-8
-4
4
8
TIME (MSEC)

FIGURE 4.3a

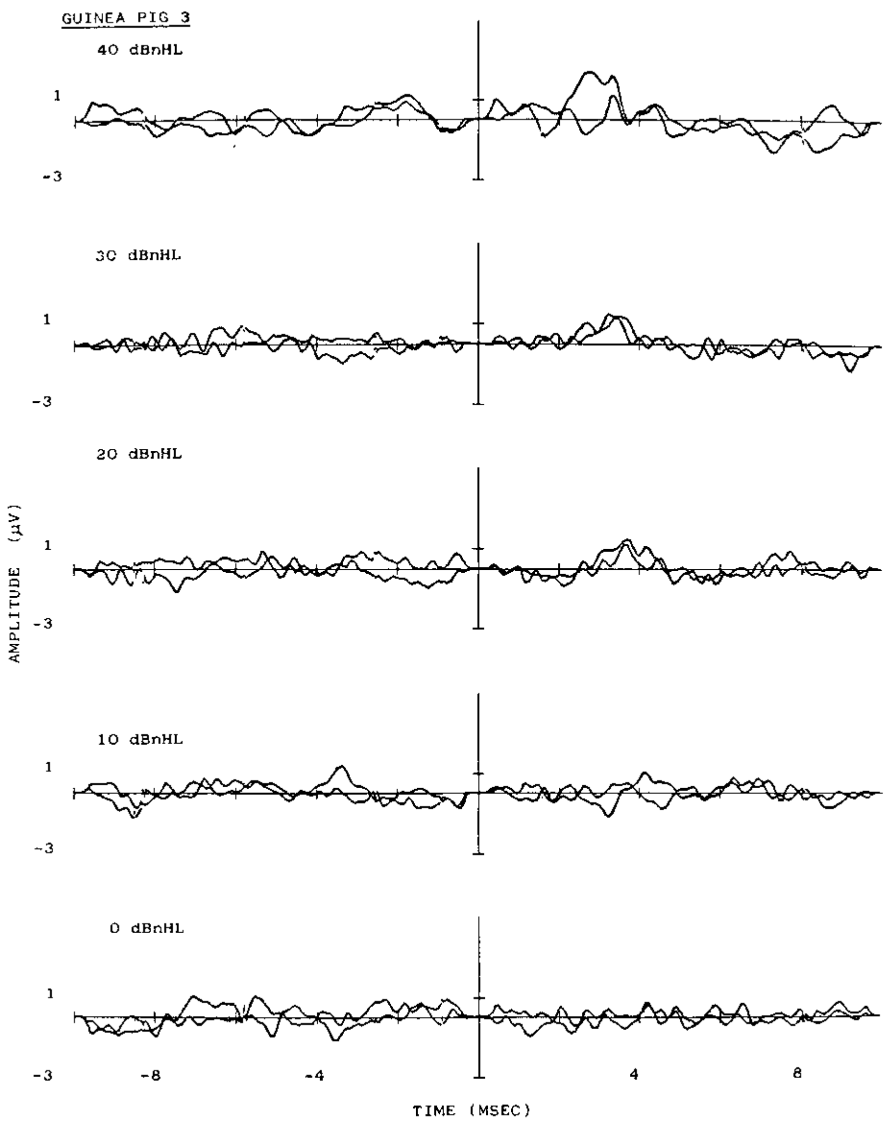

GUINEA PIG 3
40 dBnHL
30 dBnHL
20 dBnHL
10 dBnHL
0 dBnHL
1
-3
AMPLITUDE (µV)
-8
-4
4
8
TIME (MSEC)

FIGURE 4.3b

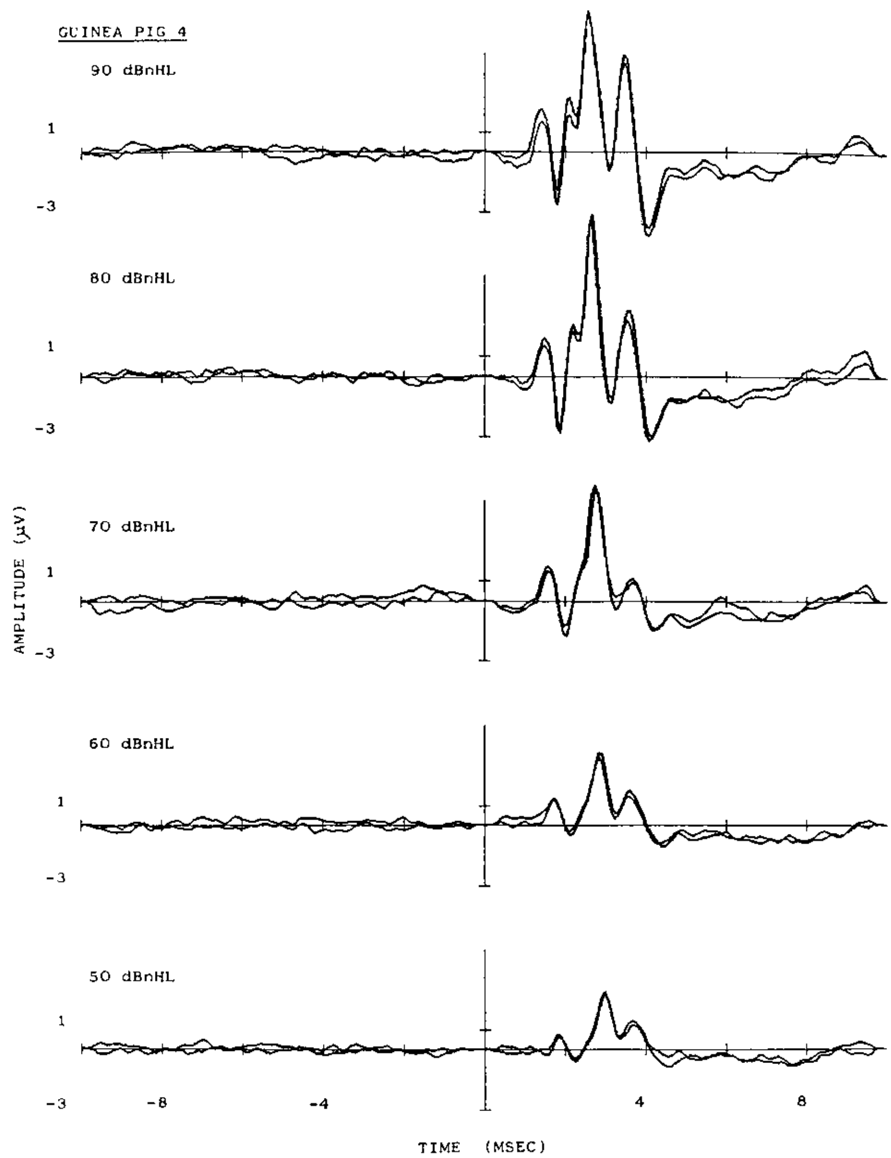

GUINEA PIG 4
90 dBnHL
80 dBnHL
70 dBnHL
60 dBnHL
50 dBnHL
1
-3
AMPLITUDE (μV)
-8
-4
4
8
TIME (MSEC)

FIGURE 4.4a

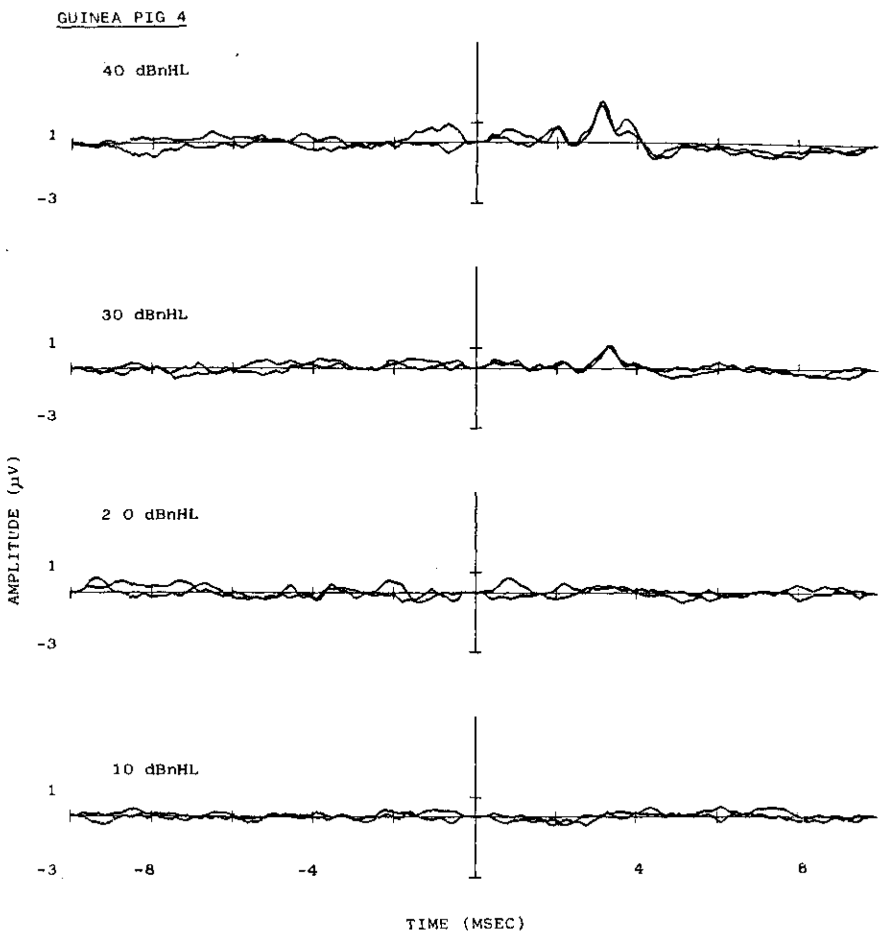

GUINEA PIG 4
40 dBnHL
30 dBnHL
2 0 dBnHL
10 dBnHL
1
-3
1
-3
1
-3
1
-3
-8
-4
4
8
AMPLITUDE (µV)
TIME (MSEC)

FIGURE 4.4b

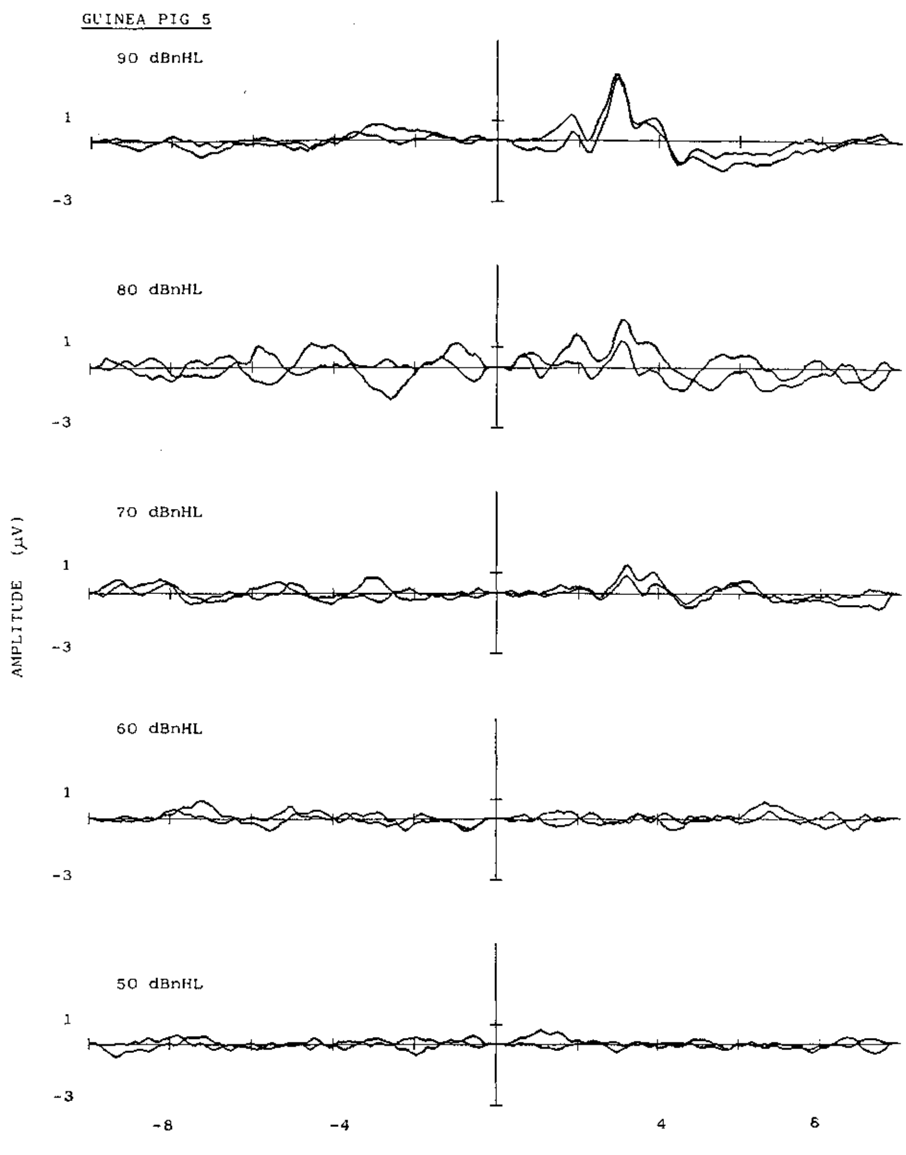

GUINEA PIG 5
90 dBnHL
80 dBnHL
70 dBnHL
60 dBnHL
50 dBnHL
AMPLITUDE (µV)
1
-3
-8
-4
4
8

FIGURE 4.5

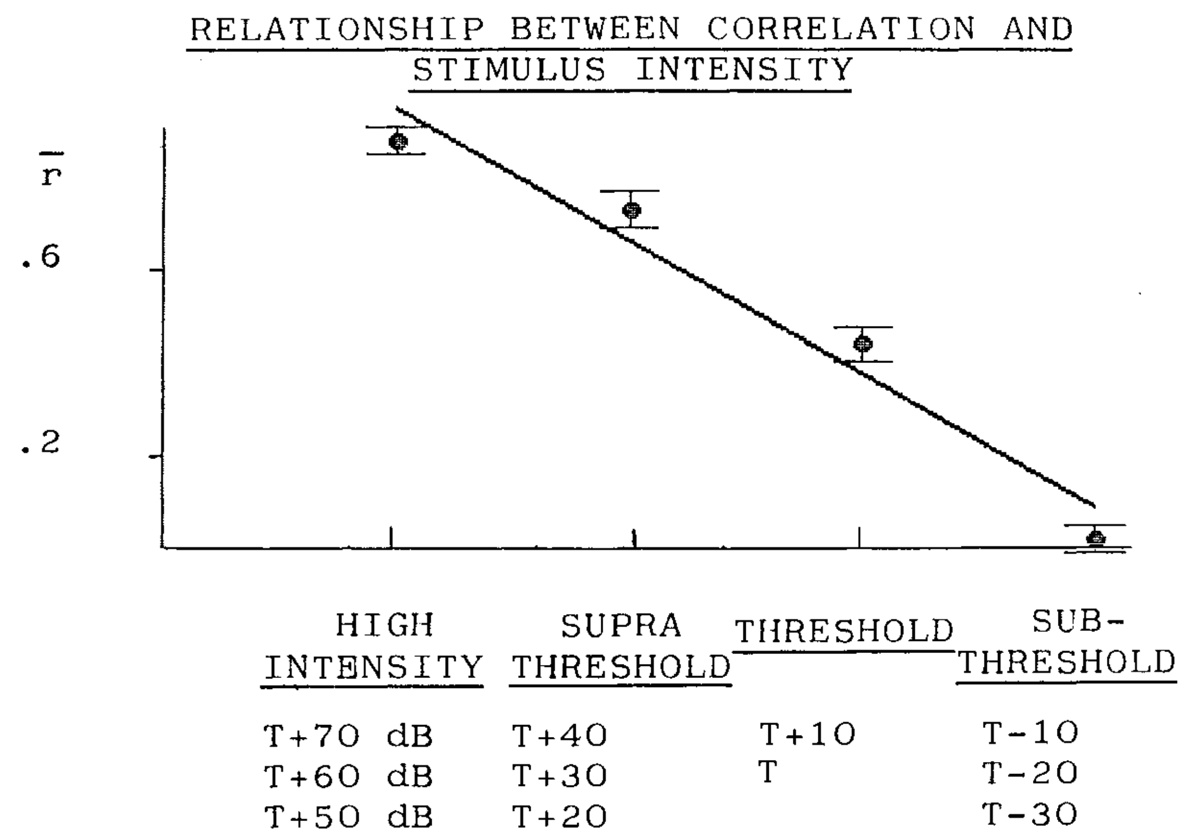


FIGURE 4.6: Pooled responses from 5 guinea-pigs. These have been divided into 4 intensity groups. Threshold for this and all subsequent figures has been based on the just detectable post-stimulus response for each animal. Using the post-stimulus coherent grand-average as a template, mean ensemble correlation co-efficients were calculated for each ensemble of 16 sweeps. The group mean and standard error at each intensity band together with the regression line have been plotted.

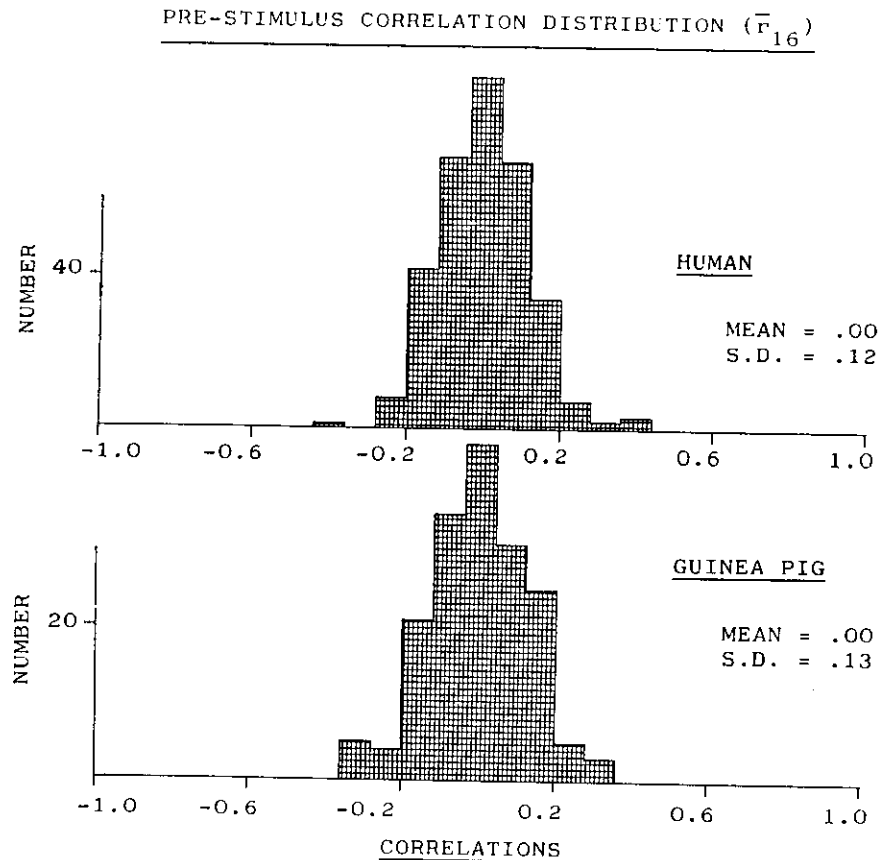


FIGURE 4.7: Human and guinea-pig pre-stimulus mean correlation distributions for 16 sweep ensembles.

(.00) or standard deviations (.12). Such behaviour suggested that the noise characteristics for the guinea pig study were similar to that observed in the human situation and further justification for using this model to investigate the signal statistics.

The relative sensitivity of the method in the guinea pig has been demonstrated in Figure 4.8 which compares the frequency distribution of post-stimulus mean correlations for 16 sweep ensembles and the pre-stimulus frequency distribution. The 1% probability level for the positive tail of the pre-stimulus frequency dsitribution (threshold) has also been included. While the pre-stimulus correlations were mainly to the left of this threshold statistic, the post-stimulus mean correlations were mostly distributed to the right. A more detailed analysis of the post-stimulus correlation distributions at 4 intensity levels was made (Figure 4.9). Threshold throughout was the just detectable level of response and the level 10dB above this. Supra-threshold referred to stimuli in the region of 20 to 30dB above the level at which a response was detected. High level responses were those obtained at intensities above supra-threshold. In contrast to the human study approximately 75% of records in the region of threshold exceeded the threshold criteria. Such a relatively high yield of significant positive correlations was in keeping with the large signal to noise ratio in the model. Sub-threshold records gave a correlation distribution similar to that obtained for unstimulated conditions.

The decreases in the mean correlation at lower stimulus levels may be attributed to 2 factors, degradation of response pattern and variations in response latency. It was therefore decided to evaluate alternative methods which might reasonably be considered sensitive to the presence of a consistent pattern. The correlation coefficient would provide a useful comparison. The forgoing template matching method assumed some prior knowledge of the pattern being investigated The alternative methods which have been investigated demanded no such requirements.

POWER ANALYSIS

A simple but widely accepted model of evoked potential generation proposes that a consistent signal is superimposed on the spontaneous E.E.G. in response to a stimulus. This suggests that signal detection techniques based on power measures would be appropriate. The power of a record in which the response has been

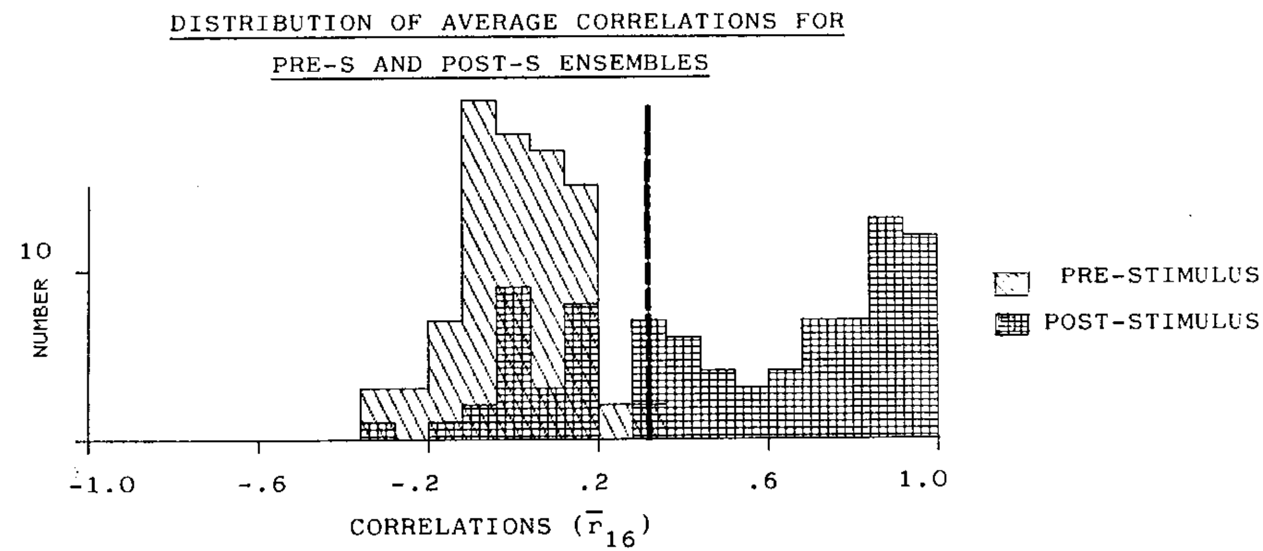


FIGURE 4.8: Comparison of mean correlation distributions from unstimulated and stimulated records. The 1% level of the positive tail of the pre-stimulus distribution has been included.

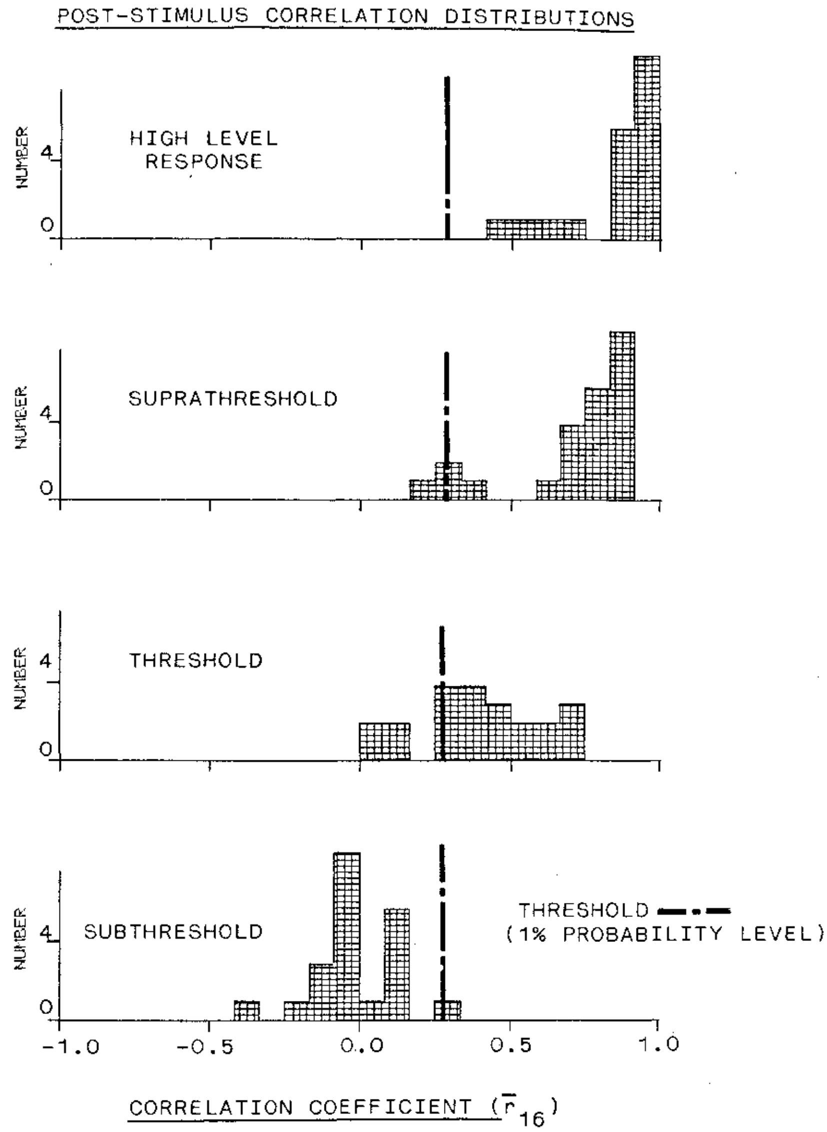


FIGURE 4.9: Frequency distribution of post-stimulus ensemble mean correlation co-efficients for 4 intensity bands. At threshold, approximately 25% of the records failed to reach the threshold criteria.

superimposed on uncorrelated spontaneous noise should exceed that of the noise source alone. The usefulness of power and amplitude measures have been investigated by Beagley, Sayers and Ross (1979). Major limitations were shown to arise because of the low signal to noise ratio and also because of the marked variability of the background noise. Nevertheless in the present study of brainstem potentials it was found instructive to examine the relationship between the cross-correlation coefficient and banded power of the coherent grand-average (Figure 4.10). A high positive correlation was obtained ($r = 0.84$, $p < .001$). The relationship between the mean cross-correlation coefficient ($\bar{r}$) and ensemble mean power, or R.M.S. was then evaluated (Figure 4.11). The mean R.M.S. for the first 15 harmonics (broad band response) and the first 8 harmonics (narrow band response) were separately studied. In contrast to the high correlations observed with the coherent grand-average R.M.S., the correlation between ensemble R.M.S. and ensemble $\bar{r}$ was relatively weak, although positive and significant. Two possible causes for the decrease in the correlation were large intersubject variability in individual responses power and large intersubject variability in background noise. The relationship was therefore investigated using a different ensemble measure, coefficient of variability. With coefficient of variability the distribution of individual response amplitudes were normalised and therefore the effects of mean signal level differences from subject to subject and from session to session were eliminated. A high **negative** correlation was obtained ($r = -.73$, $p < .001$) (Figure 4.12).

One possible source of intersession variability was change in background noise level. An estimate of the background noise occurring during a post-stimulus sweep was provided by the immediate pre-stimulus noise level. A correction of this noise contribution was achieved by subtracting the mean pre-stimulus level from the post-stimulus R.M.S. Using corrected R.M.S. level a substantial increase in the correlation between $\bar{r}$ and R.M.S. was obtained ($r = .78$, $p < .001$) (Figure 4.12). However, no significant improvement resulted when individual post-stimulus R.M.S. values were corrected by removing corresponding pre-stimulus R.M.S. values.

SPECTRAL ANALYSIS OF BRAINSTEM POTENTIALS

It is well recognised that the time domain pattern of the coherent average depends on the contributions of the amplitudes and phases of significant Fourier components. The mechanisms underlying increase in

RELATIONSHIP BETWEEN POST-S COHERENT GRAND AVERAGE POWER
AND ENSEMBLE MEAN CORRELATION COEFFICIENTS

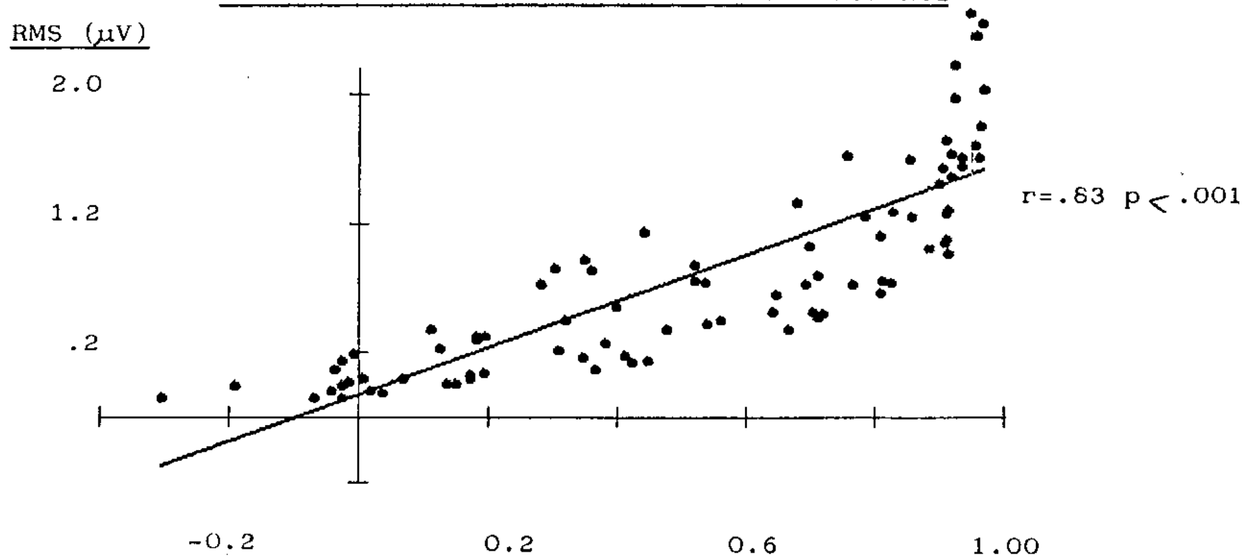


FIGURE 4.10: Coherent grand-average has been digitally filtered to 100-3,000 Hz. (harmonics 1-15).

RELATIONSHIP BETWEEN POST-S ENSEMBLE MEAN POWER
AND ENSEMBLE MEAN CORRELATION COEFFICIENT

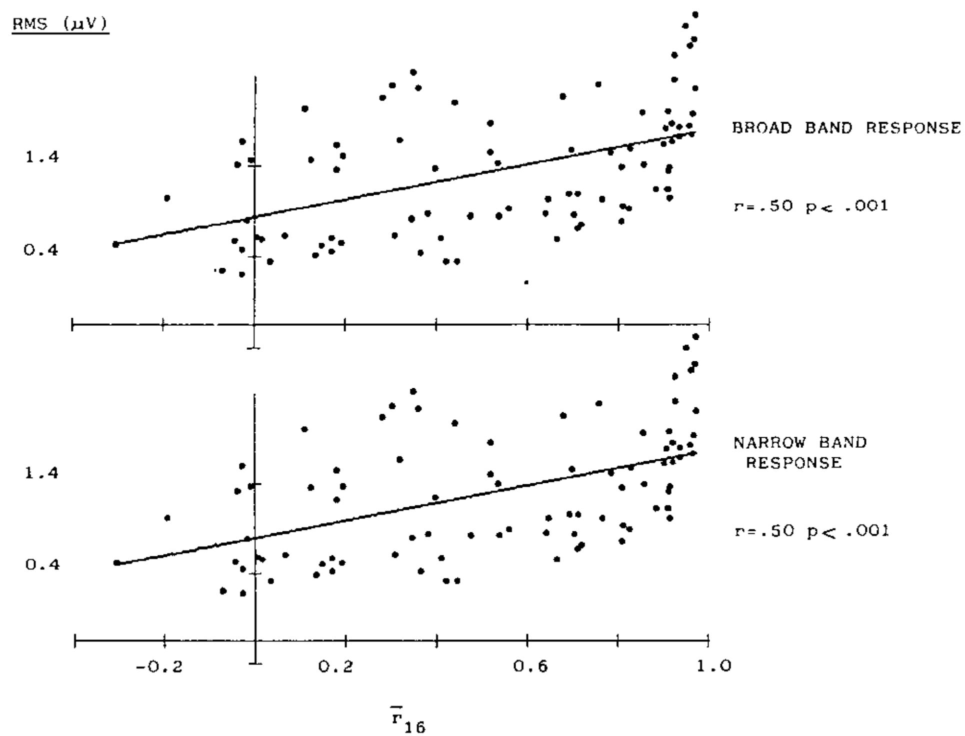


FIGURE 4.11: Individual broad-band responses have been digitally filtered to 100-3,000 Hz., narrow-band to 100-1,600 Hz., (harmonics 1-8).

RELATIONSHIP BETWEEN ENSEMBLE POWER STATISTICS
AND ENSEMBLE MEAN CORRELATION COEFFICIENT

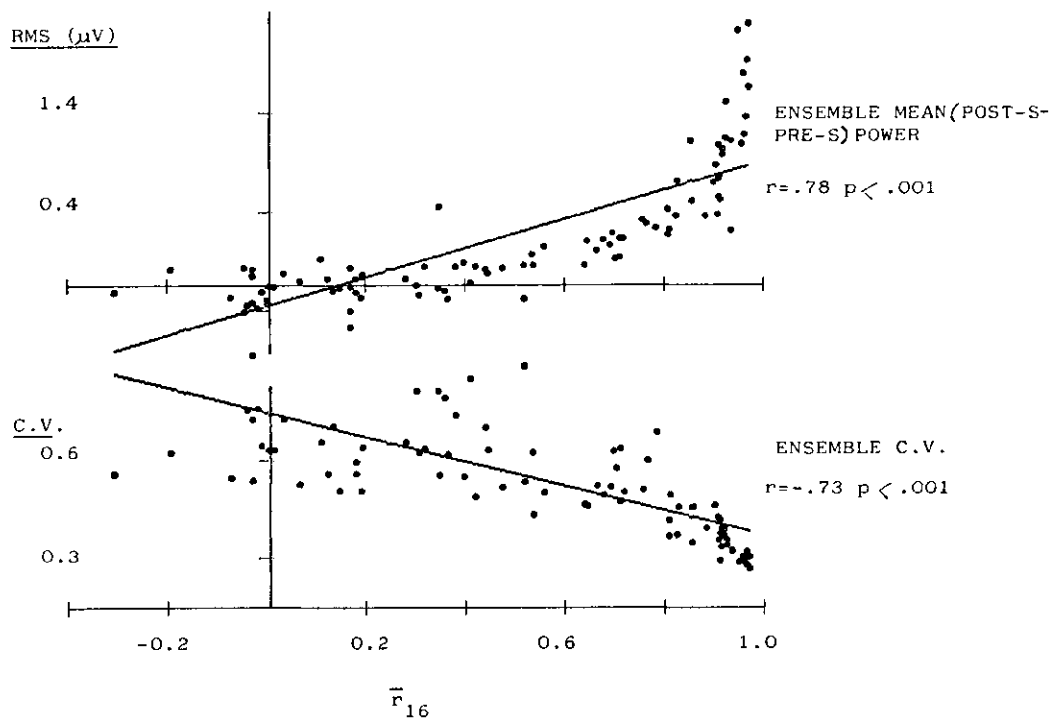


FIGURE 4.12: In the upper figure the regression line between ensemble differences in post-stimulus and pre-stimulus power and ensemble correlation co-efficient has been plotted. In the lower figure the regression line between ensemble C.V. of power and ensemble correlation co-efficient has been plotted.

pattern of the average and the increase in magnitude of the cross-correlation coefficient may be clarified by examining the contributions made by individual harmonics of each post-stimulus record. The correlation coefficient measures the fraction of power linearly held in common between the record and so is sensitive to relative amplitudes of individual spectral components and the relative phases in the 2 records,

$$r = \frac{\sum_{m=1}^{M} \text{Cross power due to harmonic } m}{(\text{Power in average} \times \text{power in sweep})^{\frac{1}{2}}}$$

(Beagley, Sayers and Ross, 1979)

HARMONIC AMPLITUDE ANALYSIS

The amplitude spectra at each intensity level were averaged and plotted together with the standard errors of the distributions (Figure 4.13). While the pre-stimulus amplitude spectra showed a systematic decrease with harmonic number, in the post-stimulus spectra there were distinctive peaks in the region of the fourth and fifth harmonics. This spectral pattern was evident over the range of intensity levels studied. At high stimulus levels the differences between pre-stimulus and post-stimulus spectra were large for harmonics one to 14. However, in the region of threshold only the first 8-10 harmonics had amplitudes which were greater than the spontaneous noise level and presumably only these were making a significant contribution to the pattern of the coherent average. As the final goal of the study was to develop a method of detecting responses in the region of threshold, it was decided to confine the main signal analysis investigation to the first 8 harmonics.

The behaviour of individual harmonics at different stimulus levels was compared. Amplitudes of all harmonics decreased with reductions in stimulus intensity (Figure 4.14). The relationship was not linear however and over a wide intensity region, from supra-threshold to sub-threshold, differences in amplitude were wholly non-significant. In order to establish confidence intervals for these amplitude measures the statistical behaviour of the corresponding harmonics of unstimulated records were investigated. The amplitude corresponding to the .05 probability level was chosen as "threshold" and calculated from the histograms of frequency distributions formed from the pooled observations on the 5 guinea pigs (Figure 4.15). While the first moments of the harmonic amplitude distributions decreased systematically with harmonic number the general form of the distributions were very similar and approximated to a Chi-squared

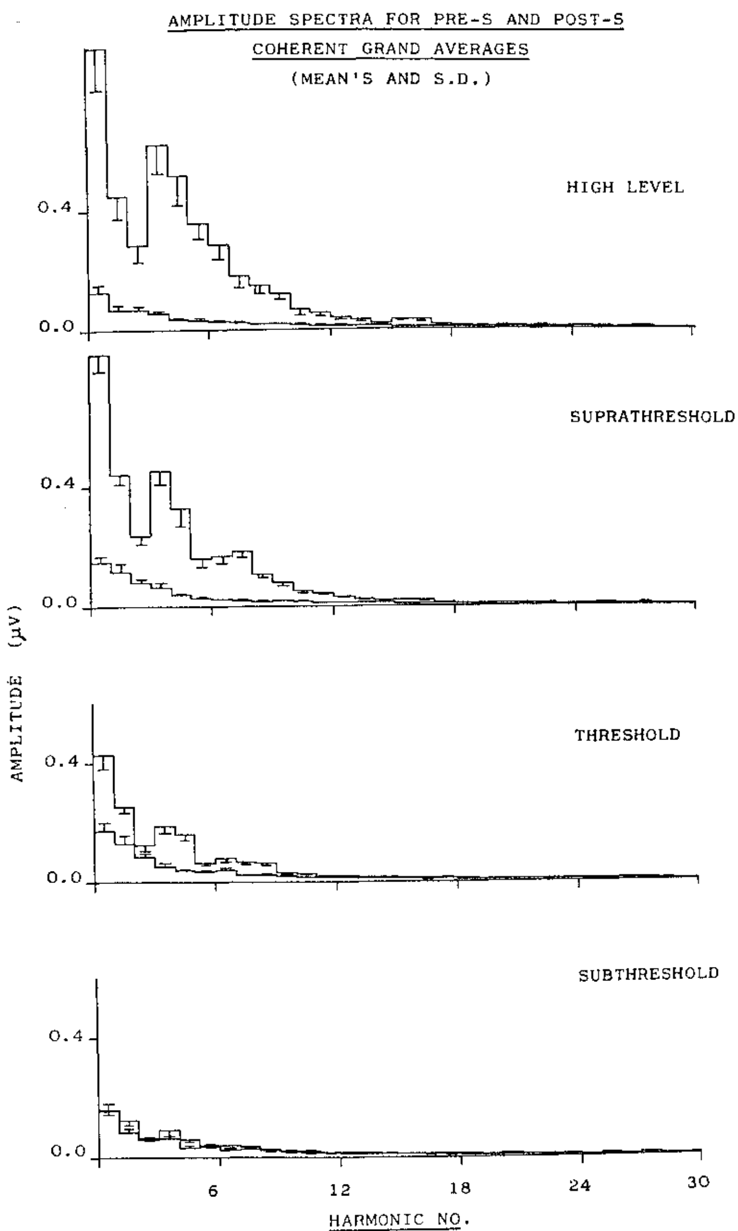


FIGURE 4.13: Mean amplitude spectra of the grand-averages for 5 guinea pigs at 4 intensity levels, together with their standard errors. Pre-stimulus is the lower amplitude level throughout. The time window for spectral analysis was 5 m sec. in this and all subsequent figures.

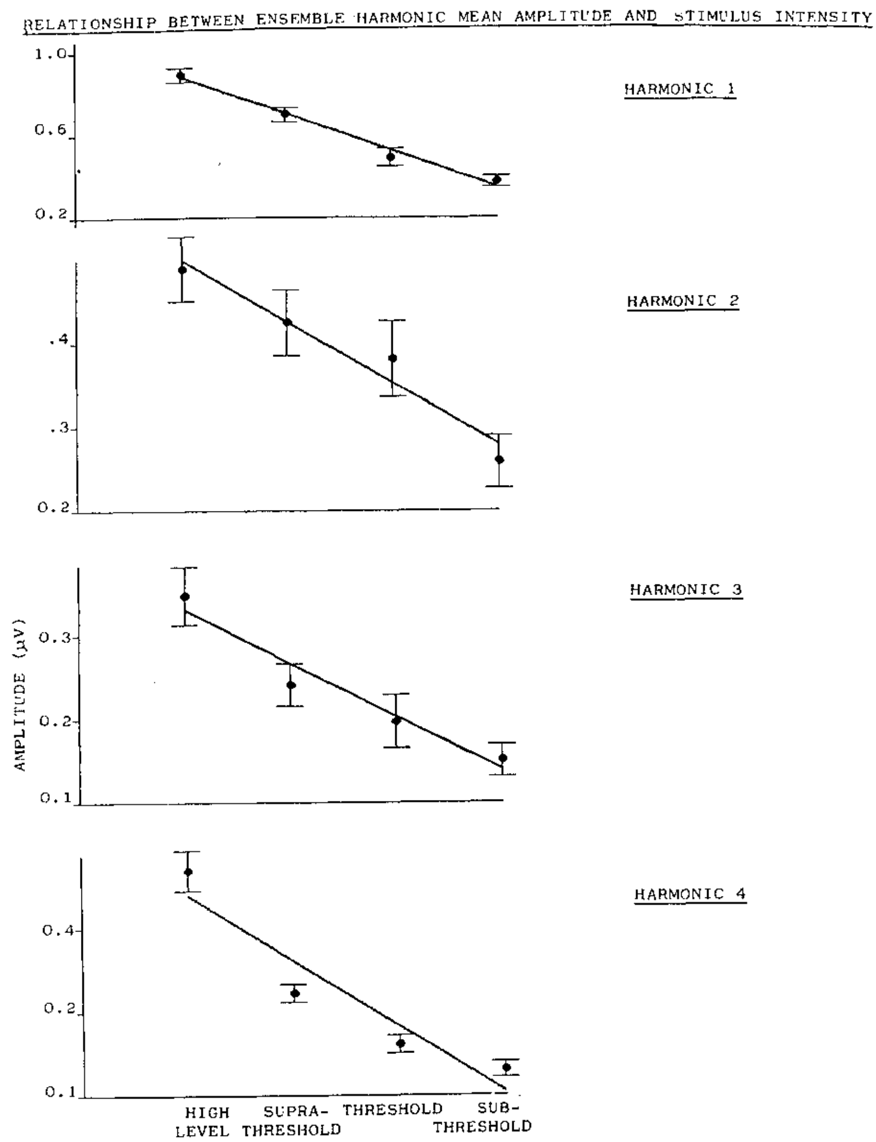


FIGURE 4.14a: In this and the following figure mean R.M.S. and standard errors for individual harmonics were calculated for each ensemble and the average for all responses at each intensity level plotted.

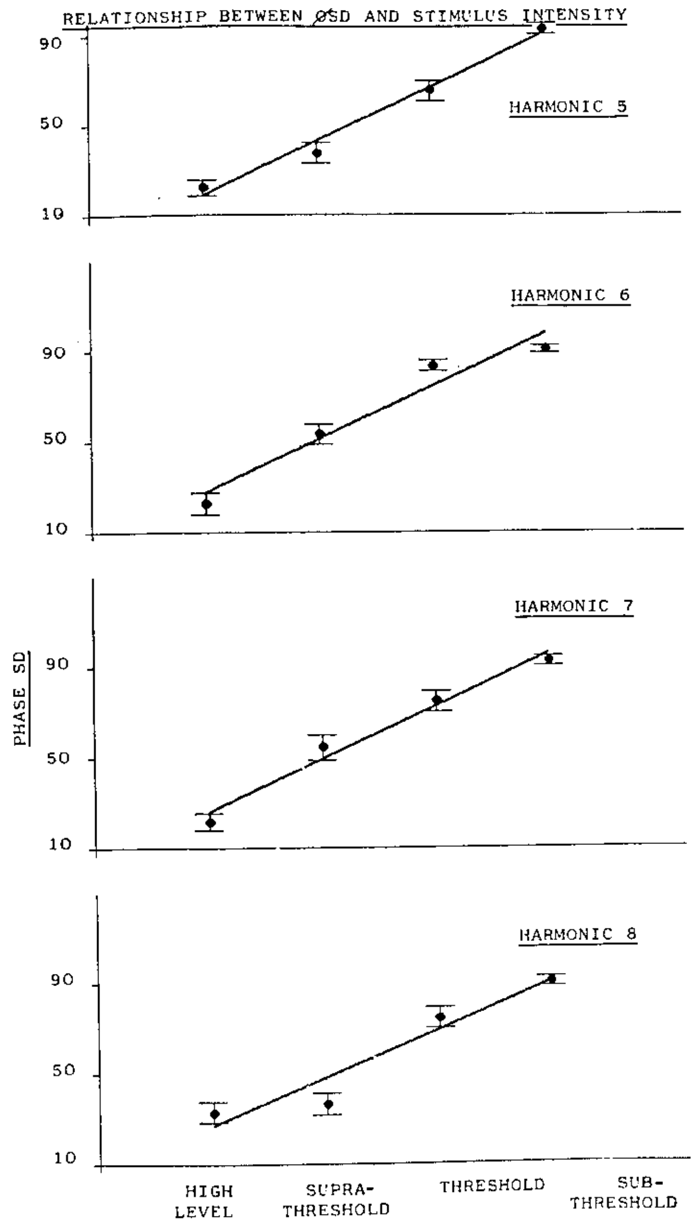


*FIGURE 4.22b

*4.14b on page 111

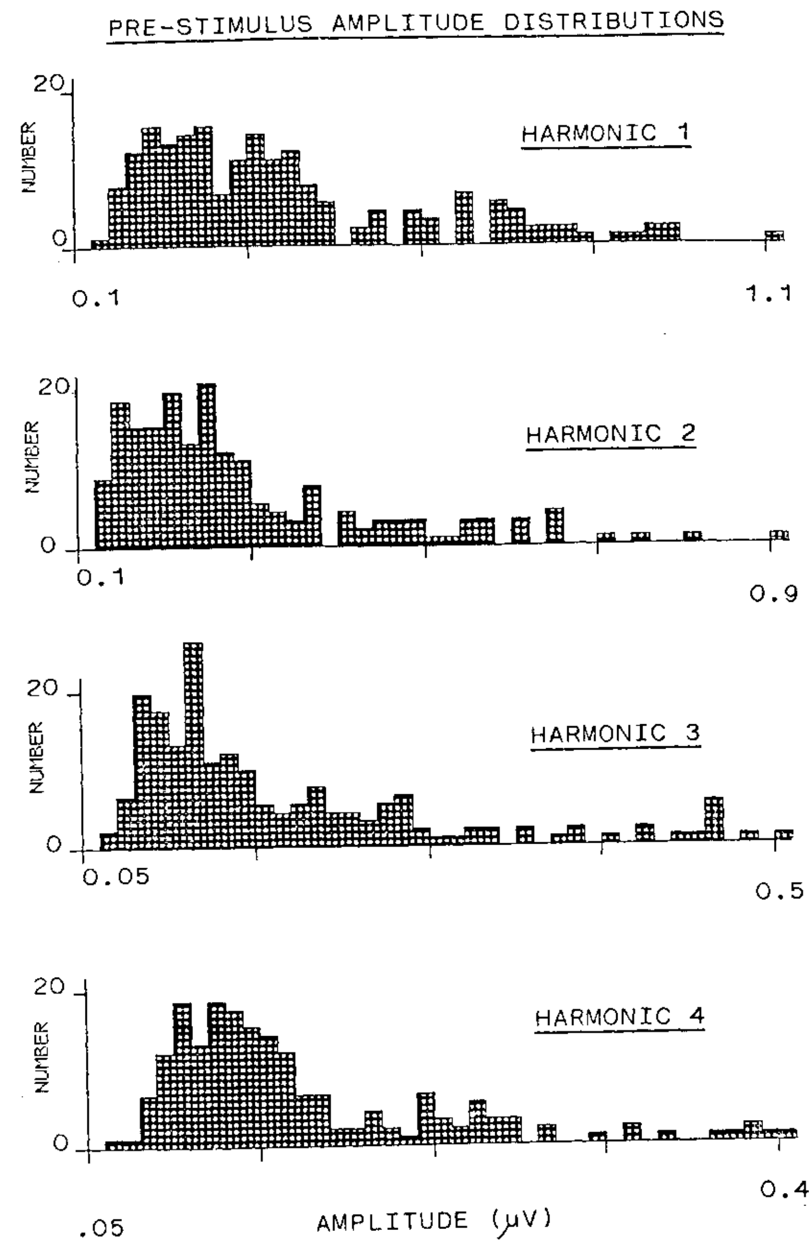


FIGURE 4.15a: In this and the following figure the frequency distribution of ensemble mean amplitudes of individual harmonics for unstimulated records have been plotted, for 88 observations.

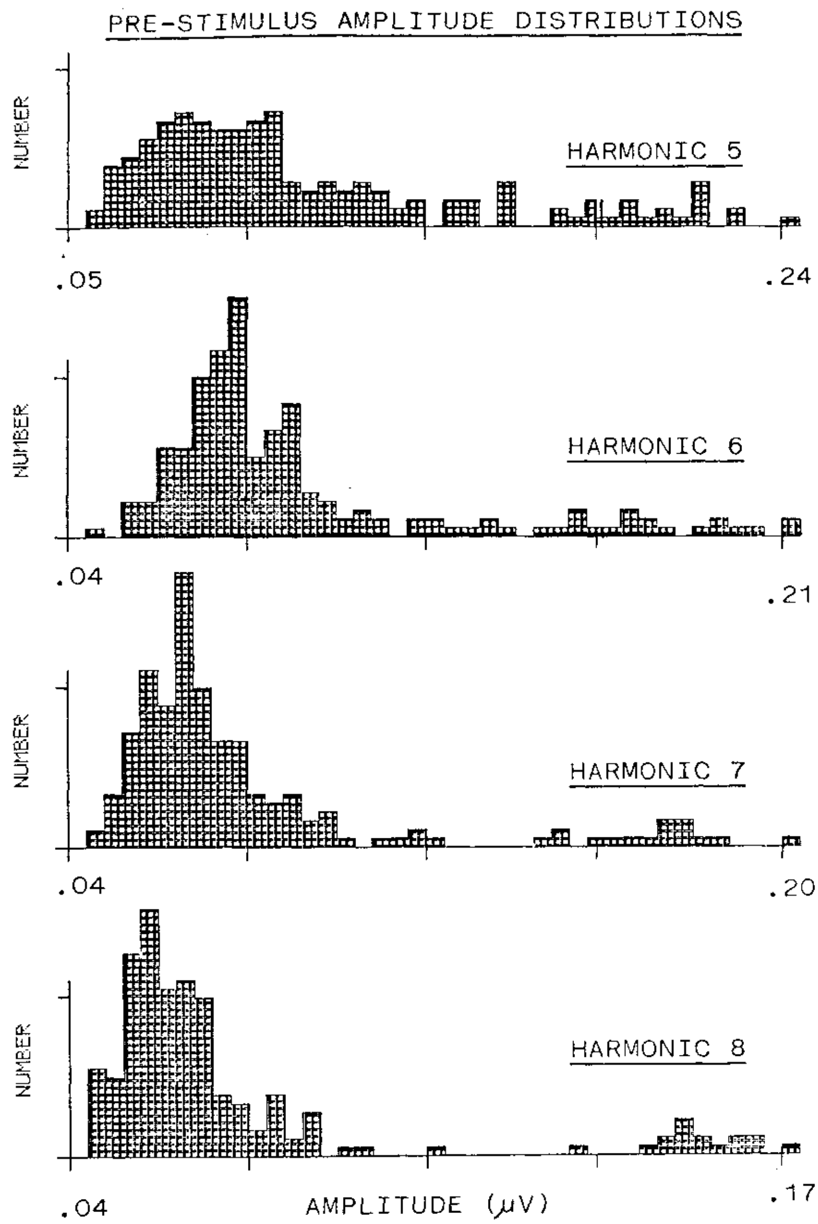

PRE-STIMULUS AMPLITUDE DISTRIBUTIONS
NUMBER
HARMONIC 5
.05
.24
NUMBER
HARMONIC 6
.04
.21
NUMBER
HARMONIC 7
.04
.20
NUMBER
HARMONIC 8
.04
AMPLITUDE (μV)
.17

FIGURE 4.15b

distribution with 2-3 degrees of freedom. The choice of the 5% level as "threshold" was quite arbitrary and by definition would lead to a number of false positive decisions. However, in view of the extreme variations in amplitude it was considered a reasonable compromise. The level of confidence can obviously be altered empirically once the most sensitive signal statistics have been delineated. The post-stimulus frequency distributions of harmonic ensemble mean amplitude have been plotted in Figure 4.16. For most harmonics high stimulus intensities produced harmonic amplitudes which exceeded the 5% level of unstimulated records. This suggested that amplitude criteria alone may be used to differentiate between no-stimulus and high intensity conditions. However the frequency distributions of harmonic amplitudes at all other stimulus intensities were much more problematic and in the region of threshold 78% of observations failed to reach the "threshold" criteria. Harmonic amplitude was evidently a very insensitive measure of auditory threshold. This was due largely to the extreme variability of spontaneous noise such that a confidence interval corresponding to the 5% probability level resulted in a large number of false negative decisions. As stated above, reducing the criterion level would have the opposite effect and give an unacceptable number of false positive decisions.

From observations of pre-post differences and the effects of correcting for mean spontaneous noise level, some improvement in the sensitivity of the method would have been expected (Figure 4.12). However, the requirement of establishing confidence intervals with a high degree of reliability would necessitate collecting many unstimulated records. Such a procedure would not only be time consuming, it would be confounded by the problems of amplitude variability.

HARMONIC PHASE ANALYSIS

One possible alternative to parameters based on measures of power and harmonic amplitude was a statistic derived from the ensemble phase distribution. Phases are however more problematic. The phase spectrum of a signal can be considered to consist of 2 independent functions of frequency. These have been illustrated for the brainstem potentials in Figure 4.17. Neither can be distinguished readily from the conventional representation of phase within the range $\pm\pi$ because of its periodic nature which leads to wrap-around effects However, by unwrapping the phase spectrum a linear trend proportional to frequency can be seen. The slope of this trend is the first

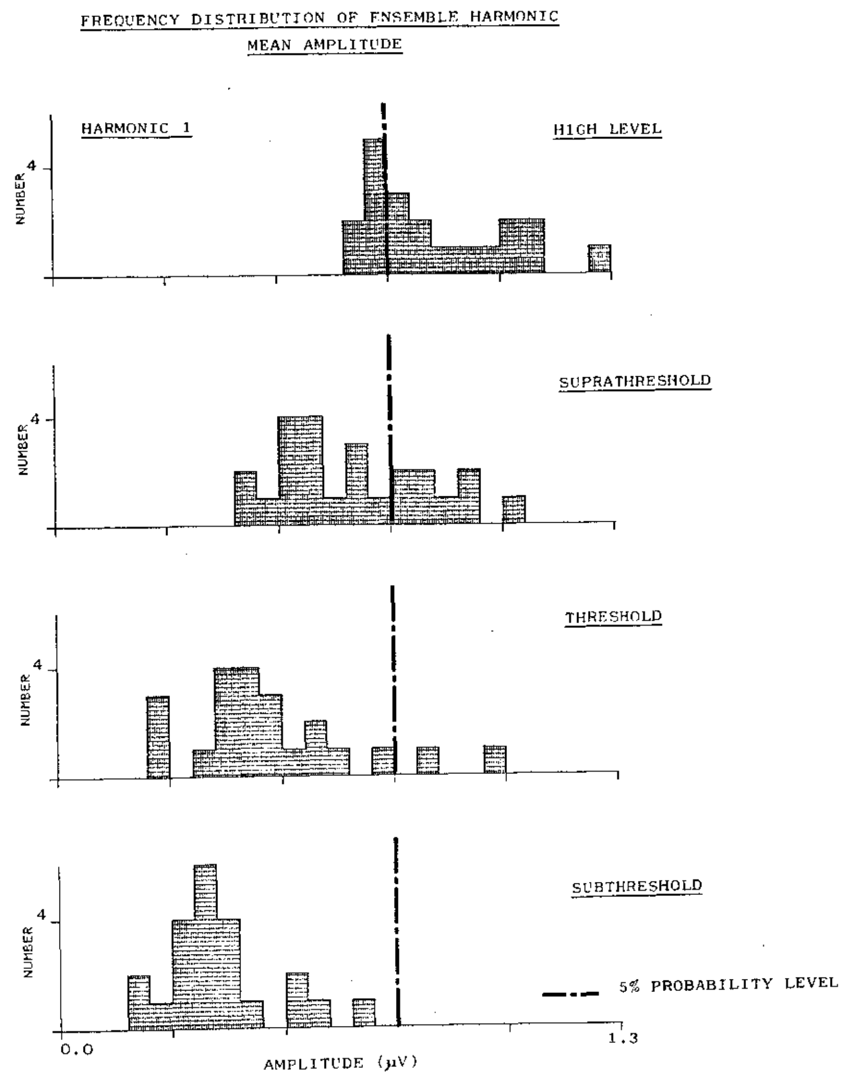


FIGURE 4.16a: In this and the following 7 figures the post-stimulus frequency distributions of ensemble mean amplitudes have been plotted for individual harmonics for the 4 stimulus intensity levels. The confidence interval for the 0.5 probability level has also been included.

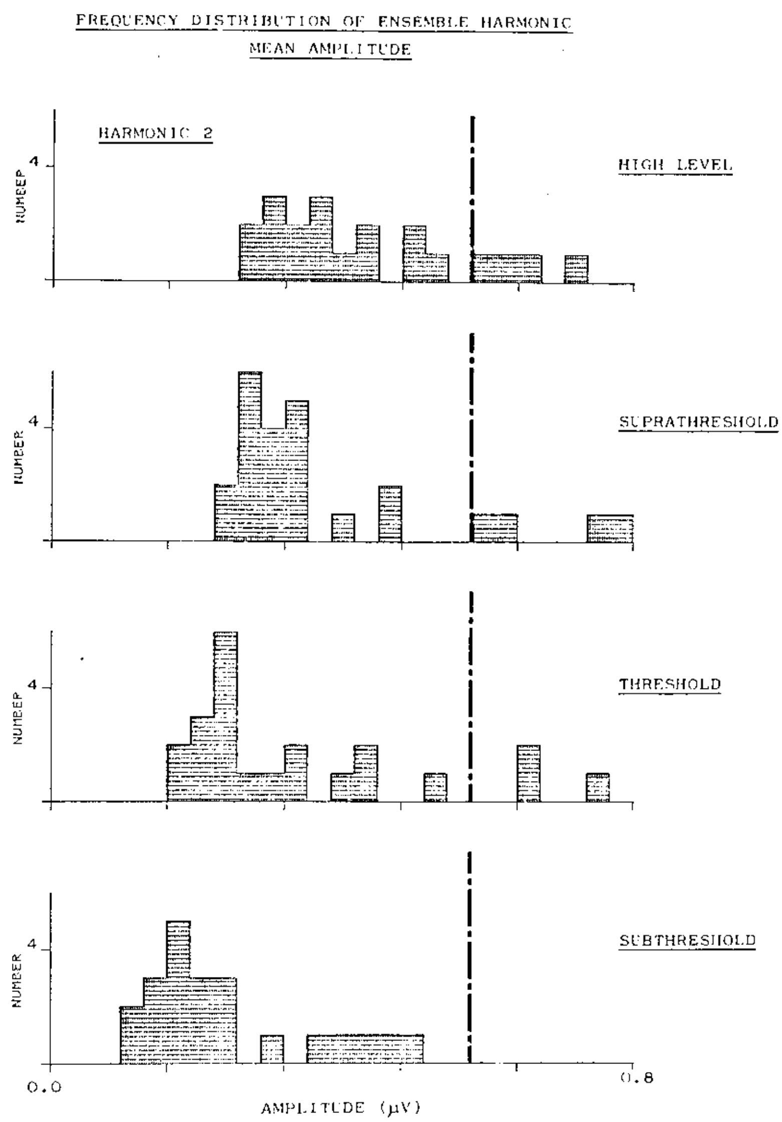

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 2
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.8
AMPLITUDE (µV)

FIGURE 4.16b


FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 3
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.5
AMPLITUDE (μV)

FIGURE 4.16c

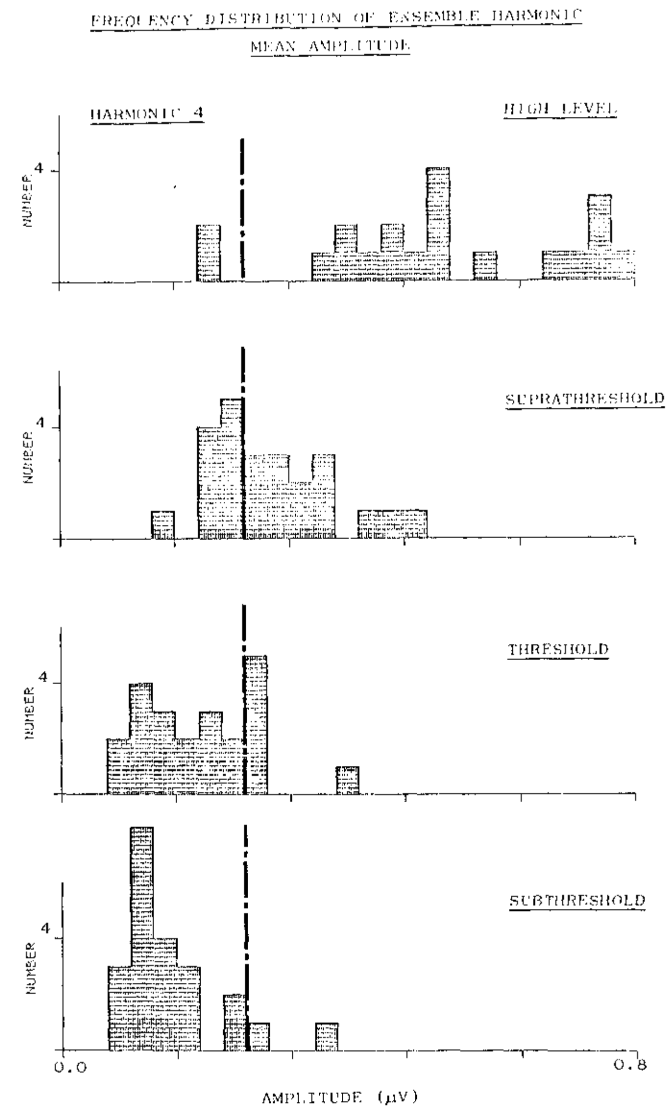

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 4
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.8
AMPLITUDE (µV)

FIGURE 4.16d

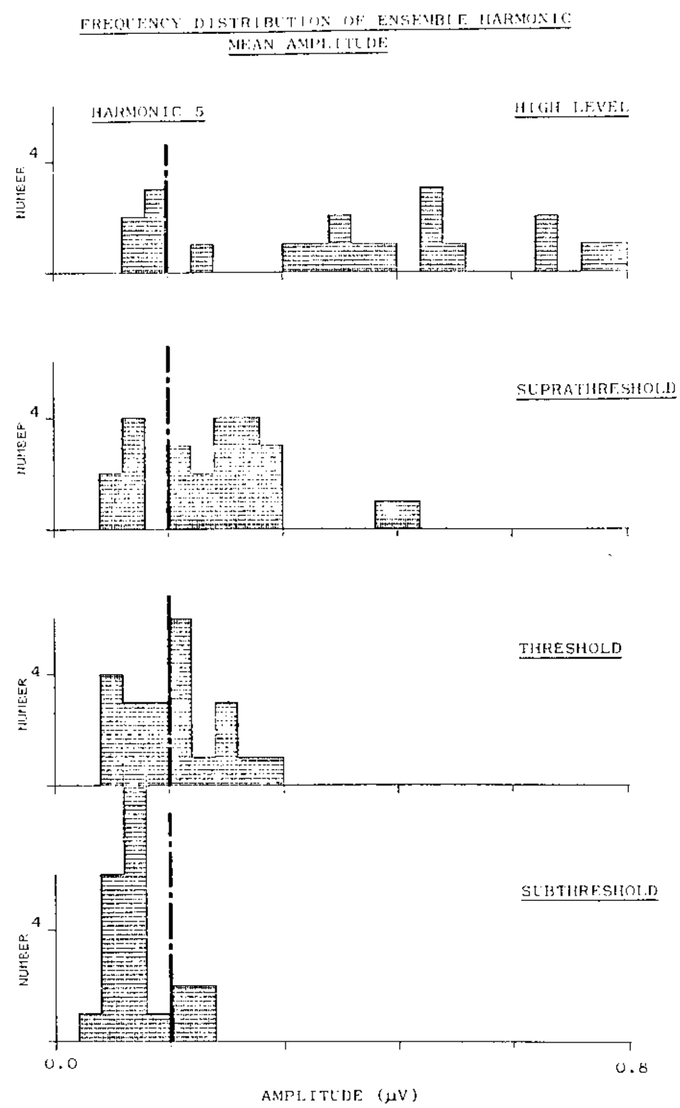

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 5
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.8
AMPLITUDE (μV)

FIGURE 4.16e

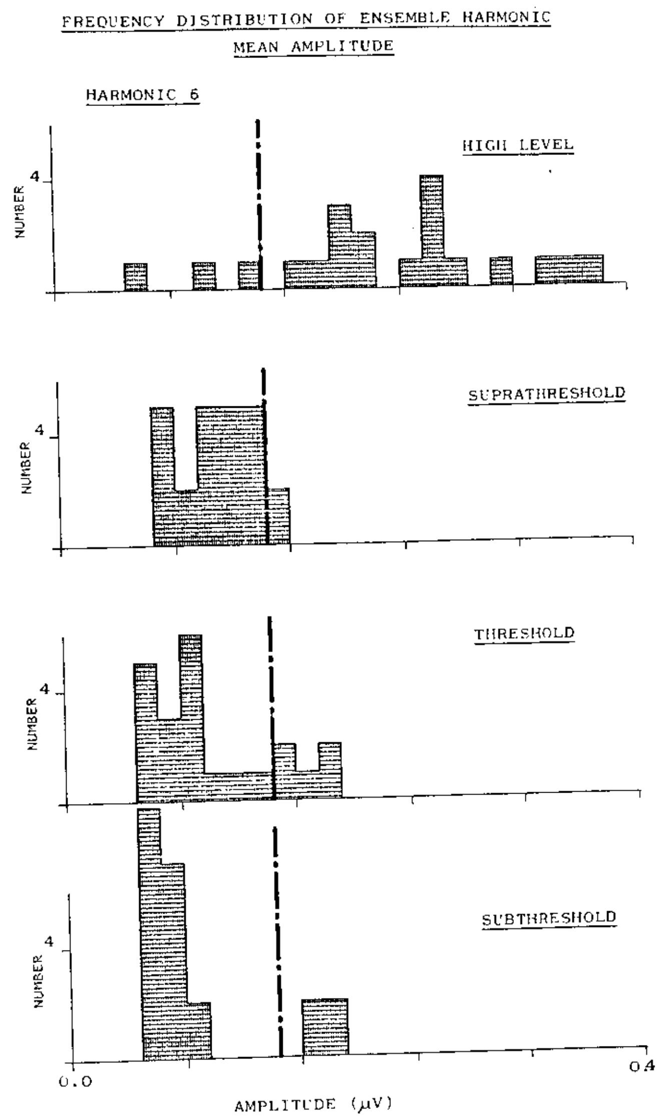

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 6
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.4
AMPLITUDE (µV)

FIGURE 4.16f

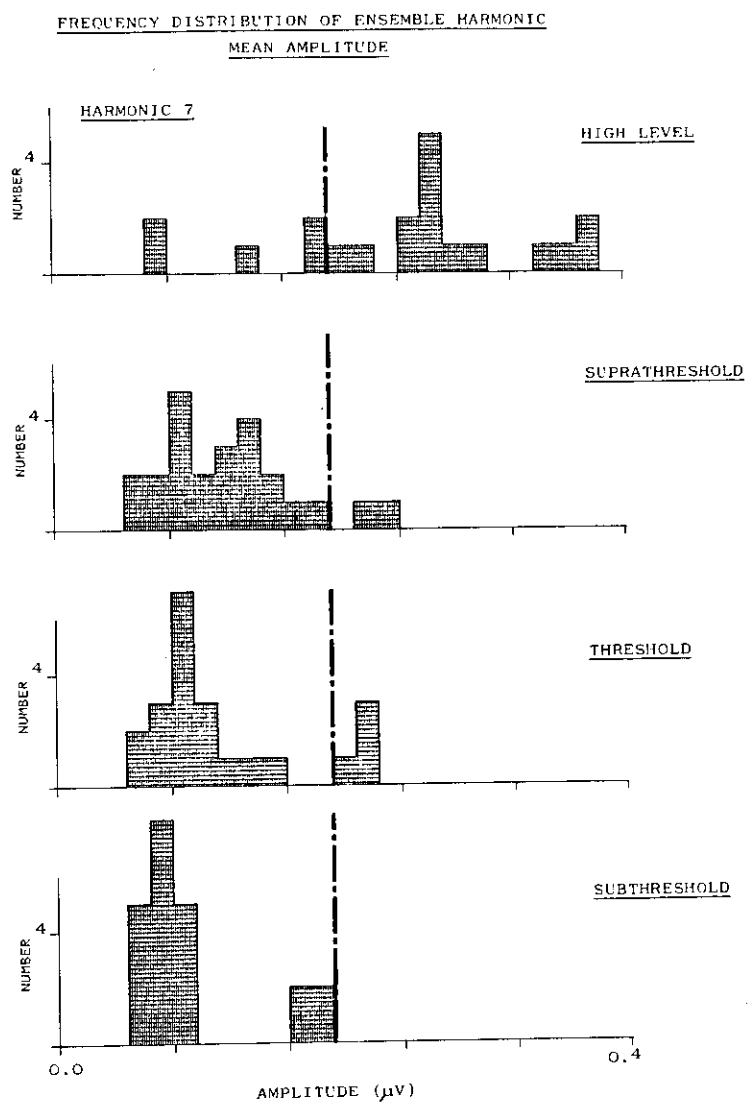

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 7
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.4
AMPLITUDE (μV)

FIGURE 4.16g

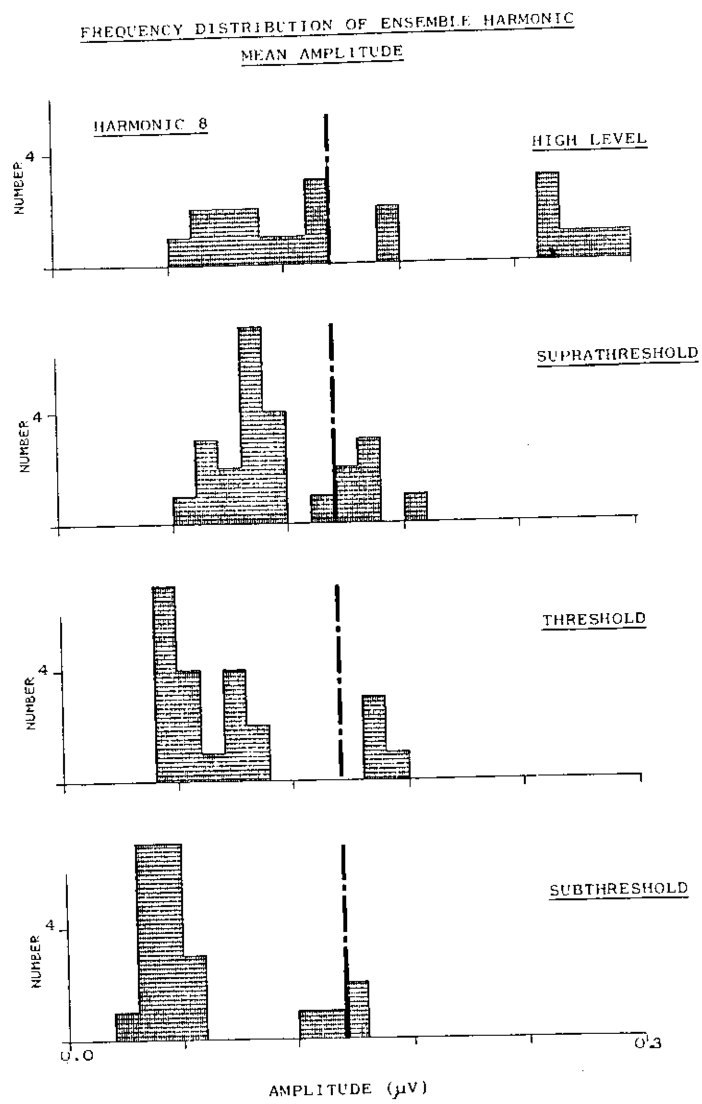

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC
MEAN AMPLITUDE
HARMONIC 8
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0.0
0.3
AMPLITUDE (μV)

FIGURE 4.16h

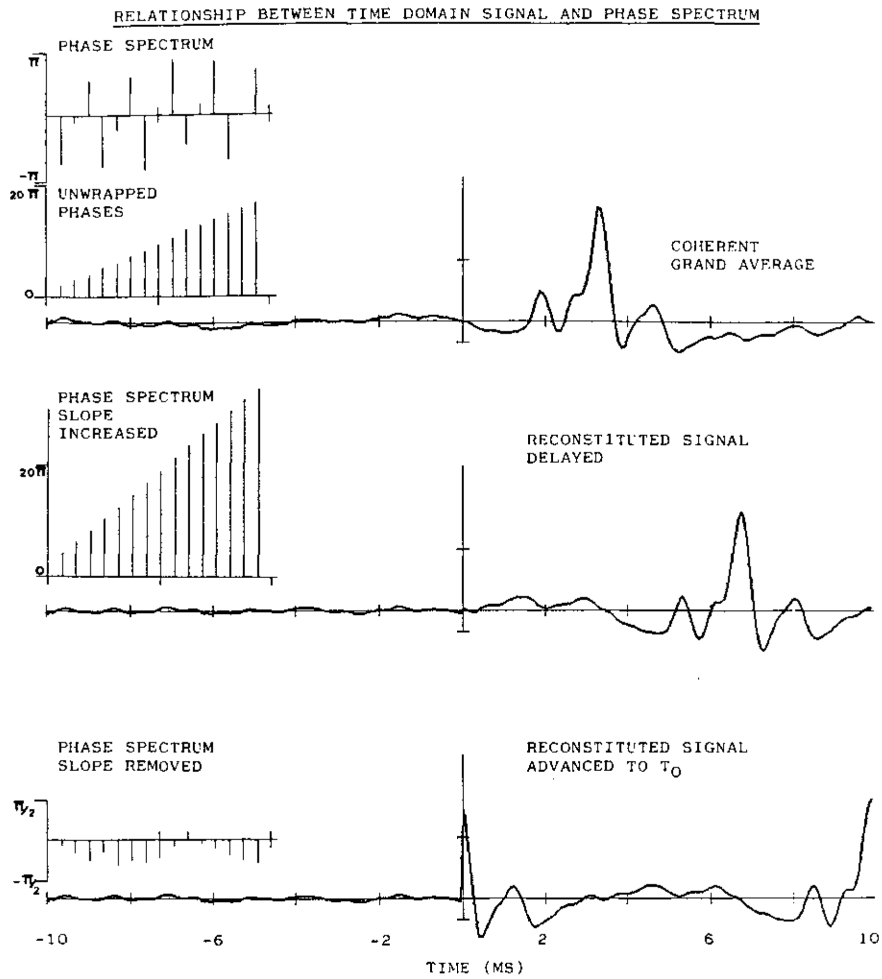


FIGURE 4.17: Phase spectrum of the coherent grand-average of a typical high level response. This figure shows the relationship between the slope of the unwrapped phase spectrum and the latency of the time-domain signal.

function of frequency and is the frequency representation of temporal delay of the signal. Removal of this trend reveals the spectrum due solely to the time domain pattern of the signal.

In a study of late cortical evoked potentials it has been shown that merely imposing the phase spectral-characteristics of the post-stimulus coherent average on an ensemble of unstimulated records formed a consistent pattern which was highly correlated with the original coherent average (Sayers and Beagley, 1974). The same effect was observed for the auditory brainstem potentials. The ensemble cross-correlations were calculated for pre-stimulus and high level post-stimulus records in each of 2 guinea pigs:

	Post-stimulus	Pre-stimulus
Guinea pig 1 $\bar{r}$	.82	-.01
Guinea pig 2 $\bar{r}$	.90	-.16

The amplitude and phase spectral values were calculated and the phases for the pre-stimulus and post-stimulus epochs of each record swopped. The time-domain record was then reconstituted and the cross-correlations between each record and the original coherent average calculated:

	Post-stimulus	Pre-stimulus
Guinea pig 1	.06	.72
Guinea pig 2	-.02	.76

The high positive correlations observed in each post-stimulus ensemble of normal records was essentially reversed for the phase-swopped ensembles. The coherent averages of the original and phase-swopped ensembles were formed and compared (Figure 4.18). The coherent average formed from the ensemble of pre-stimulus phases and post-stimulus amplitudes retained the original pattern. By contrast no recognisable response was evident in the ensemble reconstituted from the original post-stimulus amplitude spectra and pre-stimulus phases.

The relationship between ensemble mean correlation coefficient and phase pattern was further evaluated over a range of stimulus intensities by comparing the correlation/intensity functions for the two conditions of real ensembles and phase-swopped ensembles (Figure 4.19). The systematic drop in correlation value for the real post-stimulus ensembles contrasted with near zero values for untreated pre-stimulus ensembles. This relationship was reversed for spectral ensembles in which the phase values had been swopped.

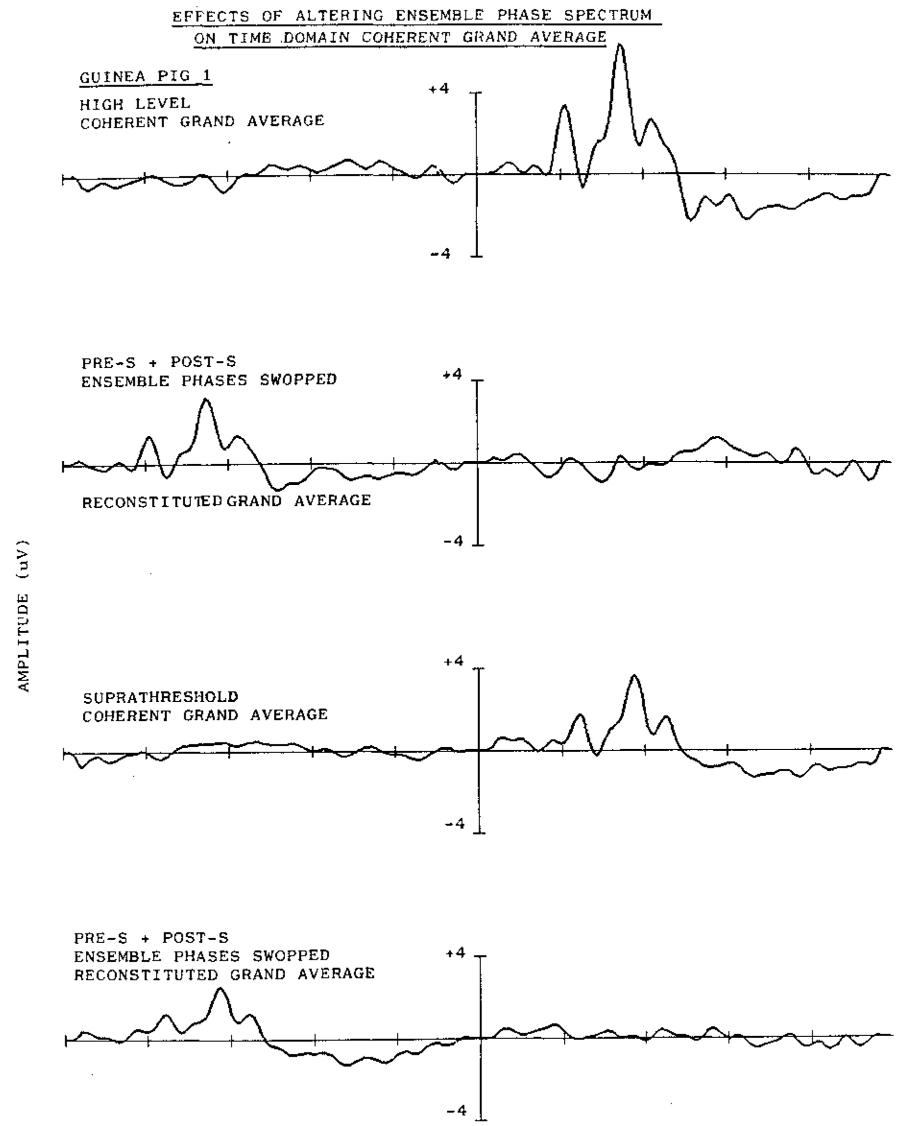


FIGURE 4.18a: In this and the following figure the contribution of ensemble phase spectra to the time-domain pattern has been demonstrated by swopping the pre-stimulus and post-stimulus ensemble phases, reconstituting the individual sweeps and forming the coherent average. The procedure has been repeated for 2 stimulus conditions.

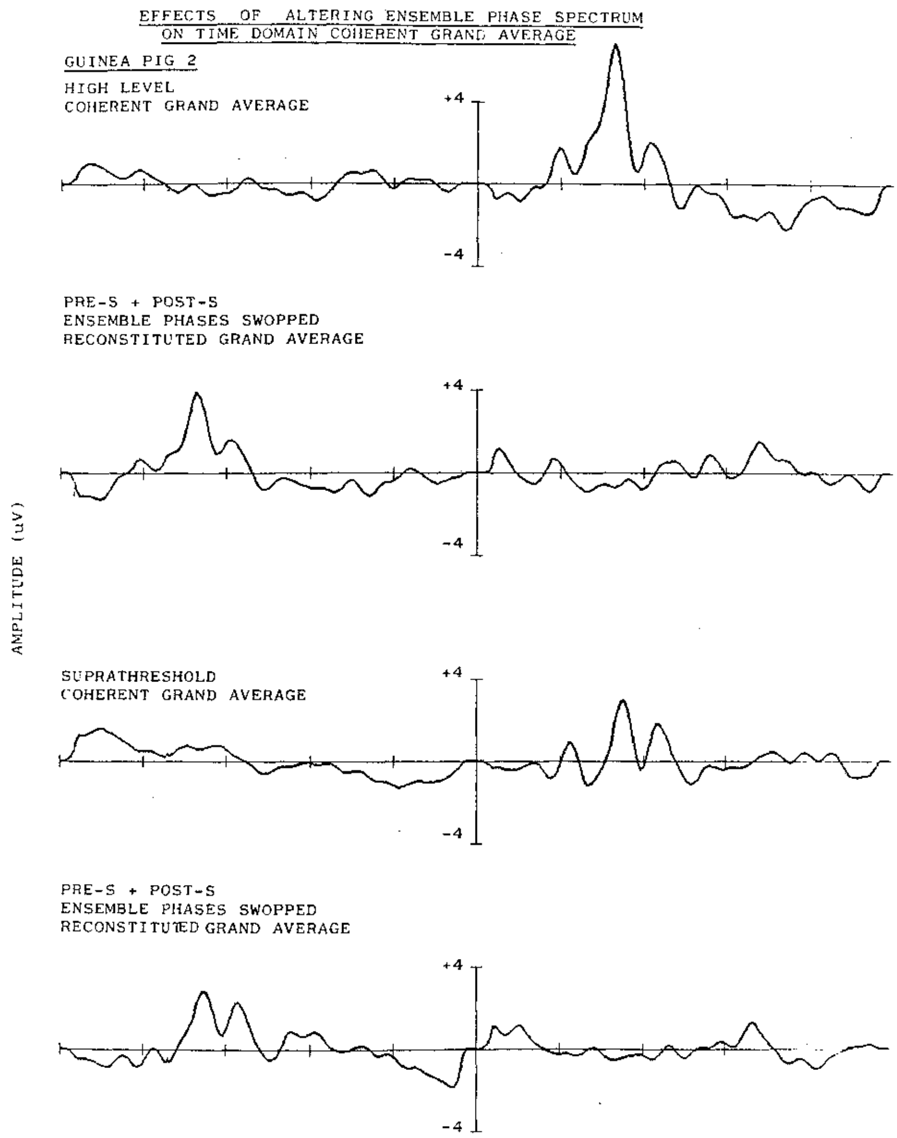

EFFECTS OF ALTERING ENSEMBLE PHASE SPECTRUM ON TIME DOMAIN COHERENT GRAND AVERAGE
GUINEA PIG 2
HIGH LEVEL COHERENT GRAND AVERAGE
+4
-4
PRE-S + POST-S ENSEMBLE PHASES SWOPPED RECONSTITUTED GRAND AVERAGE
+4
-4
AMPLITUDE (uV)
SUPRATHRESHOLD COHERENT GRAND AVERAGE
+4
-4
PRE-S + POST-S ENSEMBLE PHASES SWOPPED RECONSTITUTED GRAND AVERAGE
+4
-4

FIGURE 4.18b

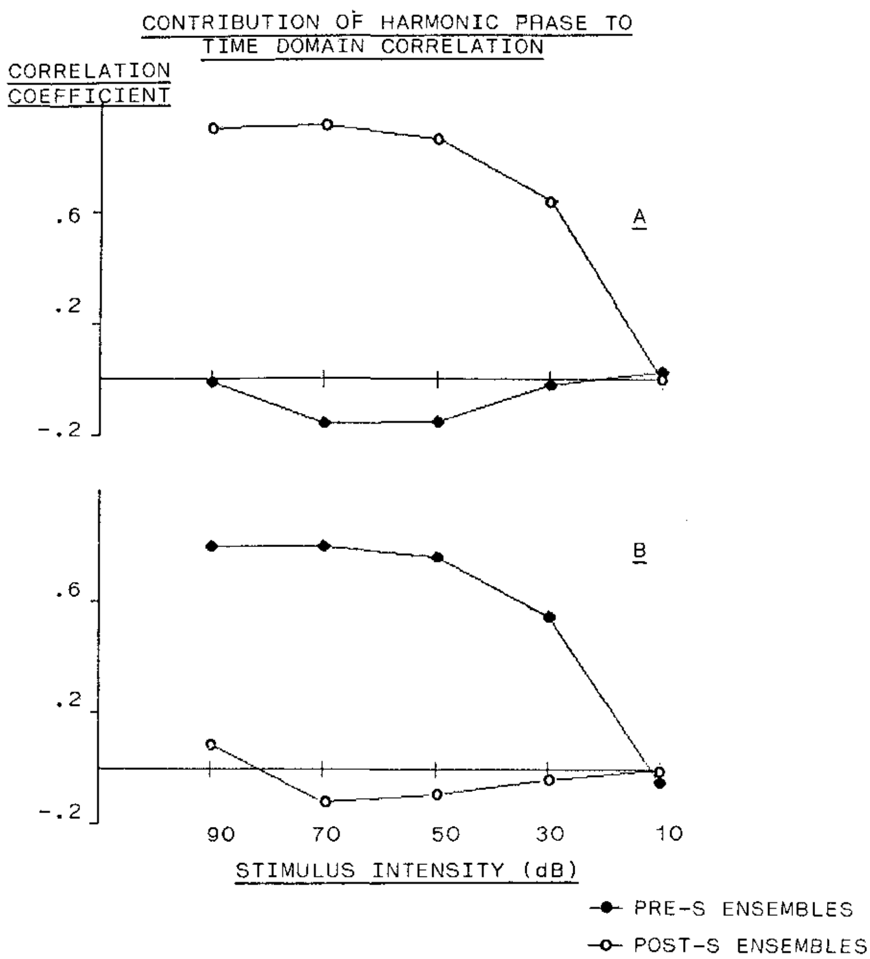


FIGURE 4.19a: In this and the following figure the contribution of harmonic phase to the time-domain cross-correlation co-efficient has been demonstrated. The upper plots (A) are the average correlations of pre-stimulus and post-stimulus ensembles obtained at discreet stimulus intensities. In the lower plots (B) the corresponding phase spectra of the pre-stimulus and post-stimulus ensembles have been swopped. Note how the high positive correlations have been transferred to the pre-stimulus ensembles.

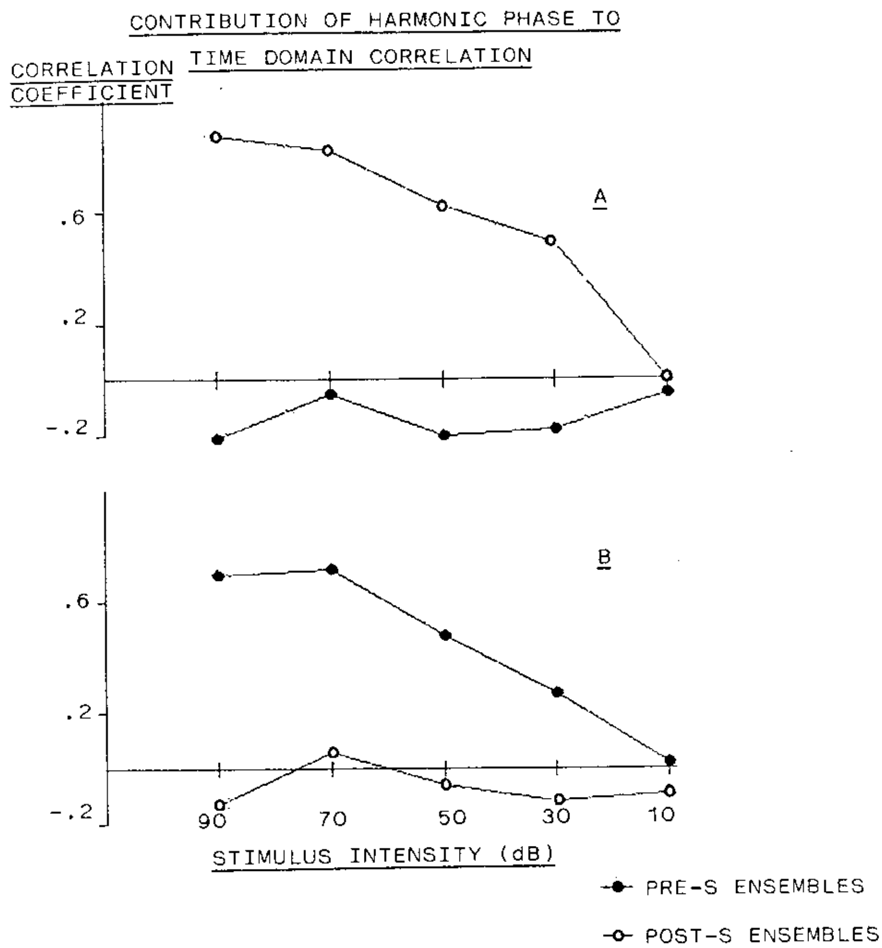

CONTRIBUTION OF HARMONIC PHASE TO
TIME DOMAIN CORRELATION
CORRELATION
COEFFICIENT
A
.6
.2
-.2
B
.6
.2
-.2
90
70
50
30
10
STIMULUS INTENSITY (dB)
PRE-S ENSEMBLES
POST-S ENSEMBLES

FIGURE 4.19b

In the present investigation of brainstem potentials the behaviour of the first and second moments of the cross-correlation distribution at different stimulus intensities (Figure 4.21) has been interpreted as evidence that the pattern observed in the coherent average recurred within most or all of the individual records obtained from supra-threshold stimuli. Such a recurring pattern implied synchronisation of activity in the time-domain which should be reflected in the phase spectra of one or more harmonics. In particular time synchronisation should be associated with constraint in the phase values of relevant harmonics, and they would be aggregated around a mean value corresponding to the phase of the corresponding harmonic in the coherent average. The existence of phase aggregation can be seen for the Fourier spectrum of brainstem potentials at high stimulus intensities in Figure 4.20. These contrasted with the widely scattered phases of sub-threshold harmonics. The phases of responses evoked by stimuli of intermediate intensity showed distributions intermediate between these two extremes.

As mentioned in the introduction the requirements of any objective method for measuring evoked potentials were that the parameters chosen do represent the observed time-domain pattern and that they may be quantified. The contribution of phase to the pattern has already been demonstrated. The histogram of frequency distribution of phase provided the basis of a quantitative statistical test of phase aggregation. The starting assumption was that for unstimulated records the ensemble of phases was randomly but uniformly distributed over the range $-\pi$ to $+\pi$. The objective therefore was to establish a test of the phases from ensembles of post-stimulus records with the null-hypothesis that the underlying estimators are uniform. The estimator chosen was the second moment, or standard deviation, of the phase distribution. If the phases of an ensemble were aggregated then the standard deviation of the distribution would be less than that for a uniform distribution.

The problem of wrap-around has already been demonstrated and this had to be taken into consideration in calculating the standard deviation of the phase distribution. The issue has been discussed in relation to the assessment of cortical evoked potentials by Ross, Beagley and Sayers, (1980). In view of the central position in a solution to the problem for the present study the matter will be fully elaborated. Phases may occasionally be grouped near one end of the range, say $+\pi$. Because of wrap-around, phases exceeding $+\pi$ will be located close to $-\pi$, that is at the other end of the distribution.

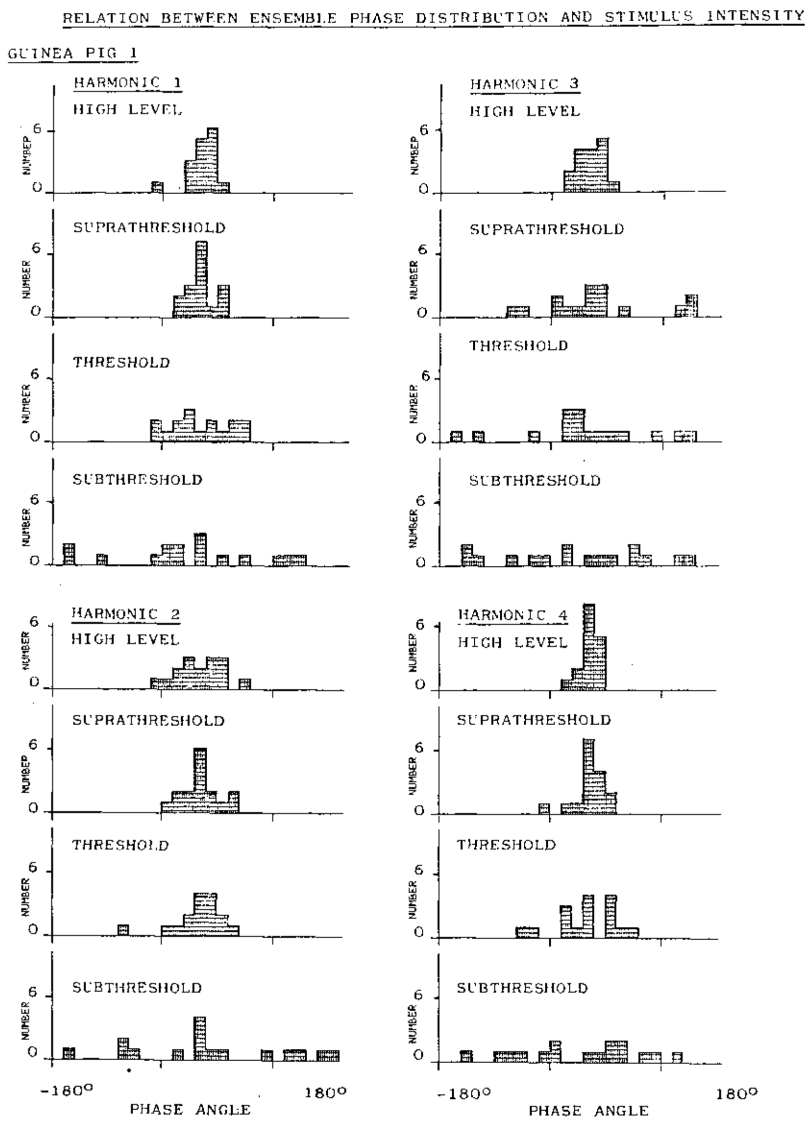


FIGURE 4.20a: In this and the following 3 figures the ensemble phase distribution of post-stimulus records at 4 discreet stimulus intensities has been plotted. Note the phase aggregation at high stimulus intensities and increasing dispersion at successively lower stimulus intensities.

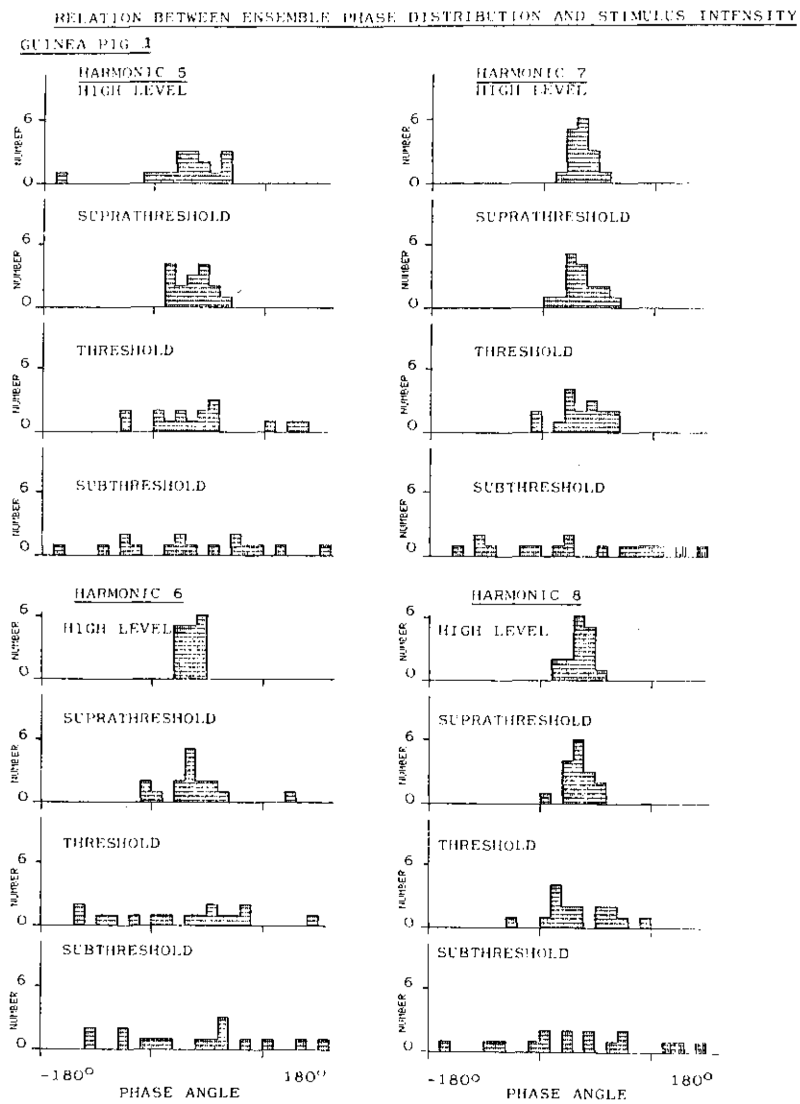

RELATION BETWEEN ENSEMBLE PHASE DISTRIBUTION AND STIMULUS INTENSITY
GUINEA PIG 1
HARMONIC 5
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
HARMONIC 6
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
HARMONIC 7
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
HARMONIC 8
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
6
0
-180°
180°
PHASE ANGLE

FIGURE 4.20b

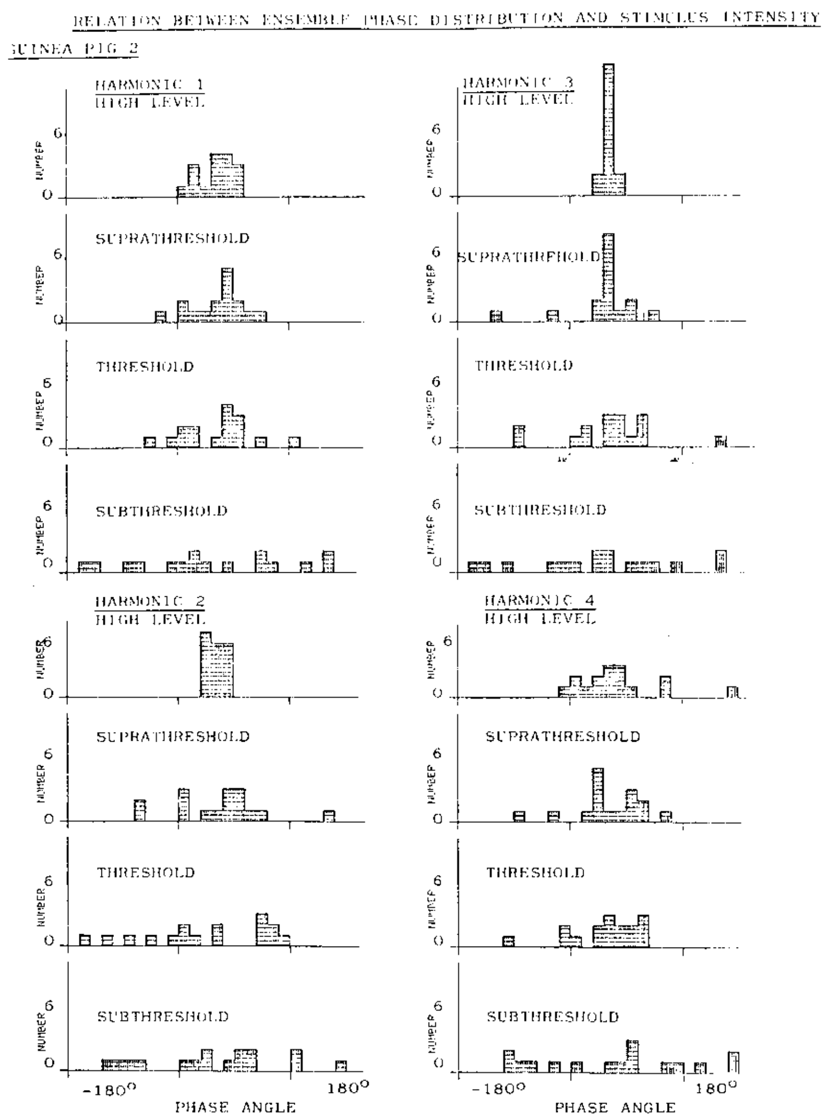

RELATION BETWEEN ENSEMBLE PHASE DISTRIBUTION AND STIMULUS INTENSITY
GUINEA PIG 2
HARMONIC 1
HIGH LEVEL
HARMONIC 3
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
HARMONIC 2
HIGH LEVEL
HARMONIC 4
HIGH LEVEL
NUMBER
6
0
-180°
180°
PHASE ANGLE

FIGURE 4.20c

RELATION BETWEEN ENSEMBLE PHASE DISTRIBUTION AND STIMULUS INTENSITY

GUINEA PIG 2

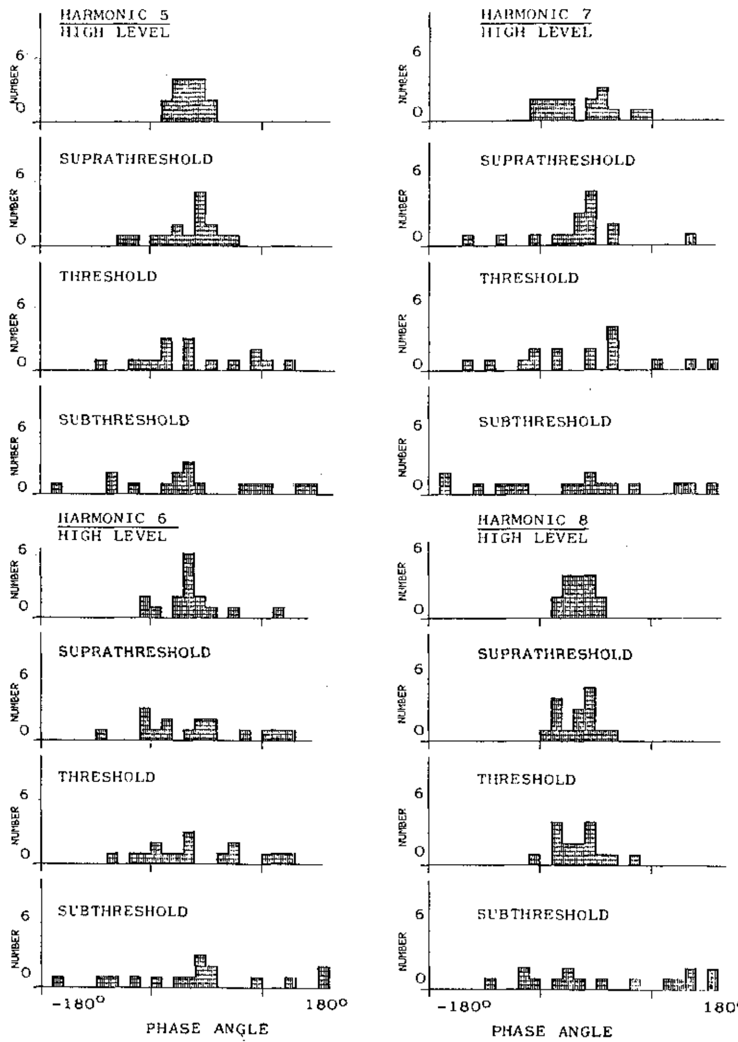


FIGURE 4.20d

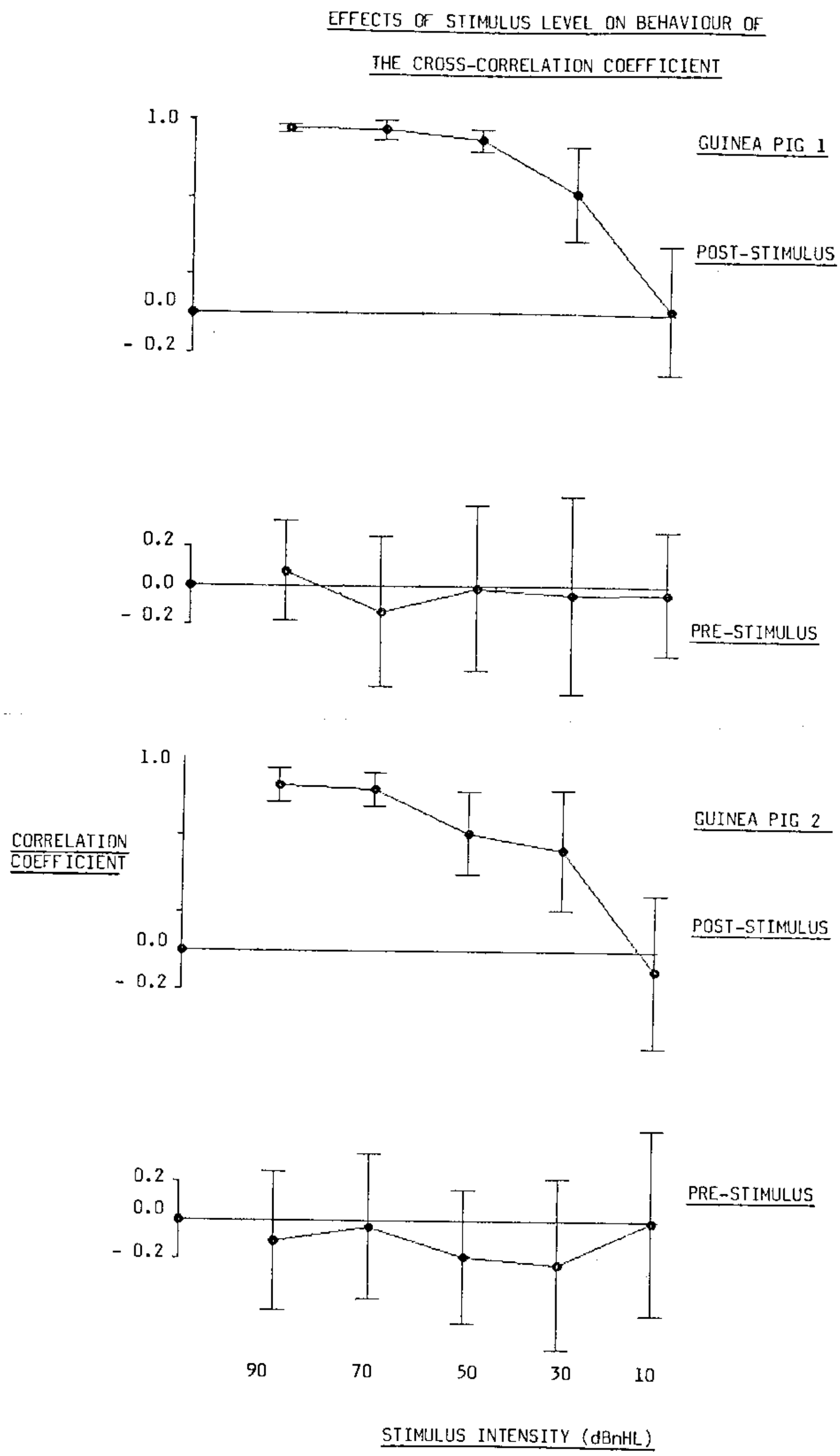

EFFECTS OF STIMULUS LEVEL ON BEHAVIOUR OF
THE CROSS-CORRELATION COEFFICIENT
1.0
0.0
- 0.2
GUINEA PIG 1
POST-STIMULUS
0.2
0.0
- 0.2
PRE-STIMULUS
1.0
CORRELATION
COEFFICIENT
0.0
- 0.2
GUINEA PIG 2
POST-STIMULUS
0.2
0.0
- 0.2
PRE-STIMULUS
90
70
50
30
10
STIMULUS INTENSITY (dBnHL)

FIGURE 4.21

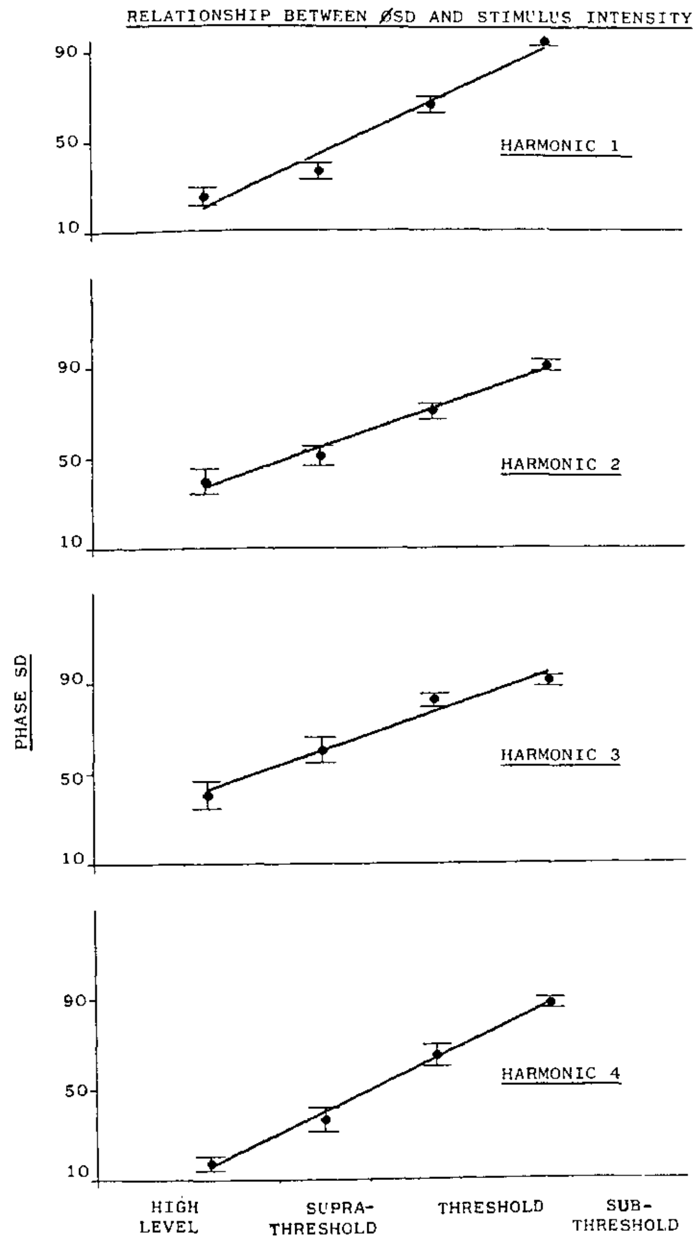
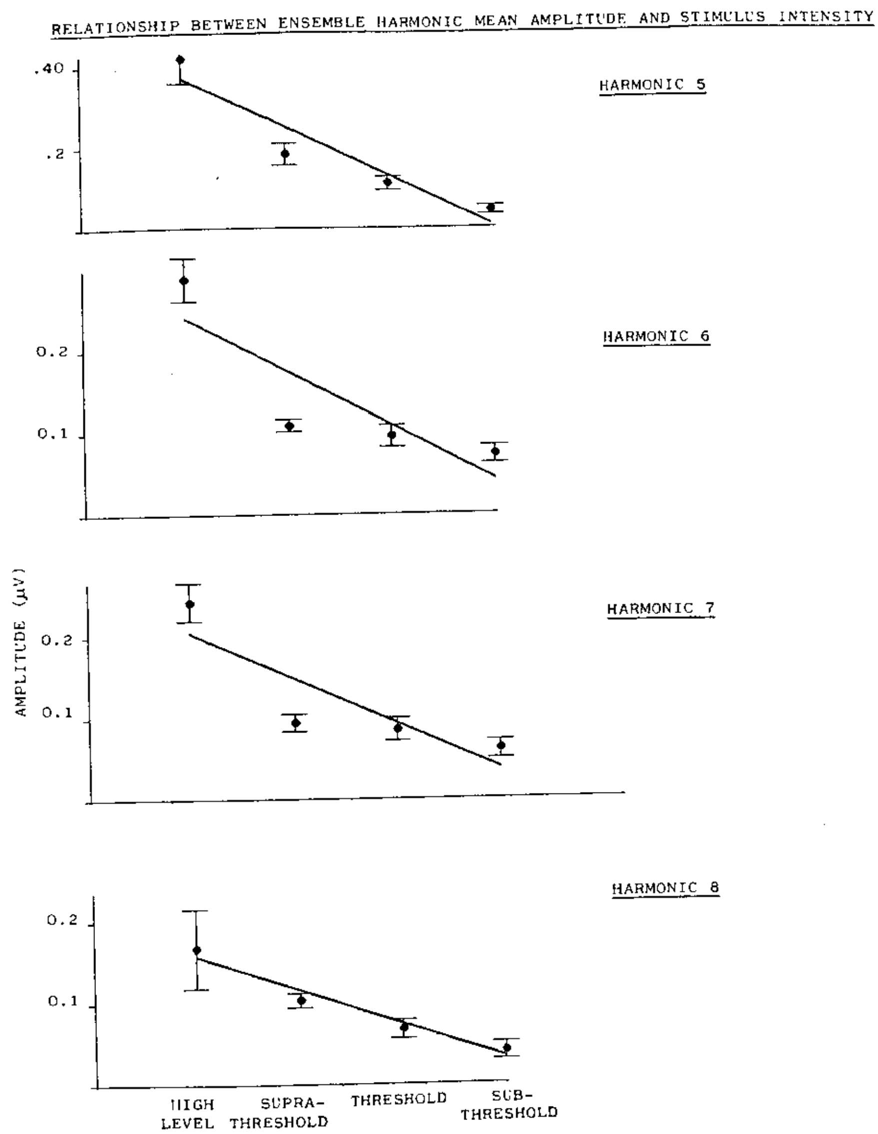


FIGURE 4.22a: In this and the subsequent figure the relationship between stimulus intensity and harmonic phase standard deviation has been examined.



RELATIONSHIP BETWEEN ENSEMBLE HARMONIC MEAN AMPLITUDE AND STIMULUS INTENSITY
.40
.2
HARMONIC 5
0.2
0.1
HARMONIC 6
AMPLITUDE (μV)
0.2
0.1
HARMONIC 7
0.2
0.1
HARMONIC 8
HIGH LEVEL
SUPRA-THRESHOLD
THRESHOLD
SUB-THRESHOLD

FIGURE 4.14b

Any calculation of standard deviation which disregarded this effect would yield incorrectly large values. In order to overcome this difficulty the phase vector approach has been used. Each phase value is assigned a magnitude of unity and defined in terms of its Cosine and Sine components. From these two orthogonal functions and their respective mean values the mean phase angle can be calculated. The differences of individual phase values from the mean can be measured directly and the standard deviation of the distribution calculated in the usual way.

The relationship between phase standard deviation and stimulus intensity for the pooled observations from the 5 guinea pigs was investigated and the results for each harmonic plotted in Figure 4.22. An inverse relationship was observed for most harmonics. However, it was also evident that some harmonics in the region of threshold showed considerably more phase constraint than others (compare harmonic 5 with 6 for threshold responses).

The method of estimating standard deviation has important consequences for the sampling statistics of this parameter. For a continuous and uniformly distributed variable defined over the range $-\pi$ to $+\pi$, with expected mean equal to zero, the expected value of standard deviation of phase can be obtained as follows:

$$\langle VAR_{\phi} \rangle = \int_{-\pi}^{\pi} (\phi)^2 . \rho(\phi) . d\phi, \text{ where } \rho(\phi) = \frac{1}{2\pi}$$

$$= \frac{\pi^2}{3}$$

$$\langle S.D \rangle = \pi/\sqrt{3}$$

$$= 104^0$$

However because of the periodic nature of the phase distribution and the method of correction for wrap-around effects in calculating the mean, the estimation of standard deviation will tend to give an underestimate of random occurrences in which the phases have been located by chance near both ends of the range. This will obviously occur more frequently when the number of observations is small. As a result, the sampling statistics of phase standard deviation shows a systematic bias dependent on sample size. The magnitude of this effect and the confidence interval need to be established empirically. To this end an analysis was made of the phase distribution of unstimulated records. Phase standard deviations of individual harmonics for 16 sweep ensembles, the size used throughout this study, have been plotted in Figure 4.23. The distributions showed a slightly longer tail in the direction of lower harmonic value but were much less widely dispersed than the corresponding amplitude distributions. Further, the distributions for different harmonics were very similar in shape and in the magnitudes of their first and second moments. It was therefore considered justifiable to pool the observations for the individual harmonics to provide a more reliable estimate of phase scatter (Figure 4.24). The mean value of standard deviation for 300 observations of 16 sweep ensembles was 94. This agreed well with the theoretical estimate (Ross, 1978). The 5% level of the negative tail of the distribution was 76 and was chosen as the confidence interval to facilitate comparison with the amplitude measures. The phase S.D. distribution of individual harmonics for post-stimulus ensembles have been plotted in Figure 4.25 and the 5% confidence interval included. All phase standard deviations obtained from high intensity stimuli exceeded the criterion for threshold. However, in contrast to the amplitude values obtained at supra-threshold and threshold, most harmonics still showed standard deviations which exceeded the criterion level, denoting a high probability of the presence of pattern in the post-stimulus records.

In Figure 4.26 the percentage of harmonics exceeding the threshold criteria for amplitude and phase have been compared for the 3 stimulus levels, high level, threshold, and sub-threshold. The relative weakness of amplitude as a measure of response occurrence can be seen. For high level responses, harmonic phase standard deviations exceeding threshold criteria occurred in 95% of observations, while for amplitude only 65% exceed threshold. The differences in the relative sensitivities of the two methods was most evident in the region of threshold where 54% of phase estimates exceeded threshold, while only 11% of the correspondong amplitude observations reached threshold. For this reason it was decided to abandon the use of amplitude as a measure of threshold and optimise the phase constraint method.

While the contribution of phase aggregation to the time-domain pattern and correlation co-efficient has been demonstrated (Figure 4.19) this relationship has been more critically evaluated. The contributions of individual harmonics to the ensemble mean correlation co-efficient were separately examined. This was achieved by randomising the phase spectra of all harmonics except the one under scrutiny, in both the template and the individual records, reconstituting the time domain waveforms and calculating the correlation co-efficient. The

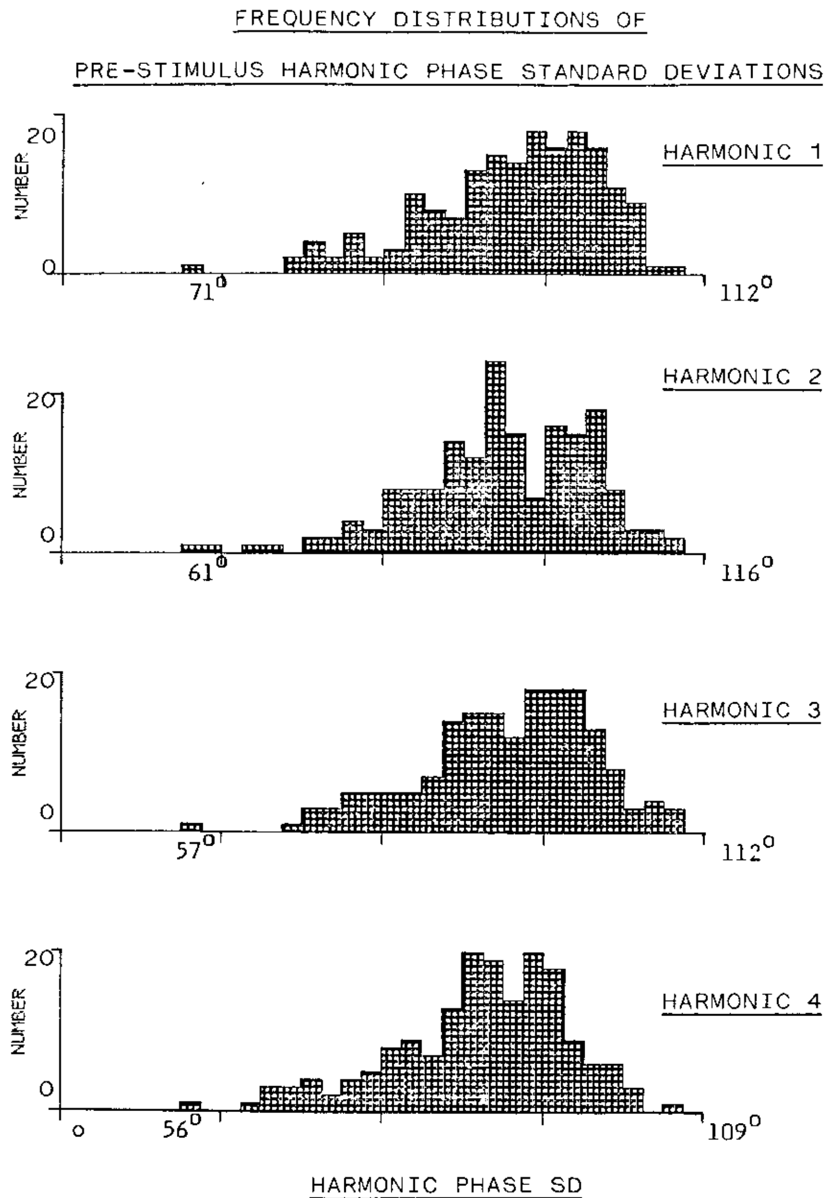


FIGURE 4.23a: In this and the following figure the histograms of frequency distribution of phase standard deviation have been plotted for 16 sweep ensembles of unstimulated records.

FREQUENCY DISTRIBUTIONS OF

PRE-STIMULUS HARMONIC PHASE STANDARD DEVIATIONS

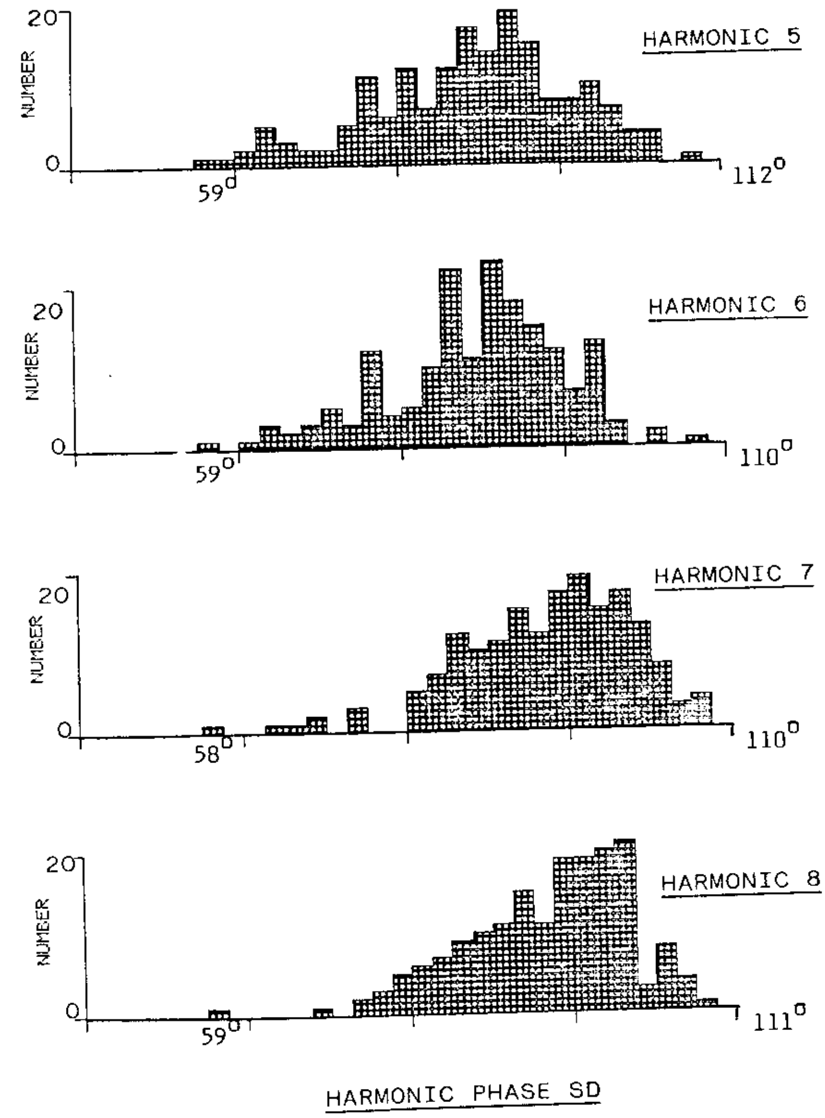


FIGURE 4.23b

FREQUENCY DISTRIBUTION OF POOLED HARMONIC PHASE SD

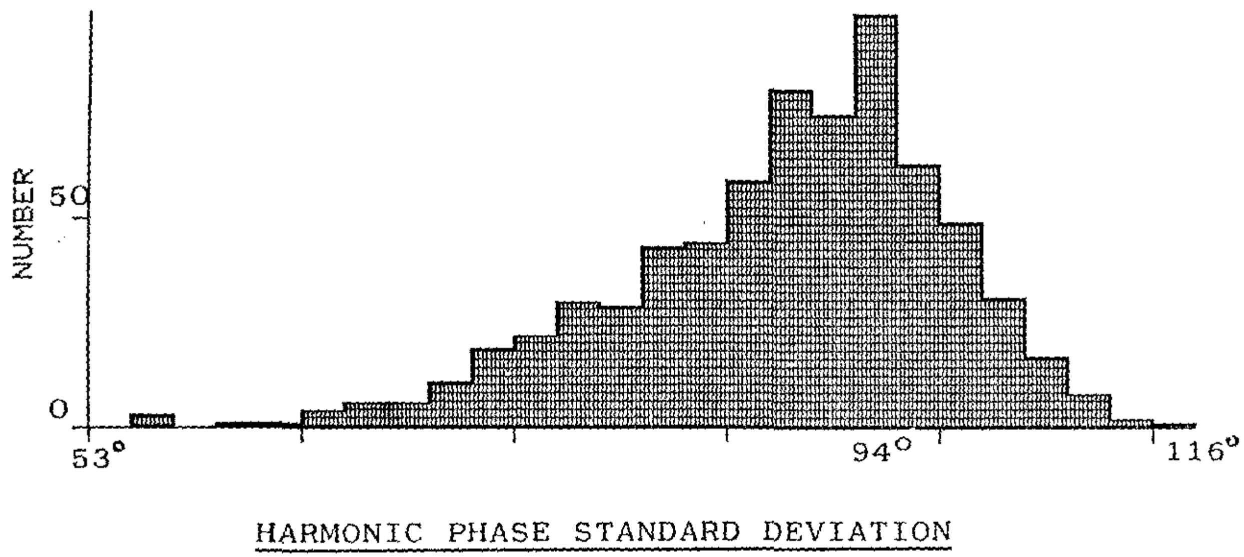


FIGURE 4.24

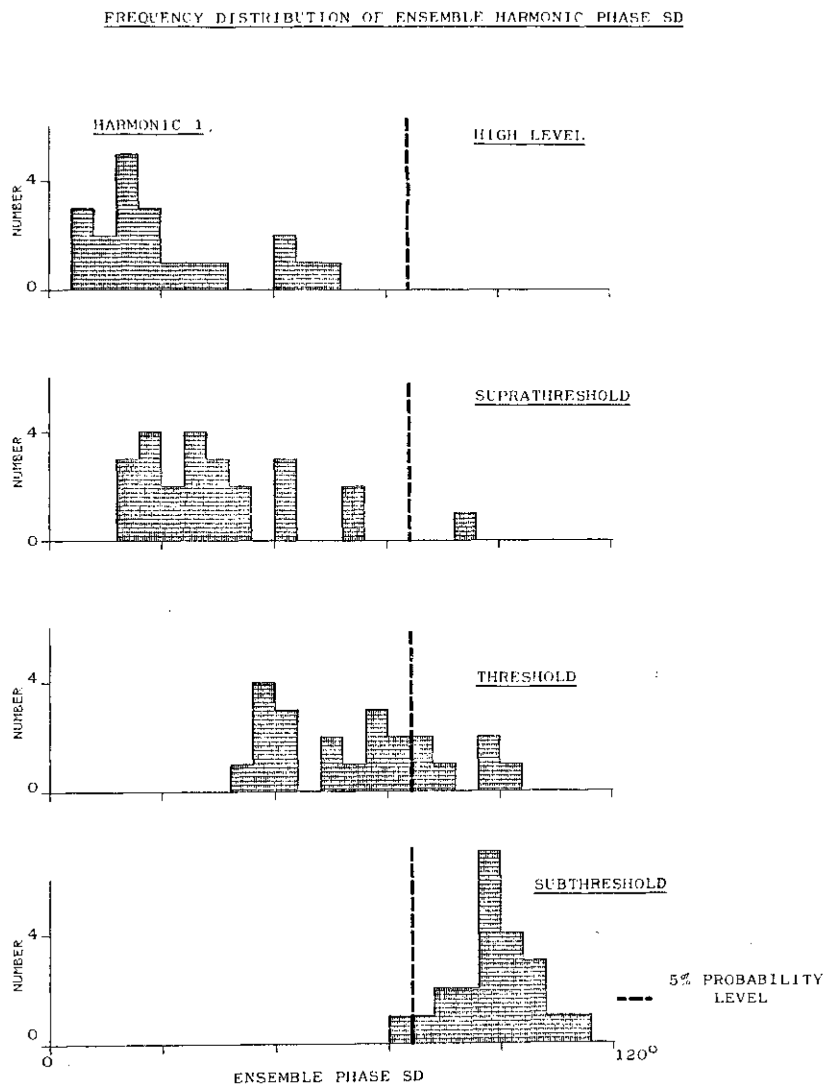


FIGURE 4.25a: In this and the following 7 figures post-stimulus frequency distributions of harmonic phase S.D. for 5 guinea pigs have been plotted for 4 stimulus intensity levels. The confidence interval associated with the 5% probability for unstimulated records has been included.

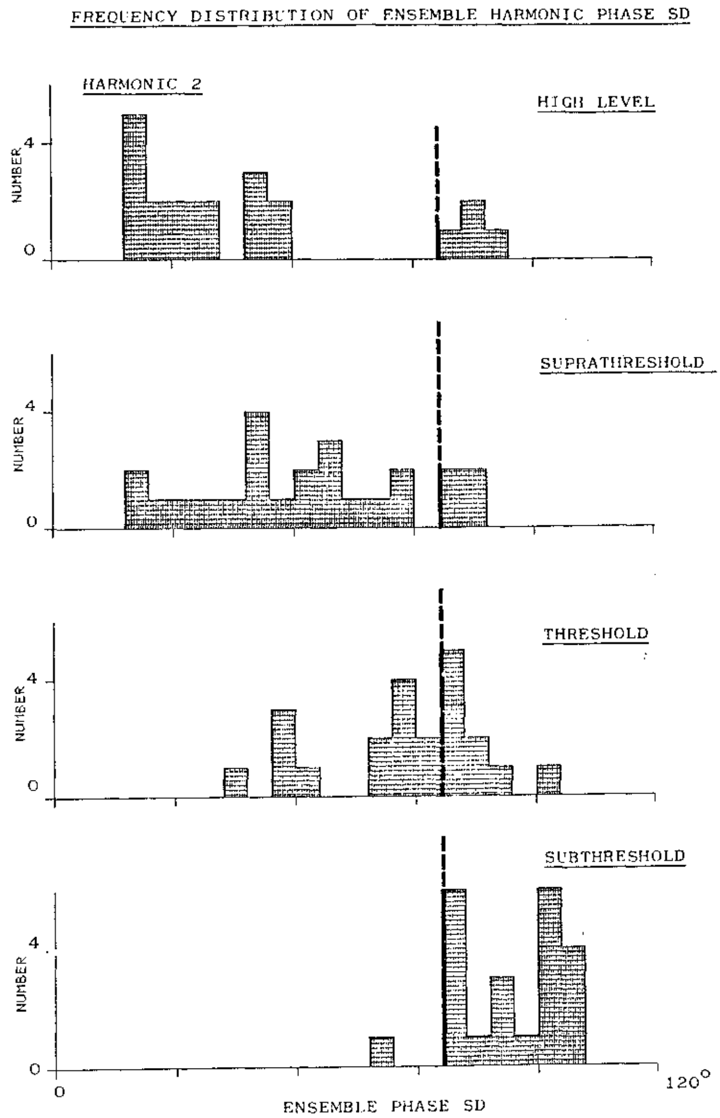

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD
HARMONIC 2
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0
0
120°
ENSEMBLE PHASE SD

FIGURE 4.25b

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD

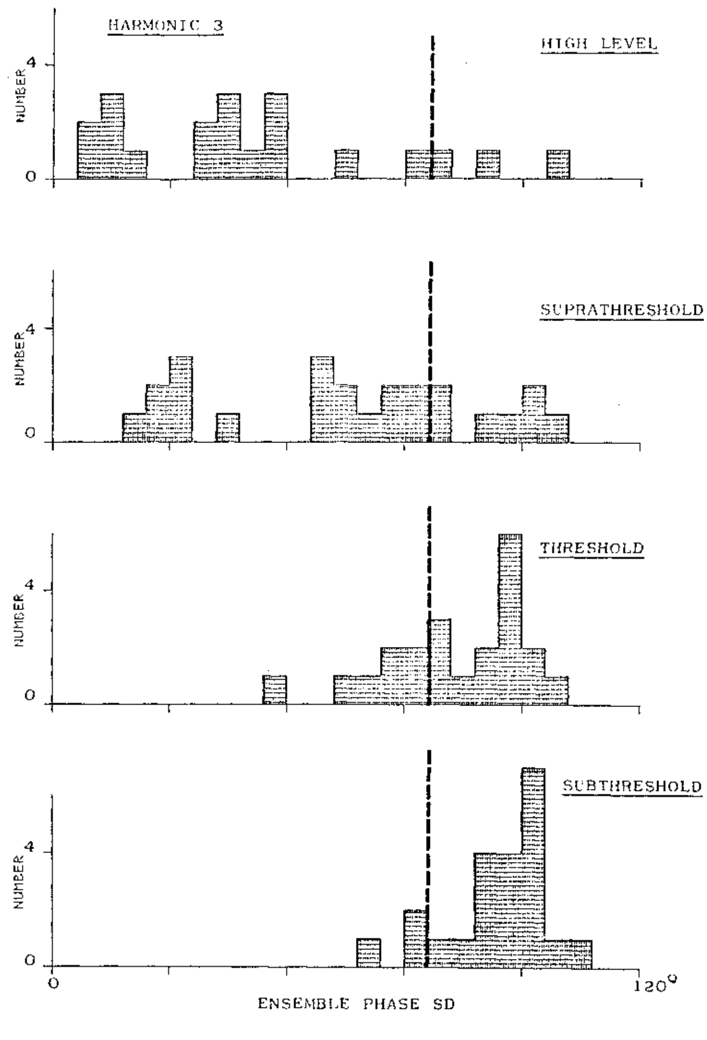


FIGURE 4.25c

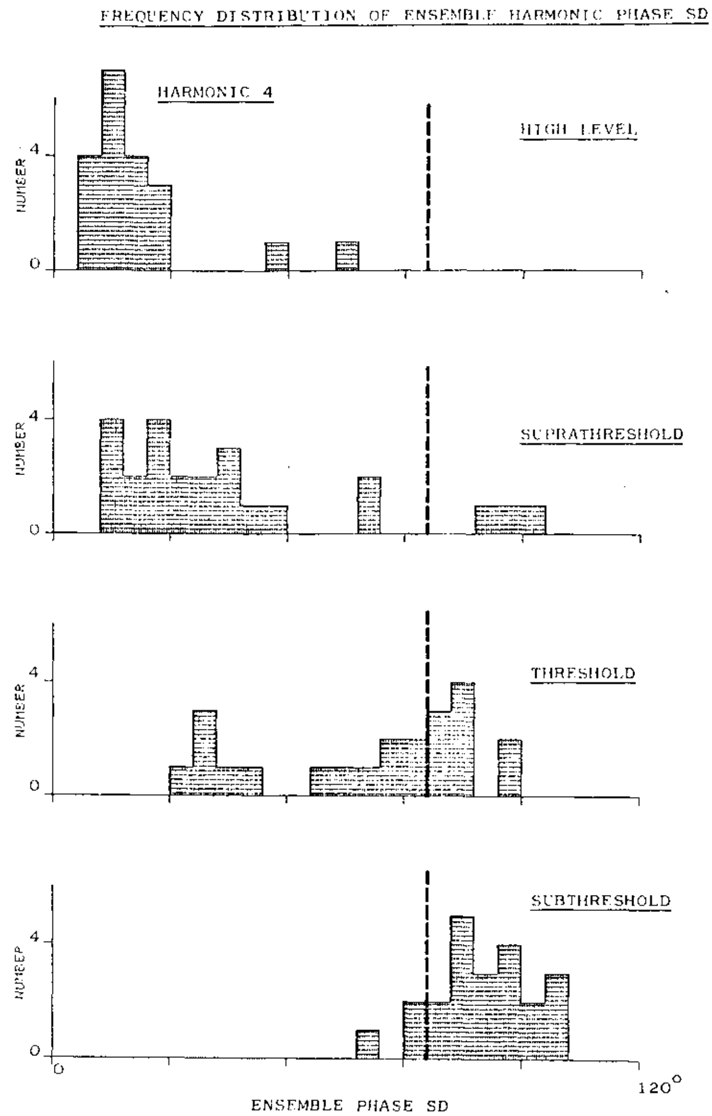
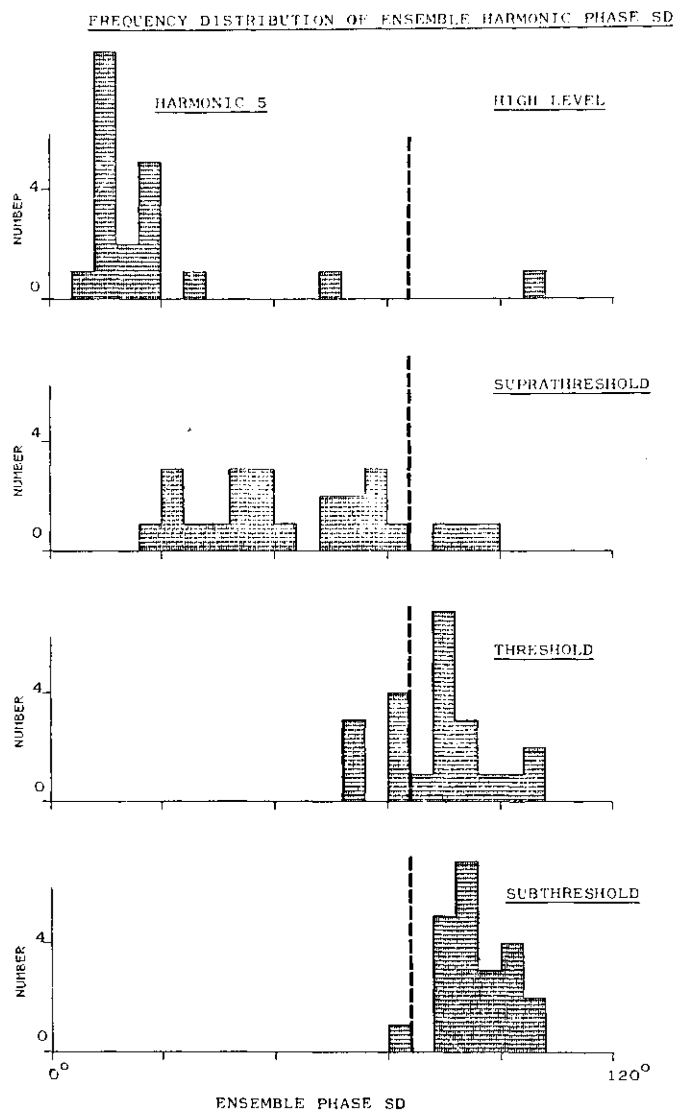

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD
HARMONIC 4
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0
120°
ENSEMBLE PHASE SD

FIGURE 4.25d



FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD
HARMONIC 5
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0
0°
120°
ENSEMBLE PHASE SD

FIGURE 4.25e

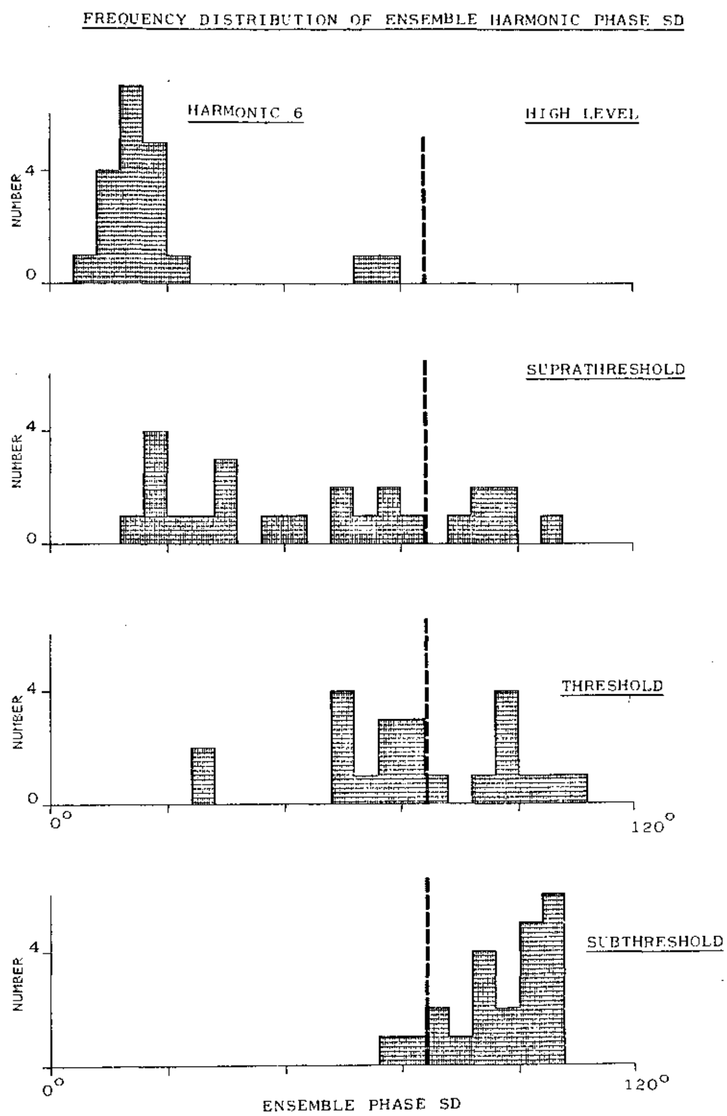

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD
HARMONIC 6
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0
0°
120°
ENSEMBLE PHASE SD

FIGURE 4.25f

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD

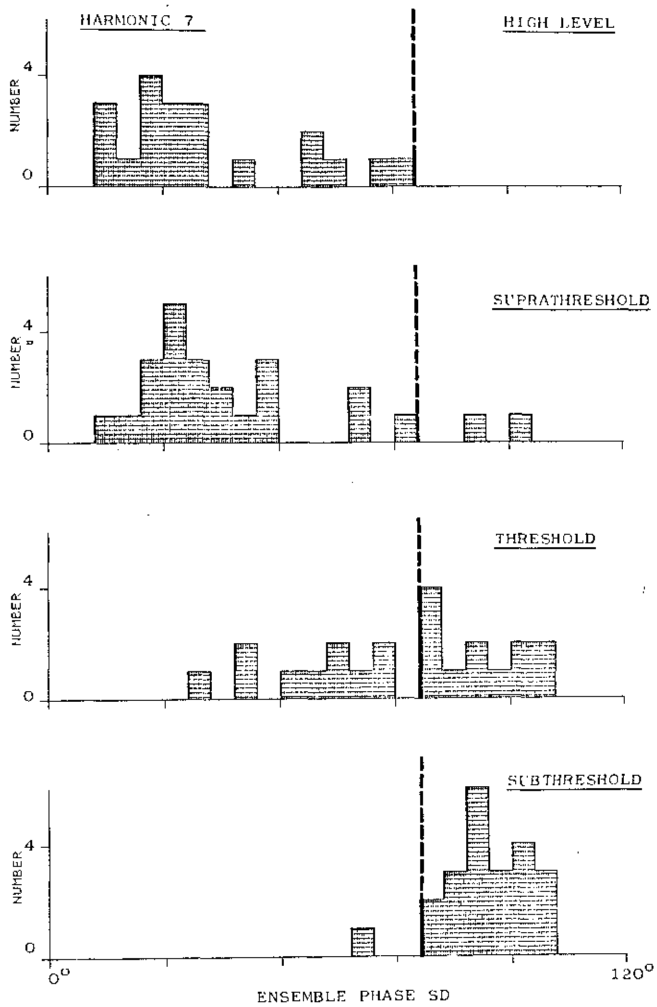


FIGURE 4.25g

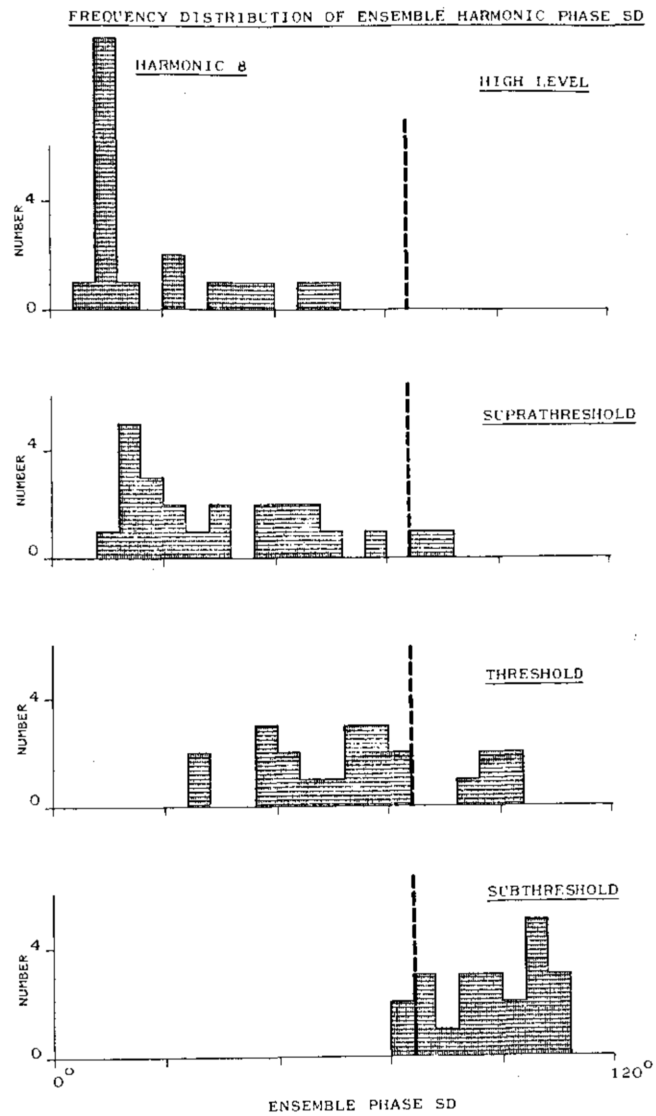

FREQUENCY DISTRIBUTION OF ENSEMBLE HARMONIC PHASE SD
HARMONIC 8
HIGH LEVEL
SUPRATHRESHOLD
THRESHOLD
SUBTHRESHOLD
NUMBER
4
0
0°
120°
ENSEMBLE PHASE SD

FIGURE 4.25h

PERCENTAGE OF HARMONICS REACHING 5% PROBABILITY LEVEL

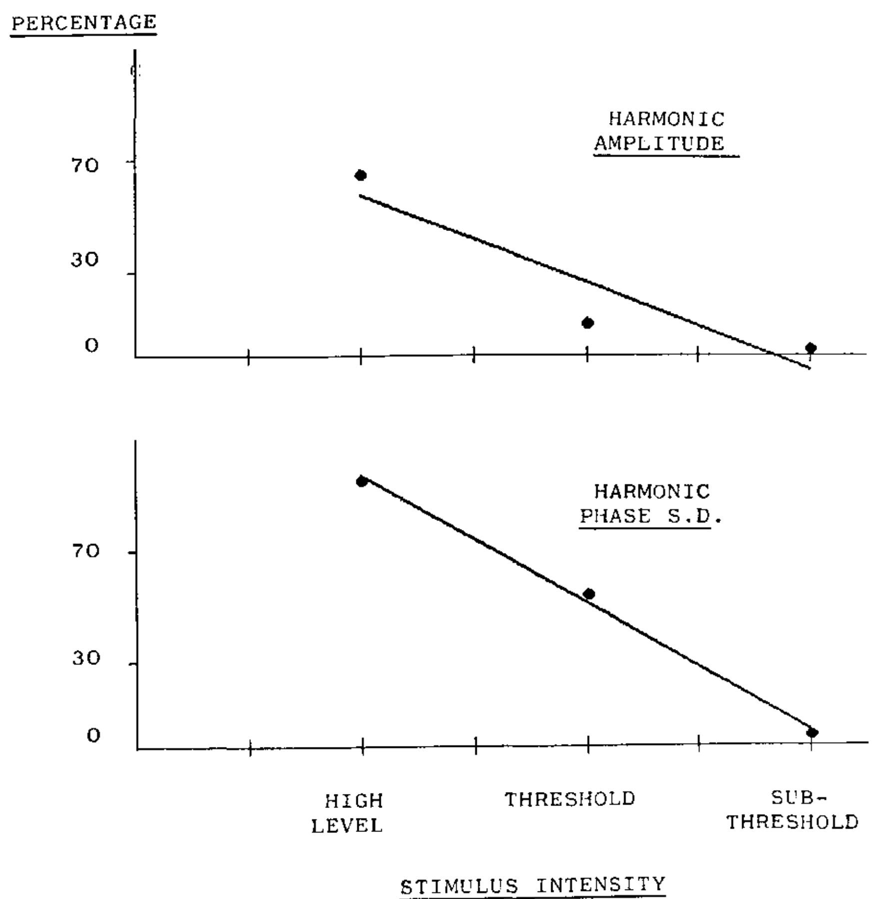


FIGURE 4.26: Comparison of relative sensitivities of harmonic ensemble mean amplitude and phase S.D. for 16 sweep ensembles at 3 stimulus levels.

procedure was repeated at 10 stimulus levels from 90 dB to 10 dB in each of the 5 guinea pigs and the results pooled (Figure 4.27). The slopes of the regression lines relating $\bar{r}$ to phase S.D. were drawn. The slope was greatest for the first harmonics (r = -.93) and the size of the slope appeared to be a function of harmonic number. This effect was presumably due to the contributions of harmonic power to the correlation co-efficient. The slope size reached its second maxima with the 4th harmonic (-.74), again probably due to the large spectral contribution made by the response in this region. The size of the correlation indicated, especially for these two harmonics, that a strong relationship existed between ensemble mean correlation co-efficient and ensemble phase standard deviation. The low correlations obtained with higher harmonics needed to be considered. Examination of the scattergram indicated that while a wide range of phase standard deviations were obtained the changes in $\bar{r}$ were small and mostly below the confidence level. This implied that a stimulus could exert a definite and quantifiable constraint on the phases of the higher frequency, low amplitude, harmonics without significantly altering the correlation co-efficient.

The relationship between correlation and phase was investigated in a little more detail for the threshold region. It was frequently noted near threshold that only one or two harmonics had significantly constrained phases. Therefore a regression analysis was made between the correlation co-efficient and the single most constrained harmonic. In the region of threshold, the relationship was examined between mean ensemble correlation co-efficient and the phase standard deviation for the most constrained harmoic of each sweep (Figure 4.28). A high correlation (r = .89) was obtained suggesting that aggregation of a single harmonic in the region of threshold may still make a significant contribution to the time-domain pattern.

In the first section it was observed that moderate filtering conferred some improvement on the sensitivity of the time-domain correlation technique. These findings suggested that it might be advantageous to attend in greater detail to the contribution made by individual harmoincs. The results of the present study of phase aggregation, while confirming such a view, also indicated that phase constraint itself might provide an accurate estimate of auditory threshold. The confidence interval for significant phase aggregation has so far been based on the 5% level of the pre-stimulus phase standard deviation distribution to allow comparison with amplitude statistics. In a fully objective method due account needed to be taken

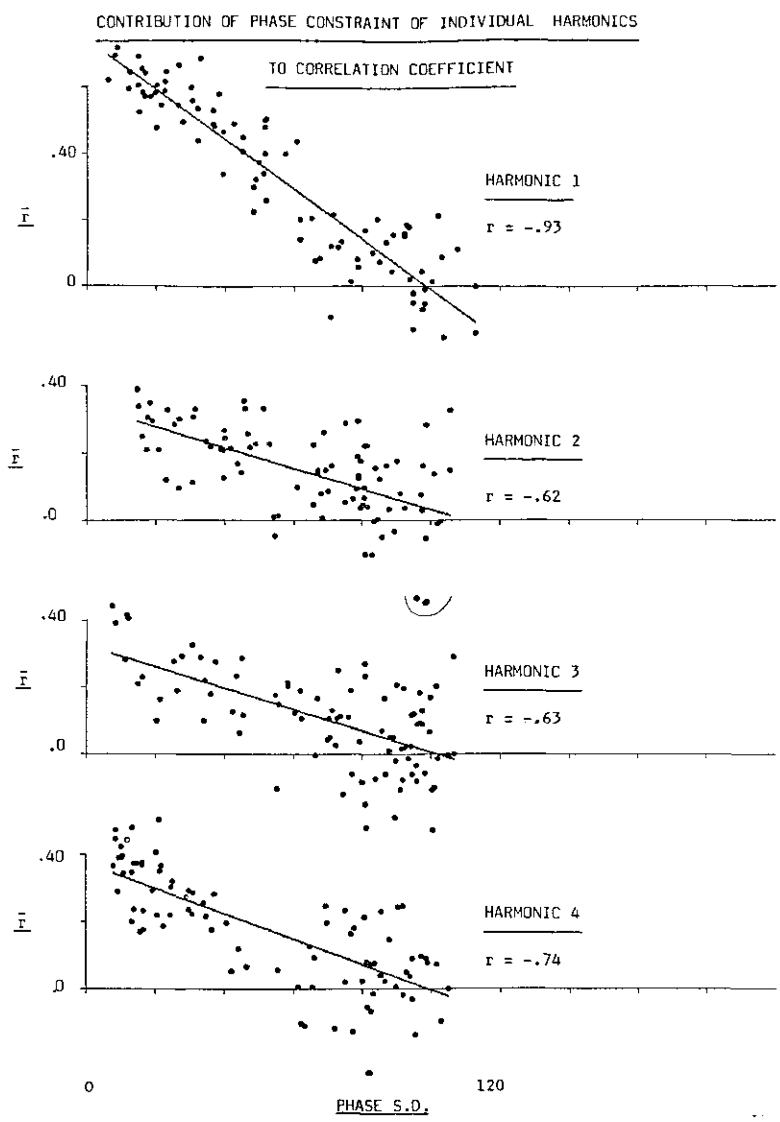


FIGURE 4.27a: In this and the subsequent figure the contributions of individual phases to the ensemble mean correlation co-efficients have been represented. This was achieved by randomising the phase spectra of all other harmonics in the template and in each record, reconstituting the time-domain waveforms and calculating the correlation co-efficient. The procedure was repeated at 10 stimulus intensities from 90 dB -10 dB in each of 5 guinea-pigs and the results pooled. Note the changes in the slope of the regression line with increasing harmonic number.

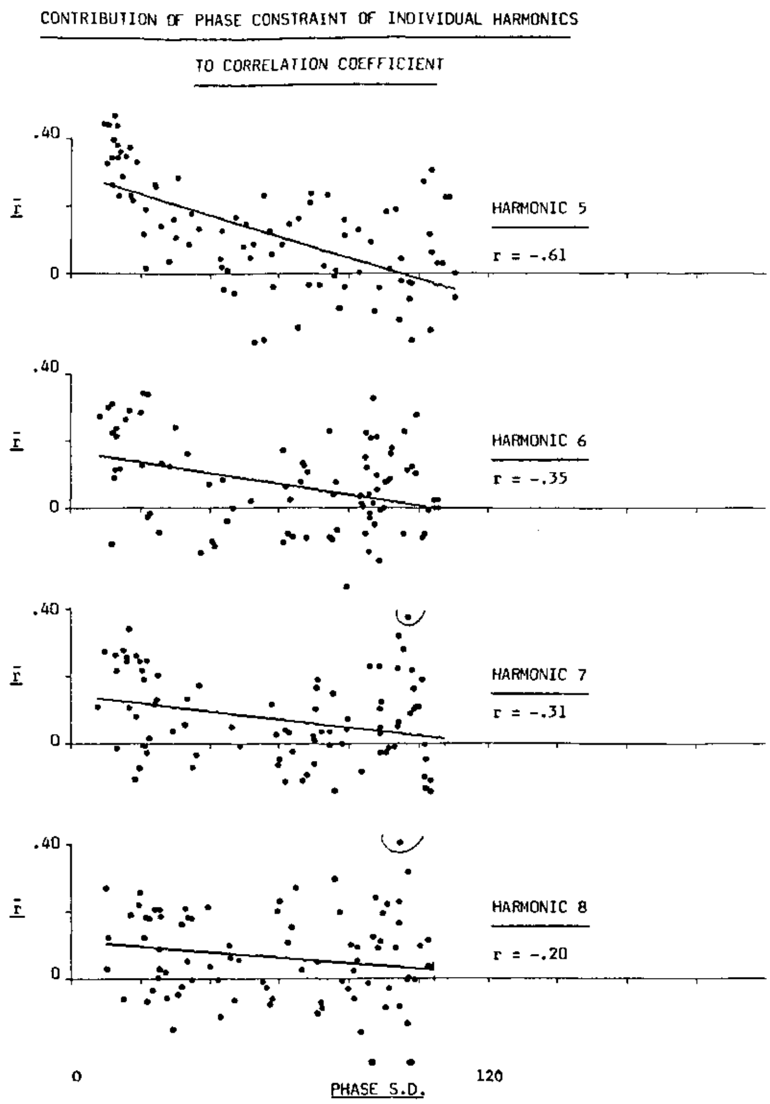

CONTRIBUTION OF PHASE CONSTRAINT OF INDIVIDUAL HARMONICS
TO CORRELATION COEFFICIENT
.40
0
HARMONIC 5
r = -.61
HARMONIC 6
r = -.35
HARMONIC 7
r = -.31
HARMONIC 8
r = -.20
0
PHASE S.D.
120

FIGURE 4.27b

RELATIONSHIP BETWEEN ENSEMBLE MEAN CORRELATION COEFFICIENT AND ENSEMBLE PHASE SD IN THE REGION OF THRESHOLD (N=22)

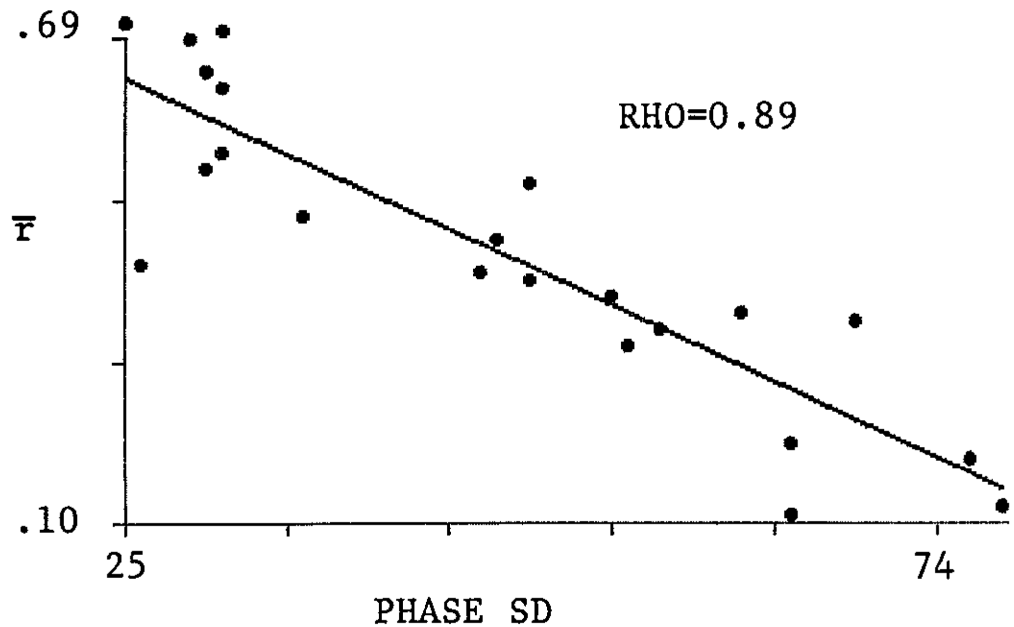


FIGURE 4.28

of falsepositive decisions arising from such a relatively high probability level. As 8 harmonics had been observed for a given ensemble this would greatly have increased the probability of making a false positive decision. Given that the 1% level of probability for a given record was chosen for the correlation method (Chapter 3), the corresponding probability level for individual harmonic phase standard deviation was .12%, giving a probability of 1% for a record consisting of 8 harmonics. Of course, consideration was given to the condition of joint occurrences in post-stimulus records to balance the low probability level of single occurrences. The confidence interval for phase standard deviation for the 1% probability level for single occurrences was 56^{o}, for 2 joint occurrences 68^{o}, and for 3 occurrences 76^{o} (Appendix).

Finally the relative sensitivities of the cross-correlation method and phase constraint method for the guinea-pig were compared (Figure 4.29). Using the correlation method approximately 77% of observations in the region of threshold exceeded the threshold criteria of $\bar{r}$. With the phase method 68% of observations exceeded the confidence interval. When one or 2 harmonics were included, the sensitivity of the phase method increased to 77% and was as sensitive as the correlation method. When one, 2, or 3 harmonics were included, then the method yielded 86% successes.

When the correlation method was used in this high signal to noise situation, a high level of agreement was obtained between the correlation results and the visual evidence of pattern in the post-stimulus records. Further a high level of agreement was found between the correlation method and the phase constraint method. It also appeared that the phase constraint method had certain advantages, enabling attention to be paid to that section of the signal in which the main pattern resided. This almost certainly accounted for the higher number of positive observations ofresponses in the threshold region. It was a debatable point whether disagreements (14%) were due to false negative decisions using the phase aggregation method or false positive decisions using conventional visual scoring.

It now remained to evaluate the sensitivity of the phase constraint method under the less favourable signal to noise conditions of human records. Before this step was taken however, one important question remained. In view of the relative sensitivity of the phase method over other frequency domain measures particularly amplitude, the question was raised whether the assumptions of superposition were more valid in relation to the auditory brainstem potentials than a synchoronisation

COMPARISON OF BEHAVIOUR OF CORRELATION AND PHASE METHODS IN REGION OF THRESHOLD

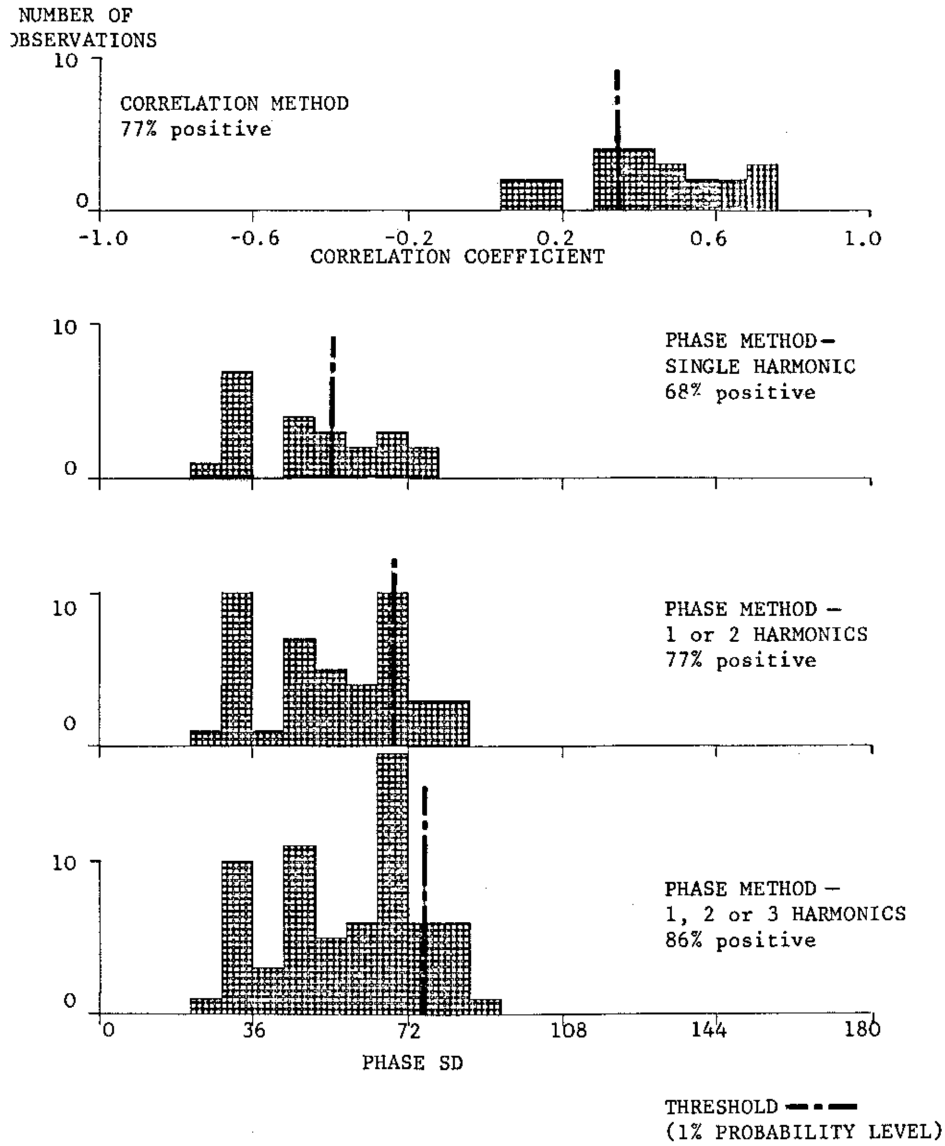


FIGURE 4.29

model of pattern generation. In the following section therefore an analysis was made of the evidence pertaining to these two hypotheses of pattern generation.

Chapter 5

A Study of the Superposition and Synchronisation Hypotheses of Brainstem Auditory Evoked Potential Generation

INTRODUCTION

Throughout the correlation study in Chapter three it was assumed that the early surface recorded far field potentials generated in the brainstem auditory pathway conformed to a superposition model of response generation. There had been several reasons for accepting such a model. Perhaps the most compelling relates to the evidence arising from simultaneous recording of compound auditory nerve activity and single units. It would appear that the shape of the gross compound nerve potential and its alteration with stimulus intensity is a function of the firing rates of single units. Many units have high spontaneous firing rates (18 spikes/sec.) and present evidence suggests that it is these which contribute most to the gross compound nerve potential. The firing rate of such a unit increases by a factor of 10-100 in response to a click stimulus and the timing of the depolarisation potentials can be described by a post-stimulus time histogram. The shape of this post-stimulus time histogram of depolarisation counts determines the shape of compound nerve potential. The N_1 potential recorded from the round window or external auditory meatus shares most of the properties of the directly recorded compound nerve (Antol-Candela and Kiang, 1978).

Changes in the shape and timing of individual components of the scalp recorded early brainstem potentails with stimulus intensity are very similar to those observed for the N_1 potential. While the precise source of the generators of the different components of these early potentials remains in some doubt, it has been generally assumed that they too are produced by an increase in the firing rateas of individual units within the brainstem auditory pathway.

However, in Chapter four the importance of phase aggregation in establishing the pattern of the coherent grand-average has been demonstrated. The aggregation of phases of significant harmonics also appeared to be of central importance to the generation of high correlations obtained between the coherent average and individual ensemble members. Phase aggregation may have been produced by a superimposed time synchronised response with a recurrent and consistent pattern. Such a pattern would have fixed characteristics of harmonic amplitude and phase. Depending on the relative amplitudes of harmonics in the background noise and added respones, the individual harmonic phase values of the pattern would be imposed on corresponding harmonics of the spontaneous activity. Alternatively phase constraint may have arisen as a result of time synchronisation of spontaneous background activity. It has already been established that the synchronisation model of pattern generation accounts well for the behaviour of the late cortical evoked potential (Beagley, Sayers and Ross, 1979). For these reasons it was decided to investigate whether the far-field auditory brainstem potentials conformed best to a superposition or synchronisation model. In the following experiment these two hypotheses have been investigated.

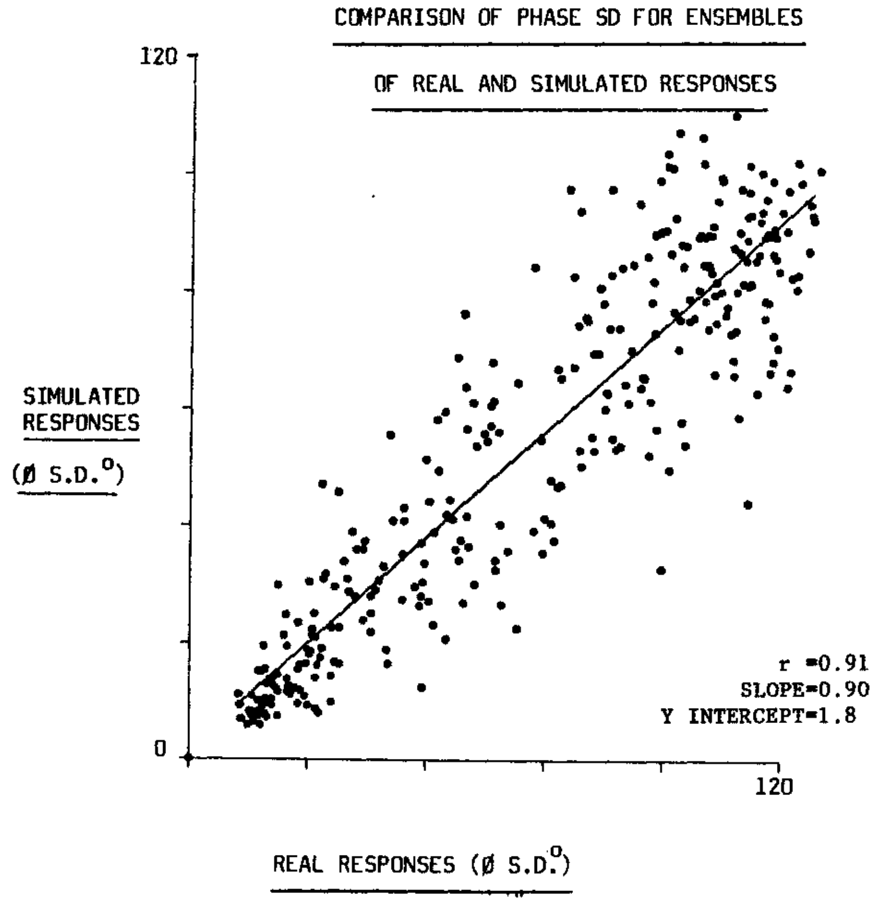
GUINEA PIG STUDY

Phase Standard Deviation

From observation of averaged records (Figure 4.1-4.4) and comparing pre-stimulus and post-stimulus epochs, it was evident that the coherent average was dominated by the true evoked response and had little noise contamination. As a test of the superposition hypothesis, ensembles of simulated responses were formed by adding this averaged response to the pre-stimulus ensemble. If an additive mechanism was correct then major similarities should have existed between such simulated responses and the corresponding ensemble of real responses. The two parameters evaluated were phase standard deviation and mean phase angle.

Harmonic phase standard deviations were calculated for simulated and real responses obtained at 10 stimulus intensities from 4 guinea-pigs. Simulated responses were formed by adding the post-stimulus coherent average obtained at each stimulus level to the corresponding pre-stimulus ensemble. A scattergram relating the simulated and real phase standard deviations was plotted and the best-fit straight line drawn (Figure 5.1). A correlation of .91 was obtained and the y-intercept was 1.8^{o} indicating a high level of agreement between these two groups of responses. The variability of different observations was attributed to the effects of the spontaneous noise. As a test of this, comparison was made between two ensembles of simulated responses in which the same averaged response was embedded in two different ensembles of spontaneous activity. The correlation coefficient was 0.90 and the general features of the scattergram were the same (Figure 5.2). As the only differences in these two groups of ensembles was in the noise it was concluded that noise variability alone could have accounted for the differences between simulated and real responses. These findings supported the superposition hypothesis.

Harmonic phase standard deviations for simulated and real responses were compared at each stimulus level (Figure 5.3 and 5.4). At high stimulus intensities all harmonics for simulated and real responses were highly constrained. Further the degree of phase aggregation at each level was very similar for both simulated and real responses. The



COMPARISON OF PHASE SD FOR ENSEMBLES
OF REAL AND SIMULATED RESPONSES
120
0
120
SIMULATED RESPONSES
(Ø S.D.°)
r =0.91
SLOPE=0.90
Y INTERCEPT=1.8
REAL RESPONSES (Ø S.D.°)

FIGURE 5.1

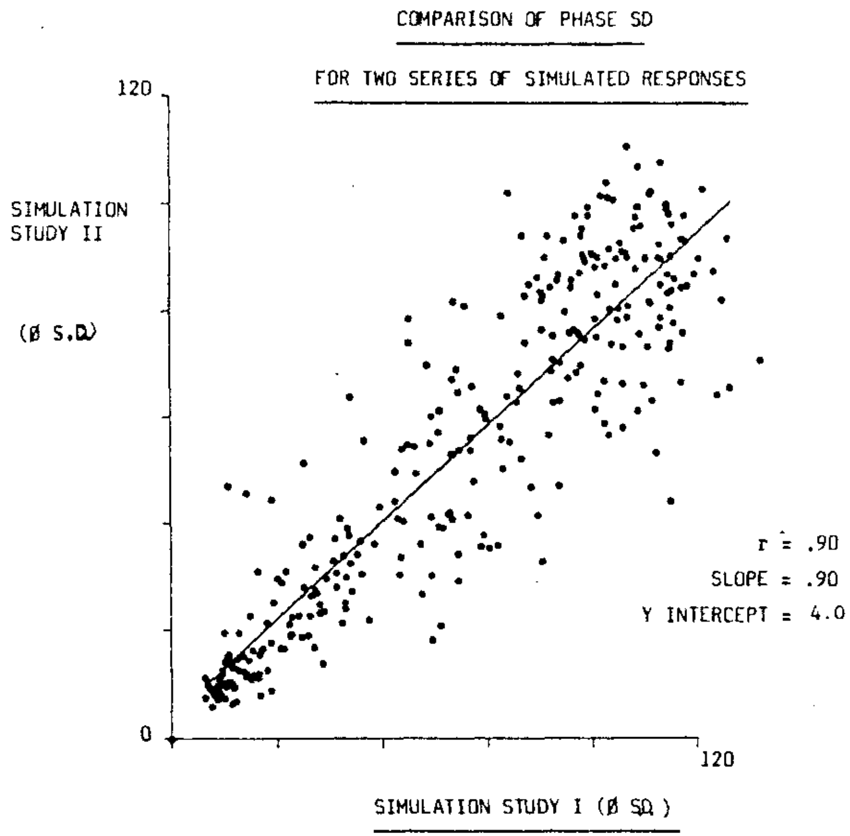

COMPARISON OF PHASE SD
FOR TWO SERIES OF SIMULATED RESPONSES
120
SIMULATION
STUDY II
(Ø S.D)
0
120
SIMULATION STUDY I (Ø SD)
r = .90
SLOPE = .90
Y INTERCEPT = 4.0

FIGURE 5.2

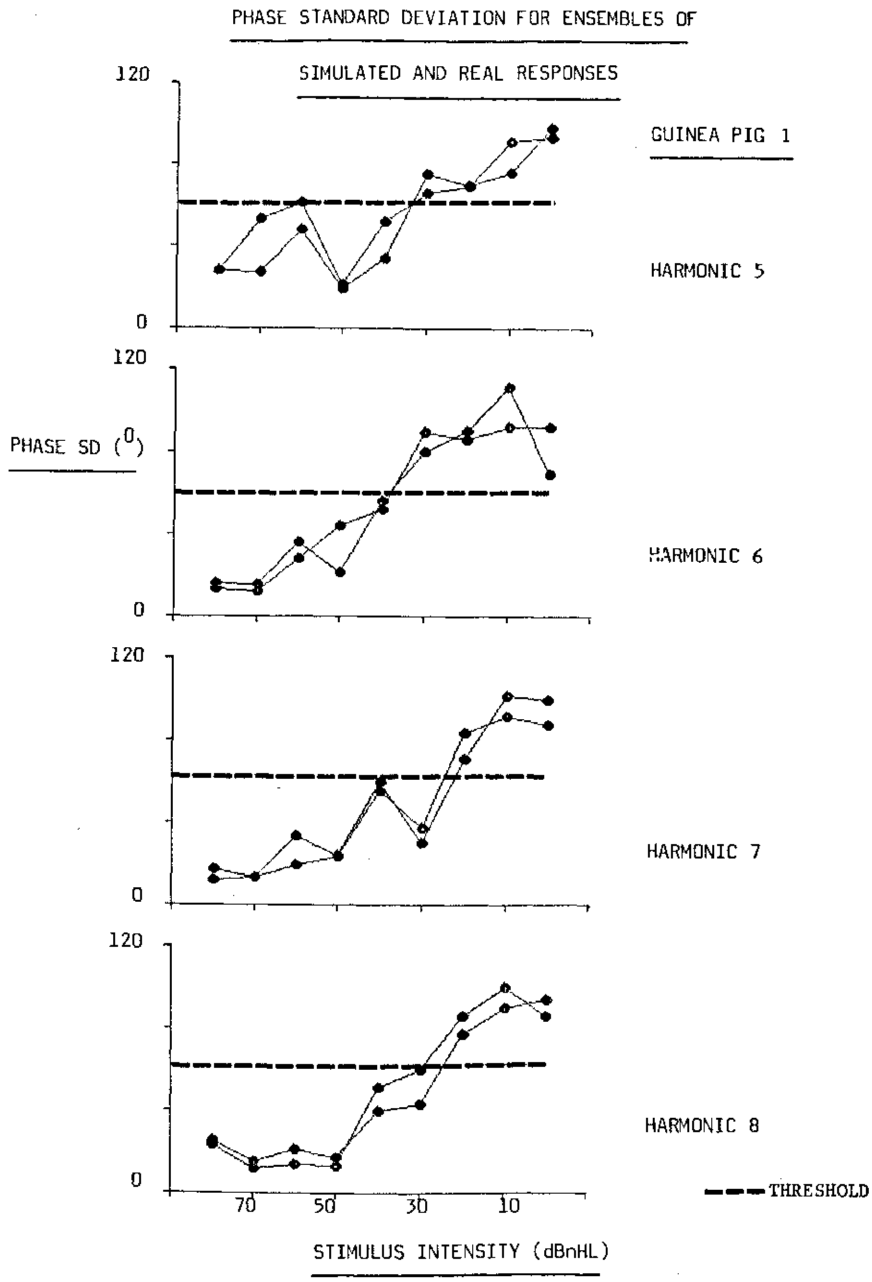


FIGURE 5.3a: In this and the following four figures comparison has been made between phase aggregations produced by simulated and real responses over the stimulus intensity range 80-0 dBnHL. The amount of phase constraint for simulated and real ensembles at most supra-threshold intensities was almost identical as was the general change with intensity.

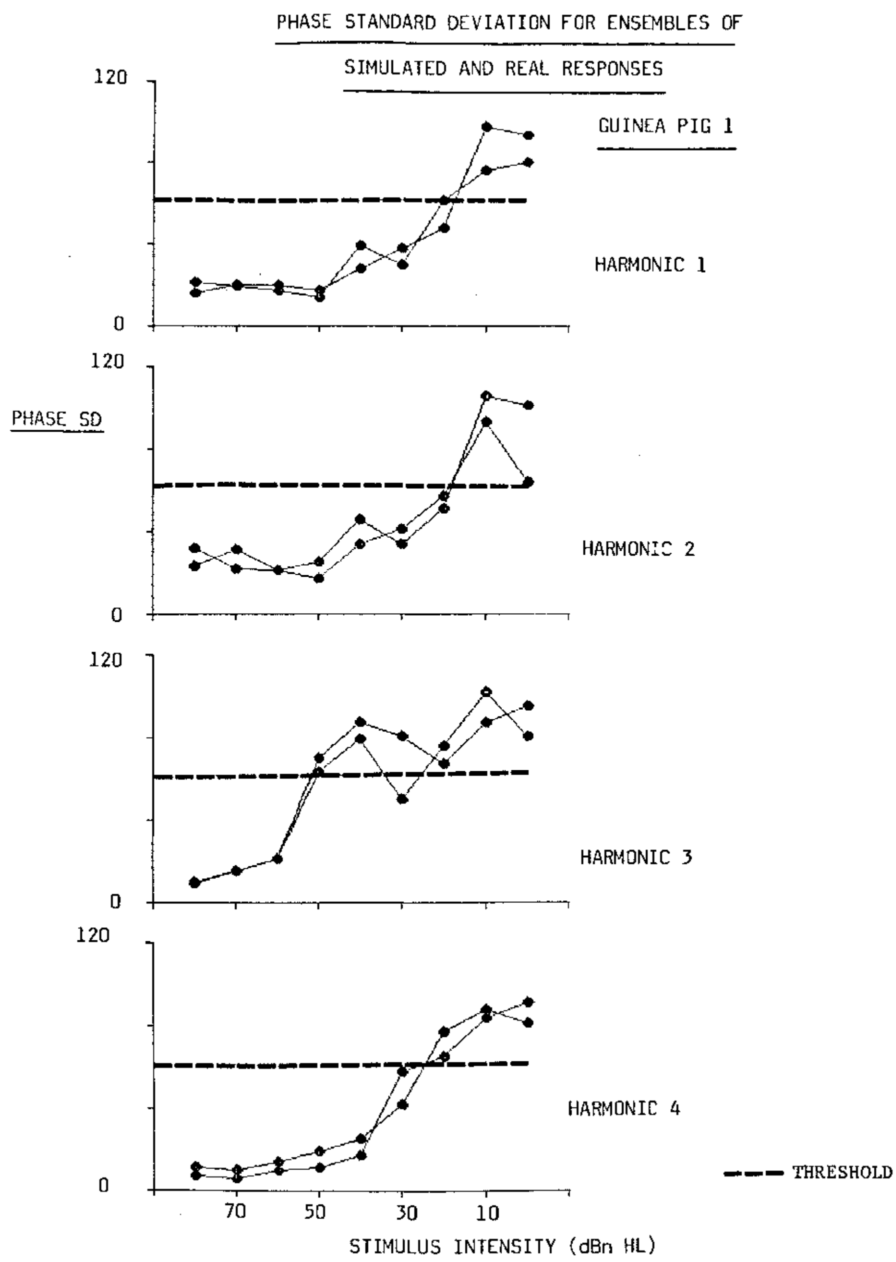

PHASE STANDARD DEVIATION FOR ENSEMBLES OF
SIMULATED AND REAL RESPONSES
GUINEA PIG 1
120
0
HARMONIC 1
120
PHASE SD
0
HARMONIC 2
120
0
HARMONIC 3
120
0
HARMONIC 4
THRESHOLD
70
50
30
10
STIMULUS INTENSITY (dBn HL)

FIGURE 5.3b

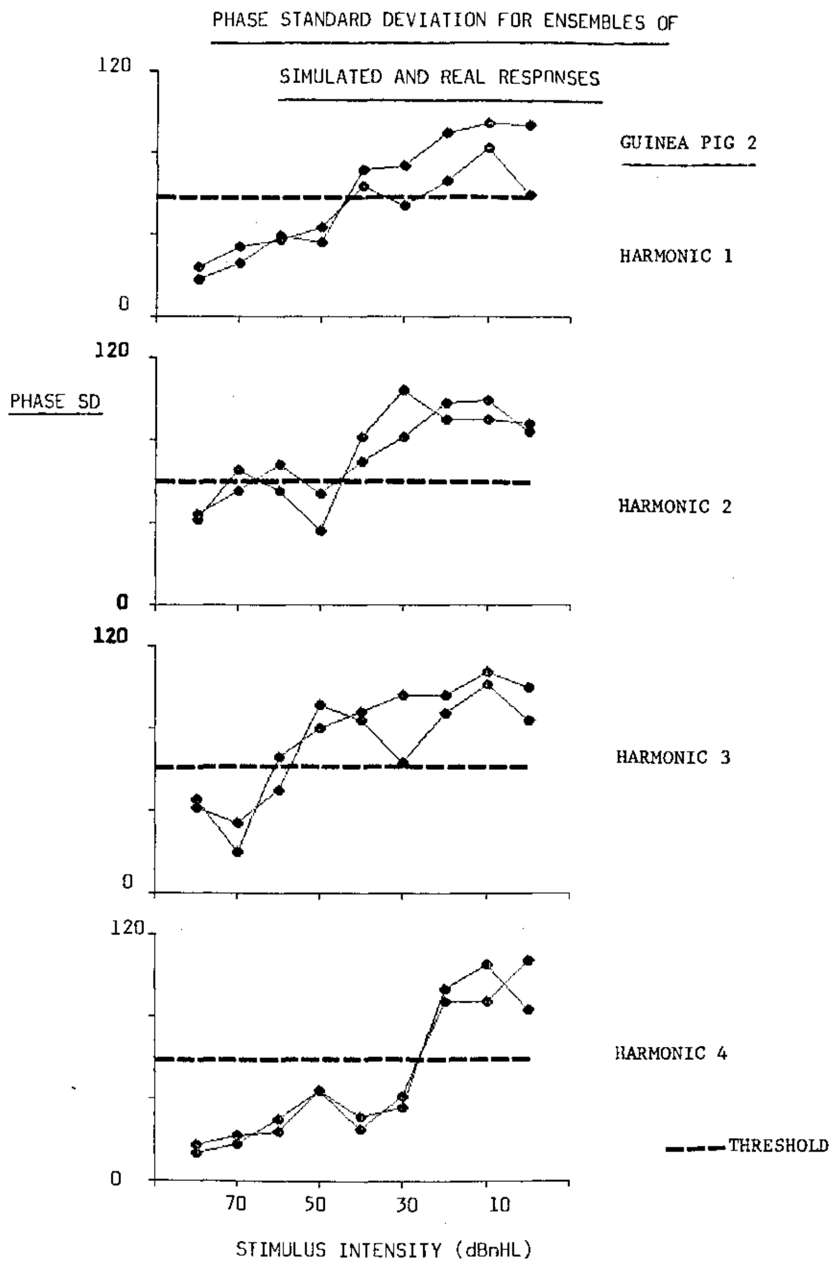

PHASE STANDARD DEVIATION FOR ENSEMBLES OF
SIMULATED AND REAL RESPONSES
GUINEA PIG 2
120
0
HARMONIC 1
PHASE SD
HARMONIC 2
HARMONIC 3
HARMONIC 4
THRESHOLD
70
50
30
10
STIMULUS INTENSITY (dBnHL)

FIGURE 5.4a

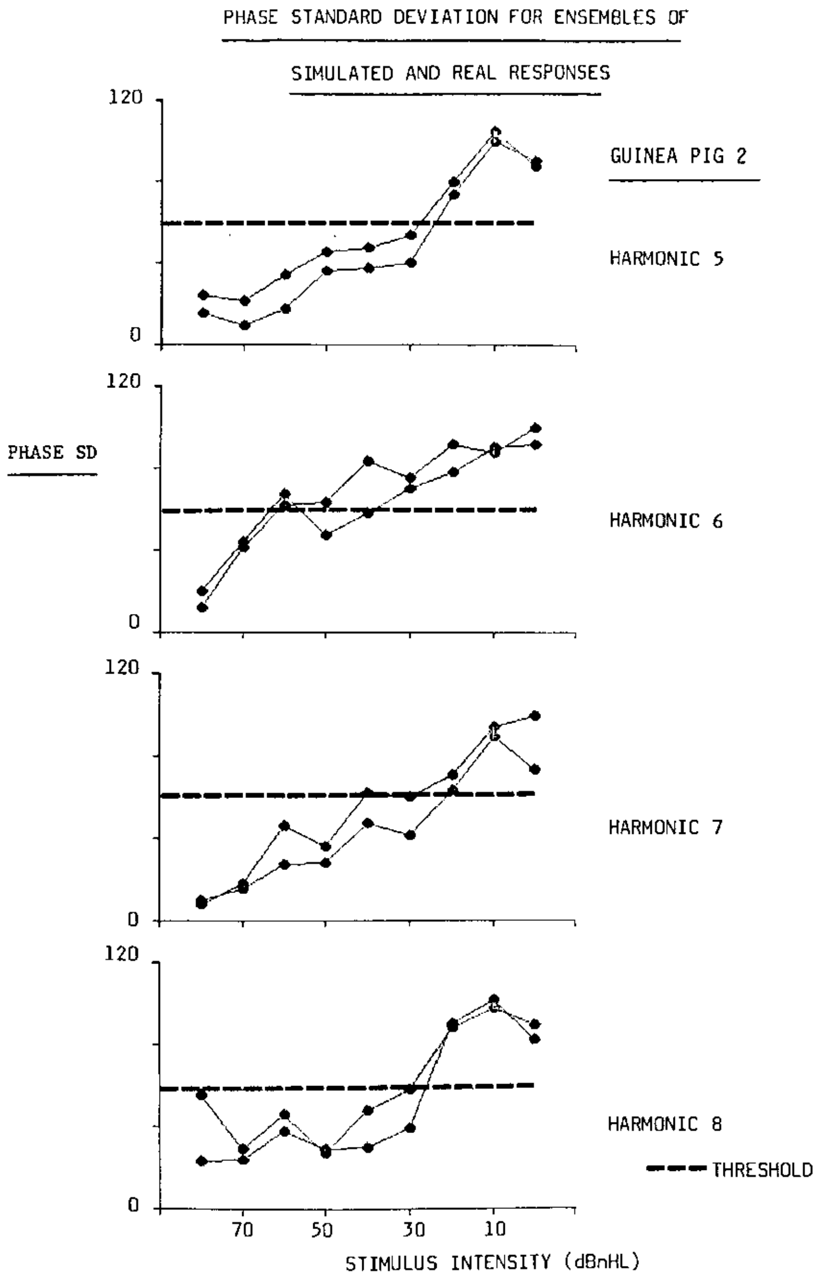

PHASE STANDARD DEVIATION FOR ENSEMBLES OF
SIMULATED AND REAL RESPONSES
GUINEA PIG 2
PHASE SD
120
0
HARMONIC 5
HARMONIC 6
HARMONIC 7
HARMONIC 8
THRESHOLD
70
50
30
10
STIMULUS INTENSITY (dBnHL)

FIGURE 5.4b

amount of phase constraint observed in the in vivo situation was reproduced simply by adding the coherent average of the response to the spontaneous background activity. The findings were also in keeping with the superposition model of pattern generation.

Mean Phase Angle

While the power and pattern of the coherent average has been shown to be critically dependant on the second moment of the phase distribution, it was also predicted that the latency shift in the time domain pattern with stimulus intensity should be related to changes in the first moment of the phase distribution. However, this must be qualified. As has been mentioned earlier, not only did the time domain pattern show a bulk latency shift with stimulus intensity, there was also a degredation of the pattern itself. It was therefore expected that all harmonics would not contribute equally to the pattern across the intensity range. By selecting harmonics which showed phase aggregations across a wide range of stimulus intensities, it was predicted that a systematic alteration in the ensemble mean would be found, corresponding to the latency changes in the time domain. Again using the same guinea-pigs, two representative harmonics were studied. The results for each animal have been plotted in Figure 5.5. For post-stimulus ensembles, harmonics showed systematic increases in mean value as stimulus intensity decreased, consistent with the increase in latency of the coherent average. Further, the slope of phase angle against stimulus intensity was much increased for later harmonics, again consistent with the observed relation between phase angle and latency of pattern in the time domain. By contrast the mean values from ensembles of pre-stimulus spontaneous activity were quite random. If the superposition model was correct then one would expect similar behaviour for both the simulated and real responses. The results for the same harmonics for simulated and real ensembles have been plotted in Figure 5.6. A high level of agreement between the simulated and real con ditions for individual harmonics was again obtained.

HUMAN STUDY

The forgoing procedure was then repeated using responses obtained from two normal hearing subjects for the range of stimulus intensities 70-10 dBnHL. However, the signal to noise ratio was very much smaller and for this reason ensembles consisting of 1,024 sweeps were investigated. Because of the dependency of the second moment of the phase S.D. distribution on ensemble size, it was first necessary to

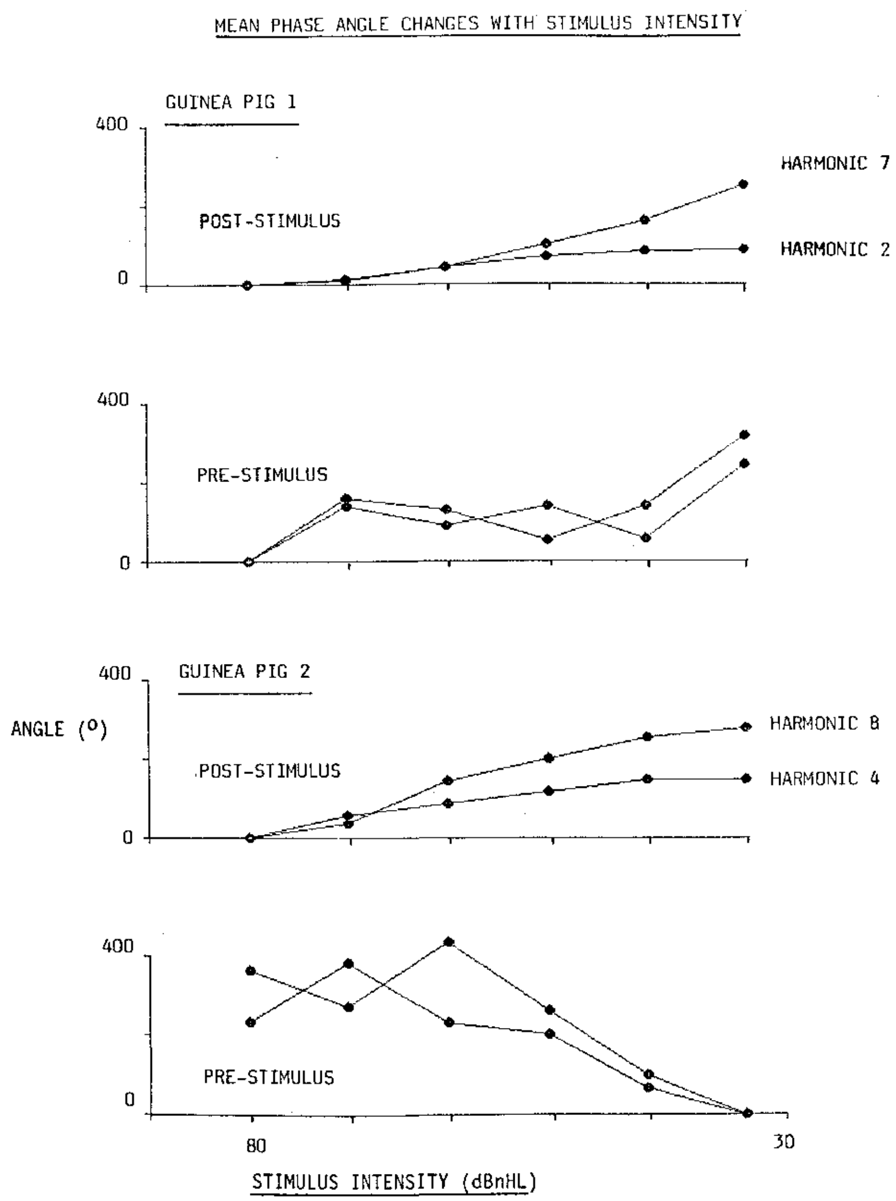


FIGURE 5.5: In each of 2 harmonics the relationship between phase angle and stimulus intensity was examined. Taking the mean phase angle at 80 dB as reference the relative positions of successive mean phase angles were plotted for pre-stimulus and post-stimulus ensembles.

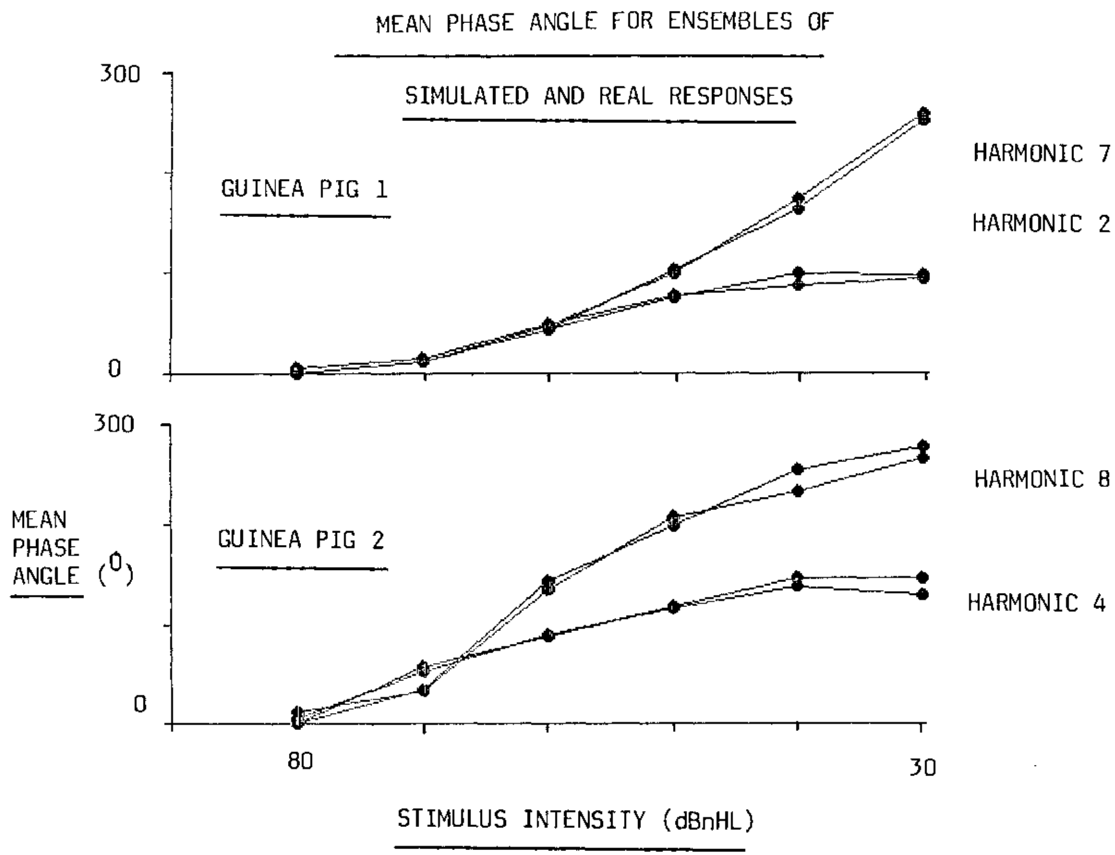


FIGURE 5.6: Comparison of simulated and real responses. For each harmonic the mean angle of the simulated response at 80 dB was taken as reference. Simulated and real responses produced almost identical man phase angles.

establish the confidence interval. For ensembles of 1,024 (Figure 5.7) the 1% confidence level was 99^o. As with the guinea-pig study simulated and real responses were compared. Figures 5.8 and 5.9 summarise the findings for individual harmonics for the two subjects. For these two human subjects marked variations were observed in phase S.D. at different stimulus intensities and between harmonics at the same stimulus intensity. Nevertheless good agreement was observed in the amount of phase constraint for simulated and real responses. Allowing for the differences in noise, the findings were consistent with those observed in the guinea-pig study.

Harmonics 5 and 6 in both subjects showed phase constraint over a wide range of stimulus intensities. It was therefore predicted that these harmonics would show a consistent change in phase angle with stimulus intensity, paralleling the observed latency shifts in the human evoked brainstem potentials (Figure 3.19). The phase angles for pre-stimulus and post-stimulus epochs were compared (Figure 5.10). Pre-stimulus harmonic phase angle showed only random variations with stimulus intensity. An almost linear change was observed in post-stimulus mean phase with stimulus intensity and in a direction consistent with the observed latency change in the time domain pattern. The values for harmonics 5 and 6 were very similar consistent with their neighbouring harmonics positions.

In conclusion the similarities in harmonic phase behaviour of simulated and real responses were consistent with the hypothesis that the evoked brainstem potentials impose a pattern on the spontaneous background E.E.G. by a mechanism of superposition. Any discrepancy observed between simulated and real conditions could be accounted for in terms of variability of the background noise.

FREQUENCY DISTRIBUTION OF SECOND MOMENT OF PHASE DISTRIBUTION

FOR 1024 SWEEP ENSEMBLES

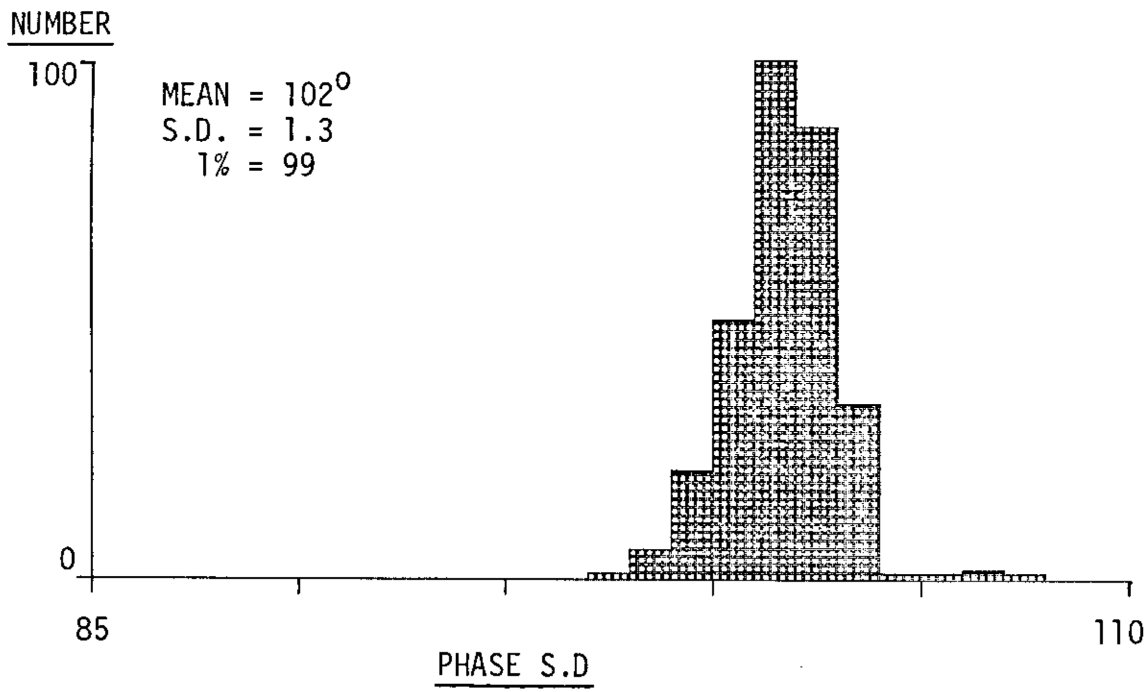


FIGURE 5.7

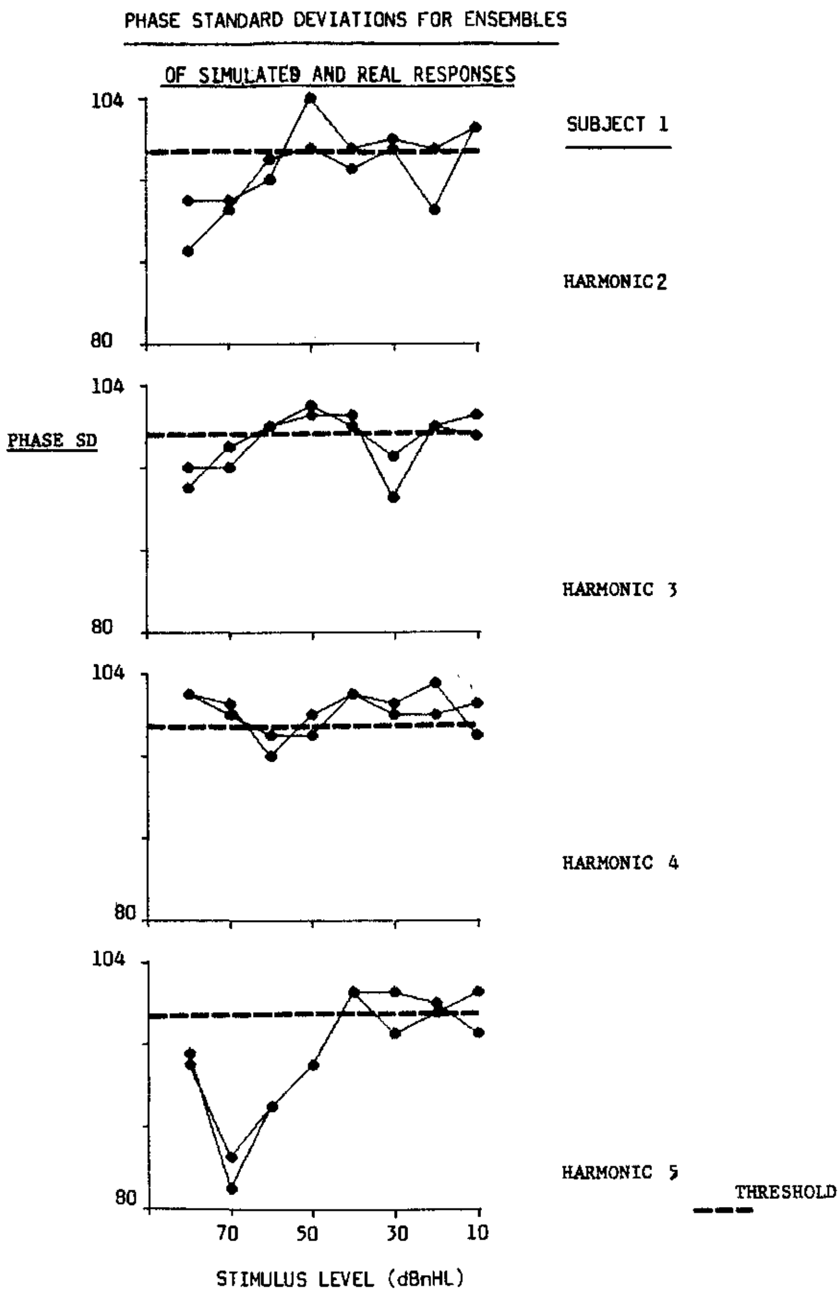


FIGURE 5.8a: In this and the following 3 figures the ensemble mean phase S.D.'s for individual harmonics have been plotted for simulated and real responses. The confidence interval associated with the 1% probability level indicates significant constraints.

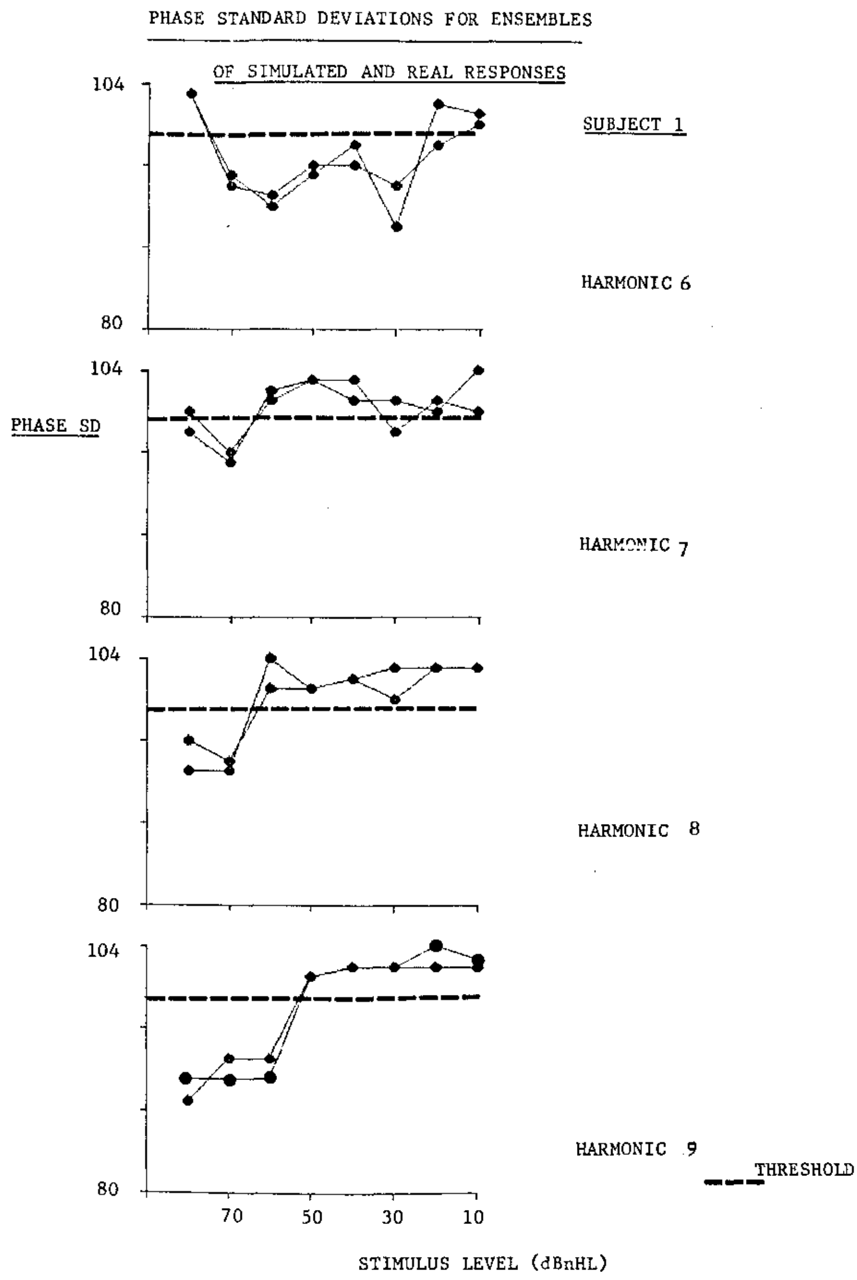

PHASE STANDARD DEVIATIONS FOR ENSEMBLES
OF SIMULATED AND REAL RESPONSES
SUBJECT 1
104
80
HARMONIC 6
104
PHASE SD
80
HARMONIC 7
104
80
HARMONIC 8
104
80
HARMONIC 9
THRESHOLD
70
50
30
10
STIMULUS LEVEL (dBnHL)

FIGURE 5.8b

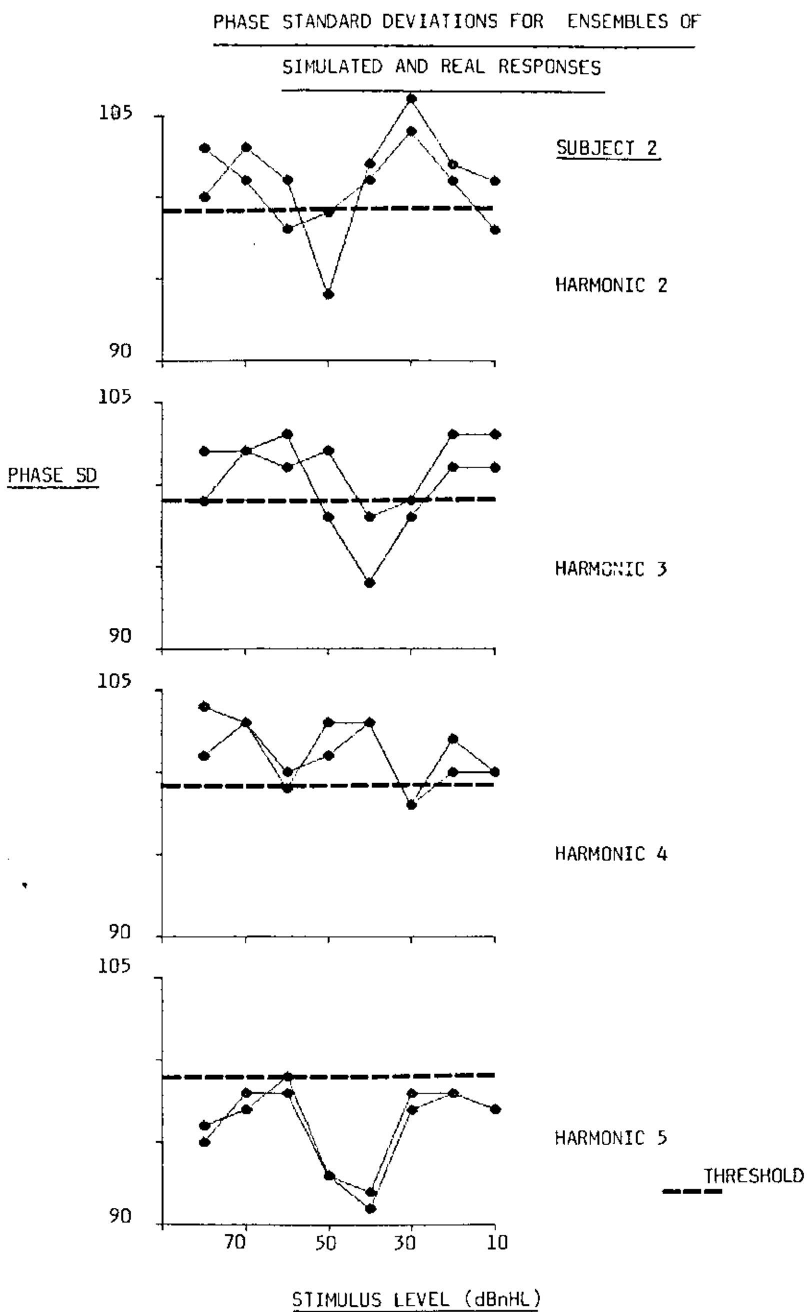

PHASE STANDARD DEVIATIONS FOR ENSEMBLES OF
SIMULATED AND REAL RESPONSES
SUBJECT 2
105
90
HARMONIC 2
105
90
PHASE SD
HARMONIC 3
105
90
HARMONIC 4
105
90
HARMONIC 5
THRESHOLD
70
50
30
10
STIMULUS LEVEL (dBnHL)

FIGURE 5.9a

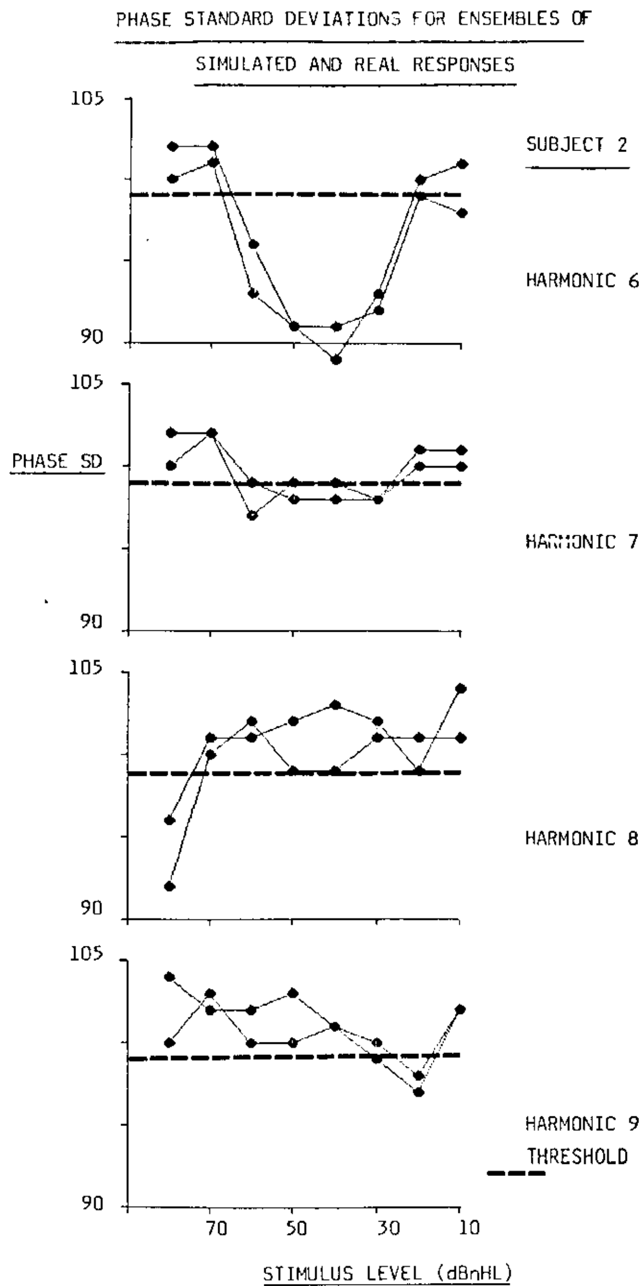

PHASE STANDARD DEVIATIONS FOR ENSEMBLES OF
SIMULATED AND REAL RESPONSES
SUBJECT 2
105
90
HARMONIC 6
105
PHASE SD
90
HARMONIC 7
105
90
HARMONIC 8
105
90
HARMONIC 9
THRESHOLD
70
50
30
10
STIMULUS LEVEL (dBnHL)

FIGURE 5.9b

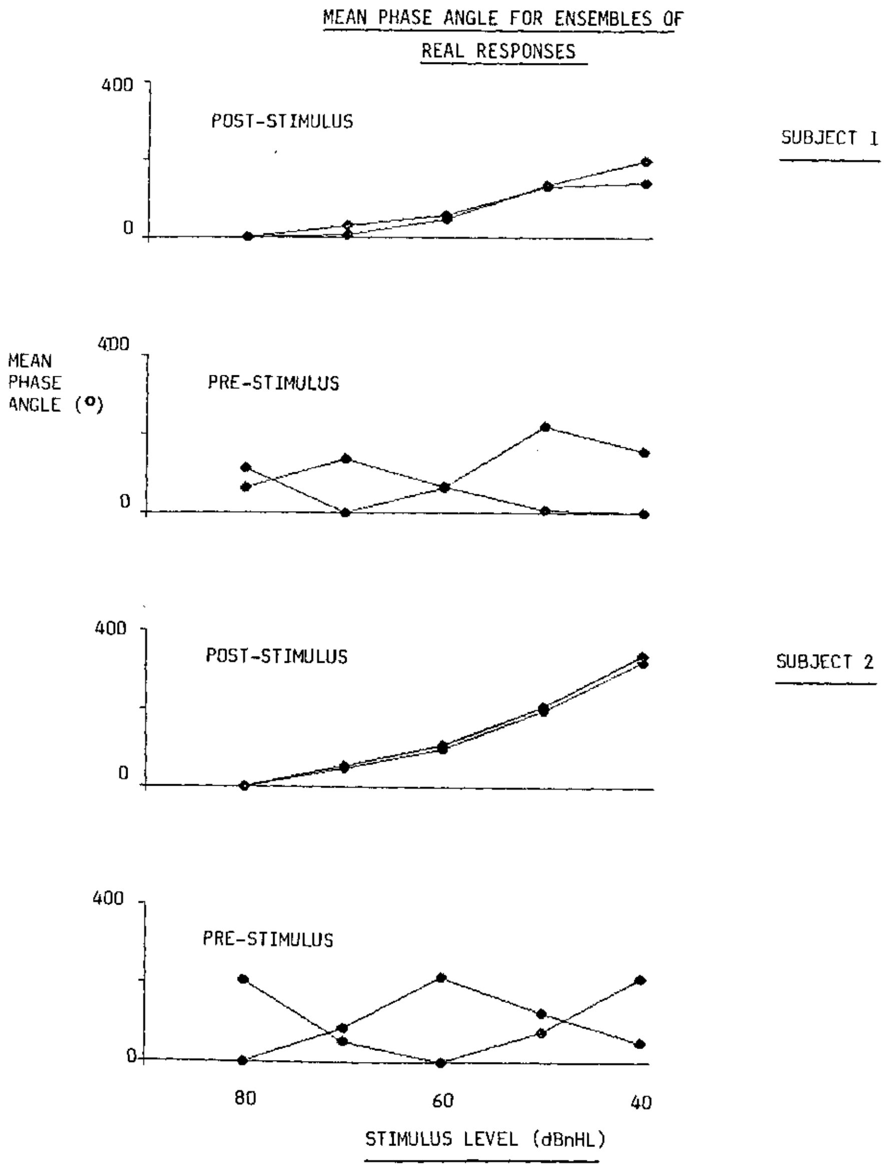


FIGURE 5.10: Behaviour of the mean phase angles of harmonics 4 and 5 at different stimulus intensities. Post-stimulus and pre-stimulus ensembles have been compared.

Chapter 6

Clinical Evaluation of the Phase Spectral Analysis Method for the Objective Detection of Auditory Threshold

INTRODUCTION

The template matching method evaluated in Chapter 3, and in which the coherent average was used as the template, assumed prior knowledge of the pattern to be detected. The limitations in the sensitivity of the method prompted a more detailed signal analysis investigation. A study of the Fourier harmonics of responses in the guinea-pig (Chapter 4) indicated that there were characteristic changes in the amplitudes and phases of individual harmonics over a range of stimulus intensities. The amplitude statistic which best characterised the presence of a response was the ensemble mean. While this altered with changes in stimulus intensity, the intersessional and intersubject variabilities were so great that the overall sensitivity of the method was considerably reduced. The phase statistic which best characterised the presence of a response was the second moment of the ensemble phase distribution (standard deviation). This statistic was much more sensitive to the occurrence of a response than amplitude and no prior knowledge of the underlying response pattern was assumed. Measurement of phase aggregation appeared to offer an alternative method of threshold evaluation. The signal analysis investigation also shed further light into the nature and behaviour of phase aggregations seen in records. The sampling statistics of phase provided important quantitive measures of phase aggregation and the results of the investigations in Chapter 5 supported the hypothesis that the scalp recorded brainstem potentials were superimposed on the background spontaneous neural and muscle activity.

SAMPLING STATISTICS AND CONFIDENCE INTERVALS FOR HUMAN BRAINSTEM POTENTIALS

The results of the guinea-pig studies indicated that phase standard deviation was a sensitive parameter for detecting the presence of a response in an ensemble of post-stimulus records. However, the sampling statistics of this parameter clearly indicated that the first moment of the frequency distribution standard deviation was a biased estimate dependent on ensemble size. It was therefore necessary at the outset of this study of normal hearing and hearing impaired subjects to establish the sampling statistics and confidence interval for phase standard deviation. To this end unstimulated E.E.G. recordings were made from 4 normal hearing subjects, ensembles of 1,024 sweeps collected, and the frequency distribution of phase S.D. for 304 ensembles formed (Figure 5.8). The mean for this ensemble size was 102^{0} and the standard deviation 1.3. The small departure of this observed sample mean, for ensemble size 1,024, from the theoretical estimate of 104^0 was attributed to the biasing effect of sample size. The empirical statistics for more appropriate sized samples for clinical use had then to be established. As mentioned in the third chapter, for reasons of economy of space and speed of analysis it was decided to utilise ensembles of 16 or 32 sweeps. The practical implementation of this entailed collecting 1,024 individual sweep records and reducing these to 16 sweep ensembles by combining them into sub-averages each consisting of 64 records. For 2,048 records ensembles of size 32 were formed again by combining 64 records into a single sub-average. Ensemble statistics of phase standard deviation for ensembles of 16 and 32 sweeps were compared with those obtained for 1,024 sweep ensembles (Figure 6.1). The effects of ensemble size on the first and second moments of the standard deviation distribution were clearly seen. The mean value of standard deviation for 16 sweep ensembles was 91 and for 32 sweep ensembles 95. The means and Standard Deviations were significantly different from 1,024 sweep ensembles and from one another,

Ensemble Statistics	16 Sweep Ensemble	32 Sweep Ensemble	Significance Level
Means	95.3	91.7	t-test t = 12.9 DF = 1.199 p<.001
Standard Deviations	9.2	6.2	F-test F = 2.2 DF = 1.199 p<.01

Although the departures of the phase S.D. distributions from normal were violations of the test requirements, the general robustness of these tests (Boneau, 1960) and the level of significance reached for the means and variances would justify the conclusion that the two distributions were significantly different.

It was interesting to compare the statistics of 16 sweep ensembles obtained from human and guinea-pig records (Figure 6.2). The shape of the frequency distribution and the first and second moments were virtually identical. This would add further support to the conclusion that the ensemble statistics of standard deviation for individual harmonics was wholly determined by the sampling statistics and similar to those observed for a band limited white noise source (Ross, 1978). As mentioned above, in order to generate ensembles of size 16 or 32, it was first necessary to combine the 1,000 or 2,000 responses

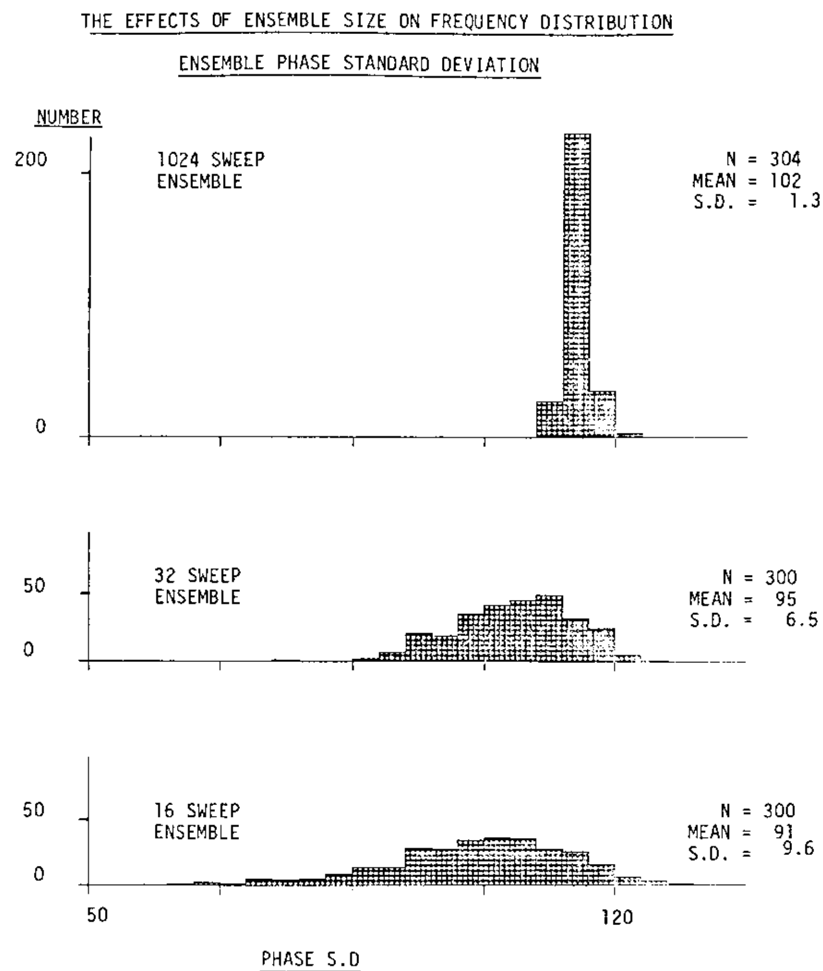

THE EFFECTS OF ENSEMBLE SIZE ON FREQUENCY DISTRIBUTION
ENSEMBLE PHASE STANDARD DEVIATION
NUMBER
200
0
1024 SWEEP
ENSEMBLE
N = 304
MEAN = 102
S.D. = 1.3
50
0
32 SWEEP
ENSEMBLE
N = 300
MEAN = 95
S.D. = 6.5
50
0
16 SWEEP
ENSEMBLE
N = 300
MEAN = 91
S.D. = 9.6
50
120
PHASE S.D

FIGURE 6.1

FREQUENCY DISTRIBUTIONS OF PHASE S.D.

FOR UNSTIMULATED RECORDS

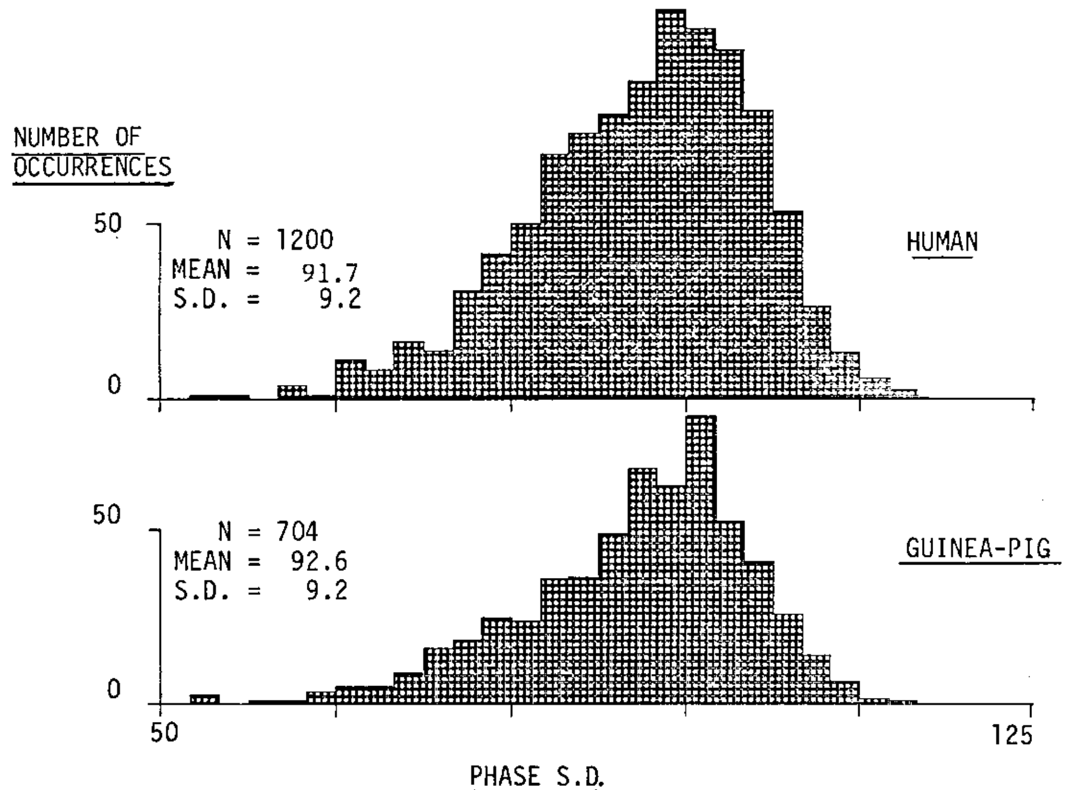


FIGURE 6.2

obtained into small sub-averages each consisting of 64 individual responses. Therefore, before establishing confidence intervals the effect of forming sub-averages on the frequency distribution of phase S.D. was first investigated. Comparison was made of the frequency distributions for single sweep ensembles and ensembles in which individual members were formed from 4, 16 and 64 sweeps. The results have been summarised in Figure 6.3. The distributions were virtually identical and no statistical differences were found in either the first or second moments when compared with single sweep ensembles.

Once the empirical statistics for phase standard deviation had been established the confidence intervals were calculated for the distribution. The confidence intervals for the .5, .1, .05, and .01 probability levels have been tabulated and indicated on the frequency distribution curves (Figure 6.4). The values for 16 sweep ensembles agreed well with those obtained earlier in the guinea-pig studies. The one per cent probability level has been chosen throughout as an arbitrary "threshold" for deciding on the presence of a response. As the first ten harmonics in each response ensemble have been examined the probability of observing the 1% probability level was increased by a factor of 10. In order to maintain the overall 1% level of probability for the ensemble the confidence interval associated with $p = .001$ was chosen for individual harmonic occurrences. The possibility of joint occurrences needed to be considered so in addition to single occurrences at the .1% level, 2 harmonic occurrences in 10 at the 1.6% level and 3 harmonic occurrences in 10 at the 5% level were included, each corresponding to overall probability of $p = .01$ for the ensemble.* The three confidence intervals associated with these probability levels (for single 59^o, joint with 2 68^o, joint with 3 harmonics 75^o) were chosen as the criteria for threshold in all subsequent investigations. Only individual values of phase S.D. less than these confidence levels were accepted as evidence of a response. It should be stressed that the choice of the 1% level has been somewhat arbitrary and it too has been the subject of further investigation.

As a final test of the reliability of the choice of confidence interval the pre-stimulus records of 34 normal hearing subjects were examined. The phase S.D. value corresponding to the .1% and .5% levels of the frequency distribution curve of 129 pre-stimulus records were 57 and 63 respectively (Figure 6.10). The corresponding values which had already been established for both the guinea-pig and human data were 59 and 63. Considering sampling effects and the small size of the

* Appendix

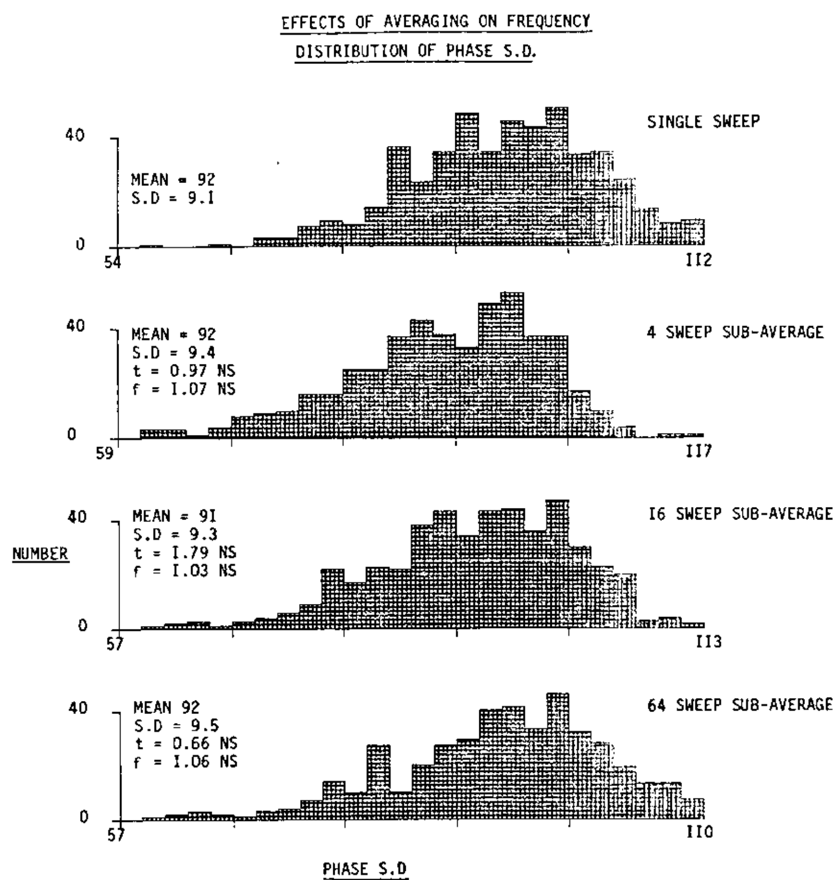

EFFECTS OF AVERAGING ON FREQUENCY
DISTRIBUTION OF PHASE S.D.
SINGLE SWEEP
40
0
MEAN = 92
S.D = 9.I
54
II2
4 SWEEP SUB-AVERAGE
40
0
MEAN = 92
S.D = 9.4
t = 0.97 NS
f = I.07 NS
59
II7
I6 SWEEP SUB-AVERAGE
40
0
NUMBER
MEAN = 9I
S.D = 9.3
t = I.79 NS
f = I.03 NS
57
II3
64 SWEEP SUB-AVERAGE
40
0
MEAN 92
S.D = 9.5
t = 0.66 NS
f = I.06 NS
57
II0
PHASE S.D

FIGURE 6.3

FREQUENCY DISTRIBUTION OF PHASE S.D.

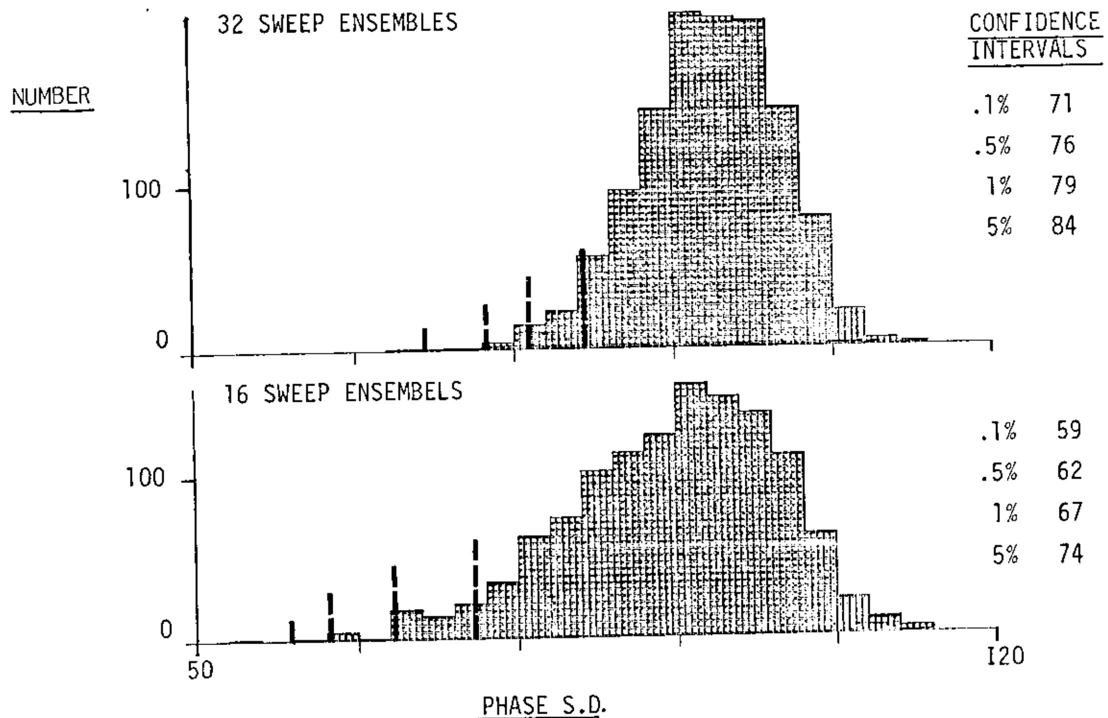


FIGURE 6.4

sample from 34 normal hearing subjects the level of agreement was very reassuring.

ANALYSIS OF RESPONSES IN NORMAL HEARING SUBJECTS

Responses to a wide range of stimulus intensities from 70 dB down to threshold were obtained from 34 normal hearing subjects. The records were grouped into 16 sweep ensembles by combining individual responses into sub-averages, each sub-average consisting of 64 individual responses. Having used the spontaneous E.E.G. as a reference to establish the empirical statistics and confidence intervals, the stimulated records were then assessed. Figure 6.5 illustrates the phase distributions of two harmonics in the post-stimulus ensembles in response to a high level stimulus in each of two subjects. In contrast to the large standard deviations for spontanenous E.E.G., post-stimulus harmonics showed aggregations in their phases which were reflected in the small standard deviations of their frequency distributions. The phase standard deviations for the first 10 harmonics obtained from the post-stimulus records of two subjects to high level stimuli have been plotted in Figure 6.6. Many harmonics showed significant phase constraint although others did not reach the criterion level for 16 sweep ensembles. Earlier observations of the amplitude spectra of the coherent grand-averages indicated that even in high intensity situations the main harmonics of the response were confined to the lower frequencies. This was even more so in the region of threshold which was the main area of interest. Therefore only the first 10 harmonics from each record were examined and the most constrained harmonic noted.

The relationship between phase standard deviation for the most constrained harmonic and stimulus intensity was then investigated and the results summarised in Figure 6.7. The observed relationship appeared to be linear in nature and the slope of change of phase standard deviation with stimulus intensity was $.5^{0}$/dB. It was found instructive to compare this phase-intensity relationship with the unstimulated conditon. Given that the lowest standard deviation value in each post-stimulus record was selected from the first 10 harmonics, the corresponding value for unstimulated records was calculated for comparison. Repeatedly selecting the most constrained harmonic from the first ten in unstimulated records would, on average, correspond to the first 10% of the frequency distribution for unstimulated records (Figure 6.4). The expected value for this portion of the frequency distribution would be the 5% level. The phase S.D.

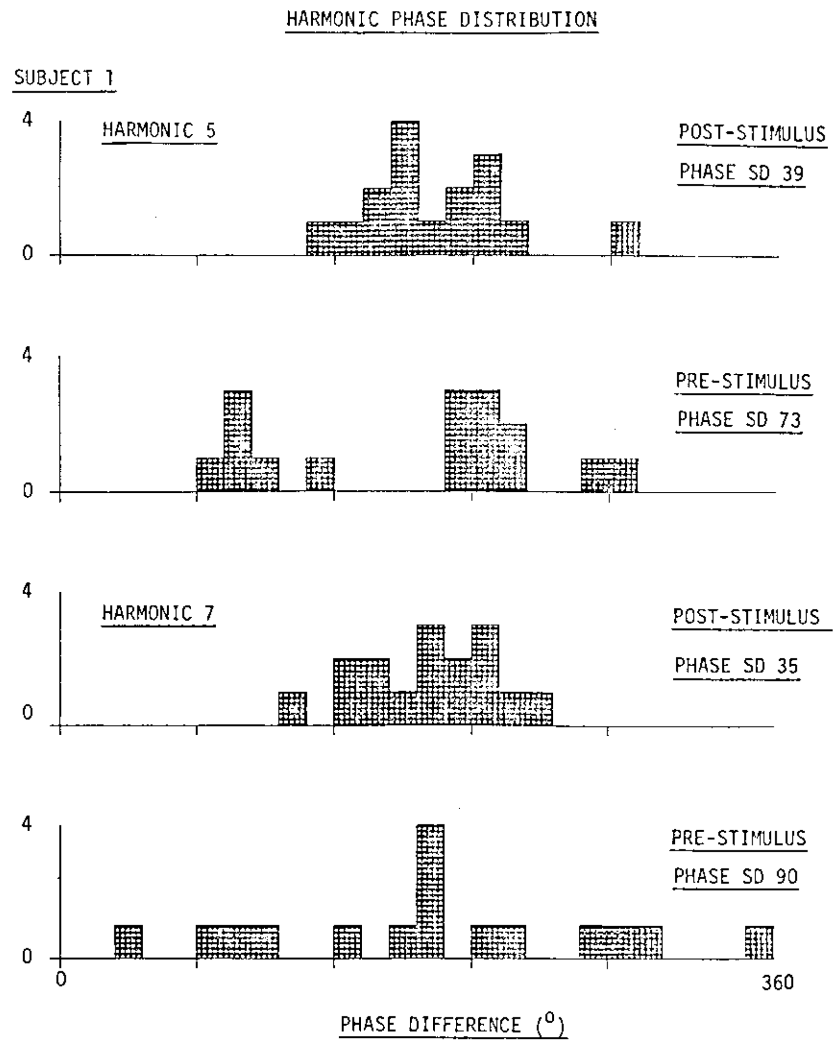
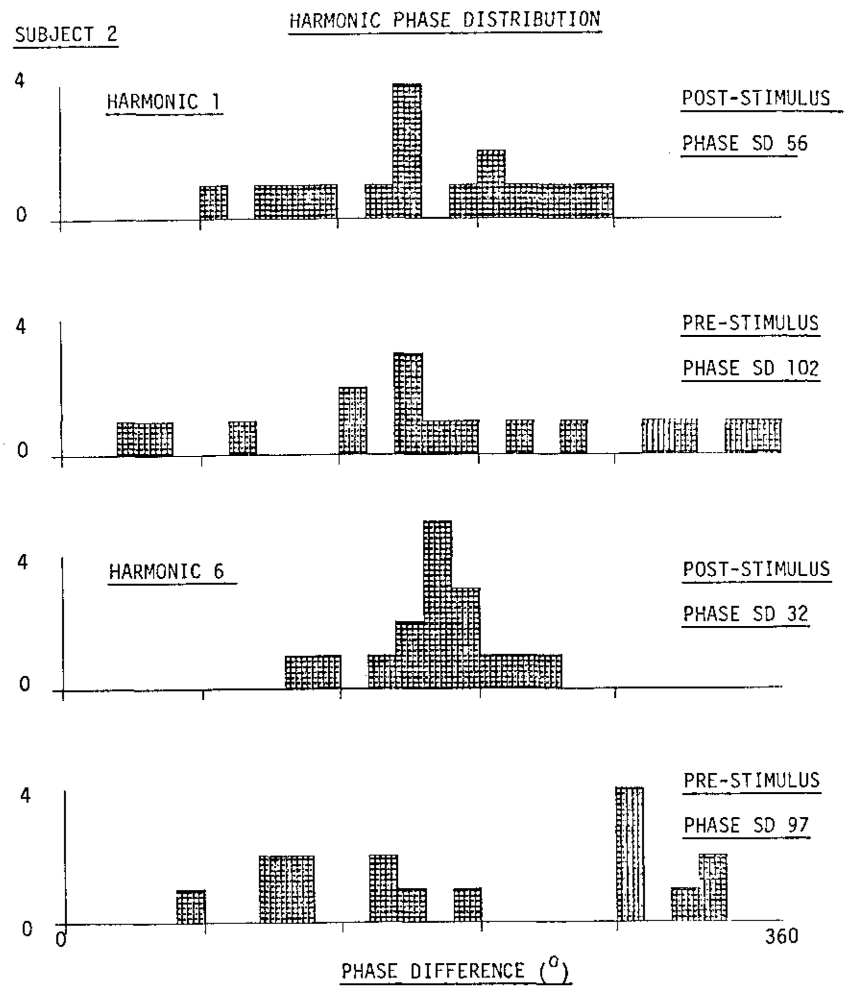

HARMONIC PHASE DISTRIBUTION
SUBJECT 1
4
0
HARMONIC 5
POST-STIMULUS
PHASE SD 39
4
0
PRE-STIMULUS
PHASE SD 73
4
0
HARMONIC 7
POST-STIMULUS
PHASE SD 35
4
0
PRE-STIMULUS
PHASE SD 90
0
360
PHASE DIFFERENCE (°)

FIGURE 6.5a



SUBJECT 2
HARMONIC PHASE DISTRIBUTION
HARMONIC 1
POST-STIMULUS
PHASE SD 56
PRE-STIMULUS
PHASE SD 102
HARMONIC 6
POST-STIMULUS
PHASE SD 32
PRE-STIMULUS
PHASE SD 97
4
0
360
PHASE DIFFERENCE (°)

FIGURE 6.5b

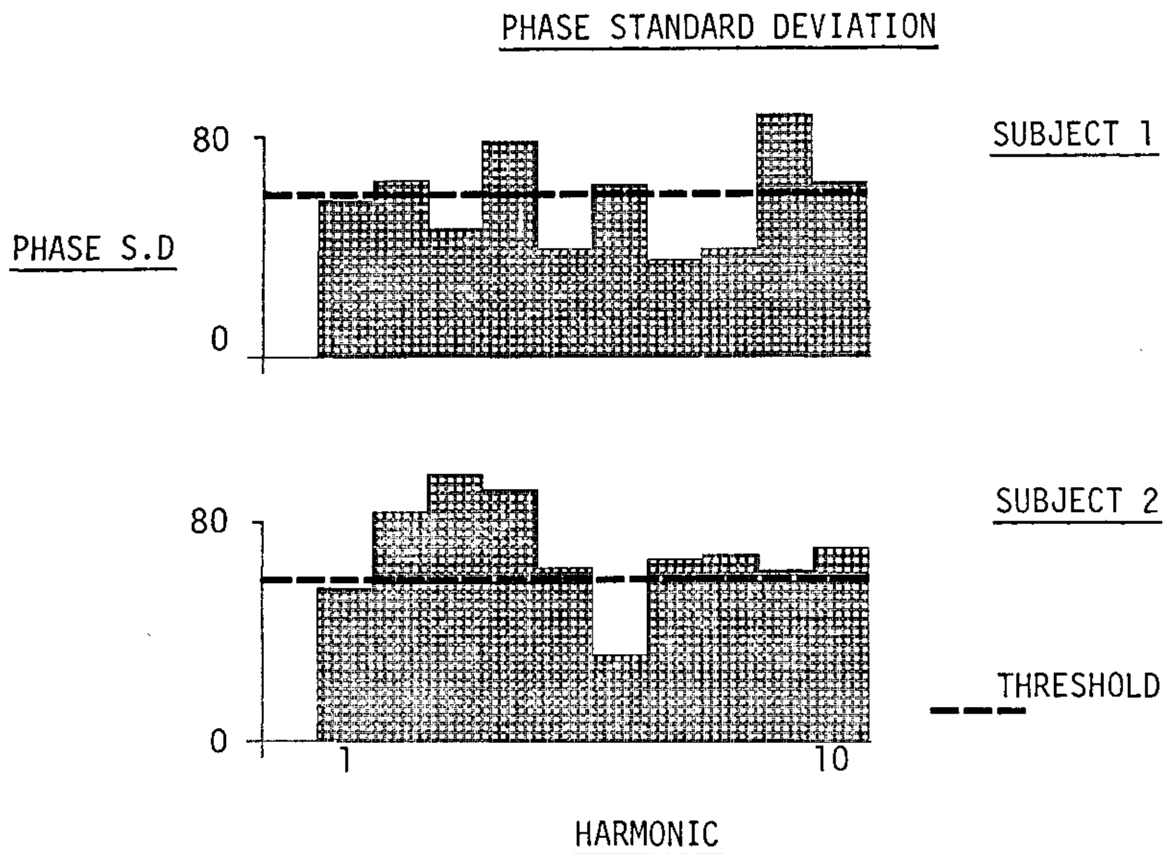


FIGURE 6.6: Harmonics with phase S.D.'s below the confidence interval regarded as significant and indicative of a response in the post-stimulus ensemble.

RELATION BETWEEN PHASE S.D. AND STIMULUS INTENSITY

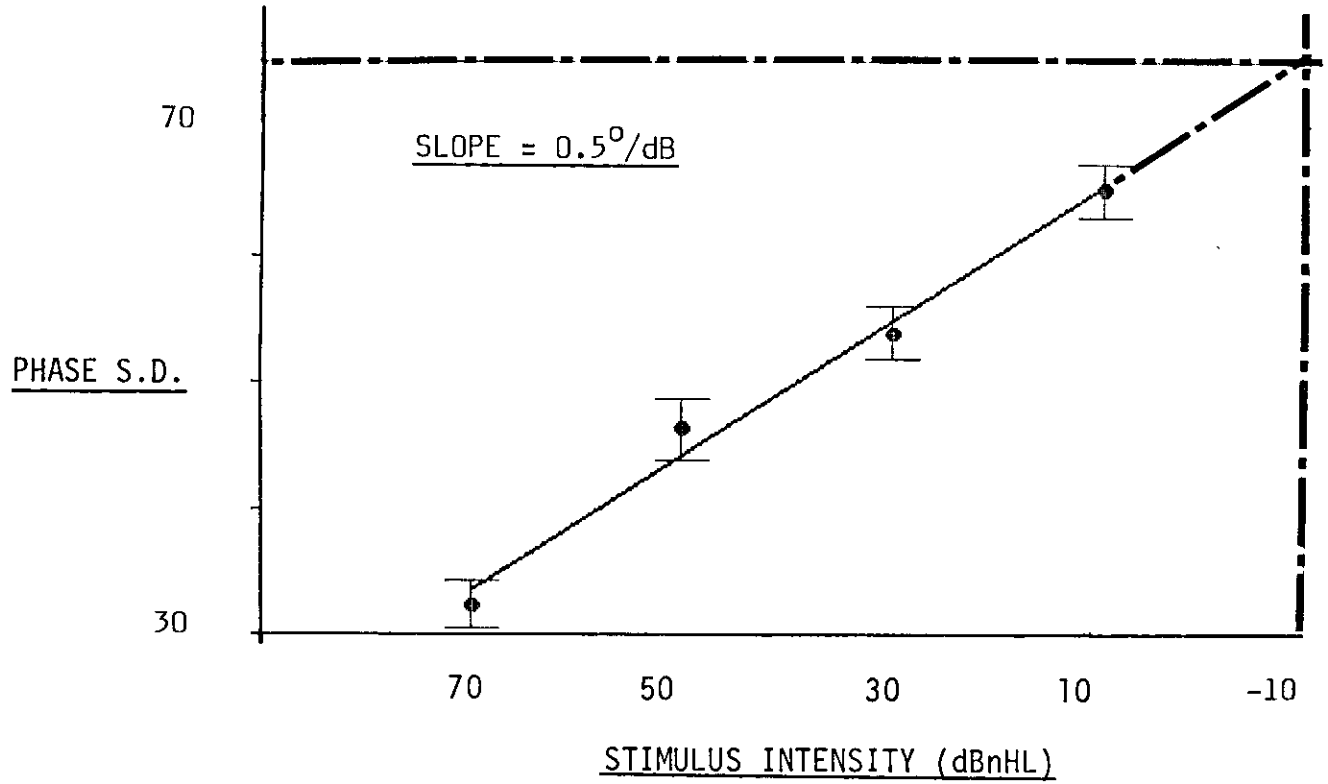


FIGURE 6.7: The expected level of phase S.D. for unstimulated records has been indicated.

corresponding to the 5% level has been included in Figure 6.7. Extrapolation of the best fit straight line relating standard deviation and stimulus intensity intercepted this level at an intensity just below threshold. This was in keeping with the linear changes in phase constraint observed at higher stimulus intensities and suggested that the phase constraint produced by the presence of a response decreased systematically throughout, from high level stimulus conditions down to sub-threshold conditions.

In Figure 6.8 the frequency distributions of phase S.D. for the most constrained harmonic for each subject at each stimulus level has been plotted together with the 1% confidence interval. On average responses down to and including 30 dB exceeded the threshold criterion. At 10 dB just under half of all observed responses exceeded this threshold criterion.

A comparison was then made between the time domain correlation statistic, reported in Chapter 3, and the behaviour of the phase standard deviation statistic observed above. Table 1 compares the correlation co-efficients obtained with the same two subjects of Figure 3.13, with the harmonics showing the greatest phase aggregations. Significant phase aggregations were observed to approximately 20 dB below the lowest intensity level at which significant correlation co-efficients were obtained. This was a typical finding.

Comparison of Phase Constraint and Correlation Statistics

Stimulus Intensity (dBnHL)	Subject 1		Subject 2	
	$\bar{r}$	ØS.D	$\bar{r}$	ØS.D
70	.38*	35*	.41*	32*
50	.57*	36*	.49*	23*
30	.17	56*	.43*	55*
10	.20	52*	.20	52*

*p<.01

TABLE 1

A regression analysis was made between ensemble mean correlation and the standard deviation value for the most constrained harmonic of each ensemble and the results plotted in Figure 6.9. A significant inverse relationship was seen between ensemble correlation co-efficient and the statistic of phase constraint ($\bar{r}$ = -.62 and the slope of the regression line -.63). The confidence intervals for p = .05 for the correlation and standard deviation parameters have also been included showing the improved sensitivity obtained with the phase constraint statistic

FREQUENCY DISTRIBUTION OF PHASE S.D

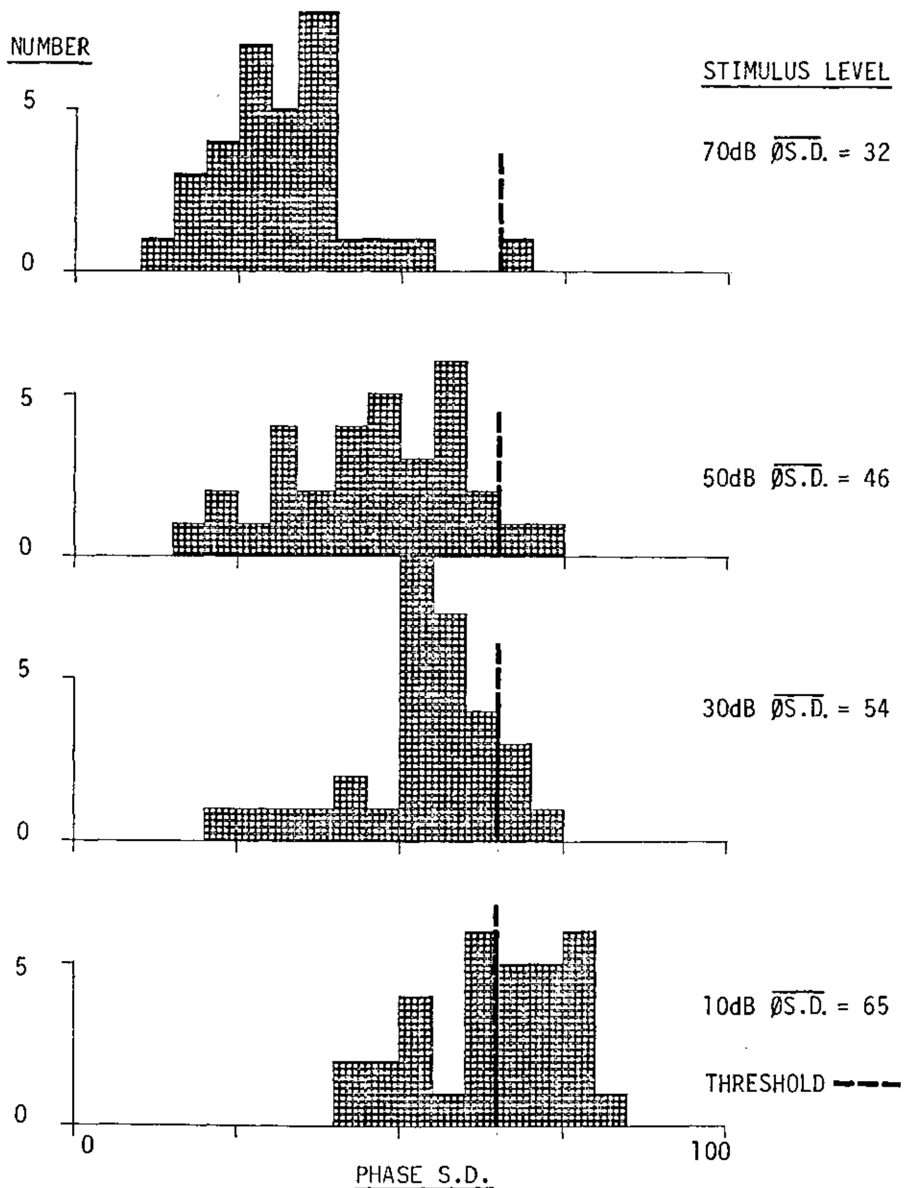


FIGURE 6.8

REGRESSION ANALYSIS OF PHASE S.D. AND $\bar{r}$

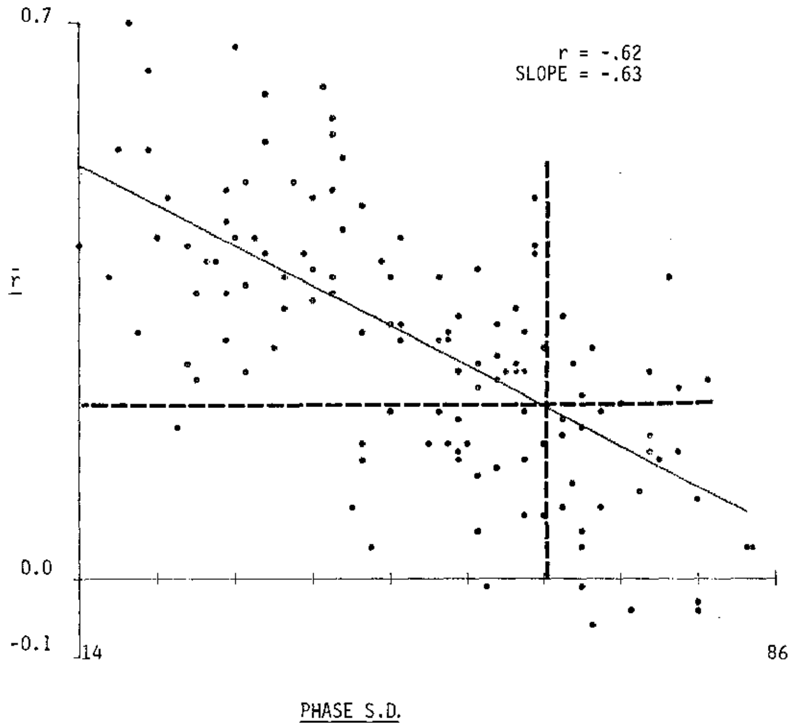


FIGURE 6.9: The 5% confidence intervals for $\bar{r}$ and phase S.D. have been indicated. Discrepancies between the two methods can be assessed from the number of points in the two diagonal quadrants, top right and bottom left. Considerably more negative $\bar{r}$ decisions were made for records which gave positive decisions using the phase constraint method.

compared with the cross-correlation co-efficient for the total of 129 observations. Only 8 phase values, (6%) were below the 5% level for records in which $\bar{r}$ exceeded the 5% level (top right quadrant). By contrast 22 observations of $\bar{r}$ (17%) were below the 5% level for records in which the phase S.D. value exceeded this probability level (bottom left quadrant).

THRESHOLD EVALUATION IN NORMAL HEARING SUBEJCTS

The region of threshold (0-40dBnHL) was more intensively studied in this group of subjects. The harmonic distribution of threshold responses exceeding the confidence interval was first established (Figure 6.10) and compared with the harmonic distribution of pooled pre-stimulus records.. A concentration of harmonic phase aggregation was observed in post-stimulus records in the frequency range 400-700 Hz (4th-7th harmonic). The frequency distribution of pre-stimulus occurrences was in keeping with the sampling statistics. The absolute number of "successful" harmonic occurrences for the region of threshold was then established. In many records two or more harmonics were significantly constrained. In other records only one harmonic showed significant phase constraint. The frequency distributions of both conditions were examined and again the main contribution to harmonic phase aggregation was in the frequency range 400-700 Hz (Figure 6.11). The relative contributions of different harmonics to response decisions was evaluated and the results summarised in Figure 6.12. Harmonic 6 gave the maximum number of positive decisions. The second most frequently contributing harmonic was harmonic 5. These two accounted for almost 75% of positive decisions. All but one decision was based on harmonics 2-8.

The amount of aggregation experienced by individual harmonics was investigated. Figure 6.13 shows the frequency distribution of phase S.D. for the three most constrained harmonics from each record over the intensity range 10-30 dBnHL. The mean for the distribution was 66° and the 75% level was 76°. Considering that three harmonics had been included from each ensemble then the appropriate confidence interval would have been the value appropriate to three joint occurrences (74°). Applying this to individual records, 70 from a total of 96, that is 73%, exceeded this confidence interval. This compared most favourably with the 75th percentile for the pooled distribution.

The frequency distribution of pooled phase S.D. for the most constrained harmonic in each ensemble was then compared with the

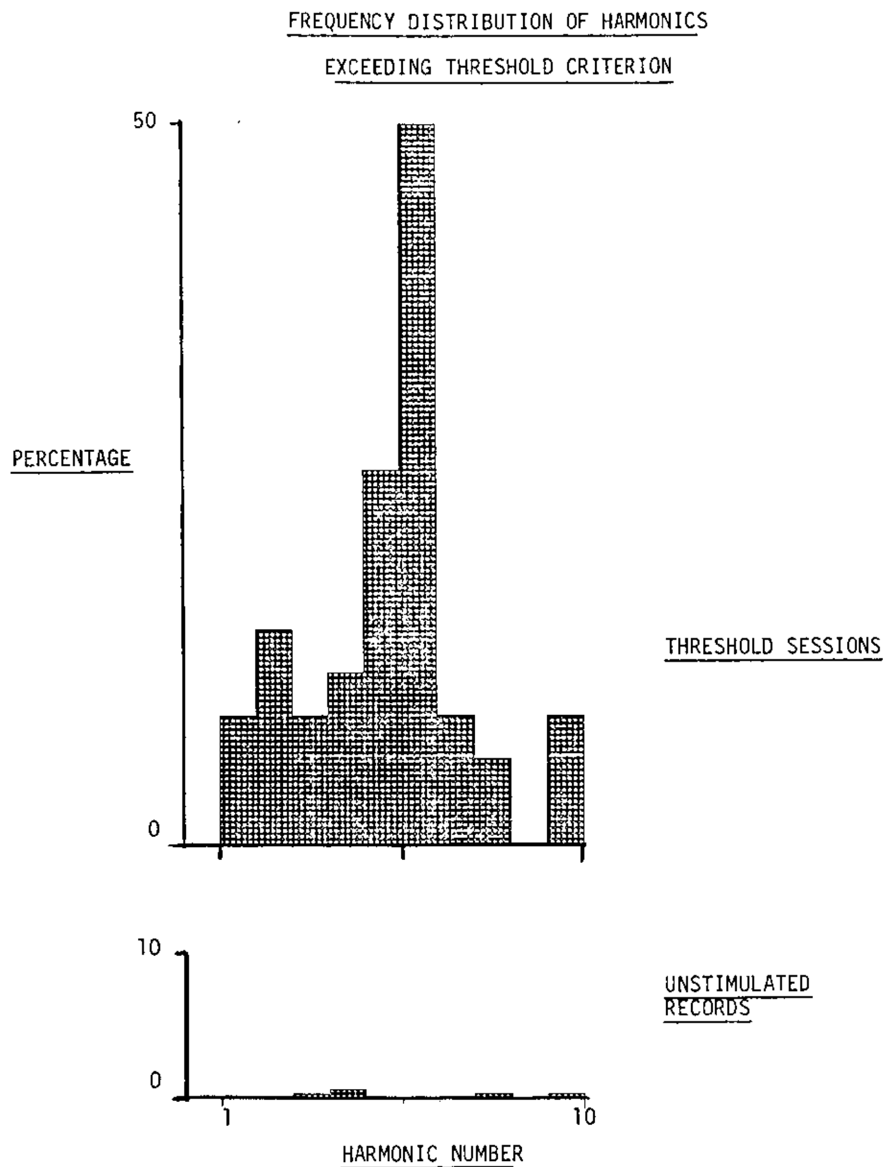


FIGURE 6.10: Percentage of harmonics exceeding the 1% probability level of unstimulated records. Threshold sessions mainly in stimulus range 10-20 dBnHL.

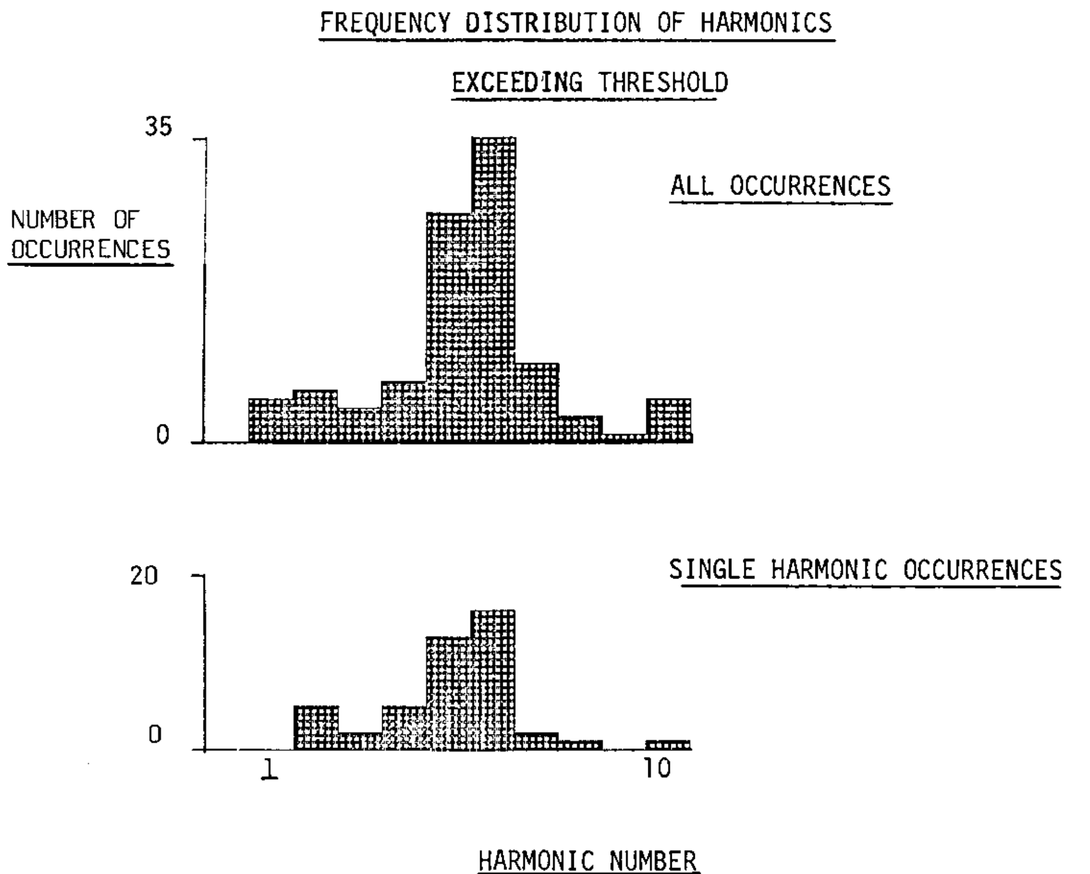


FIGURE 6.11: Frequency distribution of harmonics exceeding 1% probability in region of threshold (0-30 dBnHL). The total number of sessions examined was 66.

CUMULATIVE SUCCESS RATE FOR

HARMONICS REACHING THRESHOLD LEVEL

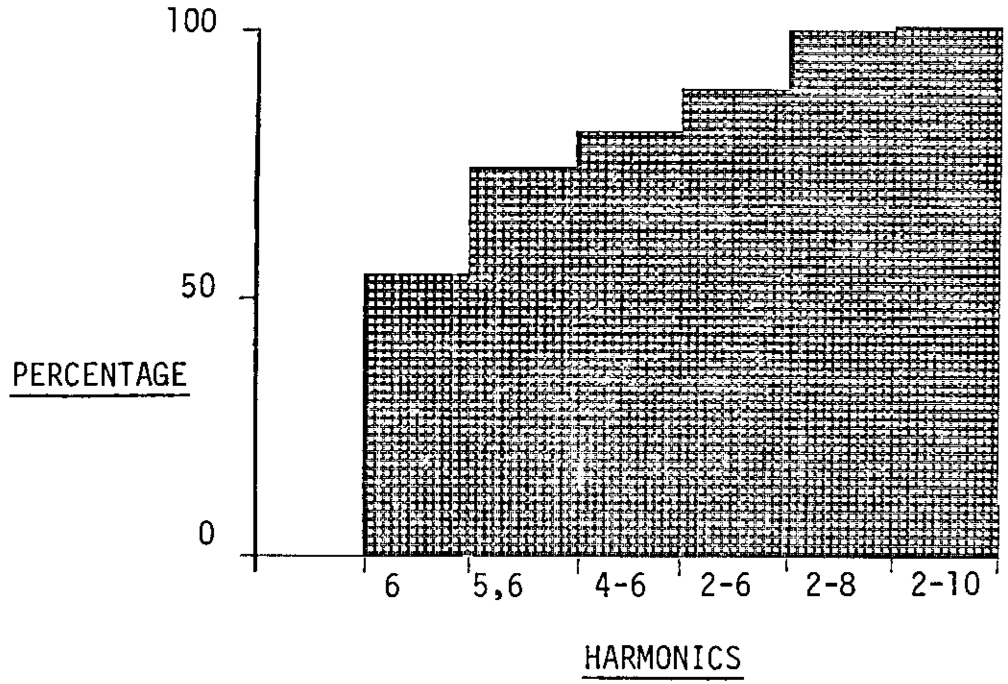


FIGURE 6.12

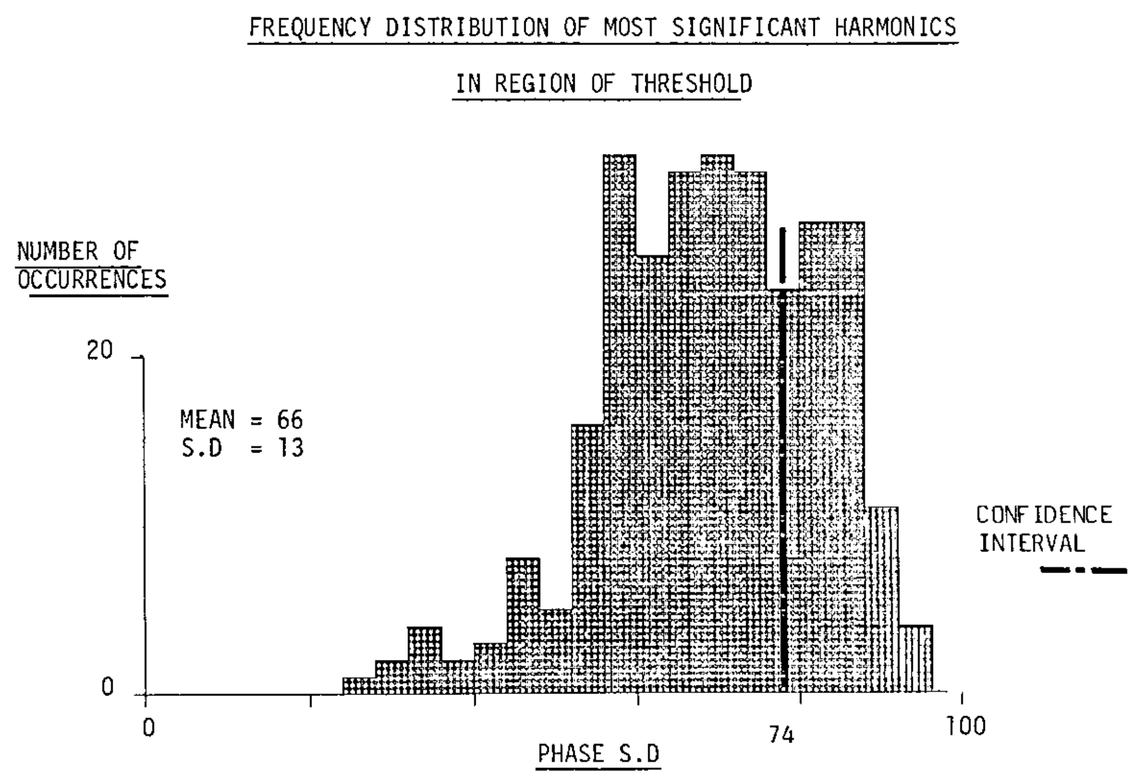


FIGURE 6.13: For each post-stimulus ensemble the three most constrained harmonics were selected. The stimulus range examined was 10-30 dBnHL.

corresponding distribution of the original ensemble mean correlation co-efficient for the same intensity range (10-30 dBnHL). The mean for the correlation distribution (.21) was well inside the confidence interval for this statistic (.33). The mean for the phase S.D. distribution was 58°, outside the confidence interval of 59° (Figure 6.14). The frequency distribution of phase S.D. was then examined separately at each of the three stimulus levels 10, 20 and 30 dBnHL (Figures 6.15, 6.16, 6.17). The advantages of attending to joint harmonic occurrences for improved threshold estimation was demonstrated. The frequency distribution of phase S.D. and associated confidence interval were again compared with the original correlation statistics,

Records exceeding Confidence Interval

Stimulus Level dBnHL	Phase S.D. %	Mean Cross-Correlation Co-efficient %
30	84	25
20	91	22
10	44	6

At these intensities the "success" rate for the phase constraint method greatly exceeded the corresponding rate for the cross-correlation method.

The phase S.D. of the most constrained harmonic gave an average threshold of 11 dB for the 34 normal hearing subjects. The corresponding level obtained using the cross-correlation method was 39 dB (Figure 6.18). The stimulus intensity at which a response could just be detected was further reduced to 15 dB by incorporating single and joint harmonic occurrences in the determination of threshold using phase aggregation method. Finally the relative sensitivities, of the phase method, the cross-correlation method and conventional visual scoring were compared (Figure 6.19). Threshold using visual method was at 11 dB with a standard deviation of 7 dB. Using the phase method, threshold was slightly higher at 15 dB and the standard deviation was 6 dB. By contrast the correlation method gave an average threshold at 39 dB with a standard deviation of 20. An improvement of approximately 25 dB in the objective detection of threshold had been achieved by using phase aggregation compared with the template matching using the cross-correlation technique.

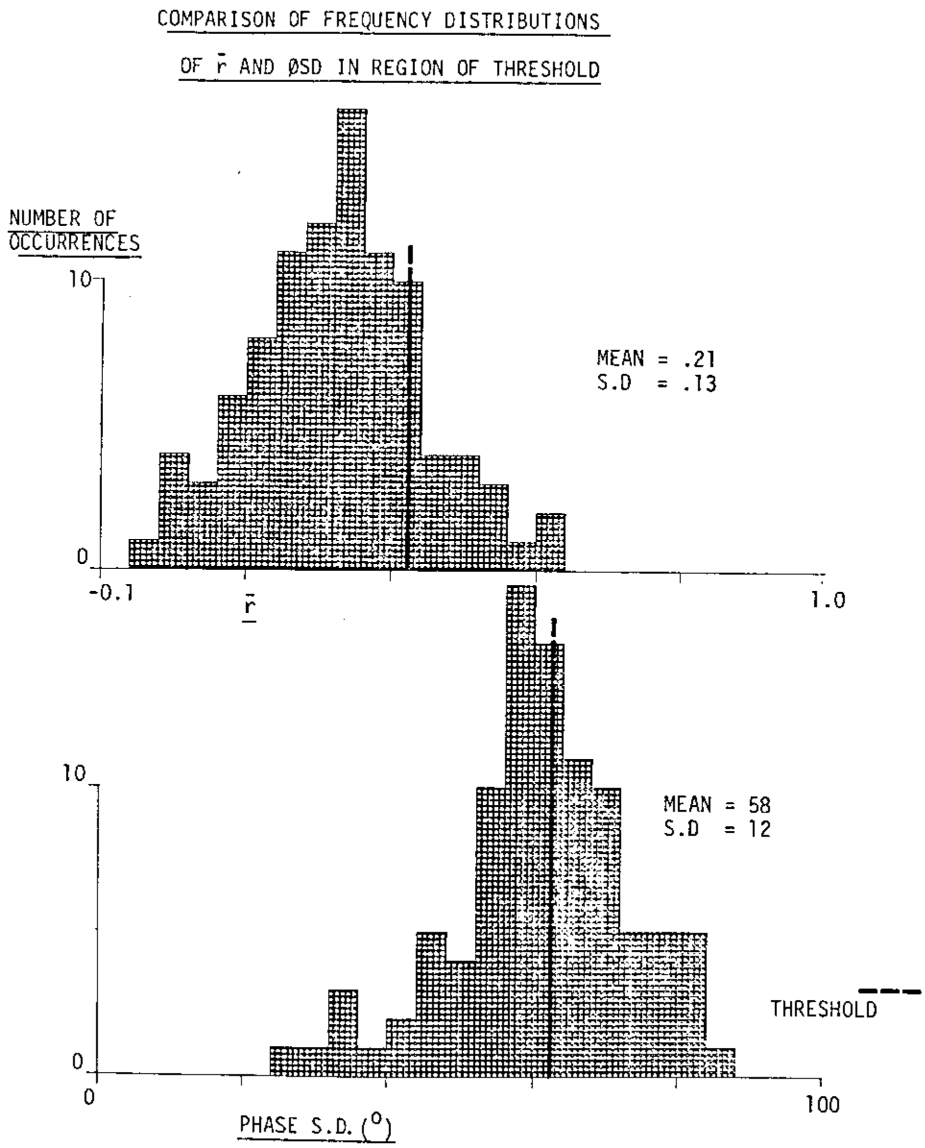


FIGURE 6.14: The phase S.D. distribution has been based on the single most constrained harmonic in each record.

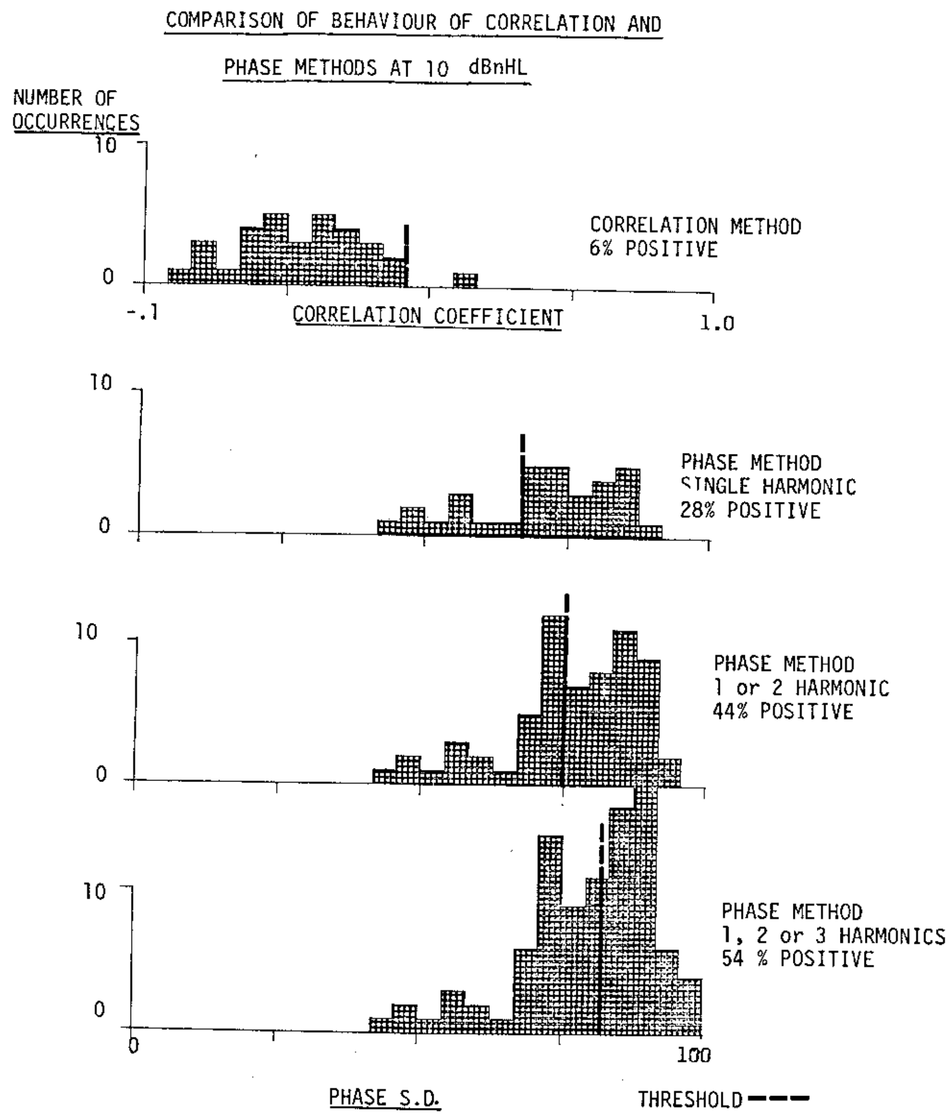


FIGURE 6.15 : In this and the next two figures the contributions of single, and joint harmonic occurrences to positive decisions have been compared.

COMPARISON OF BEHAVIOUR OF CORRELATION AND

PHASE METHODS AT 20 dBnHL

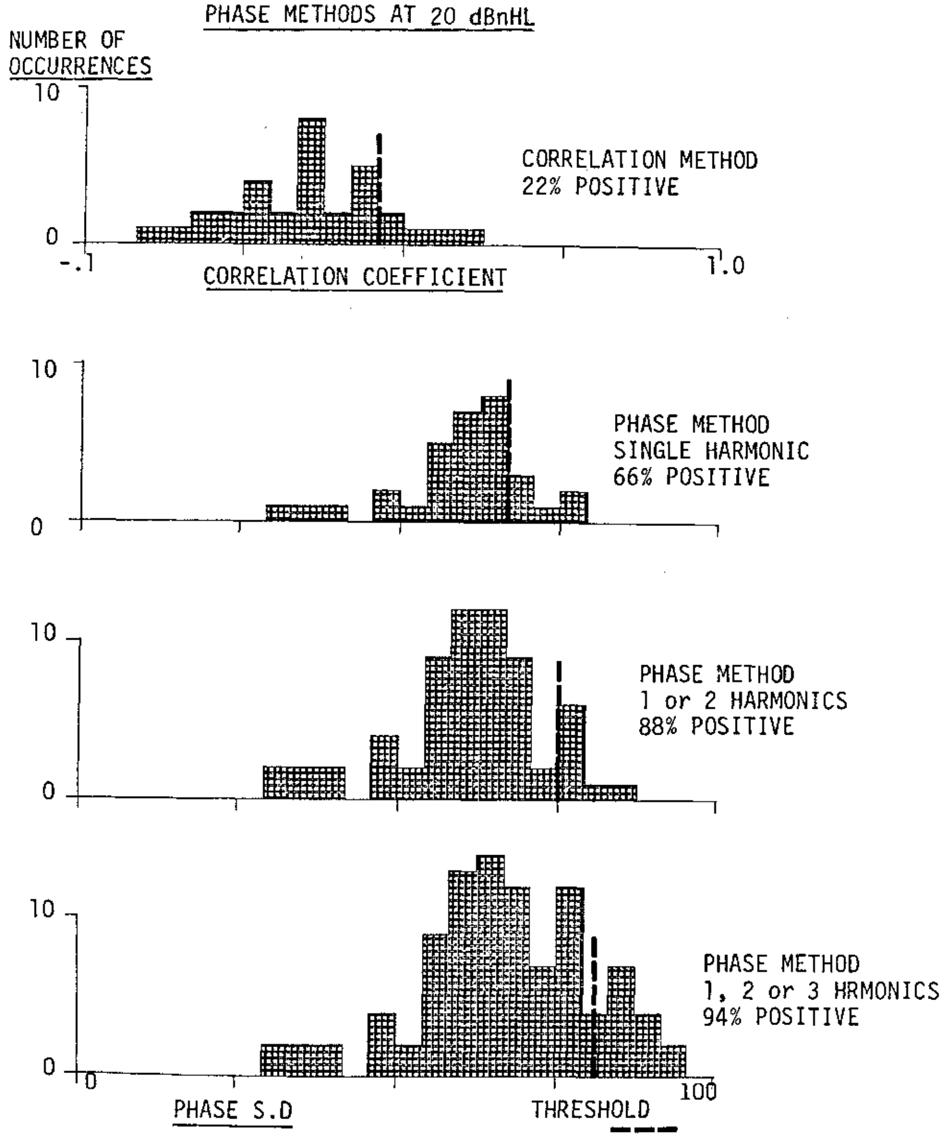


FIGURE 6.16

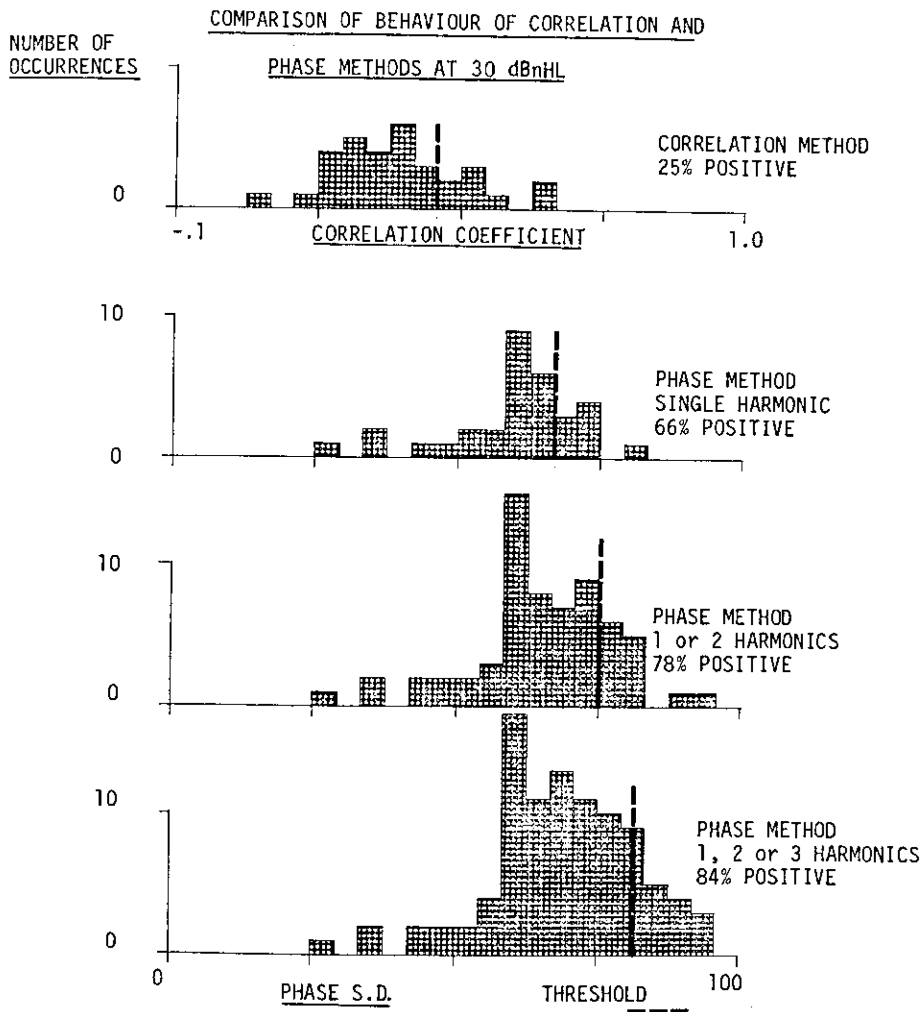

COMPARISON OF BEHAVIOUR OF CORRELATION AND
PHASE METHODS AT 30 dBnHL
NUMBER OF OCCURRENCES
0
-.1
CORRELATION COEFFICIENT
1.0
CORRELATION METHOD
25% POSITIVE
10
0
PHASE METHOD
SINGLE HARMONIC
66% POSITIVE
10
0
PHASE METHOD
1 or 2 HARMONICS
78% POSITIVE
10
0
PHASE METHOD
1, 2 or 3 HARMONICS
84% POSITIVE
0
PHASE S.D.
THRESHOLD
100

FIGURE 6.17

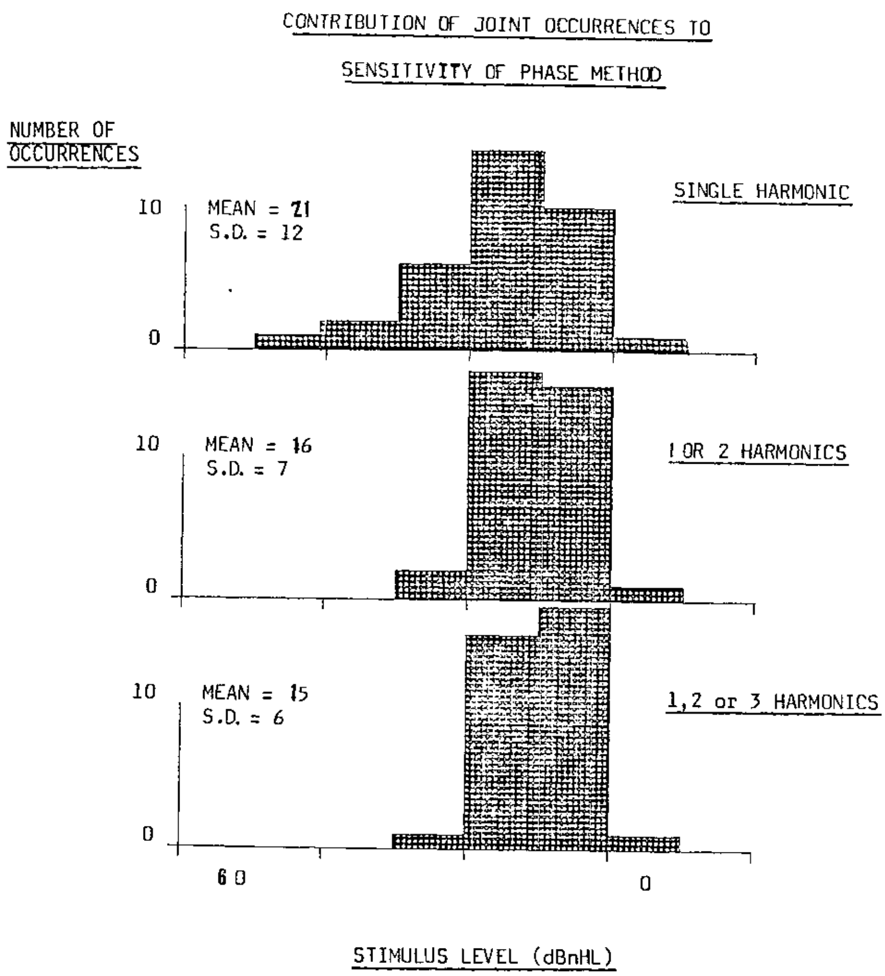

CONTRIBUTION OF JOINT OCCURRENCES TO
SENSITIVITY OF PHASE METHOD
NUMBER OF OCCURRENCES
10
0
MEAN = 21
S.D. = 12
SINGLE HARMONIC
10
0
MEAN = 16
S.D. = 7
1 OR 2 HARMONICS
10
0
MEAN = 15
S.D. = 6
1,2 or 3 HARMONICS
60
0
STIMULUS LEVEL (dBnHL)

FIGURE 6.18

DISTRIBUTION OF THRESHOLD

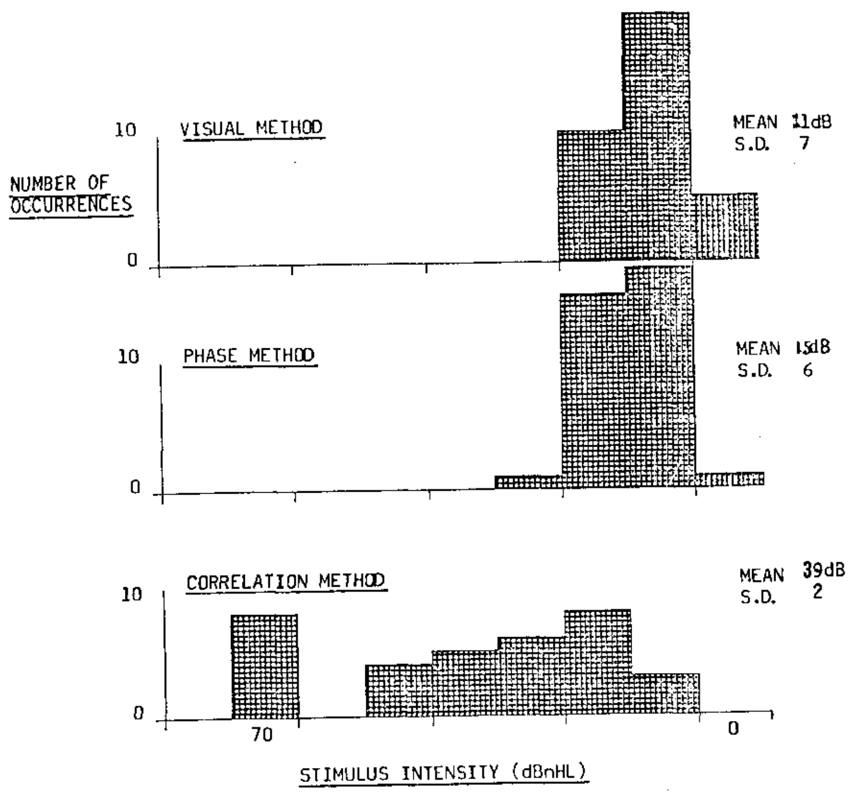


FIGURE 6.19

The choice of the 1% level as threshold criterion for the phase method gave results which were close to those obtained by independent visual scoring. Intersubject variability was exceedingly small and responses were almost exclusively at either 10 or 20 dB above subjective hearing level. A similar frequency distribution was obtained for the visual method. Throughout, the confidence interval associated with p = .01 has been used. As expected reduction in threshold was obtained when p = 0.05 was selected. The mean intensity level of threshold using p = 0.05 was 13 dB compared with 15 dB for p = 0.01.

Threshold Criteria	Distribution of Threshold 40 dB	30 dB	20 dB	10 dB	0 dB
p<.01	0	1	17	15	1
p<.05	0	0	12	20	2

The choice of the confidence interval was quite arbitrary although the small size of the improvement obtained by changing from the 1% to 5% level of confidence and the increased risk of false positive decisions favoured retaining the lower probability level.

The success of the phase aggregation method in detecting and quantifying a response event clearly indicated that phase standard deviation may be used as an objective method for the auditory brainstem potentials for establishing threshold using this procedure. Despite the bias in the sampling statistics the empirical confidence intervals for standard deviation were found to be well behaved and capable of detecting the auditory brainstem potential to within 15 dB of subjective threshold on average and to within 5 dB of the visual scoring.

It proved interesting to re-examine those records in which disagreements occurred between visual scoring and the phase aggregation method. In some in which phase S.D. gave a threshold level higher than the visual method, reducing the confidence interval to the 5% level resulted in total agreement being reached (Figure 6.20). In most however, disagreements remained (Figure 6.21):

Confidence Level	Discrepancy between Visual Method and Phase Constraint Method (Visual Score used as Reference) +20	+10	0	-10 dB
p<.01	2	11	17	4
p<.05		8	21	5

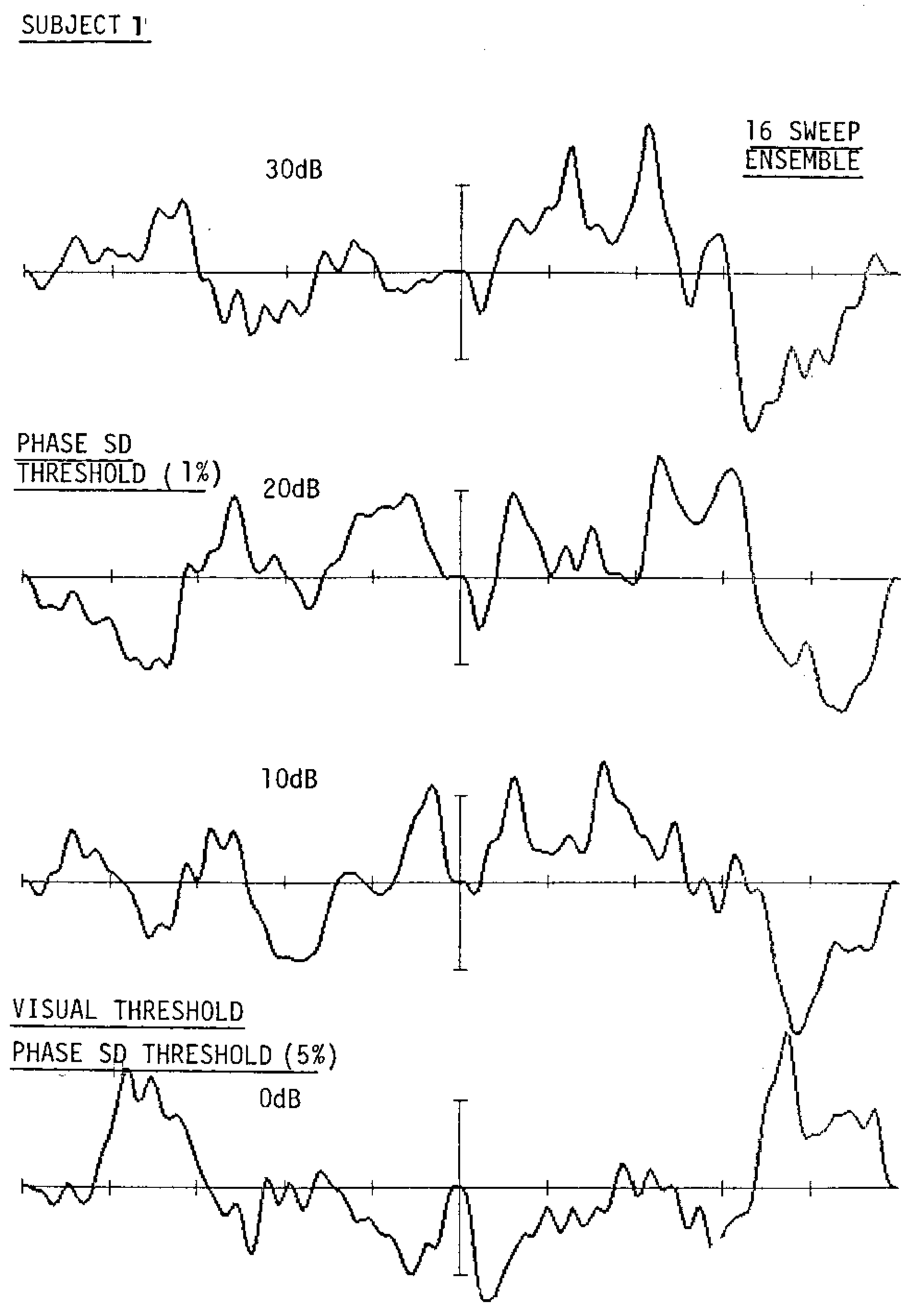


FIGURE 6.20: Normal hearing subject showing discrepancy between Subjective and Objective estimates of threshold.

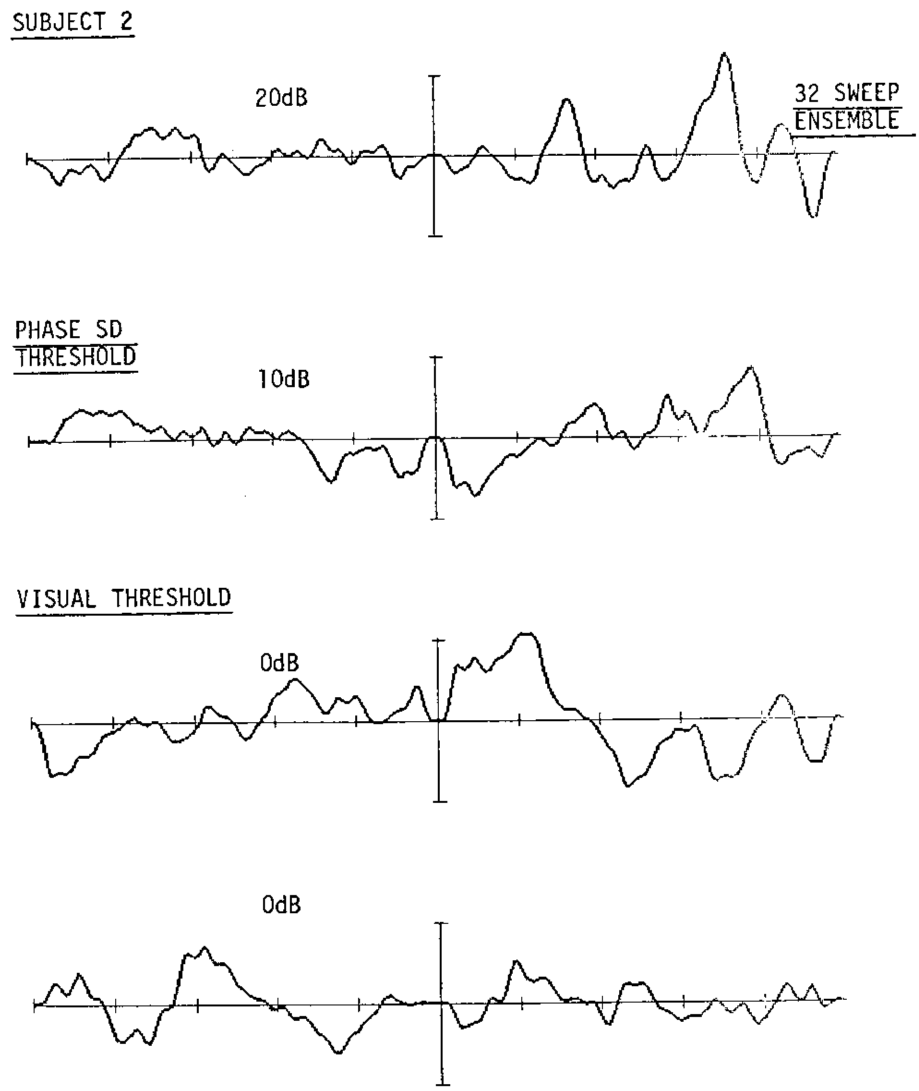


FIGURE 6.21: Normal hearing subject showing discrepancy between Subjective and Objective estimates of threshold.

It was concluded that the statistical quantification of probability that a given record belonged to either the population of supra-threshold or sub-threshold records gave more reliable discrimination than subjective decisions about the presence or absence of a response.

CLINICAL EVALUATION OF THE PHASE CONSTRAINT METHOD IN HEARING IMPAIRED CHILDREN AND ADULTS

Details of the patient group have been given in the Methods Section. Before commencing this clinical study it was decided to use ensembles of 32 rather than 16. A total of 2,048 responses were collected at each stimulus level and grouped into sub-averages, each sub-average consisting of 64 individual responses. This formed a new ensemble of size 32. The decision to use the larger number was based on earlier observation of the sampling statistics of phase S.D. Not only was the expected value reduced by smaller sample size, the variance of estimates increased greatly. Attention has almost exclusively been paid to the problem of false positive decisions, that is of rejecting the null hypothesis that a given observation did not deviate significantly from the population of unstimulated records. This Type I error has been guarded against simply by choosing the confidence interval associated with a small probability level (.01). But it had to be recognised that a second kind of error may have arisen, namely of accepting the null hypothesis when it was in fact false. For the given probability level and the relatively large variance observed in phase S.D. estimates for 16 sweep ensembles the risk of this Type II error was probably quite high.

The effects of sample size on both types of error have been well illustrated for the comparison of sample means and proportions (Fleiss, 1973). The contribution of ensemble size to the sampling statistics of phase S.D. is more complex but would appear to be very relevant for both types of error. Analogy can be made with the one tailed comparison of two samples differing in proportion in respect of some parameter. The .01 probability level for Type I error has been accepted. The probabilities of encountering Type II error are now considered. If a proportion of scores, say 25%, reach a certain level in the control sample and this same level is obtained by 85% of the comparison sample, the contribution of sample size to Type II error can be obtained directly from tables. For a probability level of .01 for Type I error,

Sample Size	16	18	22	30
Probability of Type II error (one tailed)	.30	.20	.10	.01

For sample size 16 the probability of erroneously accepting the null hypothesis is 30%, doubling the sample size reduces this to .01, the level of the Type I error. In the present clinical study it has been assumed that both types of error are equally serious. Corresponding to the control sample above, the 25th percentile of the sampling distribution of phase S.D. was 86^{o}. Examining the phase S.D. distribution for post-stimulus records at 40 dB, the most frequently observed threshold intensity, the 85th percentile was at 86^{o}. It was therefore decided to use 32 sweep ensembles as a compromise between speed of analysis and reduction of errors.

The thresholds for the auditory brainstem potentials were evaluated in 37 hearing impaired patients. Figure 6.22 shows the distribution of thresholds obtained using visual scoring and objective phase constraint methods. For both methods the maximum number of thresholds estimates were at the limits of audiometric stimulation. While it would have been desirable on theoretical grounds to have obtained the actual threshold estimate rather than indicating that it was beyond a certain level, for clinical purposes this degree of loss clearly indicated profound impairment. However, thresholds were observed over the full audiometric range which gave an opportunity to investigate the sensitivity of the method over a range of stimulus intensities. As a final assessment of the phase aggregation method a comparison was made between the visual estimation of threshold and the objective threshold. Both these estimates were obtained fully independently of one another (Figure 6.23). A remarkably high level of agreement was obtained and the correlation between the two tests was .98. On only one occasion did the discrepancy between the methods exceed 10 dB. In the great majority of cases agreement was total. The slope of the regression line was .97 and the Y-intercept 2.3 dB which might suggest that, on occasions, a samll over-estimate of threshold level was produced by the phase aggregation method.

It was decided therefore to re-examine those records in which disagreements occurred. The file with maximum discrepancy (20 dB) has been plotted in Figure 6.24. The criteria for visual threshold (40 dB) might in retrospect be open to question. Figure 6.25 shows an example of the situation in which the visual response gave a

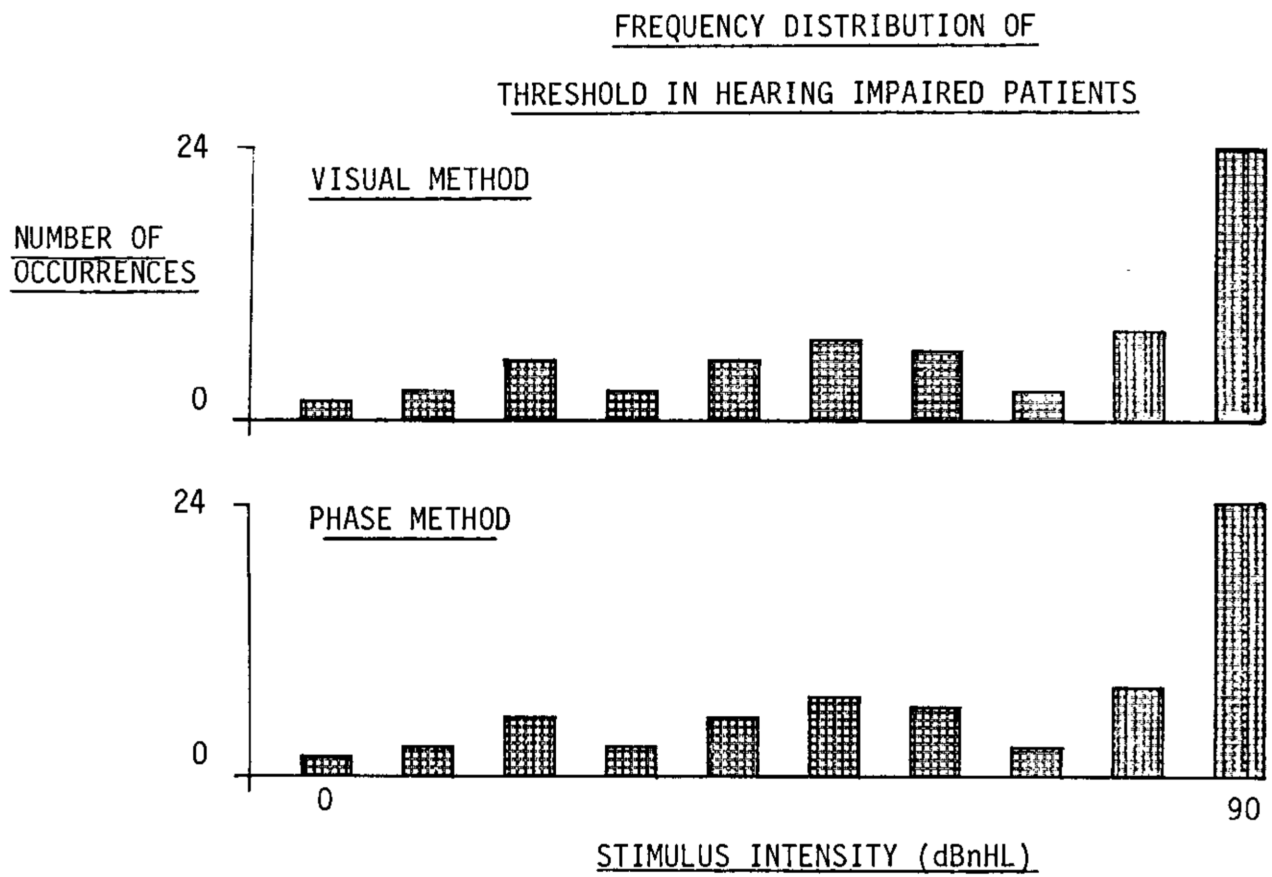

FREQUENCY DISTRIBUTION OF
THRESHOLD IN HEARING IMPAIRED PATIENTS
24
VISUAL METHOD
NUMBER OF
OCCURRENCES
0
24
PHASE METHOD
0
0
90
STIMULUS INTENSITY (dBnHL)

FIGURE 6.22

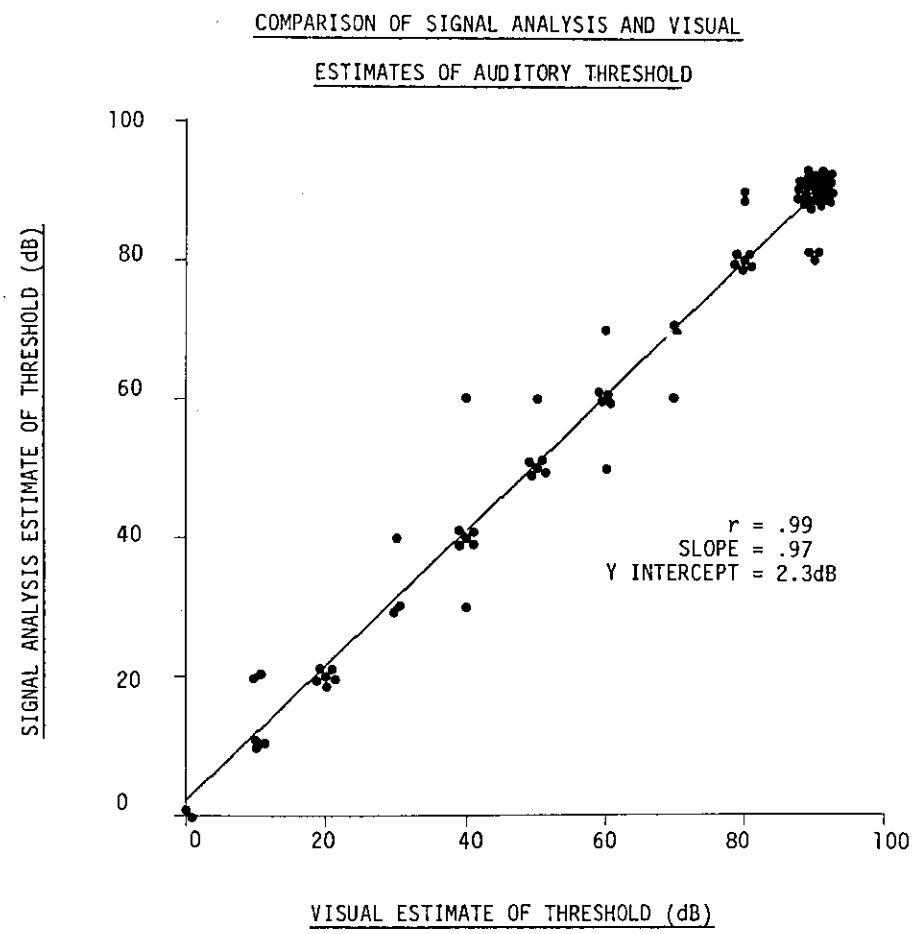

COMPARISON OF SIGNAL ANALYSIS AND VISUAL
ESTIMATES OF AUDITORY THRESHOLD
SIGNAL ANALYSIS ESTIMATE OF THRESHOLD (dB)
100
80
60
40
20
0
0
20
40
60
80
100
r = .99
SLOPE = .97
Y INTERCEPT = 2.3dB
VISUAL ESTIMATE OF THRESHOLD (dB)

FIGURE 6.23

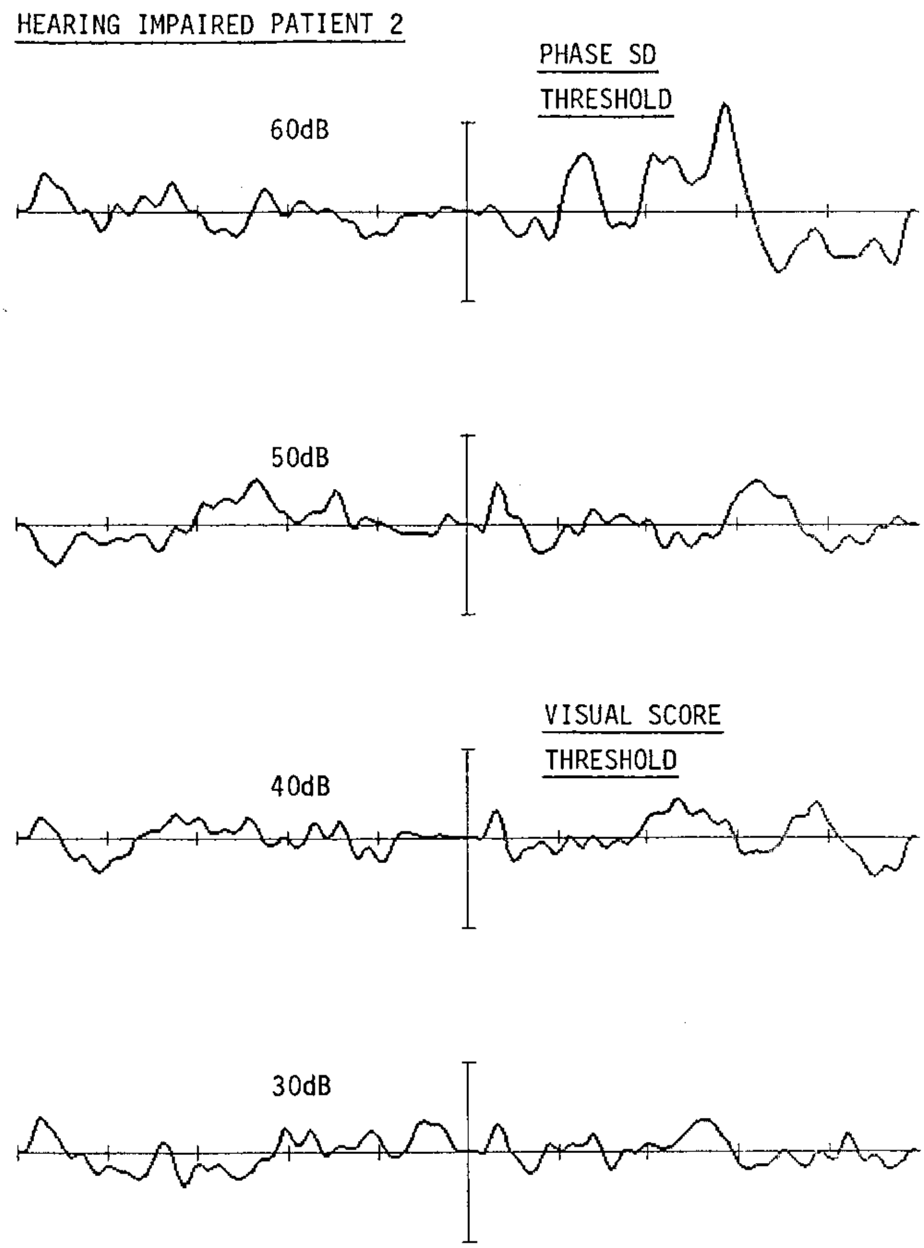


FIGURE 6.24: Hearing impaired patient showing discrepancy between Subjective and Objective estimates of threshold.

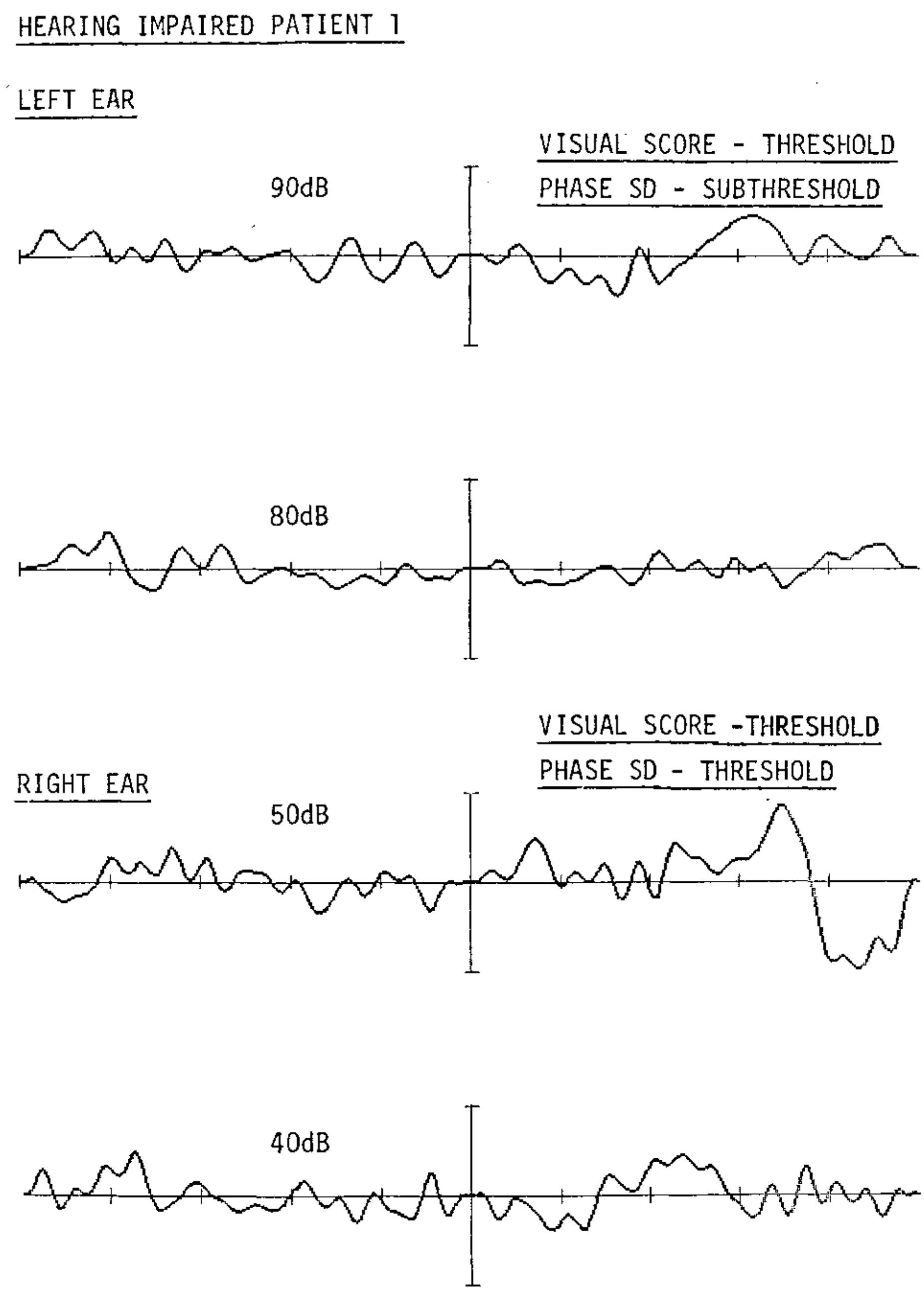


FIGURE 6.25: Hearing impaired patient showing discrepancy between Subjective and Objective estimates of threshold. Total agreement obtained for the right ear while for the left ear minimum discrepancy of 10 dB resulted.

threshold 10 dB lower than the statistical result. Again it can be seen in retrospect that the visual response was at best dubious. Of the seven decisions in which visual scoring gave a threshold lower than the phase constraint method, in only two did reduction of the significance level to 5% give a lowering of threshold and agreement between the two methods. A major advantage of the statistical method in this area of threshold was the quantification of confidence incorporated in any decision.

In conclusion, the signal statistical method provided a reliable and fully objective measure of auditory threshold. Disagreements with two highly trained observers were few, at most clinically insignificant (10 dB), and in retrospect appeared to indicate the boundary of transition between sub-threshold and threshold conditions. Signal statistics in the region of threshold provided insight into the nature of subjective decisions based on examination of the time domain pattern.

CONCLUSIONS

CONCLUSIONS

The aim of the present study was to develop a fully objective method for the detection and analysis of the far-field brainstem auditory evoked potentials. A cross-correlation method can be used as an objective basis for the determination of auditory threshold exhibited in the brainstem potentials. The method was first evaluated in a simulation study and subsequently in the results obtained from normal hearing subjects. The cross-correlations of each pre-stimulus or post-stimulus sweep with the grand-average of the specific ensemble were formed and the empirical statistic of the cross-correlation investigated as a function of stimulus intensity. The main conclusions of the simulation study were as follows:-

The confidence attached to individual correlation values depends on the behaviour of the spontaneous E.E.G. The histogram of frequency distribution $\bar{r}$, where $\bar{r}$ = mean r, is only approximately Gaussian and the spread critically dependent on the ensemble size underlying $\bar{r}$. In the present study the 1% probability level was chosen as "threshold" and the associated $\bar{r}_c$ for 16 sweep ensembles was 0.33.

The presence of a response embedded within the background E.E.G. noise produces a positive shift in the correlation distribution, the size of the shift depending on the signal to noise ratio. It was possible to reduce the E.E.G. noise by forming sub-averages and the observed improvement in correlation agreed well with the theoretical estimates and was approximately proportional to $\sqrt{n}$.

The following observations were made in a study of normal hearing subjects:

The statistic $\bar{r}$ showed a systematic inverse relationship with stimulus intensity. However, large variations in the value of $\bar{r}$ were observed at any given stimulus intensity such that at 10 dBnHL 95% failed to reach the objective criterion of threshold. Compared with visual scoring, threshold was on average 30 dB higher. A small improvement in the sensitivity of the procedure was obtained by band selective filtering of the response ensembles before correlation analysis, and threshold was on average 20 dB higher than that obtained with visual scoring.

While such filtering produced a small improvement in threshold estimation using the correlation procedure, it was perhaps not s surprising that a fixed choice of bandwidth had a variable effect. Significant increases in $\bar{r}$ were observed for some subjects, but little change was observed in others. It seemed likely that some harmonics may possibly be important in all subjects, but the relative contributions of other harmonics to the overall ocrrelation value varied from subject to subject and also from intensity level to intensity level. The problem then became one of selecting correct harmonics. More attention therefore, needed to be paid to the behaviour of individual harmonics themselves, selecting "significant" harmonics only into the pattern recognition technique.

A guinea-pig model has been utilised in a comparative signal analysis study of the brainstem potential response to auditory stimulation. Responses recorded differentially between the vertex and cervical regions were evoked by a free field click stimuli. A choice for such a model was made because of the very favourable signal to noise ratio. It was further justified through the similarity of response properties obtained, specifically:-

(i) The time domain pattern in response to high level stimulation

(ii) Amplitude and latency changes with stimulus intensity

(iii) The cross-correlation statistic $\bar{r}$ for 16 sweep ensembles.

The amplitudes and phases of significant Fourier harmonics in individual pre-stimulus and post-stimulus sweeps were separately examined. It has been found that harmonic amplitudes decrease with stimulus intensity while their phases become more widely scattered. As a measure of phase scatter, the second moment of the ensemble phase distribution (S.D.) altered more systematically with stimulus intensity than did harmonic amplitude. Correspondingly, threshold estimates based on harmonic phase standard deviation produced more satisfactory discrimination than criteria operating on harmonic amplitude. The phase standard deviation criteria of threshold agreed well with independent visual scoring of threshold.

The relative sensitivities, of the phase method the cross-correlation method and conventional visual scoring were then compared in a group of normal hearing subjects. Threshold using visual method was at 11 dB with a standard deviation of 7 dB. Using the phase method, threshold was slightly higher at 15 dB and the standard deviation was 6 dB. By contrast the correlation method gave an average threshold at 39 dB with a standard deviation of 20. An improvement of approximately 25 dB in the objective detection of threshold had been achieved by using phase aggregation compared with the template matching using the cross-correlation technique. The choice of the confidence interval for the objective methods was quite arbitrary although the small size of the improvement obtained by changing from the 1% to 5% level of significance and the increased risk of false positive decisions favoured retaining the lower probability level.

The success of the phase aggregation method in detecting and quantifying a response event clearly indicated that phase standard deviation may be used as an objective method for the auditory brainstem potentials for establishing threshold using this procedure. Despite the bias in the sampling statistics the empirical confidence intervals for standard deviation were found to be well behaved and capable of detecting the auditory brainstem potential to within 15 dB of subjective threshold on average and to within 5 dB of the visual scoring.

It proved interesting to re-examine those records in which disagreements occurred between visual scoring and the phase aggregation method. In some in which phase S.D. gave a threshold level higher than the visual method, reducing the confidence interval to the 5% level resulted in total agreement being reached. In most however, disagreements remained. It was also concluded that the statistical quantification of probability based on the ensemble histogram of frequency distribution of phase standard deviation gave a more reliable determination of threshold than subjective decisions.

As a final assessment of the phase aggregation method a comparison was made between the visual estimation of threshold and the objective threshold in a group of hearing imparied children and adults. Both these estimates were obtained fully independently of one another. A remarkably high level of agreement was obtained and the correlation between the two tests was .98. On only one occasion did the discrepancy between the methods exceed 10 dB. A major advantage of the statistical method in this area of threshold was the quantification of confidence incorporated in any decision.

In view of the relative sensitivity of the phase method over other measures, the question was raised whether the assumptions of superposition were in fact valid. Results of a comparative study of simulated and real responses supported the hypothesis that the evoked brainstem potentials imposed patterning on the spontaneous background activity by superposition.

APPENDIX

For a Binomial Random Variable with individual probability = y

(1) Probability of two or more occurrences in a sample size of a.

$$P_0 = P\ (0 \text{ occurrences}) = (1 - y)^a$$

$$P_1 = P\ (1 \text{ occurrence}) = a(1 - y)^{a-1} \times (y)$$

$\therefore$ Probability of two or more occurrences

$$= 1 - (P_0 + P_1)$$

(2) Probability of three or more occurrences in a sample size of a.

$$P_0 = (1 - y)^a$$

$$P_1 = a(1 - y)^{a-1} \times (y)$$

$$P_2 = (a-1) \times \frac{a}{2} \times (1 - y)^{a-2} \times (y)^2$$

$\therefore$ Probability of three or more occurrences

$$= 1 - (P_0 + P_1 + P_2)$$

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